2020 NATIONAL STUDENT TRIAL ADVOCACY COMPETITION (STAC)

OFFICIAL RULES

and

FACT PATTERN

Endowed by Baldwin & Baldwin, LLP
**Important Dates:**

Requests for fact pattern clarification due: January 15, 2020  
Team Participant Registration due (students must be AAJ members): February 14, 2020  
Regional Competitions: March 12 – March 15, 2020  
National Final Competition: April 16 – April 19, 2020

AAJ’s 2020 Fact Pattern is authored by A. Michael Gianantonio of Pittsburgh, PA.  
AAJ extends its thanks and appreciation to Mr. Gianantonio for developing the 2020 Fact Pattern. AAJ also extends its thanks and appreciation to our STAC co-chairs Lauren Barnes, Maria Glorioso, and Fred Schultz.

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**Please note:**

Information regarding the 2020 Student Trial Advocacy Competition is available at [www.justice.org/STAC](http://www.justice.org/STAC) and will be updated frequently.

**All questions and correspondence should be addressed to:**

Kara Yoh  
American Association for Justice  
*Formerly the Association of Trial Lawyers of America (ATLA®)*  
777 6th Street, NW  
Suite 200  
Washington, DC 20001  
Phone: (800) 622-1791 or (202) 965-3500 ext. 8612  
Fax: (202) 625-7084  
STAC@justice.org
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GENERAL INFORMATION

One of AAJ’s goals is to inspire excellence in trial advocacy through training and education for both law students and practicing attorneys. One way AAJ accomplishes this goal is by sponsoring a national student mock trial competition. This is an exceptional opportunity for law students to develop and practice their trial advocacy skills before distinguished members of the bar and bench.

Because the purpose of this competition is to give law students the opportunity to develop their trial skills, the actual merits of the plaintiff’s case and the defendant’s case presented are irrelevant to this purpose. Competition rounds are decided not on the merits of a team’s side but on the quality of a team’s advocacy.

Requests for Clarification

Requests for clarifications of the rules or fact pattern must be submitted via an online survey no later than 5:30 p.m. (EST) on January 15, 2020. A link to the survey will be posted online at www.justice.org/STAC after the fact pattern is released. Each school is limited to five (5) questions. No school, regardless of the number of teams it has in the competition, may submit more than five questions. Each subpart of a question is counted as a question.

RULE VIOLATION AND FILING OF COMPLIANTS

A competitor or coach violating any of the rules governing the national Student Trial Advocacy Competition may be penalized or disqualified. If a team wants to file a complaint under the rules, the team’s coach should immediately notify the regional coordinator at a regional competition or the final round coordinator at the final competition. The coordinator will review the complaint and make a ruling, which shall be binding for that round of competition. The coordinator’s rulings will be governed by the rules of the competition and the objectives of the program.

Complaints after a regional competition or after the national competition must be filed in writing with Kara Yoh at the address on page 2 no later than the seven (7) days following the last day of the regional or final round, as appropriate. The AAJ Law Student Services Committee will promptly consider and rule on any such complaints.

LAW SCHOOL AND STUDENT ELIGIBILITY

The competition is open to all law schools nationwide. A law school may enter up to two teams. Each team shall be comprised of four law students. A school’s selection method of its trial team(s) is left for the school to determine. However, for a student to be eligible, he or she must be enrolled for a J.D. degree and be a law student member of AAJ.
Students who graduate in December 2019 are eligible to participate only if the competition counts toward their credits for graduation and they will not be admitted to practice prior to March 2020.

Each student participant must be an AAJ student member by February 14, 2020 in order to participate.

REGISTRATION PROCEDURES

Refund Policy

Requests for a refund of a school’s registration fee were due in writing before November 15, 2019. It is inevitable that a few teams drop out of the competition in the months leading up to the regionals. Teams placed on the waiting list because the competition is full will be contacted for participation in the order that their registrations were received. Teams on the waiting list will also be issued a refund check if it is determined that the team will not be competing. Schools that registered two teams but are only able to enter one team because the competition is full will receive a refund of the registration fee for the second team.

AAJ Law Student Membership and Student Team Registration

Student team members must be AAJ members by February 14, 2020 in order to participate. This year, all students must verify their membership and register for their respective team online at www.justice.org/STACParticipantRegistration. AAJ Law Student membership dues are $15. If you have any questions about AAJ’s law student membership, or if you have any trouble becoming a member online, please call AAJ’s member hotline at (202) 965-3500, ext. 8611. If you have any questions about registering as a STAC team member, please call Kara Yoh, STAC Manager, ext. 3502.

Coach Registration

AAJ must receive the names of the coach for each team. A coach must accompany each team to the regional competitions. A coach may be a law student, but may not be a student who is competing in the competition. Coaches do not need to be members of AAJ, and should not register for the STAC event. Coaches, and other administrators traveling with the team, must complete an online survey listing the team coach that will be travelling with the team by March 2, 2020. This is the information that will be sent to the regional coordinators to communicate logistics onsite.

Student Substitution Policy

Substitution of team members after February 14, 2020 is not permitted except in the case of personal emergencies. Requests for substitution after the February 14 deadline must be made in writing with an explanation of why the substitution is needed and sent to Kara Yoh at AAJ for consideration. These requests can be made to STAC@justice.org.
REGIONAL AND FINAL COMPETITION ASSIGNMENTS

Entering teams will be assigned to one of 14 regional competitions based on geographical convenience to the extent possible. Teams from the same law school will be assigned to the same region. If a school’s second team is waitlisted, there is no guarantee that second team will be sent to the same region as the first team. Teams will be notified of any date changes when regional assignments are made. Please remember that a school’s second team will not be officially registered until one team from each law school has entered the mock trial competition. Then the second teams will be registered on a first-come, first-served basis until all the team slots are filled. If you paid for two teams and only one team is able to participate, you will receive a refund for the second team.

In order to officially compete in the competition, a team must receive its regional assignment. If a team is not informed by AAJ that it is able to compete, that team is not registered for the competition.

Coaches

A coach must accompany each team to the regional and the final competitions. The coach for a team that goes to the final competition does not have to be the person who coached the team at the regional competition.

A coach may be a law student, but may not be a student who is competing in the competition.

Only team coaches are permitted to attend the coaches’ meeting. If a coach is unable to attend, he or she must notify AAJ and the regional coordinator. Only then can students be permitted to attend in the coach’s absence.

Team Expenses

Travel expenses for the regional and final competitions are the responsibility of the participants. Teams competing in past competitions have obtained funds from law school deans and alumni associations, members of the local legal community, state and local trial associations, and AAJ law school chapters.

COMPETITION FORMAT

This is a trial skills competition. There is no motion or trial brief writing component. Each team will consist of four law students. Two students will be advocates and two students will play the witnesses for their side in each round. Advocates and witnesses may change their roles from round to round, but roles must remain consistent throughout each individual trial.
In the regional competitions:
- Each team will compete in three qualifying rounds
- The top four teams from the qualifying rounds will advance to a single elimination semifinal round
- The top two teams from the semifinal round will advance to a single elimination final round to determine which one team will advance to the National Final Competition

In the final competition:
- Each team will compete in three qualifying rounds
- The top eight teams from the qualifying rounds will advance to a single elimination quarter-final round
- The top four teams from the quarter-final round will advance to a single elimination semifinal round
- The top two teams from the semifinal round will advance to a single elimination final round

Regional Team Pairings in Qualifying Rounds

Pairing of teams in the qualifying rounds will be at random and conducted during the coaches’ meeting prior to each competition. Teams may also be pre-assigned by the regional coordinator prior to the coaches’ meeting; this practice is at the discretion of the regional coordinator. Each team will represent both plaintiff and defendant in the first two rounds. No two teams shall compete against each other more than once in the qualifying rounds. Teams from the same school will not compete against each other during any of the rounds of the regional competition or in the qualifying rounds of the national final competitions.

Team Rankings in All Other Rounds

In the semifinal round, the first-ranked team will meet the fourth-ranked team, and the second-ranked team will meet the third-ranked team.

Regional semifinal round (Normal pairings: 1 v. 4; 2 v. 3)
- Situation 1: Teams ranked 1 and 4 are from the same school
  - New pairings: 1 v. 3; 2 v. 4
- Situation 2: Teams ranked 2 and 3 are from the same school
  - New pairings: 1 v. 3; 2 v. 4

The ranking of teams to determine the semifinalists and finalists will be determined by the following factors (in this order):

1. Win/loss record
2. Number of winning votes
3. Number of total points awarded to the team
Each succeeding criterion above will be used only if the prior criterion does not fully rank the teams and will be used only to break ties created by the use of the prior criterion. In the event that all three of these criterion are tied, the regional coordinator will announce a tie-breaker.

If paired regional semifinal teams have met in the qualifying rounds, they will each represent different sides than in the previous meeting. If they have not yet met, each team will take the side they represented only once in qualifying rounds. If matched teams represented the same side only once, the winner of a coin toss will choose sides.

In the regional finals, the teams will represent a different side than in the semifinal round. If the two opposing teams each represented the same side in the semifinal round, the winner of a coin toss will choose sides.

When an odd number of teams compete at a regional competition, one randomly chosen team will receive a “bye” in each qualifying round. For ranking purposes, a bye will count as a win and the team with the bye will be deemed to have had three votes and the points equal to the average of the team’s points from the two other qualifying rounds.

**NATIONAL FINALS**

**Quarter-final round** (Normal pairings: 1 v. 8; 2 v. 7; 3 v. 6; 4 v. 5)

Situation 1: Teams ranked 1 and 8 are from the same school
New pairings: 1 v. 7; 2 v. 8; 3 v. 6; 4 v. 5

Situation 2: Teams ranked 2 and 7 are from the same school
New pairings: 1 v. 7; 2 v. 8; 3 v. 6; 4 v. 5

Situation 3: Teams ranked 3 and 6 are from the same school
New pairings: 1 v. 8; 2 v. 7; 3 v. 5; 4 v. 6

Situation 4: Teams ranked 4 and 5 are from the same school
New pairings: 1 v. 8; 2 v. 7; 3 v. 5; 4 v. 6

If teams from the same school are matched to compete based on rank in the semifinal and final rounds of a regional competition, regional hosts will re-pair teams according to the following scenarios:

**Semifinal round** (Normal pairings: 1 v. 4; 2 v. 3)

Situation 1: Teams ranked 1 and 4 are from the same school
New pairings: 1 v. 3; 2 v. 4

Situation 2: Teams ranked 2 and 3 are from the same school
New pairings: 1 v. 3; 2 v. 4
**Determination of Team Representation**

If the four national and regional semifinal teams have already met in the qualifying rounds, they will represent different sides from the previous confrontation. If they have not yet met, each team will take the side they represented only once in qualifying rounds. If matched teams represented the same side only once, the winner of a coin toss will choose sides.

The national finals semifinal teams will represent a different side than in the quarter-final round. If matched teams represented the same side in the quarter-final round, the winner of a coin toss will choose sides. The two national final teams will represent a different side than in the semifinal round. If matched teams represented the same side in the semifinal round, the winner of a coin toss will choose sides.

**THE TRIAL**

The competition this year involves the trial of a civil lawsuit. The same fact pattern will be used in the regional and final competitions. The trial judge previously ruled that the case would be bifurcated, and the case being tried in the competition is the first phase of the case—the liability phase. Only evidence relevant to the liability issue will be received. There are no pending third-party claims.

The Federal Rules of Evidence (FRE) and Federal Rules of Civil Procedure (FRCP) are the applicable rules of evidence and civil procedure. Only these rules, and the law provided in the fact pattern, shall be used in argument. Specifically, no statutory, regulatory, or case law shall be cited unless such law is provided in the fact pattern.

Students may argue based upon the comments or advisory notes to the Federal Rules of Evidence but may not cite the cases contained therein. No written briefs, motions, or trial notebooks, may be presented to the judge hearing a case. Advocates may show the judge part of the fact pattern that the judge is asked to rule on, but only at the time the judge is asked to rule on it.

No pretrial motions of any kind are allowed.

Motions for a judgment as a matter of law and evidentiary objections are permitted.

The trial will consist of the following phases by each team in this order:

- Opening statements for plaintiff followed by defendant
- Plaintiff’s case-in-chief
  - Plaintiff’s direct of plaintiff’s witness #1
  - Defendant’s cross of witness
  - Plaintiff’s redirect of witness
  - Similar for plaintiff’s witness #2
- Defendant’s case-in-chief
  - Defendant’s direct of defendant’s witness #1
  - Plaintiff’s cross of witness
• Plaintiff’s redirect of witness
• Similar for defendant’s witness #2
• Closing argument
  • Plaintiff’s closing
  • Defendant’s closing
  • Plaintiff’s rebuttal closing

Each side is limited to two live witnesses whom they may call in any order.

• Plaintiff must call Carson Gray and Tony Stork
• Defendant must call Keaton Scent and Nat Romanov

The trial has six (6) major advocacy opportunities for each team: opening statement; direct/redirect examinations (2); cross-examinations (2); and closing argument. Each attorney member of a team must handle three of the six opportunities. Opening statement and closing argument may not be done by the same person, and may not be split between team members. Each team member must do a direct and cross. Each team member does not need to play an attorney role.

During the competition, each team will represent both parties. Pairing in the qualifying rounds will be at random, with each team representing both plaintiff and defendant at least once in the three rounds.

Except in the final round, the courtrooms will be off-limits to all team members, coaches, friends, and family members who are not associated with either team competing, unless their team has already been eliminated from the competition.

No team may receive any coaching from anyone in any form during a round, including any recesses or breaks. The regional or national coordinator, as applicable, has the authority to punish any violation of this rule by disqualifying the team from the remainder of the competition.

A team may record its trial if: (1) no additional lighting is required; (2) recording of the trial does not interfere with or delay its conduct; and, (3) all participants of the round, including the presiding and scoring judges and the regional or national coordinator, as applicable, agree. All recordings are subject to the local courthouse policy and discretion.

Timing of the Trial

• Each team will have 80 minutes to complete its argument; time will be stopped during objections.
• The time limit will be strictly enforced, although it is not necessary that all time allotted be used.
• There will be no time limits for specific aspects of the trial.
• Time on cross-examination is charged against the team conducting the cross-examination.
• Time will be stopped for objections and responses to objections.
• Performance at trial will be evaluated by a panel of judges and/or attorneys, one of whom will preside over the trial as Judge, making rulings as necessary, and the remainder (up to three) of whom will act as the jury.
Facts Outside the Record

Advocates must confine the questions, and witnesses must confine their answers, to the facts provided in the fact pattern and reasonable inferences which may be drawn therefrom.

1. Definition: A fact outside the record is (1) any instance on direct examination, cross-examination, or re-direct, in which a witness introduces testimony contradictory to his or her affidavit; and/or (2) any instance on direct or re-direct examination in which an attorney offers, through witness testimony, material facts not included in or reasonably inferred from a witness’s affidavit.

2. Cross-examination: On cross-examination, a witness commits no violation when he or she testifies to material facts not included in his or her affidavit as long as the witness’s answer is responsive to the question posed. Attorneys who ask questions to which the witness’s affidavit does not provide an answer risk receiving an unfavorable answer in trial. Notwithstanding the preceding rules, nothing in this section is intended to prevent attorneys from attempting to challenge a witness’s credibility by demonstrating an omission through use of the witness’s affidavit.

3. Material facts: No inferred fact may be material, which is defined (a) as a fact that changes the merits of either side of the case or (b) that bears on the credibility of any witness or litigant. The latter is defined to include any background information about a witness or litigant.

4. Reasonable inference: A witness’s answer does not qualify as a reasonable inference merely because it is consistent with statements in the witness’s affidavit. A reasonable inference must be a conclusion that a reasonable person would draw from a particular fact or set of facts contained in the fact pattern documents.

5. Affidavit: An affidavit includes not only a witness’s sworn statement, but any document in which the witness has stated his or her beliefs, knowledge, opinions or conclusions or a document which a witness relied upon to form his or her conclusions.

Except during closing argument, no party may make an objection that the opposing team is going outside the record. Instead, a party may address instances of testimony outside the record by means of impeachment of the offending witness or by contradiction using another witness or document.

When true and if asked, witnesses must admit that the “facts” they have testified to are not in their deposition or otherwise in the record: “yes, I did not say that in my deposition.” Witnesses may not qualify this response; for example, a witness may not say he or she was not asked about the issue at deposition or that the facts were contained in some portion of the deposition omitted from the record.

Like all officers of the court, who are bound by the Rules of Professional Conduct prohibiting deceit, dishonesty, or misrepresentation, coaches and team members must play fairly and ethically. Invention and use of a material fact outside the record is considered cheating and will result in judges reflecting this in their scoring.
This is a competition about trial advocacy skills—doing what you can with the facts provided and the witnesses in the courtroom. The coordinators will instruct the judges on the significance of facts outside the record and impeachment efforts, and that judges should reflect a violation of this rule in their scoring.

**Witnesses**

Any witness may be played by a person of either gender. Before the opening statement, each team should notify the other team of the gender of each witness they intend to call and any witness they could call but are choosing not to call.

Expert witnesses are assumed to have access to and have read all documents in the fact pattern. A lay witness can only attest to his or her deposition and related exhibits.

All depositions are signed and sworn. The same attorney conducting direct examination of a witness shall also conduct any redirect examination.

The only lawyer who may object during witness testimony is the lawyer who will be examining that witness.

Witnesses may not be recalled. Witnesses will not be sequestered.

**JURY INSTRUCTIONS**

The instructions provided in the fact pattern are the only instructions that will be given. The instructions are the only statements of the applicable substantive law. Instructions will not be eliminated or modified. No additional instructions may be tendered or will be given.

**EXHIBITS**

Participants are free to enlarge any diagram, statement, exhibit, or portion of the fact pattern if it is identical to the item enlarged, or if any changes provide no advantage to the party intending to use it. Participants may, subject to the presiding judge’s ruling, use common household items such as a measuring tape, flashlight, or serving bowl as demonstrative evidence. Such items are subject to security restrictions imposed by the courthouse and may not cost more than $20. The use of computers, projectors, and other electronic equipment for demonstrative purposes is prohibited during the trial. Participants must clear all such demonstrative evidence with the regional or national coordinator, as applicable, at the coaches’ meeting preceding the competition.

In addition, subject to rulings of the court, counsel and witnesses may draw or make simple charts or drawings during examination, opening or closing, but not in advance of the trial, for the purpose of illustrating testimony or argument. These materials may not be written or drawn in advance of the segment during which they are being used.

No charts or drawings may reflect facts outside the record.

All exhibits are stipulated as authentic and genuine for purposes of trial.
SCORING CRITERIA

Performances at trial will be evaluated by a panel of three or more judges and/or attorneys, one of whom will preside as the trial judge, with the others sitting as jurors. To the extent that there are more than three scoring judges, all scores may be used. This may result in teams being awarded fractions of votes and points. The most a team can win is three votes and 180 points per trial.

An example of this would be as follows: Team A is in a trial with five judges, with all judges’ votes and points counting. Team A wins the trial, with 4 votes in favor of A’s side. Team A is awarded the following point totals from each judge: 55, 57, 53, 58, and 48. Team A’s votes and points are calculated using the formula below:

Votes: $4 \times 0.6 \left(\frac{3}{5} \text{ to equalize to three votes}\right) = 2.4$

Points: $271 \times 0.6 \left(\frac{3}{5} \text{ to equalize to a portion of 180 possible}\right) = 162.6$

To the extent a courtroom has three or more judges, the trial judge may elect not to participate in scoring. The trial judge will rule on any objections or motions for judgment as a matter of law.

Each member of the jury may award up to ten points in each phase of trial for each party. A sample score sheet is attached.

If at the end of the trial, an evaluator awards the same number of points to both the plaintiff and the defendant, the evaluator will award one additional point to either the plaintiff or the defendant for effectiveness of objections and/or overall case presentation in order to break the tie. There is a section on the score sheet where evaluators can indicate who should win the trial in the event of a tie.

Evaluators have been instructed not to score teams on the merits of the case.

The following criteria for scoring trial performances are set forth to assist both judges and student advocates. Evaluators are not limited to these criteria and may consider other aspects of strategy, technique, and so forth, which they view as important.

Evaluator Shortage

For each match, there must be three votes from evaluators. In the event that, due to circumstances beyond AAJ’s control, there are not three evaluators in a particular match, “ghost” evaluator(s) will be used to score the round. The vote of a ghost evaluator is determined by calculating the average of all other evaluators in the session.

Suggested Evaluation Criteria

OPENING STATEMENT

Did Counsel:
1. Generally confine statement to an outline of the evidence that would be presented?
2. Clearly present counsel’s theory of the case?
3. Persuasively present counsel’s theory of the case?
4. Personalize self and client?
5. Allow opposing attorney to make argument during opening statement?
6. Make unnecessary objections?

EXAMINATION OF WITNESSES

Did Counsel:
1. Ask questions that generated minimal valid objections?
2. Make/fail to make objections with tactical or substantial merit?
3. Respond appropriately to objections?
4. Know the rules of evidence and express that knowledge clearly?
5. Develop rapport with the witness?
6. Maintain appropriate general attitude and demeanor?
7. Address the court and others appropriately?
8. Demonstrate awareness of ethical considerations?

Did Direct-Examiner:
9. Use leading questions unnecessarily?
10. Develop testimony in an interesting and coherent fashion?
11. Follow up on witness’ answers?
12. Present the witness in the most favorable light?

Did Cross-Examiner:
13. Appropriately use leading questions?
14. Control witness?
15. Follow up on answers and elicit helpful testimony?
16. Use impeachment opportunities?

CLOSING ARGUMENT

Did Counsel:
1. Present a cohesive theory of the case, pulling all the positive arguments together?
2. Deal effectively with the weakness(es) in his or her own case?
3. Make an argument that was persuasive?
4. Have an effective style of presentation?
5. Utilize the law effectively in the argument?
6. Inappropriately interrupt the argument of the opposing counsel?
7. Properly confine rebuttal to rebuttal matters?
8. Effectively counter the opponent’s speech in rebuttal

Discrepancies in Remaining Match Time

Often, bailiffs are unavailable to keep time for rounds. In such cases, one or more judges in each match should be instructed to keep time according to the timekeeping rules. Additionally, judges may ask the respective teams to assist with this process. Teams may also keep track of time used for their own purposes. They may not, however, report their time used or that of an opposing team to the bailiff or judge for any purpose, unless they were instructed to do so. Moreover, time use improperly reported by any team may not be considered or used by a bailiff or judge for any purpose.

Notwithstanding this limitation, in the event that the match judge or judges declare the time
remaining as less than the team requires for closing or other parts of the trial, the coach or
team member (whoever records the time discrepancy¹) should immediately consult with the
Regional Coordinator during the break, who should then evaluate the circumstances and
decide the amount of time remaining. Neither the team coach nor the team member should
discuss the discrepancy with the match judge. Should the team be unable to consult with the
Regional Coordinator before completion of the trial and the team requires additional time to
complete the trial, the team may elect to complete the trial beyond the time allotted. When
the trial is complete, the time will be evaluated by the Regional Coordinator. The team will
lose two points from the number of total overall points for that round (as tallied on the ‘Trial
Score Sheet’) for every five minutes—or fraction thereof—of time in excess of its allotment.

**Viewing of Score Sheets by Teams**

Viewing of the score sheets is done at the discretion of the Regional Coordinator. Each team
will have the right to view their score sheets for each round. Team coaches may only view
score sheets once the third round has commenced. This should be done one team at a time.
Participating students should be unaware of how they were scored until the qualifying rounds
are completed, and the semi-final teams are announced. Teams are not allowed to take score
sheets with them or make any markings to the score sheets. Teams may view score sheets
only in the presence of the Regional Coordinator. If team coaches require a copy of their
score sheets, they should notify the Regional Coordinator and email AAJ staff.

¹ Note that coaches and team members may not communicate during rounds
2020 STUDENT TRIAL ADVOCACY COMPETITION (STAC)
JUDGE’S SCORE SHEET

Teams are to be scored on their trial skills only, NOT on the merits of the case.
Do not give half-points. Do not tie teams. There must be a winner.
Do not write your name on this score sheet, and do not share your score with the participating students or coaches.

ROUND:

REGIONAL LOCATION: ________________________________

TEAM ____ -- PLAINTIFF

<table>
<thead>
<tr>
<th></th>
<th>Good</th>
<th>Average</th>
<th>Poor</th>
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<tbody>
<tr>
<td>Opening Statement</td>
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<td>Direct Exam of Plaintiff's Expert Witness</td>
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<td>Cross Exam of Defendant's Lay Witness</td>
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<td>Cross Exam of Defendant's Expert Witness</td>
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<td>Summation</td>
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Total points awarded to PLAINTIFF ____________________________

TEAM ____ -- DEFENDANT

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<th>Good</th>
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<th>Poor</th>
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2020 AAJ Fact Pattern

CARSON GRAY

v.

EDISON AUTOMOBILE COMPANY

Prepared by A. Michael Gianantonio

of Robert Peirce & Associates

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IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF STEELTON  

CARSON GRAY;  
   Plaintiff,  

v.  

EDISON AUTOMOBILE COMPANY;  
   Defendant.

COMPLAINT

AND NOW, comes Plaintiff, Carson Gray, and files the within Complaint, the following of which is a statement:

I. PARTIES

1. Plaintiff, Carson Gray, is an adult individual residing at 5064 Yoh Avenue, Steelton, in the District of Steelton.

2. Defendant, Edison Automobile Company ("Edison"), is a Delaware corporation with a business address of 125 Hyperloop Drive, Los Francisco, in the state of California.

3. At all times relevant hereto, Edison acted through its employees, agents, contractors and/or subcontractors.

II. FACTS

4. In 2015, Edison commenced a pilot program in Steelton for its autonomously driving automobiles.

5. After making numerous representations to local, state, and national authorities that Edison had suitable technology to test these vehicles in a "real world" situation, Steelton granted Edison permission to utilize the city as Edison’s laboratory.
6. Edison simultaneously began pilot programs in Lone Star and Buffalo-Niagara.

7. Edison was working in partnership with Lyber, an internet-based ride sharing platform that outsourced passenger transportation to a network of independently operating drivers.

8. Lyber users could utilize an app on their smart phone to call for transportation; a Lyber driver would then pick up the user and take the user to his or her destination.

9. It was Edison’s hope to replace Lyber drivers with fully automated vehicles that no longer required a driver to operate.

10. In February 2017, a fleet of 15 Edison self-driving vehicles began operating in Steelton, providing rides to Lyber users.

11. In March 2017, an Edison vehicle, working in partnership with Lyber in Buffalo-Niagara, was en route to pick up a Lyber user, when the Edison vehicle left the street and drove on the sidewalk for several hundred feet.

12. Darren Ryan, the local engineer in charge of Buffalo-Niagara operations sent multiple communications to Edison suggesting that the all autonomous vehicles be taken out of service until a full inquiry could be made.

13. Keaton Scent, founder of Edison and lead engineer on the project, determined a full stop on the project was not necessary and kept all Edison vehicles in service.

14. In the later afternoon hours of September 4, 2017, Carson Gray was in a parking space on Webster Street in Penn’s Woods.
15. The parking space was on-street parking and Carson Gray’s motorcycle was legally parked in the on-street parking space.

16. At the same time, an Edison autonomous vehicle was making a right from Pennsylvania Avenue and continued onto Webster Street to pick up a passenger at the corner of Webster Street and New York Avenue.

17. There was a designated Lyber pick-up area located adjacent to the parking space where Carson Gray’s motorcycle was parked.

18. Carson Gray had not moved from the parking space where the motorcycle was parked, when suddenly, and without warning, the Edison autonomous vehicle struck Carson.

19. As a result of the collision, Carson suffered multiple injuries including, but not limited to, a fractured right tibia, a fractured right femur, a fractured left tibia, a fractured pelvis, and a closed head injury.

20. All of Carson’s injuries were caused by the negligence of Defendant Edison.

COUNT I

Negligence

21. Plaintiff incorporates by reference all previous Paragraphs of the Complaint as if set forth in their entirety herein.

22. As a motorist on a public thoroughfare, Edison owed Carson a duty of care.

23. Edison breached its duty to Carson insofar as:

   a) Edison knew, or should have known, that its vehicles were not capable of operating in a manner in which they would obey all Steelton’s traffic laws;
b) Edison knew, or should have known, that there was a problem in the self-driving vehicle software based upon the incident occurring in Buffalo-Niagara; and

c) Edison knew, or should have known, that its vehicles were prone to prematurely leave their lane of traffic.


25. As a result of this collision, Carson suffered significant and severe injuries.

WHEREFORE, Plaintiff demands judgment against Defendant, in an amount in excess of the prevailing arbitration limits, exclusive of prejudgment interest, post-judgment interest and costs; for punitive damages; and for such other relief as this Court seems fit to award.

A JURY TRIAL IS DEMANDED

Respectfully submitted

/s/ Luna Swatkins
Attorney for Plaintiff
IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF STEELTON

CARSON GRAY;

Plaintiff,

v.

EDISON AUTOMOBILE COMPANY;

Defendant.

ANSWER AND AFFIRMATIVE DEFENSES

AND NOW, comes Defendant, Edison Automobile Company (“EAC”), and files the within Answer and Affirmative Defenses, the following of which is a statement:

ANSWER

1-2. The averments of Paragraphs 1 through 2 of Plaintiff’s Complaint are admitted.

3. As the averments of Paragraph 3 of Plaintiff’s Complaint, constitute conclusions of law, no responsive pleading is required.

4. The averments of Paragraph 4 of Plaintiff’s Complaint are denied as stated. While EAC’s vehicles were first deployed in August 2015, EAC commenced its driverless Highway Integrated Transportation program (“HIT”) in first quarter 2011. After a series of rigorous in-house testing, closed course testing, and driver-assisted testing, the fully autonomous vehicles were put into service in Steelton in August 2015.

5. The averments of Paragraph 5 of Plaintiff’s Complaint are denied as stated. EAC rigorously tested its autonomous vehicles and presented verified, empirical information to Steelton and other local, state, and federal regulatory agencies that the vehicles were safe for use on public roadways because they were and are.

7-8. The averments of Paragraphs 7 through 8 of Plaintiff’s Complaint are admitted.

9. The averments of Paragraph 9 are denied. EAC hoped to work in conjunction with Lyber and Lyber’s drivers, not to replace Lyber drivers. Further, EAC’s vehicles will have numerous other impacts on the automotive industry that will increase safety and reduce the number of vehicle crashes.

10. The averments of Paragraph 10 of Plaintiff’s Complaint are admitted.

11. The averments of Paragraph 11 of Plaintiff’s Complaint are denied. Rather, an EAC vehicle did not “leave the street” but was impacted by icy road conditions that caused the vehicle to move onto a sidewalk; the vehicle traveled a short distance before becoming able to stop, and there were no injuries or collisions.

12. The averments of Paragraph 12 of Plaintiff’s Complaint are admitted in part and are denied in part. While it is admitted that Darren Ryan sent an email communication suggesting that EAC consider removing autonomous vehicles from the road, Darren Ryan was under scrutiny at the time based upon several allegations made by coworkers of Darren Ryan creating a hostile work environment.

13. The averments of Paragraph 13 of Plaintiff’s Complaint are denied as stated. Keaton Scent concluded a full halt of the project was not necessary after an intensive internal review that was conducted in cooperation with Buffalo-Niagara authorities. All autonomous vehicles were withdrawn from service during the time of the investigation, which lasted for three weeks.
14. The averments of Paragraph 14 of Plaintiff’s Complaint are denied. Witness statements indicated that Carson Gray was parked at a curb on Webster Street and pulled out in front of the autonomous vehicle, thus causing the collision.

15-17. The averments of Paragraphs 15 through 17 of Plaintiff’s Complaint are admitted in part and denied in part. Carson Gray was not operating the motorcycle, and as an unlicensed driver, should not have been on the motorcycle. However, it is admitted that immediately prior to the incident that vehicle in question made a right hand turn from Pennsylvania Avenue onto Webster Street and that there is a traffic light controlling the intersection of Webster and New York.

18-19. The averments of Paragraph 18 of Plaintiff’s Complaint are denied. Carson Gray suffered injury as a result of Carson’s own negligence.

20. As Paragraph 20 of Plaintiff’s Complaint is an incorporation paragraph, no responsive pleading is necessary.

21-24. As the averments of Paragraphs 21 through 24 of Plaintiff’s Complaint constitute conclusions of law, no responsive pleading is required. However, EAC was not negligent and Carson Gray’s injuries were caused by Carson’s own negligence.

**AFFIRMATIVE DEFENSES**

1. Plaintiff’s Complaint fails to set forth a cause of action upon which relief may be granted.

2. Plaintiff’s Complaint is barred by Plaintiff’s own negligence.

3. Plaintiff’s claims were caused or contributed by the superseding and intervening acts of persons, entities, or circumstances beyond the control of Defendant.

4. Plaintiff failed to adhere to Steelton’s traffic laws.
5. Plaintiff was an unlicensed motorcycle driver.

6. Plaintiff was not wearing a helmet at the time of the collision.

4. Defendant owed no duty to Plaintiff.

WHEREFORE, Defendant, Edison Automobile Company, respectfully requests that this Honorable Court enter judgment against Plaintiff and dismiss Plaintiff’s Complaint in its entirety.

A JURY TRIAL IS DEMANDED

Respectfully submitted

/s/ Allie Blue
Attorney for Defendant
IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF STEELTON

CARSON GRAY;

Plaintiff,

v.

EDISON AUTOMOBILE COMPANY;

Defendant.

STIPULATIONS

AND NOW, comes the parties to this matter, and file the within Stipulations to be used at trial, which shall have the binding effect of being taken as established facts if so offered:

1. On September 4, 2017, Carson Gray did not possess a valid motorcycle license.

2. As of September 4, 2017, Carson Gray had completed all safety training and courses required to obtain said license.

3. Carson Gray received a motorcycle license on August 11, 2018.

4. Carson Gray had a valid Steelton automobile license.

5. Steelton motor vehicle laws require licensed motorcycle drivers of less than two years of driving experience to wear a helmet.

6. At the time Darren Ryan sent his emails of April 14, 2017, Edison had opened an investigation into Mr. Ryan concerning employee allegations that Mr. Ryan created a hostile work environment.
7. Mr. Ryan and Edison reached a mutual separation agreement on September 1, 2017, whereby Mr. Ryan was granted early retirement.

8. The mutual separation agreement is confidential and inadmissible.

9. All Edison autonomous vehicles are equipped with video monitoring equipment.

10. All video footage from the vehicle in question from September 4, 2017, was given to the National Transportation Safety Board ("NTSB") for analysis; the NTSB subsequently lost all footage and there no other copies of the footage available.

11. Darren Ryan is unavailable for trial.

12. Chaz Shanton was deposed during discovery but is unavailable for trial. The parties agree that Chaz Shanton is unavailable to testify, as that term is defined by the Federal Rules of Civil Procedure and the Federal Rules of Evidence.

13. The parties agree that Chaz Shanton’s deposition may be used at trial and the deposition testimony itself is not subject to a hearsay objection. As such, the deposition testimony may be used for any purpose so long as the intended use is otherwise admissible under the Federal Rules of Evidence.

14. The District Court for the District of Steelton follows the Federal Rules of Evidence.

15. The District Court for the District of Steelton follows the Federal Rules of Civil Procedure.

16. The depositions are signed and sworn to by each respective deponent as being accurate and authentic.
17. The expert reports were produced by the parties simultaneously before trial. Experts have reviewed all documents contained within this case file and may testify to the same; however, the expert’s testimony is limited by the applicable rules of Civil Procedure.

18. The expert reports have been prepared and signed by each respective expert.

18. Plaintiff must call Carson Gray and Tony Stork as witnesses.

19. Defendant must call Keaton Scent and Nat Romanov, as witnesses.

20. This case has been bifurcated into a liability phase and a damages phase.

For purposes of this trial, the parties will try the liability phase only.
IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF STEELTON

CARSON GRAY;

Plaintiff, 

v.

EDISON AUTOMOBILE COMPANY;

Defendant.

JOINT EXHIBIT LIST

AND NOW, comes the parties to this matter, by and through their respective
counsel, and submit the following proposed joint exhibit list. The parties agree the
identified exhibits are authentic and admissible subject to objection on grounds that the
proposed exhibit is otherwise inadmissible under the pertinent rules of evidence.

1. Motorcycle registration for Carson Gray;
2. April 2017 emails between Darren Ryan and Keaton Scent;
   Is Now”;
4. January 8, 2018 Steelton Post-Gazette newspaper article entitled
   “Superloop Shut Down Pending Feds’ Investigation”;
5. Medication fact sheets for clonazepam, paroxetine, and alprazolam.
Deposition of Carson Gray

And now, this 6th day of June, 2019, Carson Gray, being duly sworn by the undersigned appeared at the offices of MurdockPunxy, LLP, for the purposes of deposition by oral questioning.

(Questioning by Allie Blue)

Q. Good morning. We met earlier today before your deposition, but for purposes of the record, can you please state your name?

A. Sure, my name is Carson Gray.

Q. Carson, have you ever been deposed before?

A. No.

Q. Have you ever given testimony before in a civil or criminal case?

A. What is the difference? I am not sure I understand.

Q. Okay, sure. A civil case is like the case you filed against my client. A criminal case is a case in which you are accused of violating a law.

A. Okay, I have testified at a criminal case before.

Q. What was the nature of that case?

A. I was charged with driving under the influence a few years back.

Q. Were you convicted?

A. No, halfway through my trial it was determined because I was first time offender, I was eligible for a something called the accentuated rehab program

By Ms. Swatkins

You mean the accelerated rehabilitative disposition program, ARD?

A. Yes.

By Ms. Blue
Q. Okay, so you were admitted into the ARD program. Do you know what that means?
A. From what I understand I was never convicted of a crime, and because I met all of the requirements of the program, my record has been expunged. I have been sober for three years now.

Q. Alright, are there any other testimony or lawsuits that you have been a part of?
A. No.

Q. Great. So there are a couple of ground rules that I would like to set up before we begin. First, when I ask you a question, I expect you to tell me what you know when you answer that question. I do not want to you guess or speculate, okay?
A. Sure.

Q. So if you answer one of my questions, we can agree that you have provided a full answer, right, and that you are not leaving anything out?
A. Okay. I agree.

Q. If you do not hear me or the question that I ask, please ask me to repeat it and I will be happy to do so, alright?
A. Yes.

Q. Similarly, if I ask you a question and you do not understand it, please ask me to rephrase my question. Can you do that?
A. I can.

Q. So anytime that you answer one of my questions, I am going to assume that you both heard and understood the question I asked, is that fair?
A. Yes.

Q. Okay, so let’s start with the hard questions, how old are you?
A. I am 31.
Q. So, at the time of the accident you would have been 29?
A. Yes.

Q. And when were you born?

Q. Where do you currently live?
A. 5064 Yoh Avenue in Steelton.

Q. Is that the same address you lived at when you were involved in the accident in September 2017?
A. Yes.

Q. How long have you been at that address?
A. Just over two years. I moved there right before the accident from my hometown of Asbury Park.

Q. How far away is Asbury Park?
A. I’d say about a thousand miles or so. It’s back east.

Q. Had you ever been to Steelton before?
A. No. I was looking to make a clean start. I got a job here working for Dr. Googlay.

Q. Who is Dr. Googlay?
A. It is actually a what. Dr. Googlay is a website that people can use to check their medical symptoms and get information about various medical conditions and medications and things like that.

Q. What do you do at Dr. Googlay?
A. I am in advertising. I sell advertising space to companies that may be interested in advertising on the site.

Q. Is this something you have been trained to do?
A. Yes, I went to college where I majored in marketing and minored in Spanish. I then went to work for Rick’s, which is a sporting goods store, which is where I worked until when I moved to Steelton.

Q. You mentioned earlier that you moved here to get, I think you said, a clean start. Can you explain what you mean by that?

A. Sure, I just felt like I was in a rut. I was not happy with my life and I started finding comfort in drinking. I was in a long-term relationship and when my partner left me, I really went into a tailspin. I was drinking every night, and then I got pulled over after I had a couple too many at the bar.

Q. I see, and you mentioned that you no longer drink?

A. That is correct. I started seeing a counselor and I was diagnosed with depression and anxiety. I began taking Paxil for the depression, and I would take Klonopin on a daily basis to help with the anxiety. I also have prescription for Xanax, but I only take that if I am having a panic attack.

Q. Were you taking these medications at the time of the accident?

A. Well, I take my Paxil and Klonopin every morning when I wake up. I did not take any Xanax that day.

Q. It is my understanding that your prescription bottle for Xanax was found at the accident scene, can you explain that?

A. Well, yeah, I mean, I always have some with me. Panic attacks are not something that you can tell are going to happen.

Q. So you are sure that you did not take any Xanax that day.

A. 100%. It had been some time since I had panic attack prior to the accident.

Q. Do you have them now?
A. Almost daily, ever since the accident. I probably have two or three a week.

Q. And do you know why?

A. I believe it is trauma from the accident. There are times that I am in traffic and all of sudden I just start to lose it.

Q. How do you handle it?

A. I take a Xanax. That is why I have them.

Q. Well, do you continue to drive after taking the medication?

A. I do.

Q. Well, is that something you should be doing on that type of medicine?

A. I have never had anybody tell me not to. It does not affect my ability to drive.

Q. Have you been in any other motor vehicle accident since September 2017?

A. Yes, one, I hit a patch of ice and lost control of my vehicle. It wasn’t anything major, but it was scary.

Q. And what type of vehicle do you drive now?

A. That depends. In the summer and nice days in the fall and spring I drive my motorcycle. On days that the weather does not permit, I will drive my car.

Q. And it is also my understanding that you have received some traffic citations related to your motorcycle driving, is that accurate?

A. It is not. I had one citation.

Q. What was that for?

A. Driving without a helmet, which is completely false.

Q. Why is it false?
A. I had just pulled into Portini Sisters to get a sandwich. I took my helmet off and a cop showed up and gave me a ticket. Said he been following me for a couple of blocks and that I was not wearing a helmet. He must have had me confused with somebody else.

Q. Well did you challenge the citation?

A. I did, but you can’t fight city hall. The traffic court judge said it was a he said/she said argument, and she found in favor of the cop. Big surprise there.

Q. And when did this happen?

A. About six months ago.

Q. Okay, and before we move on to the day of the accident, there is one last thing I want to ask you about. You mentioned a few times you moved to Steelton to get a clean start. Did you have any problems at your job at Rick’s?

A. No. Not once. I worked there for five years without a single complaint about me. I received a raise and a bonus every year.

Q. Okay. Thank you. Let’s move on to the day of the accident. It’s my understanding that at the time of the accident, you were not licensed to operate a motorcycle in Steelton, is that correct?

A. Yes.

Q. And yet when you were struck, you were sitting on a motorcycle, correct?

A. That is correct, but I was not operating the motorcycle.

Q. Let’s talk about that. First, the motorcycle you were sitting on was registered in your name, right?

A. Yes.

Q. And it was titled in your name as well, right?
A. Yes, I purchased it. I had recently received a pretty decent bonus from Dr. Googlay because I made a big sale to Perdue. I had always wanted a motorcycle, so I went out and bought one. I guess I got ahead of myself as I had not been licensed to drive one, and I had to take the test.

Q. Did you ever drive a motorcycle before?
A. When I was a kid and into my teens I was pretty big into dirt bike racing.

Q. Do you mean BMX?
A. No, I mean real dirt bike racing. So, for a very long time, I was riding dirt bikes, which are essentially motorcycles specifically made for racing on dirt tracks.

Q. And you do not need a license to ride them?
A. No, not at that age, and those types of racing.

Q. So how did you get the motorcycle home if you did not have a license?
A. The dealership was nice enough to deliver it to my house.

Q. And when did you take your license test?
A. About three weeks after the motorcycle was delivered.

Q. But you did not drive the motorcycle prior to that?
A. No, I did not. It would have been illegal.

Q. Where was the test?
A. At the Steelton Department of Motor Vehicles testing center.

Q. How far away from your home is that?
A. About three miles.

Q. And how did you get the motorcycle to the testing center?
A. I have a good friend I worked with at Dr. Googlay who drove it for me.

Q. And does this good friend have a name?
A. Yes. Vince Strugalski.

Q. Did Vince have a license?

A. Yes, but Strugs did not have a motorcycle, so after I did not pass the test, I let him keep it until I did.

Q. Strugs?

A. It’s what we called Vince. A lot easier than saying Strugalski.

Q. And you answered one of my questions, which is I understand that you did not pass the motorcycle licensing exam, right?

A. That is correct. I failed by a point. It was really disheartening.

Q. And it is my understanding that Mr. Strugalski kept the vehicle until the time of the accident, correct?

A. Yes.

Q. Do you know where Mr. Strugalski is now?

A. I do not. I am not sure if anybody does. He was one of those guys who was always around until he wasn’t. Nobody has seen or heard from him in over a year.

Q. Just so I understand, the person with whom you entrusted your brand-new motorcycle until you passed the license test just picked up and vanished, and you have not seen or heard from him since, is that right?

A. As incredible as it sounds, that is the truth. He showed up for work one day, said he was going out to lunch and never came back.

Q. I mean, was he kidnapped, was there foul play?

A. I really have no idea. Corporate said that they got an email from him saying that he just decided he had enough, and he wasn’t coming back to work. I went to his house that night to see what
happened, and he was gone. I looked into his windows and all of his stuff was gone. He just kind of vanished.

Q. So, what were you doing on it at the time of the accident?
A. I was just sitting on it. Thinking about what it would be like to get out on the road. I needed some motivation for the test.

Q. You would agree with me that the motorcycle was on, right?
A. It was on. Strugs had just pulled in to the spot about five minutes before the accident and I wanted to sit on it while it was running. It wasn’t in gear, and I had no intention of taking it for a ride.

Q. You are aware that a witness in the police accident report told the investigating officer they had seen you remove the kick stand and it appeared that you began to pull out into traffic?
A. I am aware of that, but it did not happen. I don’t have a license.

Q. And to be clear, you were not wearing a helmet at the time you were struck?
A. Well, considering that I was not planning on riding it, no, I was not.

Q. You are aware there was not a helmet found at the scene either, right?
A. I have no idea. I really can’t tell you one way or the other.

Q. Do you know if Mr. Strugalski was wearing a helmet when he pulled up?
A. I don’t know.

Q. Really? You seem to remember everything else about that day, but you can’t remember that?
A. I told you, I don’t remember.

Q. Tell me what you remember about the conditions that day.
A. What do you mean conditions?

Q. What time of day was it? What was the weather like? Was it still light outside? Those types of things.
A. It was after work. I leave around 5:30 p.m. every day unless I have project or something big that I am working on.

Q. Let me stop you right there. Do you know if you left work around 5:30 p.m. that day?

A. I don’t know for sure.

Q. Well, do you know if you were working on a project or anything that would have required you to stay later?

A. Not that I recall.

Q. Alright, what was the weather like?

A. It was a sunny, warm day. I remember being really hot, but I do not recall the exact temperature.

Q. Do you know what time you met Mr. Strugalski?

A. It must have been around 6:00 p.m. I walked to the spot where I was meeting him, and it is about a half an hour walk.

Q. How do you know you walked?

A. I remember it being a nice day and thinking that since fall and winter were coming, there might not be too many more like it, so I wanted to get out an enjoy it while the weather held up.

Q. Do you remember if it was still sunny, or was it starting to get dark?

A. It was still sunny outside. It usually does not start getting dark around here until around 8:00 p.m. at that time of year.

Q. Did you get to your meeting location at the same time as Mr. Strugalski?

A. No. Strugs pulled up where I was waiting. He wanted to grab a beer and talk, so I agreed to hang out and listen. Because he brought my motorcycle, I decided to just sit on it for a minute or two.

Q. I thought you said you were sober?

A. I am. Just because Strugs wanted a beer doesn’t mean I needed to drink one.
Q. But you were still meeting Strugs at a bar?
A. Yes.
Q. And after you got on the bike, what happened?
A. Well, the bike was facing forward, so I could not see behind me, which is the direction that car that hit me came from. At that point I remember Strugs saying, “Hey, there is one of those self-driving cars.” They had been around for a while, but they had just recently started letting them operate without an actual operator in the vehicle. I turned around and I saw the vehicle was not slowing down. Before I knew what happened, I woke up in the hospital.
Q. Do you remember where the motorcycle was parked?
A. Yes. It was in a space on the street.
Q. Well, wasn’t the motorcycle actually parked in a designated Lyber pick-up spot?
A. No, it was not. It was parked abutting the designated spot, but not in it.
Q. Tell me about your injuries. What happened as a result of the collision?
A. I broke both of my legs. Dislocated my sacroiliac joint and suffered a significant closed head injury. I was unable to work for six months because of the pain I was in.
Q. Have you recovered from your injuries as of today?
A. I suppose, I mean, I am still sore every now and then, and sometimes I walk with a limp. Also, I think I mentioned it earlier, I have more frequent panic attacks.
Q. So, if the accident did not happen, when were you scheduled to take motorcycle license test next?
Q. And it is my understanding that you were eventually able to pass the test, is that correct?
A. I did. Once I healed from all my injuries and completed all of my physical therapy, I was able to pass the test with flying colors the next time that I took it.
WHEREUPON the deposition was concluded.
Deposition of Keaton Scent

And now, this 11th day of June, 2019, Keaton Scent, being duly sworn by the undersigned appeared at the offices of the Swatkins Law Firm, for the purposes of deposition by oral questioning.

(Questioning by Luna Swatkins)

Q. Good afternoon Keaton.
A. Hello.

Q. We are here today to take your deposition in the case involving Carson Gray. Is this the first time that you have given deposition testimony?
A. No, I have been deposed and testified many times before.

Q. Alright, so this is nothing new to you then, is it?
A. No, unfortunately when you want to change the world, you have to deal with nuisances like this from time to time.

Q. Well, I’m sure Carson Gray does not think this is a nuisance given that Carson was struck by one of your vehicles and suffered very significant injuries.
A. Obviously that is not what I meant. I am very sorry that Carson was hurt, but Carson was doing something Carson was not supposed to do, and that is how people get hurt sometimes.

Q. Well, we will talk about that later, I am more interested in starting with some background. Can you tell me more about the times you have testified?
A. I have testified in depositions like this probably at least twenty times. Sometimes dealing with injuries, sometimes dealing with work place issues, and sometimes dealing with cases against other companies. I have also testified multiple times before Congress concerning Edison’s projects.

Q. How many times have you testified before Congress?
A. Probably five or six.
Q. And of those five or six, have any been about self-driving vehicles?
A. Yes. Once.

Q. Why were you before Congress to testify about self-driving vehicles?
A. To discuss how safe they are. To help bring about change in motor vehicle regulations so that we could make the roads safer through better technology.

Q. When did you testify about autonomous vehicles in Congress?
A. It was probably a few months ago.

Q. So that was after Carson’s accident?
A. Yes, it was.

Q. And what did you tell Congress about Carson’s accident?
A. It did not come up.

Q. What do you mean it did not come up? Weren’t you there to discuss the safety of your self-driving vehicles?
A. I was, and the cars are safe. Carson did not come up because after a thorough internal investigation, we did not do anything wrong. Carson, an unlicensed driver, pulled out in front of our vehicle. Even with all of the safety features we place on these cars, it could not stop in time. It was a very unfortunate accident, but there was nothing Edison could have done to prevent it.

Q. Okay, and like I said, we will get into that more as we go on. However, I understand that you are either the head of, or responsible for, running at least seven different companies, is that correct?
A. Yes.

Q. So when I ask you a question today about the accident involving Carson, I want you to tell me what you know, or to be more specific, what you have knowledge of, alright?
A. That is fair.
Q. I do not want to guess as to what might be true.
A. I can do that.

Q. Also, I do not want you to answer my question if you don’t understand it, is that fair?
A. Yes.

Q. That is very important, because if you answer a question, everyone here is going to believe that you understood the question, and in answering the question, you provided all the knowledge you had about that question, okay?
A. Yes. My lawyers talked to me about that.

Q. Stop right there. I do not want to know what you and your lawyers discussed. That is privileged.
A. Okay.

Q. So, in addition to Edison, you also, as you alluded to, own several own other companies, correct?
A. Own or control.

Q. I would like to talk to you about Superloop for minute.
A. Uh, I don’t know what that has to do with anything, but okay.

Q. Well, you own that particular company?
A. Yes.

Q. And what is Superloop?
A. It is a company working on the revolution of transportation. We are working on technology called hyperloop.

Q. What is hyperloop, you know, in layman’s terms?
A. Hyperloop is a way of transporting people or cargo very quickly between two points.

Q. How does it work?
A. Very simply, in fact. Hyperloop transportation involves a sealed system of tubes that create a vacuum through which the vehicle can be propelled at very high speeds since there is not any other force such as friction slowing the vehicle down. But surely, you do not want to know about that, do you?

Q. Well actually, it is my understanding that Superloop recently had an incident during testing in which one of the test vehicles was involved in a major accident, is that accurate?

A. It is.

Q. What happened?

A. We are not sure yet, and I really cannot get into details while the federal investigation is still underway. What I can tell you, is that we believe one of the vacuum seals failed, and there was an event with the vehicle and a subsequent crash.

Q. Okay, that is fine, but there is one thing that I did want to ask you about concerning the Superloop incident.

A. I will answer if I can.

Q. Thank you. Weren’t you warned that the vacuum seals were faulty?

A. No.

Q. No?

A. We received information from one of our lead engineers that he believed that the seals could fail under certain conditions. However, at the time the engineer reported that information, he was under investigation that he was making unwanted sexual advances toward several of his subordinates. We investigated these concerns, but we did not determine them to be credible, and believed they were an attempt to distract us from the HR investigation that was ongoing against him.
Q. What was this engineer’s name?
A. I am not at liberty to divulge that.

Q. I ask only because one of the things that we are aware of is that the federal investigation began as a result of a whistleblower complaint against your company, is that right?
A. There was a so-called whistleblower.

Q. And my understanding is that the whistleblower was the same engineer that tried to warn you about the vacuum seals failing, right?
A. I cannot answer that.

Q. If you can’t answer that, okay, but you would agree that you have put forth in the public that the whistleblower was a disgruntled employee who was terminated for sexual harassment, correct?
A. Yes, that much is true. But I cannot say if they are the same person.

By Ms. Blue
Counsel, I have allowed you significant leeway on this line of questioning, move on.

By Ms. Swatkins

Q. Let’s talk about Edison now, okay?
A. Okay.

Q. When did you first start looking into designing, manufacturing, and putting into service self-driving cars?
A. It was probably around 10 years ago when the technology, which was already present, was affordable enough to make it practical. I mean, people have been fooling around with this technology since the mid-twentieth century. In fact, back in ‘95, a vehicle engineered by Carnegie Mellon University was able to drive across the country with just under 100% being performed without any driver input.
Q. Can you provide me with a background as to how these vehicles, in general, operate?

A. I guess the most basic way to explain it is this. The cars are equipped with multiple and varying types of sensors. First, there is radar, which is used to determine the position of other vehicles within a close proximity to the self-driving vehicle. The cars also have video cameras that are used to detect traffic signals, other vehicles, and pedestrians. We also use LIDAR, which…

Q. Wait, really quickly, what is LIDAR?

A. LIDAR is an acronym that stands for light detection and ranging. That is used to detect travel lanes and measure distances of surrounding objects such as road edges. Finally, there are sensors in the wheels that assist with parking by detecting curbs and the like.

Q. So how do all of these sensors allow a car to operate without driver input?

A. Like with anything else today, all of these sensors report their respective information to a central computer. The computer, and the software that it runs, uses the information to plot a safe path, control speed, and avoid obstacles, all while traveling where the vehicle is lawfully meant to be traveling.

Q. Does the computer control the car then?

A. In a matter of speaking, yes. After processing all of the information from sensors and determining how the vehicle should move, the computer then sends the appropriate information to the vehicle’s accelerator, brakes, and steering.

Q. So in other words, there are multiple, complicated systems, that have to work in harmony to ensure that the vehicle can operate safely?

A. Yes, there are, which is why we spent so long developing and testing our self-driving cars before putting them on the road.

Q. And when did you first start testing them?
A. Probably in 2010 or so. We ran a lot of computer simulations first, and then began outfitting test vehicles with sensors and the computer. We obviously did not put the vehicles on the road at first. We had a closed test track that was utilized for several years with cooperation from various federal agencies to ensure that the vehicles were meeting safety milestones before putting them in service in real world conditions.

Q. Do you recall when you first put the vehicles on the road for testing in real world conditions?
A. Yes. In 2015 we started testing in Steelton, Buffalo-Niagara, and Lone Star.

Q. Can you tell me how the vehicles were tested?
A. Sure. We didn’t just send these things out onto the street untested and without a driver. Each vehicle had an operator behind the wheel and in the passenger seat to monitor the vehicle’s systems. Both occupants were engineers who worked on the program from the inception. The engineer in the driver’s seat was able to take control of the vehicle at any time there was a perceived risk. The engineer in the passenger seat served as redundancy to the engineer in the driver’s seat in case the engineer in the driver’s seat did not appreciate the risk.

Q. And how long did this test phase last, with the two occupants?
A. About a year. We went thirteen months with the vehicles on the road and zero incidents. We received approval from the federal and state regulatory authorities to put the vehicles into driverless operation sometime in March 2017, and they worked flawlessly.

Q. You mean with the exception of the one that hit Carson Gray?
A. I would still say they worked flawlessly. As I understand it, Carson pulled out on the motorcycle directly in front of a Lyber designated pick-up point and it would not have mattered if there was no driver or if the ghost of Bill Ford himself was behind the wheel.
Q. Okay, well, supernatural happenings aside, I assume that you recorded the level of automation on the vehicles before eliminating the drivers?
A. We did.
Q. And what were those levels?
A. The first three months, the vehicles were at a 91.3% automation rate, meaning that the driver had to take control 8.7% of the time. The next three months were at 96.7% and the final months were at 99.5%.
Q. So the vehicles still had to be controlled .5% of time by the driver?
A. That is a little deceiving. The instruments pick up any time a driver takes over and there are just some situations in which the driver decided to grab the wheel for one reason or another.
Q. You mean like hitting a pedestrian?
A. No, I mean like, just forgetting where they are and setting their hands on the wheel.
Q. I would like to talk to you for a bit about some concerns raised by Darren Ryan in some emails to you, okay?
A. Sure, another disgruntled, so-called whistleblower. Darren was a troubled employee who we had to let go.
Q. Why was Darren let go?
A. Darren had a propensity to harass subordinates. After counseling Darren multiple times on why Darren’s behavior was unacceptable, myself and our VP of HR made the decision to part ways with Darren. And the terms of that separation are confidential so I cannot talk about it.
Q. So letting Darren go had nothing to do about the emails Darren sent you putting Edison on notice about small vehicle detection glitches?
A. Darren’s emails were a smoke screen. Darren knew what was going on and was trying to angle for the best exit possible. Darren’s concerns were not credible.

Q. Well, they were credible enough that you asked your Buffalo-Niagara team to look into them, right?

A. Listen, I said they were not credible. How do you think we determined they were not credible? The team investigated and found one isolated incident in a simulation from 2014.

Q. Can you explain what you mean by that?

A. We ran a lot of simulations on the software, almost like a video game, is probably the best way for me to explain it. And in one of those simulations, the virtual car bumped into a bicycle while pulling into a parking space.

Q. Well didn’t Darren report to you that when out in the field during the two-driver testing that you mentioned, Darren had to take control of the vehicle several times to avoid collisions with bicycles on the road?

A. Darren did, and we reviewed the tapes from those incidents and determined there was no danger.

Q. When did this happen?

A. April 2017.

Q. And where are those tapes now?

A. We are only required to keep the footage from the tapes for a year following the date upon which the footage is filmed. They are erased and taped over.

Q. So you taped over the tapes that you say can prove your company is blameless?

A. I do not need tapes to prove we are blameless. We have never once been faulted for a single accident.
Q. It is my understanding that Darren also raised concerns about an incident that occurred in March 2017, when one of the Edison vehicles left the roadway and drove on the sidewalk. Is that accurate?
A. No.
Q. Well, why not? You agree with me that there was an incident in Buffalo-Niagara where one of your vehicles ended upon the sidewalk, right?
A. I agree with your basic premises that a car ended up on the sidewalk, but it was through no fault of the vehicle or its systems. That day there was an unexpected temperature drop and it was raining. The road conditions got bad quickly and the vehicle hit some black ice and slid up on to a curb. I think there were something like 30-40 ice-related accidents that day. It seems like we did better than the human drivers.
Q. Didn’t you only have 10 vehicles on the road that day?
A. Yes, what’s your point?
Q. How many vehicles were being driven by humans at that time?
A. I don’t have that information.
Q. And what about the tapes from the vehicle concerning Carson’s accident; do you have those?
A. All of that information was given to the NTSB. It is my understanding that they are unable to locate the tapes.
Q. And the investigator in charge of the NTSB investigation into this accident, isn’t that person a former Edison employee?
A. Yes, but that was fifteen years ago.
Q. And you are saying Edison did nothing wrong with respect to the collision with Carson Gray?
A. As I understand it, Carson, an unlicensed motorcycle driver, who was not wearing a helmet, pulled out in front of our vehicle.

Q. Okay, I have no further questions.

WHEREUPON the deposition was concluded.
Deposition of Chaz Shanton

And now, this 22nd day of April, 2019, Chaz Shanton, being duly sworn by the undersigned appeared at the Swatkins Law Offices, for the purposes of deposition by oral questioning.

(Questioning by Luna Swatkins)

Q. Good morning Chaz. I am here to ask you some questions about a motor vehicle accident that occurred on September 4, 2017.

A. Okay.

Q. This isn’t a test, so it is okay if you don’t know an answer.

A. Alright, I am a little bit nervous.

Q. No need to be nervous. I don’t expect we are going to be that long, but if you need anything you let myself or Ms. Blue know, okay?

Q. And are you being represented by counsel here today?

A. I am not. Should I be?

Q. Well, that is your call, but we just want to talk about what you do and don’t remember about the accident. You are not on the hook for anything here, alright? Do you want to continue?

A. Sure, no problem. I just wanted to make sure I am not in trouble. And now that you said that and it is recorded, you can’t do anything to me. I saw that on a TV show once.

Q. Umm. Okay. So, can you state your name and address for the record, please?

A. Chaz Shanton, and I live in Steelton at 178 Clay Street.

Q. Chaz, how old are you?

A. Right now I am 22.

Q. And are you a student?

A. Yes, I am just finishing up my senior year at Steelton Tech.
Q. Are you sticking around or leaving town?
A. I got a job lined up at a think tank in DC. It is my hope to be a lobbyist one day.

Q. Great. What is your major?
A. History.

Q. And what do you remember about the accident on September 4, 2017?
A. Not much.

Q. Alright, well let’s go back to that day and we can see what you do and don’t know.
A. That sounds good.

Q. What do you remember about that day?
A. Well, I do remember it was Labor Day, so we did not have school. I probably would have sat around with my friends playing the new Madden. It just came out the week before.

Q. What is Madden?
A. It’s a football video game. A new version comes out every year. I remember Tom Brady was on the cover and I really hoped he got hit by the Madden Jinx.

Q. Okay, what is the Madden Jinx?
A. Every year there is football player on the cover of the game. And almost every year, the player on the cover gets hurt. And I did not want to see those guys win another title.

Q. What did you do after you finished playing Madden?
A. I remember that we went to this new bar that just opened up. It was called Montana Max’s. It was Mexican Monday and they had killer tacos and three-dollar margaritas.

Q. How old were you at the time?
A. I was twenty.

Q. If the legal drinking age is 21, how were you able to get a three-dollar margarita?
A. I had a killer fake ID. This freshman graphic arts student in the dorm made it.

Q. Alright. Do you remember what time you got to Max’s?
A. It was probably about three or four in the afternoon?

Q. How many margaritas did you have?
A. Probably three or four. They water them down when they are on special like that.

Q. Did you have any other drinks?
A. I had a couple of Coronas. Because you can’t have a margarita if you don’t have a Corona.

Q. I see. Did you eat anything?
A. I probably had five or six tacos. They were only a dollar on Mexican Mondays.

Q. And what time did you leave Max’s?
A. I think it would have been between six and seven.

Q. Were you intoxicated?
A. Well, I wasn’t driving anywhere if that is what you mean.

Q. No, it’s not. I am trying to understand if you were drunk or not. And by you telling me you were not driving anywhere, I assume the answer is yes.
A. I wasn’t that bad. I had a bit of a buzz going, but nothing that really impaired me too much.

Q. Well, it was enough for you to say you would not drive an automobile, right?
A. Well, I’m not dumb. Impairment begins with the first drink you know. I wanted to go to DC and it would be hard to make a career with a DUI.

Q. But underage drinking was okay?
A. It was college. We all drank.

Q. Do you remember a motor vehicle accident that day?
A. I sure do.
Q. Tell me what you remember.
A. We had called a Lyber and were heading toward the pick-up spot. There was this person on a motorcycle revving the engine. I remember the person was not wearing a helmet.

Q. How do you remember he was not wearing a helmet?
A. I always notice that when I see somebody on a motorcycle without a helmet. It is an example of Darwinism at its finest.

Q. Okay, and what happened next.
A. Somebody mentioned that they thought we might be getting one of the driverless Lybers, and pointed it out coming down the street. That was pretty exciting because I had never been in one before, and the rides were free for you allowing them to use you as a guinea pig.

Q. What happened next?
A. Well, I bent down to tie my shoe because it was untied, and then I heard some commotion and screeching brakes.

Q. What did you do?
A. I looked up and I saw the Lyber was stopped pulling into its space, and the motorcycle was out on the street and driver was on the road, still without a helmet.

Q. Did you actually see the motorcycle driver get hit?
A. I did not. I just assumed the driver pulled out in front of the car.

Q. You assumed. Did you actually see the driver operate the motorcycle?
A. I saw the driver on the bike.

Q. But did you see the driver actually drive it?
A. No, but why else would the driver be sitting on it?

Q. Did you see anybody else there by the parking spot?
A. Yeah, there was this weird dude checking out the bike. He was holding a helmet in his hand.

Q. Did you give a statement to the police?
A. Yes.

Q. What did you tell them?
A. That somebody driving a motorcycle pulled out in front of the Lyber and got hit.

Q. But you would agree you never actually saw that, right?
A. No, I did not see it, but it was pretty apparent.

Thank you, those all of the questions that I have.

By Ms. Blue

Q. Just to confirm, did you actually see the impact?
A. No.

Q. And the screeching of the tires, do you know if that happened before or after the impact.
A. I don’t know.

Q. What about the revving of the bike, did you hear that immediately before the impact?
A. Immediately before, I don’t think so, but I am not sure.

Thank you, no further questions.

WHEREUPON the deposition was concluded.
November 22, 2019

Luna Swatkins, Esquire  
The Swatkins Law Offices  
1877 Asbury Park Drive  
District of Steelton, USA 12345

Re: Gray v. Edison

Dear Ms. Swatkins:

Pursuant to your request, I have thoroughly reviewed the file materials concerning this unfortunate incident. Based upon a reasonable degree of professional certainty, it is my opinion that Edison’s conduct fell below the standard of care of automotive engineering. Based upon the documents you have provided me, Edison knew, or should have known, that there was the potential for its vehicles to strike pedestrians and other vehicles.

In preparation for offering this testimony, I have reviewed, in detail, all of the materials that you have provided to me. This includes the depositions of Carson Gray, Keaton Scent, Chaz Shanton, and all of the materials that are included on the joint witness list. It is my understanding that Edison will be offering testimony that will be meant to counter my conclusions, though I do not see how that is possible. This is an open and shut case.

Autonomous Vehicles (AVs) are nothing new on the road. The vast majority of passenger vehicles on the road today have some form of automation from brake assist to cruise control to blind spot monitoring. However, what we are dealing with presently in this most unusual situation is a vehicle that actually operates on its own, without driver input, and without the safety that years of driver knowledge would present.

Nowhere is this more apparent than the recent automobile crash involving a Tesla during which the driver was involved in an automobile crash while the vehicle was engaged in “autopilot” mode. Although I recognize this crash occurred after the incident involved herein, it nonetheless demonstrates the dangers of using automated technology. In the Tesla crash, the individual relied upon the technology and did not respond to emergency alerts telling him to take control of the vehicle.

It is my understanding of these types of accidents, based upon studying them for the past several years, that so called “autonomous vehicles” sometimes have trouble detecting lane markings that can be confusing to even human drivers. That this accident occurred on a spot on the street that had sudden changes in traffic marking, from parking spots to a designated Lyber pick-up area, is not surprising. It is my belief that this was the likely cause of the vehicle’s error.
The above chart is the Society of Automotive Engineer’s designation for AVs. It sets forth six different categories of automated features found in vehicles. Levels 0-2 have been in public use for some time now, but still require a driver in all senses for safe operation of the vehicle. Levels 3-5 are where things begin to get tricky in that purportedly a driver may not be necessary, but that does not necessarily make the vehicle safe. Clearly it could not be considered Level 5 because of the Buffalo-Niagara incident.

Based upon my review of the evidence, with a reasonable degree of professional certainty, the Edison vehicles should have been taken out of service as early as March of 2017, and should have had more testing after the complaints by Darren Ryan based upon the simulations.

First, the March Buffalo-Niagara incident demonstrates that the vehicles had the same propensity to crash in poor conditions as one driven by a human driver. There is no utility in letting a vehicle drive on the road without a driver if it is not making travel safer. Further, there is little evidence to review about this accident, as all we know is that it happened. The video footage is gone, and we have no other data presented by Edison to back up its claim that the vehicles were safe to operate.

More importantly, the decision to ground the vehicles, so to speak, should have been made based upon Darren Ryan’s concerns about the potential to strike individuals like Carson Gray. In a computer simulation, in which the vehicle was presented with information indistinguishable from a real-world

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**SAE J3016™ LEVELS OF DRIVING AUTOMATION**

<table>
<thead>
<tr>
<th>Level 0</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
<th>Level 4</th>
<th>Level 5</th>
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<tbody>
<tr>
<td>You are driving when these automated driving features are engaged – even if your feet are on the pedals and you are not steering.</td>
<td>You are driving when these automated driving features are engaged – even if you are seated in “The driver’s seat.”</td>
<td>You must constantly supervise these support features; you must steer, brake or accelerate as needed to maintain safety.</td>
<td>You are not driving when these automated driving features are engaged – even if you are seated in “The driver’s seat.”</td>
<td>When the feature requests, you must drive.</td>
<td>These automated driving features will not require you to take over driving.</td>
</tr>
<tr>
<td>These features are limited to providing warnings and momentary assistance.</td>
<td>These features provide steering OR brake/acceleration support to the driver.</td>
<td>These features provide steering AND brake/acceleration support to the driver.</td>
<td>These features can drive the vehicle under limited conditions and will not operate unless all required conditions are met.</td>
<td>This feature can drive the vehicle under all conditions.</td>
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<td>Exemplary Features:</td>
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<tr>
<td>automatic emergency braking</td>
<td>lane centering OR</td>
<td>lane centering AND</td>
<td>traffic jam</td>
<td>local driverless taxi</td>
<td>same as level 4 but feature can drive everywhere in all conditions.</td>
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<tr>
<td>blind spot warning</td>
<td>adaptive cruise control</td>
<td>adaptive cruise control at the same time</td>
<td>control</td>
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<td>lane departure warning</td>
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STAC 44
scenario, the AV actually struck a bike. While a bike and motorcycle are not identical, they are certainly similar. Darren Ryan states in his emails that this is an event that Darren believed could be duplicated, and that further testing would be needed. While Keaton Scent tacitly acknowledges the issue and promises further testing, we have seen no evidence of that testing other than the words of Keaton.

A reasonably prudent company would have listened to its engineer and taken the vehicle out of service at that time to further test whether or not it could or would strike other similar vehicles or pedestrians. Edison did not, and in my opinion, based upon those emails, the identical issue happened here as it did in the simulation. It appears the simulated vehicle became confused about a bike lane and travel lane and swerved into the bike lane. This caused the vehicle to hit a parked bike.

It is my opinion, within a reasonable degree of professional certainty, that this is the accident scenario that played out with Carson. Based upon my review of the records, Plaintiff’s version of the events is reasonable.

As such, Edison did not act within the standard of care, and Edison’s actions directly caused Carson to get hurt.

Very truly yours,

Tony Stork
CURRICULUM VITAE

Tony Stork
177a Bleecker St.
Asbury Park, ST

Education

1998 Carnegie Mellon University
BS in mechanical engineering, magna cum laude

2000 California Institute for Technology
MS in Advanced Computer Technology

Work History

2000-2012
Lead Technical Engineer, Edsel Motor Operations

Responsibilities included development, testing, and implantation of autonomous safety devices for use in automobiles. I worked on developing blind spot sensor technology programs and adaptive cruise control programs. The two technologies that I oversaw have been utilized and implemented by several major automobile companies in their current gen vehicles.

2012-present
Principal, Automotive Investigations Group

I founded a forensic automobile research company that reviews automobile accidents for the federal government, automobile companies, industry companies, and private parties. Part of the work of AIG includes serving as a litigation consultant. Our litigation work is split evenly between work for plaintiffs and defendants.

Organizations:

Society of Automotive Engineers
Cal Tech Alumni Association.
CMU Alumni Association

Publications

Automated Vehicles: A Shining Future or the Terminator? Modern Cars, July 2015
Is Your Car a Better Driver Than You? Automotive Track, September 2010

Prior Testimony

I have testified in 20 prior lawsuits involving various automobile accidents. I have testified 13 times on behalf of the plaintiff and seven times on behalf of the defendant. My rate is $650 per hour with an $8000 flat fee for trial testimony plus lodging and transportation.
November 22, 2019

Allie Blue, Esquire
Covfefe and Associates
257 Wilderness Drive
District of Steelton, USA 12345

Re: Carson Gray Claim

Dear Ms. Blue:

Thank you for asking me to consult on behalf of your client, Edison Automobile Company, a true American innovator. I am a licensed professional engineer who has been involved in the automobile industry for twenty years. I have designed automated systems for vehicles such as lane assist devices and blind spot monitoring.

I am prepared to offer my opinions concerning this matter. Before doing so, I wanted to let you know that I have relied upon my knowledge, expertise and experience in the field, as well as all of the depositions that you sent me. These are the depositions of Carson Gray, Keaton Scent and Chaz Shanton. I have also reviewed all of the documents contained on the joint witness list.

I can say, with professional certainty, that Edison Automobile did nothing wrong. They properly tested the vehicle, and it is my belief that the accident was caused by Carson Gray. My opinions follow.

First, I would like to clear up some common misconceptions about autonomous vehicles (“AVs”). We, as the automobile industry, have been experimenting with automated drive systems for almost as long as the automobile has been around. In fact, as early as 1979 Hans Moavec created an automated cart that was successfully able to cross a chair filled room. Of course, it took five hours, but the industry has made tremendous strides since then.

For instance, Ernst Dickmanns in 1987 was able to outfit a Mercedes Benz VaMoR (which was a larger conversion van type vehicle) with cameras and sensors. His trials with the vehicles eventually led to a Mercedes S class making a 1,600-kilometer trip from Munich to Odense, Denmark. The vehicle even reached speeds of 112 miles per hour. More recently, in 1995, a group of Carnegie Mellon engineers were able to drive a 1990 Pontiac from Pittsburgh to Los Angeles with an autonomous driving percentage of 98.2%.

In fact, most vehicles on the road today have some automated features that we take for granted as actually being automated features. In that regard, most vehicles today have cruise control, which will regulate speed. Some vehicles have lane assist, which will help either keep a vehicle in its lane of travel, or warn the driver when they’ve left it.

To help us better understand the operation of automated and autonomous vehicles, the Society of Automotive Engineers (“SAE”) has developed six levels of automation to help clarify the difference between certain systems that are presently available and may become available in the future. The
examples of cruise control and lane keeping assist are Level 1 types of automated driving. There are computer systems at play, but driver assistance is still necessary.

The Edison vehicle at issue, on the other hand, is essentially a Level 5 type vehicle. SAE classifies these types of vehicles as vehicles where the driving is performed by an automated system under all roadway and environmental conditions. Although the vehicles may have technically been considered Level 4 vehicles when the engineers were in the vehicles, they were still most likely at Level 5 since the engineers were a redundancy.

These vehicles provide tremendous advantages over human drivers. For instance, many accidents related to human error, such as tailgating, rubbernecking, and distracted driving, will be eliminated. It is clear that Edison is working for the betterment of public transportation.

With respect to the unfortunate, unavoidable incident involving Carson Gray, it is my opinion, within a reasonable degree of professional certainty, that Edison acted reasonably, and the vehicle was involved in an unavoidable collision that was most likely caused by Carson Gray.

Edison correctly followed the engineering design process. The engineering design process is as follows:

1. Define the problem;
2. Perform background research;
3. Brainstorm, evaluate, and choose a solution;
4. Develop and prototype a solution;
5. Test the solution; and
6. Communicate the solution

First, Edison defined the problem. As I stated above, the availability of AVs would make the roadway a safer place. The next step is to perform background research. It is clear that Edison followed up on this step based upon the use of the most up to date equipment such as LIDAR, cameras and other sensors utilized by the vehicle.

The brainstorming and prototype development were also present in that Edison built off of the scientific discovery of others and built its prototype with the above equipment. Obviously, Edison tested the vehicle as development began in 2010 and it was not even until late 2015 that the vehicles were put into service on the roadway. Then, the vehicles were driven for 13 months without incident and an increasing improved autonomous driving rate.

These results were then communicated to the various regulatory authorities, which is the last step, and Edison received approval to put the vehicles in service without drivers. I am aware that an employee made a complaint about the vehicles and recommended that they be taken out of service until further
testing could be done. This was not necessary, in my opinion. First, the incident in question occurred in a simulation, not in real world conditions. While the vehicle in the simulation nudged a bicycle, it appears from the successful testing and lack of any further incidents that this concern was unfounded. Second, I understand that one of the vehicles in the Buffalo-Niagara region was involved in a weather-related incident, when it lost control due to icy conditions. AVs are no different than human drivers in these situations as mother nature can lay foil even the most safely designed and engineered vehicle.

Finally, based upon my understanding of the records, this incident occurred not due to any malfunction of the Edison vehicle, but because of the negligence of Carson Gray. Carson was an unlicensed motorcycle driver. Witness statements indicate that Carson, who was not wearing a helmet, pulled out in front of the Edison vehicle. While it would have been beneficial to have reviewed the tapes, which I understand have been lost, it is my opinion, within a reasonable degree of professional certainty, that the Edison vehicle did not malfunction, and the most likely reason Carson was hit was due to the fact that Carson probably pulled out in front of the vehicle.

Thank you for the opportunity to review this most interesting case.

Very truly yours,

Nat Romanov, P.E.
CURRICULUM VITAE

Nat Romanov
2713 Red Room Way
Barnes, IA

Education

Massachusetts Institute of Technology 1995
B.S. with a major in Electrical Engineering and Computer Sciences

Massachusetts Institute of Technology 1997
Master of Science in Computation for Design and Optimization

Massachusetts Institute of Technology 1999
Sc.D. Electrical Engineering

Professional Registrations

Registered Engineer in Steelton, MA, NY and IA

Work History

1999 to 2001
Massachusetts Institute of Technology

Tenure track professor of computer science. Taught courses focused on automation of industrial machinery.

2001 to 2008
University of Steelton

Tenure track professor of electrical engineering and computer science. Instructed students on AI technology in industrial machinery for more efficient production design.

2008-Present
RCC, Inc.

CEO and lead engineer of multifaceted engineering consultant firm that investigates and discovers primary cause of automated equipment failure.
Prior Testimony

I have testified approximately fifty times before this trial. Eighty percent of my work is spent representing defendants. I have testified about autonomous automobile systems three times in the past. My hourly rate is $700 per hour.
## TITLE CERTIFICATE

### A VEHICLE INFORMATION

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<thead>
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<th>Vehicle Identification Number</th>
<th>Title Number</th>
<th>Registration Plate Number</th>
</tr>
</thead>
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<tr>
<td>0HFD123ABC456D789</td>
<td>98765432109 ST</td>
<td>GRAYDAY</td>
</tr>
</tbody>
</table>

### B VEHICLE OWNER INFORMATION

<table>
<thead>
<tr>
<th>last Name (or Full Business Name)</th>
<th>First Name</th>
<th>Middle Name</th>
<th>PA Dl/Photo ID# or Bus. ID#</th>
<th>Date of Birth</th>
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</thead>
<tbody>
<tr>
<td>GRAY CARSON</td>
<td>CARSON</td>
<td>—</td>
<td></td>
<td>01/08/1988</td>
</tr>
</tbody>
</table>

Current Street Address

5064 Yoh Avenue

City: Steelton

State: ST

Zip Code: 12345

### C SIGNATURE

I hereby certify under penalty of law that ALL information is TRUE and CORRECT and that I understand that any misstatement of fact is a misdemeanor of the third degree punishable by a fine up to $2,500 and/or imprisonment up to one year (18 St.C.S. Section 4904[b]).

/s/ Carson Gray 10/15/2017

Applicant’s Signature  Date  Telephone Number

Co-Applicant’s Signature  Date  Telephone Number

Visit us at [www.dmv.steelton.gov](http://www.dmv.steelton.gov) or call us at 412-555-5555. TTY callers — please dial 711 to reach us.
Hey, Keaton, I know you are busy with all those shady tax things that you rich people like to do, but we have a real problem here with the Mark 1s. For the second time yesterday one of the Mark 1s drifted too close to a bicycle that was traveling on the road. I had to take control of the vehicle. This is the second time this happened to me when I was out in the field. I know a couple of other members of the team have mentioned other incidents, but they are too afraid to tell you about it. I have since performed some analytics and I think the LIDAR is having trouble recognizing the bicycles. I think we need to put a halt on the testing so we can figure this out so nobody gets killed. We don’t want another hyperloop situation on our hands.

Darren
Darren, have you been drinking again, because I cannot for the life of me imagine why you are emailing me at 3 in the morning. I looked at the tapes. From what I could tell, the bike swerved at you.

Also, you know rich people don’t pay taxes. Me and Bezos think we might actually get money back this year.

-K
From: Ryan, Darren
Sent: April 14, 2017 9:13
To: Scent, Keaton
Subject: Problems with Mark 1s

If you looked at the tapes, you know damn well that the bicycle did not swerve at us. This is a problem and I think we need to shut down the program until we fix it.

Darren
Scent, Keaton

From: Scent, Keaton
Sent: April 14, 2017; 9:16
To: Ryan, Darren
Subject: Problems with Mark 1s

Look Darren, there is nothing wrong. And maybe this is the wrong time to bring it up, but I am hearing some more complaints about your behavior. I don’t need another Christmas party incident on my hands, do you get it? Do you know how much that cost me?

-K
Scent, Keaton

From: Ryan, Darren
Sent: April 14, 2017 9:18
To: Scent, Keaton
Subject: Problems with Mark 1s

That’s a low blow and you know it. I can only apologize so many times for what happened. I have been a model employee since then. And don’t think I can’t see what you are doing. Your vanity project is threatened by a real concern and now you want to manufacture some issues against the only person who is brave enough to tell you there are real issues.

I want my objection to the continuation of the project noted.
Darren
Scent, Keaton

From: Scent, Keaton
Sent: April 14, 2017; 13:02
To: Ryan, Darren
Subject: Problems with Mark 1s
Noted

-K
Darren, an HR representative will be coming to meet with you concerning the persistent complaints I seem to be hearing. Please make time available for next Monday so that we can get to the bottom of these rumors.

-K
So yu actually didit. Yoe went and created an isse. You will her from my lawyer.
Self-driving cars no longer just exist in the movies any longer. After obtaining federal and state regulatory authority, Edison’s self-driving vehicles are now fully autonomous. That means the next time you order a Lyber ride, you may not actually have a driver.

“This is a momentous time for Steelton,” said Keaton Scent, the eccentric billionaire owner of Edison told the Gazette over the phone. “We engineered the heck out of these things, worked out all of the kinks, and now they are ready to go.” When asked about the kinks, Scent would not provide details, saying only that Edison experiences the normal issues associated with changing the world.

When asked about public safety, Scent had this to say, “These vehicles are actually safer than those being driven by you and me.” Other members of our community are not so sure. Local North Side resident Tony Yinzer told the Gazette, “You know, them there vehicles scare me. I don’t trust them.”

As to changing the world, we will have to wait and see.
Embattled CEO and self-proclaimed disruptor Keaton Scent woke up this morning to a new set of headaches. Following several incidents on Scent’s hyperloop project, key federal investigators have shut down any further testing and work on the project until a full investigation can be completed into the most recent incident which cost the lives of two Edison workers.

The hyperloop is a proposed means of transportation that permits a passenger vehicle to travel quickly between two points. The vehicle travels through sealed tube in which a vacuum is created allowing the vehicle to travel free of any air resistance or friction.

“We need to see what Edison is actually doing with respect to its engineering processes,” said NTSB agent Chase Antonio. “We’re hearing whispers that corners have been cut, but without a full investigation, we can’t know for sure,” said another NTSB representative speaking on a condition of anonymity.

Scent is facing his own problems here in Steelton as well. Last year one of Edison’s self-driving cars was involved in a collision with a local motorist. Although no fault has been attributed to Edison yet, it has certainly shaken Steelton’s faith in the company.
Klonopin tablets are available as scored tablets with a K-shaped perforation containing 0.5 mg of clonazepam and unscored tablets with a K-shaped perforation containing 1 mg or 2 mg of clonazepam. Each tablet also contains lactose, magnesium stearate, microcrystalline cellulose and corn starch, with the following colorants: 0.5 mg—FD&C Yellow No. 6 Lake; 1 mg—FD&C Blue No. 1 Lake and FD&C Blue No. 2 Lake.

Chemically, clonazepam is 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one. It is a light yellow crystalline powder. It has a molecular weight of 315.72 and the following structural formula:

![Chemical Structure of Clonazepam]

CLINICAL PHARMACOLOGY

Pharmacodynamics: The precise mechanism by which clonazepam exerts its antiseizure and antianxiety effects is unknown, although it is believed to be related to its ability to enhance the activity of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. Convulsions produced in rodents by pentylenetetrazol or, to a lesser extent, electrical stimulation are antagonized, as are convulsions produced by photic stimulation in susceptible baboons. A taming effect in aggressive primates, muscle weakness and hypnosis are also produced. In humans, clonazepam is capable of suppressing the spike and wave discharge in absence seizures (petit mal) and decreasing the frequency, amplitude, duration and spread of discharge in minor motor seizures.

Pharmacokinetics: Clonazepam is rapidly and completely absorbed after oral administration. The absolute bioavailability of clonazepam is about 90%. Maximum plasma concentrations of clonazepam are reached within 1 to 4 hours after oral administration. Clonazepam is approximately 85% bound to plasma proteins. Clonazepam is highly metabolized, with less than 2% unchanged clonazepam being excreted in the urine. Biotransformation occurs mainly by reduction of the 7-nitro group.
to the 4-amino derivative. This derivative can be acetylated, hydroxylated and glucuronidated. Cytochrome P-450 including CYP3A, may play an important role in clonazepam reduction and oxidation. The elimination half-life of clonazepam is typically 30 to 40 hours. Clonazepam pharmacokinetics are dose-independent throughout the dosing range. There is no evidence that clonazepam induces its own metabolism or that of other drugs in humans.

Pharmacokinetics in Demographic Subpopulations and in Disease States: Controlled studies examining the influence of gender and age on clonazepam pharmacokinetics have not been conducted, nor have the effects of renal or liver disease on clonazepam pharmacokinetics been studied. Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Thus, caution should be exercised when administering clonazepam to these patients.

Clinical Trials: Panic Disorder: The effectiveness of Klonopin in the treatment of panic disorder was demonstrated in two double-blind, placebo-controlled studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IIIR) with or without agoraphobia. In these studies, Klonopin was shown to be significantly more effective than placebo in treating panic disorder on change from baseline in panic attack frequency, the Clinician’s Global Impression Severity of Illness Score and the Clinician’s Global Impression Improvement Score.

Study 1 was a 9-week, fixed-dose study involving Klonopin doses of 0.5, 1, 2, 3 or 4 mg/day or placebo. This study was conducted in four phases: a 1-week placebo lead-in, a 3-week upward titration, a 6-week fixed dose and a 7-week discontinuation phase. A significant difference from placebo was observed consistently only for the 1 mg/day group. The difference between the 1 mg dose group and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 74% of patients receiving clonazepam 1 mg/day were free of full panic attacks, compared to 56% of placebo-treated patients.

Study 2 was a 6-week, flexible-dose study involving Klonopin in a dose range of 0.5 to 4 mg/day or placebo. This study was conducted in three phases: a 1-week placebo lead-in, a 6-week optimal-dose and a 6-week discontinuation phase. The mean clonazepam dose during the optimal dosing period was 2.3 mg/day. The difference between Klonopin and placebo in reduction from baseline in the number of full panic attacks was approximately 1 panic attack per week. At endpoint, 62% of patients receiving clonazepam were free of full panic attacks, compared to 37% of placebo-treated patients.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of race or gender.

INDICATIONS AND USAGE

Seizure Disorders: Klonopin is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic seizures. In patients with absence seizures (petit mal) who have failed to respond to succinimides, Klonopin may be useful.
In some studies, up to 30% of patients have shown a loss of anticonvulsant activity, often within 3 months of administration. In some cases, dosage adjustment may reestablish efficacy.

**Panic Disorder:** Klonopin is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Klonopin was established in two 6- to 9-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The effectiveness of Klonopin in long-term use, that is, for more than 9 weeks, has not been systematically studied in controlled clinical trials. The physician who elects to use Klonopin for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

**CONTRAINDICATIONS**

Klonopin should not be used in patients with a history of sensitivity to benzodiazepines, nor in patients with clinical or biochemical evidence of significant liver disease. It may be used in patients with open angle glaucoma who are receiving appropriate therapy but is contraindicated in acute narrow angle glaucoma.

**WARNINGS**

*Interference With Cognitive and Motor Performance:* Since Klonopin produces CNS depression, patients receiving this drug should be cautioned against engaging in hazardous occupations requiring mental alertness, such as operating machinery or driving a motor vehicle. They should also be warned about the concomitant use of alcohol or other CNS-depressant drugs during Klonopin therapy (see PRECAUTIONS: Drug Interactions and Information for Patients).

*Suicidal Behavior and Ideation:* Antiepileptic drugs (AEDs), including Klonopin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43% compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events Per 1000 Patients</th>
<th>Drug Patients with Events Per 1000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
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<td>Psychiatric</td>
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</tr>
<tr>
<td>Other</td>
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<td>1.9</td>
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</tr>
<tr>
<td>Total</td>
<td>2.4</td>
<td>4.3</td>
<td>1.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Klonopin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

**Pregnancy Risks:** Data from several sources raise concerns about the use of Klonopin during pregnancy.

**Animal Findings:** In three studies in which Klonopin was administered orally to pregnant rabbits at doses of 0.2, 1, 5 or 10 mg/kg/day (low dose approximately 0.2 times the maximum recommended human dose of 20 mg/day for seizure disorders and equivalent to the maximum dose of 4 mg/day for panic disorder, on a mg/m² basis) during the period of organogenesis, a similar pattern of malformations (cleft palate, open eyelid, fused sternebrae and limb defects) was observed in a low, non-dose-related incidence in exposed litters from all dosage groups. Reductions in maternal weight gain occurred at dosages of 5 mg/kg/day or greater and reduction in embryo-fetal growth occurred in one study at a dosage of 10 mg/kg/day. No adverse maternal or embryo-fetal effects were observed in mice and rats following administration during organogenesis of oral doses up to 15 mg/kg/day or 40 mg/kg/day, respectively (4 and 20 times the maximum recommended human dose of 20 mg/day for seizure disorders and 20 and 100 times the maximum dose of 4 mg/day for panic disorder, respectively, on a mg/m² basis).

**General Concerns and Considerations About Anticonvulsants:** Recent reports suggest an association between the use of anticonvulsant drugs by women with epilepsy and an elevated incidence of birth defects in children born to these women. Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these are also the most commonly prescribed anticonvulsants; less systematic or anecdotal reports suggest a possible similar association with the use of all known anticonvulsant drugs.

In children of women treated with drugs for epilepsy, reports suggesting an elevated incidence of birth defects cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodologic problems in obtaining adequate data on drug teratogenicity in humans; the possibility also exists that other factors (eg, genetic factors or the epileptic condition itself) may be more important than drug therapy in leading to birth defects. The great majority of mothers on anticonvulsant medication deliver normal infants. It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy; however, it cannot be said with any confidence that even mild seizures do not pose some hazards to the developing embryo or fetus.

**General Concerns About Benzodiazepines:** An increased risk of congenital malformations associated with the use of benzodiazepine drugs has been suggested in several studies.
There may also be non-teratogenic risks associated with the use of benzodiazepines during pregnancy. There have been reports of neonatal flaccidity, respiratory and feeding difficulties, and hypothermia in children born to mothers who have been receiving benzodiazepines late in pregnancy. In addition, children born to mothers receiving benzodiazepines late in pregnancy may be at some risk of experiencing withdrawal symptoms during the postnatal period.

Advice Regarding the Use of Klonopin in Women of Childbearing Potential: In general, the use of Klonopin in women of childbearing potential, and more specifically during known pregnancy, should be considered only when the clinical situation warrants the risk to the fetus.

The specific considerations addressed above regarding the use of anticonvulsants for epilepsy in women of childbearing potential should be weighed in treating or counseling these women.

Because of experience with other members of the benzodiazepine class, Klonopin is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency in the treatment of panic disorder, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Patients should also be advised that if they become pregnant during therapy or intend to become pregnant, they should communicate with their physician about the desirability of discontinuing the drug.

Withdrawal Symptoms: Withdrawal symptoms of the barbiturate type have occurred after the discontinuation of benzodiazepines (see DRUG ABUSE AND DEPENDENCE).

PRECAUTIONS

General: Worsening of Seizures: When used in patients in whom several different types of seizure disorders coexist, Klonopin may increase the incidence or precipitate the onset of generalized tonic-clonic seizures (grand mal). This may require the addition of appropriate anticonvulsants or an increase in their dosages. The concomitant use of valproic acid and Klonopin may produce absence status.

Laboratory Testing During Long-Term Therapy: Periodic blood counts and liver function tests are advisable during long-term therapy with Klonopin.

Risks of Abrupt Withdrawal: The abrupt withdrawal of Klonopin, particularly in those patients on long-term, high-dose therapy, may precipitate status epilepticus. Therefore, when discontinuing Klonopin, gradual withdrawal is essential. While Klonopin is being gradually withdrawn, the simultaneous substitution of another anticonvulsant may be indicated.
**Caution in Renally Impaired Patients:** Metabolites of Klonopin are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function.

**Hypersalivation:** Klonopin may produce an increase in salivation. This should be considered before giving the drug to patients who have difficulty handling secretions. Because of this and the possibility of respiratory depression, Klonopin should be used with caution in patients with chronic respiratory diseases.

**Information for Patients:** A Klonopin Medication Guide must be given to the patient each time Klonopin is dispensed, as required by law. Patients should be instructed to take Klonopin only as prescribed. Physicians are advised to discuss the following issues with patients for whom they prescribe Klonopin:

**Dose Changes:** To assure the safe and effective use of benzodiazepines, patients should be informed that, since benzodiazepines may produce psychological and physical dependence, it is advisable that they consult with their physician before either increasing the dose or abruptly discontinuing this drug.

**Interference With Cognitive and Motor Performance:** Because benzodiazepines have the potential to impair judgment, thinking or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Klonopin therapy does not affect them adversely.

**Suicidal Thinking and Behavior:** Patients, their caregivers, and families should be counseled that AEDs, including Klonopin, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

**Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with Klonopin (see WARNINGS: Pregnancy Risks). Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 (see PRECAUTIONS: Pregnancy).

**Nursing:** Patients should be advised not to breastfeed an infant if they are taking Klonopin.

**Concomitant Medication:** Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

**Alcohol:** Patients should be advised to avoid alcohol while taking Klonopin.

**Drug Interactions:** Effect of Clonazepam on the Pharmacokinetics of Other Drugs:** Clonazepam does not appear to alter the pharmacokinetics of phenytoin, carbamazepine
or phenobarbital. The effect of clonazepam on the metabolism of other drugs has not been investigated.

**Effect of Other Drugs on the Pharmacokinetics of Clonazepam:** Literature reports suggest that ranitidine, an agent that decreases stomach acidity, does not greatly alter clonazepam pharmacokinetics.

In a study in which the 2 mg clonazepam orally disintegrating tablet was administered with and without propantheline (an anticholinergic agent with multiple effects on the GI tract) to healthy volunteers, the AUC of clonazepam was 10% lower and the C_{max} of clonazepam was 20% lower when the orally disintegrating tablet was given with propantheline compared to when it was given alone.

Fluoxetine does not affect the pharmacokinetics of clonazepam. Cytochrome P-450 inducers, such as phenytoin, carbamazepine and phenobarbital, induce clonazepam metabolism, causing an approximately 30% decrease in plasma clonazepam levels. Although clinical studies have not been performed, based on the involvement of the cytochrome P-450 3A family in clonazepam metabolism, inhibitors of this enzyme system, notably oral antifungal agents, should be used cautiously in patients receiving clonazepam.

**Pharmacodynamic Interactions:** The CNS-depressant action of the benzodiazepine class of drugs may be potentiated by alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, antianxiety agents, the phenothiazines, thioxanthenes and butyrophenone classes of antipsychotic agents, monoamine oxidase inhibitors and the tricyclic antidepressants, and by other anticonvulsant drugs.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenicity studies have not been conducted with clonazepam.

The data currently available are not sufficient to determine the genotoxic potential of clonazepam.

In a two-generation fertility study in which clonazepam was given orally to rats at 10 and 100 mg/kg/day (low dose approximately 5 times and 24 times the maximum recommended human dose of 20 mg/day for seizure disorder and 4 mg/day for panic disorder, respectively, on a mg/m^2 basis), there was a decrease in the number of pregnancies and in the number of offspring surviving until weaning.

**Pregnancy:** **Teratogenic Effects:** Pregnancy Category D (see WARNINGS: Pregnancy Risks).

To provide information regarding the effects of in utero exposure to Klonopin, physicians are advised to recommend that pregnant patients taking Klonopin enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on this registry can also be found at the website http://www.aedpregnancyregistry.org/.

**Labor and Delivery:** The effect of Klonopin on labor and delivery in humans has not been specifically studied; however, perinatal complications have been reported in...
children born to mothers who have been receiving benzodiazepines late in pregnancy, including findings suggestive of either excess benzodiazepine exposure or of withdrawal phenomena (see WARNINGS: Pregnancy Risks).

**Nursing Mothers:** Mothers receiving Klonopin should not breastfeed their infants.

**Pediatric Use:** Because of the possibility that adverse effects on physical or mental development could become apparent only after many years, a benefit-risk consideration of the long-term use of Klonopin is important in pediatric patients being treated for seizure disorder (see INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION).

Safety and effectiveness in pediatric patients with panic disorder below the age of 18 have not been established.

**Geriatric Use:** Clinical studies of Klonopin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Because clonazepam undergoes hepatic metabolism, it is possible that liver disease will impair clonazepam elimination. Metabolites of Klonopin are excreted by the kidneys; to avoid their excess accumulation, caution should be exercised in the administration of the drug to patients with impaired renal function. Because elderly patients are more likely to have decreased hepatic and/or renal function, care should be taken in dose selection, and it may be useful to assess hepatic and/or renal function at the time of dose selection.

Sedating drugs may cause confusion and over-sedation in the elderly; elderly patients generally should be started on low doses of Klonopin and observed closely.

**ADVERSE REACTIONS**
The adverse experiences for Klonopin are provided separately for patients with seizure disorders and with panic disorder.

**Seizure Disorders:** The most frequently occurring side effects of Klonopin are referable to CNS depression. Experience in treatment of seizures has shown that drowsiness has occurred in approximately 50% of patients and ataxia in approximately 30%. In some cases, these may diminish with time; behavior problems have been noted in approximately 25% of patients. Others, listed by system, are:

**Neurologic:** Abnormal eye movements, aphonia, choreiform movements, coma, diplopia, dysarthria, dysdiadochokinesia, “glassy-eyed” appearance, headache, hemiparesis, hypotonia, nystagmus, respiratory depression, slurred speech, tremor, vertigo

**Psychiatric:** Confusion, depression, amnesia, hallucinations, hysteria, increased libido, insomnia, psychosis (the behavior effects are more likely to occur in patients with a
history of psychiatric disturbances). The following paradoxical reactions have been observed: excitability, irritability, aggressive behavior, agitation, nervousness, hostility, anxiety, sleep disturbances, nightmares and vivid dreams

Respiratory: Chest congestion, rhinorrhea, shortness of breath, hypersecretion in upper respiratory passages

Cardiovascular: Palpitations

Dermatologic: Hair loss, hirsutism, skin rash, ankle and facial edema

Gastrointestinal: Anorexia, coated tongue, constipation, diarrhea, dry mouth, encopresis, gastritis, increased appetite, nausea, sore gums

Genitourinary: Dysuria, enuresis, nocturia, urinary retention

Musculoskeletal: Muscle weakness, pains

Miscellaneous: Dehydration, general deterioration, fever, lymphadenopathy, weight loss or gain

Hematopoietic: Anemia, leukopenia, thrombocytopenia, eosinophilia

Hepatic: Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase

Panic Disorder: Adverse events during exposure to Klonopin were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, CIGY dictionary terminology has been used to classify reported adverse events, except in certain cases in which redundant terms were collapsed into more meaningful terms, as noted below.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials:

Adverse Events Associated With Discontinuation of Treatment:

Overall, the incidence of discontinuation due to adverse events was 17% in Klonopin compared to 9% for placebo in the combined data of two 6- to 9-week trials. The most common events (≥1%) associated with discontinuation and a dropout rate twice or greater for Klonopin than that of placebo included the following:
Table 2  Most Common Adverse Events (≥1%) Associated with Discontinuation of Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Klonopin (N=574)</th>
<th>Placebo (N=294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Depression</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Intellectual Ability Reduced</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Adverse Events Occurring at an Incidence of 1% or More Among Klonopin-Treated Patients:

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of panic disorder from a pool of two 6- to 9-week trials. Events reported in 1% or more of patients treated with Klonopin (doses ranging from 0.5 to 4 mg/day) and for which the incidence was greater than that in placebo-treated patients are included.

The prescriber should be aware that the figures in Table 3 cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 3  Treatment-Emergent Adverse Event Incidence in 6- to 9-Week Placebo-Controlled Clinical Trials*

<table>
<thead>
<tr>
<th>Clonazepam Maximum Daily Dose</th>
<th>All Klonopin Groups N=574 %</th>
<th>Placebo N=294 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event by Body System</td>
<td>&lt;1mg n=96 %</td>
<td>1-&lt;2mg n=129 %</td>
</tr>
<tr>
<td>Central &amp; Peripheral Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence†</td>
<td>26</td>
<td>35</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Coordination Abnormal†</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ataxia†</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dysarthria†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Memory Disturbance</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>
### Clonazepam Maximum Daily Dose

<table>
<thead>
<tr>
<th>Adverse Event by Body System</th>
<th>&lt;1mg n=96 %</th>
<th>1-&lt;2mg n=129 %</th>
<th>2-&lt;3mg n=113 %</th>
<th>≥3mg n=235 %</th>
<th>All Klonopin Groups N=574 %</th>
<th>Placebo N=294 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervousness</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Intellectual Ability Reduced</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Emotional Lability</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Libido Decreased</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Confusion</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td><strong>Respiratory System</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection†</td>
<td>10</td>
<td>10</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>4</td>
<td>2</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Coughing</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Pharyngitis</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Gastrointestinal System</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation†</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>2</td>
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</tr>
<tr>
<td>Appetite Decreased</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal Pain†</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Adverse Event by Body System</td>
<td>1mg-%</td>
<td>1-&lt;2mg-%</td>
<td>2-&lt;3mg-%</td>
<td>≥3mg-%</td>
<td>All Klonopin Groups-%</td>
<td>Placebo-%</td>
</tr>
<tr>
<td>-----------------------------</td>
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<td>----------</td>
<td>--------</td>
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</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>9</td>
<td>6</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>4</td>
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<tr>
<td>Allergic Reaction</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Resistance Mechanism</td>
<td></td>
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<tr>
<td>Disorders</td>
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<tr>
<td>Influenza</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Urinary System</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Micturition Frequency</td>
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<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Urinary Tract Infection†</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Vision Disorders</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Reproductive Disorders‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Colpitis</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ejaculation Delayed</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Impotence</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* Events reported by at least 1% of patients treated with Klonopin and for which the incidence was greater than that for placebo.

† Indicates that the p-value for the dose-trend test (Cochran-Mantel-Haenszel) for adverse event incidence was ≤0.10.

‡ Denominators for events in gender-specific systems are: n=240 (clonazepam), 102 (placebo) for male, and 334 (clonazepam), 192 (placebo) for female.
Commonly Observed Adverse Events:

Table 4 Incidence of Most Commonly Observed Adverse Events* in Acute Therapy in Pool of 6- to 9-Week Trials

<table>
<thead>
<tr>
<th>Adverse Event (Genentech Preferred Term)</th>
<th>Clonazepam (N=574)</th>
<th>Placebo (N=294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>37%</td>
<td>10%</td>
</tr>
<tr>
<td>Depression</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td>Coordination Abnormal</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Treatment-emergent events for which the incidence in the clonazepam patients was ≥5% and at least twice that in the placebo patients.

Treatment-Emergent Depressive Symptoms:

In the pool of two short-term placebo-controlled trials, adverse events classified under the preferred term “depression” were reported in 7% of Klonopin-treated patients compared to 1% of placebo-treated patients, without any clear pattern of dose relatedness. In these same trials, adverse events classified under the preferred term “depression” were reported as leading to discontinuation in 4% of Klonopin-treated patients compared to 1% of placebo-treated patients. While these findings are noteworthy, Hamilton Depression Rating Scale (HAM-D) data collected in these trials revealed a larger decline in HAM-D scores in the clonazepam group than the placebo group suggesting that clonazepam-treated patients were not experiencing a worsening or emergence of clinical depression.

Other Adverse Events Observed During the Premarketing Evaluation of Klonopin in Panic Disorder:

Following is a list of modified CIGY terms that reflect treatment-emergent adverse events reported by patients treated with Klonopin at multiple doses during clinical trials. All reported events are included except those already listed in Table 3 or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and events reported only once and which did not have a substantial probability of being acutely life-threatening. It is important to emphasize that, although the events occurred during treatment with Klonopin, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency. These adverse events were reported infrequently, which is defined as occurring in 1/100 to 1/1000 patients.

Body as a Whole: weight increase, accident, weight decrease, wound, edema, fever, shivering, abrasions, ankle edema, edema foot, edema periorbital, injury, malaise, pain, cellulitis, inflammation localized

Cardiovascular Disorders: chest pain, hypotension postural
Central and Peripheral Nervous System Disorders: migraine, paresthesia, drunkenness, feeling of enuresis, paresis, tremor, burning skin, falling, head fullness, hoarseness, hyperactivity, hypoesthesia, tongue thick, twitching

Gastrointestinal System Disorders: abdominal discomfort, gastrointestinal inflammation, stomach upset, toothache, flatulence, pyrosis, saliva increased, tooth disorder, bowel movements frequent, pain pelvic, dyspepsia, hemorrhoids

Hearing and Vestibular Disorders: vertigo, otitis, earache, motion sickness

Heart Rate and Rhythm Disorders: palpitation

Metabolic and Nutritional Disorders: thirst, gout

Musculoskeletal System Disorders: back pain, fracture traumatic, sprains and strains, pain leg, pain nape, cramps muscle, cramps leg, pain ankle, pain shoulder, tendinitis, arthralgia, hypertonia, lumbago, pain feet, pain jaw, pain knee, swelling knee

Platelet, Bleeding and Clotting Disorders: bleeding dermal

Psychiatric Disorders: insomnia, organic disinhibition, anxiety, depersonalization, dreaming excessive, libido loss, appetite increased, libido increased, reactions decreased, aggressive reaction, apathy, attention lack, excitement, feeling mad, hunger abnormal, illusion, nightmares, sleep disorder, suicide ideation, yawning

Reproductive Disorders, Female: breast pain, menstrual irregularity

Reproductive Disorders, Male: ejaculation decreased

Resistance Mechanism Disorders: infection mycotic, infection viral, infection streptococcal, herpes simplex infection, infectious mononucleosis, moniliasis

Respiratory System Disorders: sneezing excessive, asthmatic attack, dyspnea, nosebleed, pneumonia, pleurisy

Skin and Appendages Disorders: acne flare, alopecia, xeroderma, dermatitis contact, flushing, pruritus, pustular reaction, skin burns, skin disorder

Special Senses Other, Disorders: taste loss

Urinary System Disorders: dysuria, cystitis, polyuria, urinary incontinence, bladder dysfunction, urinary retention, urinary tract bleeding, urine discoloration

Vascular (Extracardiac) Disorders: thrombophlebitis leg

Vision Disorders: eye irritation, visual disturbance, diplopia, eye twitching, styes, visual field defect, xerophthalmia

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Clonazepam is a Schedule IV controlled substance.

Physical and Psychological Dependence: Withdrawal symptoms, similar in character to those noted with barbiturates and alcohol (eg, convulsions, psychosis, hallucinations,
behavioral disorder, tremor, abdominal and muscle cramps) have occurred following abrupt discontinuance of clonazepam. The more severe withdrawal symptoms have usually been limited to those patients who received excessive doses over an extended period of time. Generally milder withdrawal symptoms (e.g., dysphoria and insomnia) have been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months. Consequently, after extended therapy, abrupt discontinuation should generally be avoided and a gradual dosage tapering schedule followed (see DOSAGE AND ADMINISTRATION). Addiction-prone individuals (such as drug addicts or alcoholics) should be under careful surveillance when receiving clonazepam or other psychotropic agents because of the predisposition of such patients to habituation and dependence.

Following the short-term treatment of patients with panic disorder in Studies 1 and 2 (see CLINICAL PHARMACOLOGY: Clinical Trials), patients were gradually withdrawn during a 7-week downward-titration (discontinuance) period. Overall, the discontinuance period was associated with good tolerability and a very modest clinical deterioration, without evidence of a significant rebound phenomenon. However, there are not sufficient data from adequate and well-controlled long-term clonazepam studies in patients with panic disorder to accurately estimate the risks of withdrawal symptoms and dependence that may be associated with such use.

OVERDOSAGE

Human Experience: Symptoms of clonazepam overdosage, like those produced by other CNS depressants, include somnolence, confusion, coma and diminished reflexes.

Overdose Management: Treatment includes monitoring of respiration, pulse and blood pressure, general supportive measures and immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of no known value.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for resedation, respiratory depression and other residual benzodiazepine effects for an appropriate period after treatment. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose. The complete flumazenil package insert, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, should be consulted prior to use.

Flumazenil is not indicated in patients with epilepsy who have been treated with benzodiazepines. Antagonism of the benzodiazepine effect in such patients may provoke seizures.

Serious sequelae are rare unless other drugs or alcohol have been taken concomitantly.
DOSE AND ADMINISTRATION

Clonazepam is available as a tablet. The tablets should be administered with water by swallowing the tablet whole.

**Seizure Disorders: Adults:** The initial dose for adults with seizure disorders should not exceed 1.5 mg/day divided into three doses. Dosage may be increased in increments of 0.5 to 1 mg every 3 days until seizures are adequately controlled or until side effects preclude any further increase. Maintenance dosage must be individualized for each patient depending upon response. Maximum recommended daily dose is 20 mg.

The use of multiple anticonvulsants may result in an increase of depressant adverse effects. This should be considered before adding Klonopin to an existing anticonvulsant regimen.

**Pediatric Patients:** Klonopin is administered orally. In order to minimize drowsiness, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses. Dosage should be increased by no more than 0.25 to 0.5 mg every third day until a daily maintenance dose of 0.1 to 0.2 mg/kg of body weight has been reached, unless seizures are controlled or side effects preclude further increase. Whenever possible, the daily dose should be divided into three equal doses. If doses are not equally divided, the largest dose should be given before retiring.

**Geriatric Patients:** There is no clinical trial experience with Klonopin in seizure disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of Klonopin and observed closely (see PRECAUTIONS: Geriatric Use).

**Panic Disorder: Adults:** The initial dose for adults with panic disorder is 0.25 mg bid. An increase to the target dose for most patients of 1 mg/day may be made after 3 days. The recommended dose of 1 mg/day is based on the results from a fixed dose study in which the optimal effect was seen at 1 mg/day. Higher doses of 2, 3 and 4 mg/day in that study were less effective than the 1 mg/day dose and were associated with more adverse effects. Nevertheless, it is possible that some individual patients may benefit from doses of up to a maximum dose of 4 mg/day, and in those instances, the dose may be increased in increments of 0.125 to 0.25 mg bid every 3 days until panic disorder is controlled or until side effects make further increases undesired. To reduce the inconvenience of somnolence, administration of one dose at bedtime may be desirable.

Treatment should be discontinued gradually, with a decrease of 0.125 mg bid every 3 days, until the drug is completely withdrawn.

There is no body of evidence available to answer the question of how long the patient treated with clonazepam should remain on it. Therefore, the physician who elects to use Klonopin for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

**Pediatric Patients:** There is no clinical trial experience with Klonopin in panic disorder patients under 18 years of age.
Geriatric Patients: There is no clinical trial experience with Klonopin in panic disorder patients 65 years of age and older. In general, elderly patients should be started on low doses of Klonopin and observed closely (see PRECAUTIONS: Geriatric Use).

HOW SUPPLIED
Klonopin tablets are available as scored tablets with a K-shaped perforation—0.5 mg, orange (NDC 0004-0068-01); and unscored tablets with a K-shaped perforation—1 mg, blue (NDC 0004-0058-01); 2 mg, white (NDC 0004-0098-01)—bottles of 100.

Imprint on tablets:

0.5 mg — 1/2 KLONOPIN (front)
ROCHE (scored side)

1 mg — 1 KLONOPIN (front)
ROCHE (reverse side)

2 mg — 2 KLONOPIN (front)
ROCHE (reverse side)

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Distributed by:

Genentech USA, Inc.
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Medication Guide

KLONOPIN® (KLON-oh-pin)
(clonazepam)

Tablets

Read this Medication Guide before you start taking KLONOPIN and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

KLONOPIN can cause serious side effects. Because stopping KLONOPIN suddenly can also cause serious problems, do not stop taking KLONOPIN without talking to your healthcare provider first.

What is the most important information I should know about KLONOPIN?

Do not stop taking KLONOPIN without first talking to your healthcare provider. Stopping KLONOPIN suddenly can cause serious problems.

KLONOPIN can cause serious side effects, including:

1. KLONOPIN can slow your thinking and motor skills
   - Do not drive, operate heavy machinery, or do other dangerous activities until you know how KLONOPIN affects you.
   - Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking KLONOPIN until you talk to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, KLONOPIN may make your sleepiness or dizziness worse.

2. Like other antiepileptic drugs, KLONOPIN may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.
   - Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
     - thoughts about suicide or dying
     - attempt to commit suicide
     - new or worse depression
     - new or worse anxiety
     - feeling agitated or restless
     - panic attacks
     - trouble sleeping (insomnia)
     - new or worse irritability
     - acting aggressive, being angry, or violent
     - acting on dangerous impulses
     - an extreme increase in activity and talking (mania)
     - other unusual changes in behavior or mood
How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

**Do not stop KLONOPIN without first talking to a healthcare provider.**

Stopping KLONOPIN suddenly can cause serious problems. Stopping KLONOPIN suddenly can cause seizures that will not stop (status epilepticus).

### 3. KLONOPIN may harm your unborn or developing baby.

- If you take KLONOPIN during pregnancy, your baby is at risk for serious birth defects. These defects can happen as early as in the first month of pregnancy, even before you know you are pregnant. Birth defects may occur even in children born to women who are not taking any medicines and do not have other risk factors.

- Children born to mothers receiving benzodiazepine medications (including KLONOPIN) late in pregnancy may be at some risk of experiencing breathing problems, feeding problems, hypothermia, and withdrawal symptoms.

- Tell your healthcare provider right away if you become pregnant while taking KLONOPIN. You and your healthcare provider should decide if you will take KLONOPIN while you are pregnant.

- If you become pregnant while taking KLONOPIN, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can register by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.

- KLONOPIN can pass into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take KLONOPIN. You and your healthcare provider should decide if you will take KLONOPIN or breast feed. You should not do both.

### 4. KLONOPIN can cause abuse and dependence.

- Do not stop taking KLONOPIN all of a sudden. Stopping KLONOPIN suddenly can cause seizures that do not stop, hearing or seeing things that are not there (hallucinations), shaking, and stomach and muscle cramps.
Talk to your doctor about slowly stopping KLONOPIN to avoid getting sick with withdrawal symptoms.

Physical dependence is not the same as drug addiction. Your healthcare provider can tell you more about the differences between physical dependence and drug addiction.

**KLONOPIN is a federally controlled substance (C-IV) because it can be abused or lead to dependence. Keep KLONOPIN in a safe place to prevent misuse and abuse. Selling or giving away KLONOPIN may harm others, and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines or street drugs.**

**What is KLONOPIN?**

KLONOPIN is a prescription medicine used alone or with other medicines to treat:

- certain types of seizure disorders (epilepsy) in adults and children
- panic disorder with or without fear of open spaces (agoraphobia) in adults

It is not known if KLONOPIN is safe or effective in treating panic disorder in children younger than 18 years old.

**Who should not take KLONOPIN?**

Do not take KLONOPIN if you:

- are allergic to benzodiazepines
- have significant liver disease
- have an eye disease called acute narrow angle glaucoma

Ask your healthcare provider if you are not sure if you have any of the problems listed above.

**What should I tell my healthcare provider before taking KLONOPIN?**

Before you take KLONOPIN, tell your healthcare provider if you:

- have liver or kidney problems
- have lung problems (respiratory disease)
- have or have had depression, mood problems, or suicidal thoughts or behavior
- have any other medical conditions

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Taking KLONOPIN with certain other medicines can cause side effects or affect
how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

**How should I take KLONOPIN?**

- Take KLONOPIN exactly as your healthcare provider tells you. KLONOPIN is available as a tablet.
- Do not stop taking KLONOPIN without first talking to your healthcare provider. Stopping KLONOPIN suddenly can cause serious problems.
- **KLONOPIN tablets** should be taken with water and swallowed whole.
- If you take too much KLONOPIN, call your healthcare provider or local Poison Control Center right away.

**What should I avoid while taking KLONOPIN?**

- KLONOPIN can slow your thinking and motor skills. Do not drive, operate heavy machinery, or do other dangerous activities until you know how KLONOPIN affects you.
- Do not drink alcohol or take other drugs that may make you sleepy or dizzy while taking KLONOPIN until you talk to your healthcare provider. When taken with alcohol or drugs that cause sleepiness or dizziness, KLONOPIN may make your sleepiness or dizziness worse.

**What are the possible side effects of KLONOPIN?**

See “What is the most important information I should know about KLONOPIN?”

KLONOPIN can also make your seizures happen more often or make them worse. Call your healthcare provider right away if your seizures get worse while taking KLONOPIN.

The most common side effects of KLONOPIN include:

- Drowsiness
- Problems with walking and coordination
- Dizziness
- Depression
- Fatigue
- Problems with memory

These are not all the possible side effects of KLONOPIN. For more information, ask your healthcare provider or pharmacist.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store KLONOPIN?**

- Store KLONOPIN between 59°F to 86°F (15°C to 30°C)

*Keep KLONOPIN and all medicines out of the reach of children.*

**General Information about KLONOPIN**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use KLONOPIN for a condition for which it was not prescribed. Do not give KLONOPIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about KLONOPIN. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about KLONOPIN that is written for health professionals.

For more information, go to [www.gene.com/gene/products/information/klonopin](http://www.gene.com/gene/products/information/klonopin) or call 1-888-835-2555.

**What are the ingredients in KLONOPIN?**

Active ingredient: clonazepam

Inactive ingredients:

- Tablets:
  - 0.5 mg tablets contain lactose, magnesium stearate, microcrystalline cellulose, corn starch, FD&C Yellow No. 6 Lake
  - 1 mg tablets contain lactose, magnesium stearate, microcrystalline cellulose, corn starch, FD&C Blue No. 1 Lake and FD&C Blue No. 2 Lake
  - 2 mg tablets contain lactose, magnesium stearate, microcrystalline cellulose, corn starch

Issued: Month Year

This Medication Guide has been approved by the U.S. Food and Drug Administration.
PAXIL®
(paroxetine hydrochloride)
Tablets and Oral Suspension

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of PAXIL or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PAXIL is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

PAXIL (paroxetine hydrochloride) is an orally administered psychotropic drug. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (-)-trans-4R-(4'-fluorophenyl)-3S-[3',4'-methylenedioxyphenoxy] methyl] piperidine hydrochloride hemihydrate and has the empirical formula of C\textsubscript{19}H\textsubscript{20}FNO\textsubscript{3} \cdot HCl \cdot 1/2H\textsubscript{2}O. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:

![Structural formula of paroxetine hydrochloride]

Paroxetine hydrochloride is an odorless, off-white powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Tablets: Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 10 mg—yellow (scored); 20 mg—pink (scored); 30 mg—blue, 40 mg—green. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of...
the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake.

**Suspension for Oral Administration:** Each 5 mL of orange-colored, orange-flavored liquid contains paroxetine hydrochloride equivalent to paroxetine, 10 mg. Inactive ingredients consist of polacrilin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methylparaben, propylparaben, sodium citrate dihydrate, citric acid anhydrous, sodium saccharin, flavorings, FD&C Yellow No. 6 aluminum lake, and simethicone emulsion, USP.

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics:** The efficacy of paroxetine in the treatment of major depressive disorder, social anxiety disorder, obsessive compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. In vitro studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. In vitro radioligand binding studies indicate that paroxetine has little affinity for muscarinic, alpha1-, alpha2-, beta-adrenergic-, dopamine (D2)-, 5-HT1-, 5-HT2-, and histamine (H1)-receptors; antagonism of muscarinic, histaminergic, and alpha1-adrenergic receptors has been associated with various anticholinergic, sedative, and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine’s major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

**Pharmacokinetics:** Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets of PAXIL daily for 30 days. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6, and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

In a meta-analysis of paroxetine from 4 studies done in healthy volunteers following multiple dosing of 20 mg/day to 40 mg/day, males did not exhibit a significantly lower C\text{max} or AUC than females.

**Absorption and Distribution:** Paroxetine is equally bioavailable from the oral suspension and tablet.

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male subjects (n = 15) received 30 mg tablets daily for 30 days, steady-state paroxetine concentrations were achieved by approximately
10 days for most subjects, although it may take substantially longer in an occasional patient. At steady state, mean values of \( C_{\text{max}} \), \( T_{\text{max}} \), \( C_{\text{min}} \), and \( T_{1/2} \) were 61.7 ng/mL (CV 45%), 5.2 hr. (CV 10%), 30.7 ng/mL (CV 67%), and 21.0 hours (CV 32%), respectively. The steady-state \( C_{\text{max}} \) and \( C_{\text{min}} \) values were about 6 and 14 times what would be predicted from single-dose studies. Steady-state drug exposure based on \( \text{AUC}_{0-24} \) was about 8 times greater than would have been predicted from single-dose data in these subjects. The excess accumulation is a consequence of the fact that 1 of the enzymes that metabolizes paroxetine is readily saturable.

The effects of food on the bioavailability of paroxetine were studied in subjects administered a single dose with and without food. AUC was only slightly increased (6%) when drug was administered with food but the \( C_{\text{max}} \) was 29% greater, while the time to reach peak plasma concentration decreased from 6.4 hours post-dosing to 4.9 hours.

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the in vitro protein binding of phenytoin or warfarin.

**Metabolism and Excretion:** The mean elimination half-life is approximately 21 hours (CV 32%) after oral dosing of 30 mg tablets daily for 30 days of PAXIL. In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to \( C_{\text{min}} \) values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate, and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS: Drugs Metabolized by CYP2D6).

Approximately 64% of a 30-mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10-day post-dosing period.

**Other Clinical Pharmacology Information:**

*Specific Populations: Renal and Liver Disease:* Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below
30 mL/min. were approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min. and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C\text{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment, and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

**Elderly Patients:** In a multiple-dose study in the elderly at daily paroxetine doses of 20, 30, and 40 mg, C\text{min} concentrations were about 70% to 80% greater than the respective C\text{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

**Drug-Drug Interactions:** In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone, and atomoxetine (see PRECAUTIONS: Drug Interactions).

**Clinical Trials**

**Major Depressive Disorder:** The efficacy of PAXIL as a treatment for major depressive disorder has been established in 6 placebo-controlled studies of patients with major depressive disorder (aged 18 to 73). In these studies, PAXIL was shown to be significantly more effective than placebo in treating major depressive disorder by at least 2 of the following measures: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item, and the Clinical Global Impression (CGI)-Severity of Illness. PAXIL was significantly better than placebo in improvement of the HDRS sub-factor scores, including the depressed mood item, sleep disturbance factor, and anxiety factor.

A study of outpatients with major depressive disorder who had responded to PAXIL (HDRS total score <8) during an initial 8-week open-treatment phase and were then randomized to continuation on PAXIL or placebo for 1 year demonstrated a significantly lower relapse rate for patients taking PAXIL (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

**Obsessive Compulsive Disorder:** The effectiveness of PAXIL in the treatment of obsessive compulsive disorder (OCD) was demonstrated in two 12-week multicenter placebo-controlled studies of adult outpatients (Studies 1 and 2). Patients in all studies had moderate to severe OCD (DSM-IIIR) with mean baseline ratings on the Yale Brown Obsessive Compulsive Scale (YBOCS) total score ranging from 23 to 26. Study 1, a dose-range finding study where patients were treated with fixed doses of 20, 40, or 60 mg of paroxetine/day demonstrated that daily doses of paroxetine 40 and 60 mg are effective in the treatment of OCD. Patients receiving doses of 40 and 60 mg paroxetine experienced a mean reduction of approximately 6 and 7 points, respectively, on the YBOCS total score which was significantly greater than the approximate 4-point reduction at 20 mg and a 3-point reduction in the placebo-treated patients. Study 2 was a flexible-dose study comparing paroxetine (20 to 60 mg daily) with clomipramine (25 to 250 mg
daily). In this study, patients receiving paroxetine experienced a mean reduction of approximately 7 points on the YBOCS total score, which was significantly greater than the mean reduction of approximately 4 points in placebo-treated patients.

The following table provides the outcome classification by treatment group on Global Improvement items of the Clinical Global Impression (CGI) scale for Study 1.

| Outcome Classification (%) on CGI-Global Improvement Item for Completers in Study 1 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Outcome Classification          | Placebo (n = 74) | PAXIL 20 mg (n = 75) | PAXIL 40 mg (n = 66) | PAXIL 60 mg (n = 66) |
| Worse                           | 14%             | 7%               | 7%               | 3%               |
| No Change                       | 44%             | 35%              | 22%              | 19%              |
| Minimally Improved              | 24%             | 33%              | 29%              | 34%              |
| Much Improved                   | 11%             | 18%              | 22%              | 24%              |
| Very Much Improved              | 7%              | 7%               | 20%              | 20%              |

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

The long-term maintenance effects of PAXIL in OCD were demonstrated in a long-term extension to Study 1. Patients who were responders on paroxetine during the 3-month double-blind phase and a 6-month extension on open-label paroxetine (20 to 60 mg/day) were randomized to either paroxetine or placebo in a 6-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Panic Disorder: The effectiveness of PAXIL in the treatment of panic disorder was demonstrated in three 10- to 12-week multicenter, placebo-controlled studies of adult outpatients (Studies 1-3). Patients in all studies had panic disorder (DSM-IIIR), with or without agoraphobia. In these studies, PAXIL was shown to be significantly more effective than placebo in treating panic disorder by at least 2 out of 3 measures of panic attack frequency and on the Clinical Global Impression Severity of Illness score.

Study 1 was a 10-week dose-range finding study; patients were treated with fixed paroxetine doses of 10, 20, or 40 mg/day or placebo. A significant difference from placebo was observed only for the 40 mg/day group. At endpoint, 76% of patients receiving paroxetine 40 mg/day were free of panic attacks, compared to 44% of placebo-treated patients.

Study 2 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) and placebo. At endpoint, 51% of paroxetine patients were free of panic attacks compared to 32% of placebo-treated patients.

Study 3 was a 12-week flexible-dose study comparing paroxetine (10 to 60 mg daily) to placebo in patients concurrently receiving standardized cognitive behavioral therapy. At endpoint, 33% of the paroxetine-treated patients showed a reduction to 0 or 1 panic attacks compared to 14% of placebo patients.
In both Studies 2 and 3, the mean paroxetine dose for completers at endpoint was approximately 40 mg/day of paroxetine.

Long-term maintenance effects of PAXIL in panic disorder were demonstrated in an extension to Study 1. Patients who were responders during the 10-week double-blind phase and during a 3-month double-blind extension phase were randomized to either paroxetine (10, 20, or 40 mg/day) or placebo in a 3-month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

**Social Anxiety Disorder:** The effectiveness of PAXIL in the treatment of social anxiety disorder was demonstrated in three 12-week, multicenter, placebo-controlled studies (Studies 1, 2, and 3) of adult outpatients with social anxiety disorder (DSM-IV). In these studies, the effectiveness of PAXIL compared to placebo was evaluated on the basis of (1) the proportion of responders, as defined by a Clinical Global Impression (CGI) Improvement score of 1 (very much improved) or 2 (much improved), and (2) change from baseline in the Liebowitz Social Anxiety Scale (LSAS).

Studies 1 and 2 were flexible-dose studies comparing paroxetine (20 to 50 mg daily) and placebo. Paroxetine demonstrated statistically significant superiority over placebo on both the CGI Improvement responder criterion and the Liebowitz Social Anxiety Scale (LSAS). In Study 1, for patients who completed to week 12, 69% of paroxetine-treated patients compared to 29% of placebo-treated patients were CGI Improvement responders. In Study 2, CGI Improvement responders were 77% and 42% for the paroxetine- and placebo-treated patients, respectively.

Study 3 was a 12-week study comparing fixed paroxetine doses of 20, 40, or 60 mg/day with placebo. Paroxetine 20 mg was demonstrated to be significantly superior to placebo on both the LSAS Total Score and the CGI Improvement responder criterion; there were trends for superiority over placebo for the 40 mg and 60 mg/day dose groups. There was no indication in this study of any additional benefit for doses higher than 20 mg/day.

Subgroup analyses generally did not indicate differences in treatment outcomes as a function of age, race, or gender.

**Generalized Anxiety Disorder:** The effectiveness of PAXIL in the treatment of Generalized Anxiety Disorder (GAD) was demonstrated in two 8-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients with Generalized Anxiety Disorder (DSM-IV).

Study 1 was an 8-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day with placebo. Doses of 20 mg or 40 mg of PAXIL were both demonstrated to be significantly superior to placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to the 20 mg/day dose.

Study 2 was a flexible-dose study comparing paroxetine (20 mg to 50 mg daily) and placebo.
PAXIL demonstrated statistically significant superiority over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score. A third study, also flexible-dose comparing paroxetine (20 mg to 50 mg daily), did not demonstrate statistically significant superiority of PAXIL over placebo on the Hamilton Rating Scale for Anxiety (HAM-A) total score, the primary outcome. Subgroup analyses did not indicate differences in treatment outcomes as a function of race or gender. There were insufficient elderly patients to conduct subgroup analyses on the basis of age.

In a longer-term trial, 566 patients meeting DSM-IV criteria for Generalized Anxiety Disorder, who had responded during a single-blind, 8-week acute treatment phase with 20 to 50 mg/day of PAXIL, were randomized to continuation of PAXIL at their same dose, or to placebo, for up to 24 weeks of observation for relapse. Response during the single-blind phase was defined by having a decrease of ≥2 points compared to baseline on the CGI-Severity of Illness scale, to a score of ≤3. Relapse during the double-blind phase was defined as an increase of ≥2 points compared to baseline on the CGI-Severity of Illness scale to a score of ≥4, or withdrawal due to lack of efficacy. Patients receiving continued PAXIL experienced a significantly lower relapse rate over the subsequent 24 weeks compared to those receiving placebo.

**Posttraumatic Stress Disorder:** The effectiveness of PAXIL in the treatment of Posttraumatic Stress Disorder (PTSD) was demonstrated in two 12-week, multicenter, placebo-controlled studies (Studies 1 and 2) of adult outpatients who met DSM-IV criteria for PTSD. The mean duration of PTSD symptoms for the 2 studies combined was 13 years (ranging from .1 year to 57 years). The percentage of patients with secondary major depressive disorder or non-PTSD anxiety disorders in the combined 2 studies was 41% (356 out of 858 patients) and 40% (345 out of 858 patients), respectively. Study outcome was assessed by (i) the Clinician-Administered PTSD Scale Part 2 (CAPS-2) score and (ii) the Clinical Global Impression-Global Improvement Scale (CGI-I). The CAPS-2 is a multi-item instrument that measures 3 aspects of PTSD with the following symptom clusters: Reexperiencing/intrusion, avoidance/numbing and hyperarousal. The 2 primary outcomes for each trial were (i) change from baseline to endpoint on the CAPS-2 total score (17 items), and (ii) proportion of responders on the CGI-I, where responders were defined as patients having a score of 1 (very much improved) or 2 (much improved).

Study 1 was a 12-week study comparing fixed paroxetine doses of 20 mg or 40 mg/day to placebo. Doses of 20 mg and 40 mg of PAXIL were demonstrated to be significantly superior to placebo on change from baseline for the CAPS-2 total score and on proportion of responders on the CGI-I. There was not sufficient evidence in this study to suggest a greater benefit for the 40 mg/day dose compared to the 20 mg/day dose.

Study 2 was a 12-week flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo. PAXIL was demonstrated to be significantly superior to placebo on change from baseline for the CAPS-2 total score and on proportion of responders on the CGI-I.

A third study, also a flexible-dose study comparing paroxetine (20 to 50 mg daily) to placebo, demonstrated PAXIL to be significantly superior to placebo on change from baseline for CAPS-2 total score, but not on proportion of responders on the CGI-I.
The majority of patients in these trials were women (68% women: 377 out of 551 subjects in Study 1 and 66% women: 202 out of 303 subjects in Study 2). Subgroup analyses did not indicate differences in treatment outcomes as a function of gender. There were an insufficient number of patients who were 65 years and older or were non-Caucasian to conduct subgroup analyses on the basis of age or race, respectively.

**INDICATIONS AND USAGE**

**Major Depressive Disorder:** PAXIL is indicated for the treatment of major depressive disorder.

The efficacy of PAXIL in the treatment of a major depressive episode was established in 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III category of major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials). A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: Change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, and a suicide attempt or suicidal ideation.

The effects of PAXIL in hospitalized depressed patients have not been adequately studied.

The efficacy of PAXIL in maintaining a response in major depressive disorder for up to 1 year was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who elects to use PAXIL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

**Obsessive Compulsive Disorder:** PAXIL is indicated for the treatment of obsessions and compulsions in patients with obsessive compulsive disorder (OCD) as defined in the DSM-IV. The obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of PAXIL was established in two 12-week trials with obsessive compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of obsessive compulsive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials). Obsessive compulsive disorder is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients assigned to paroxetine showed a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who elects to use PAXIL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

**Panic Disorder:** PAXIL is indicated for the treatment of panic disorder, with or without
agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of PAXIL was established in three 10- to 12-week trials in panic disorder patients whose diagnoses corresponded to the DSM-IIIR category of panic disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who prescribes PAXIL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Social Anxiety Disorder: PAXIL is indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of 1 or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation, or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning, or social activities or relationships, or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of PAXIL was established in three 12-week trials in adult patients with social anxiety disorder (DSM-IV). PAXIL has not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY: Clinical Trials).

The effectiveness of PAXIL in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well-controlled trials. Therefore, the physician who elects to prescribe PAXIL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Generalized Anxiety Disorder: PAXIL is indicated for the treatment of Generalized Anxiety
Disorder (GAD), as defined in DSM-IV. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

The efficacy of PAXIL in the treatment of GAD was established in two 8-week placebo-controlled trials in adults with GAD. PAXIL has not been studied in children or adolescents with Generalized Anxiety Disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following 6 symptoms:

- Restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, sleep disturbance.

The efficacy of PAXIL in maintaining a response in patients with Generalized Anxiety Disorder, who responded during an 8-week acute treatment phase while taking PAXIL and were then observed for relapse during a period of up to 24 weeks, was demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who elects to use PAXIL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Posttraumatic Stress Disorder: PAXIL is indicated for the treatment of Posttraumatic Stress Disorder (PTSD).

The efficacy of PAXIL in the treatment of PTSD was established in two 12-week placebo-controlled trials in adults with PTSD (DSM-IV) (see CLINICAL PHARMACOLOGY: Clinical Trials).

PTSD, as defined by DSM-IV, requires exposure to a traumatic event that involved actual or threatened death or serious injury, or threat to the physical integrity of self or others, and a response that involves intense fear, helplessness, or horror. Symptoms that occur as a result of exposure to the traumatic event include reexperiencing of the event in the form of intrusive thoughts, flashbacks, or dreams, and intense psychological distress and physiological reactivity on exposure to cues to the event; avoidance of situations reminiscent of the traumatic event, inability to recall details of the event, and/or numbing of general responsiveness manifested as diminished interest in significant activities, estrangement from others, restricted range of affect, or sense of foreshortened future; and symptoms of autonomic arousal including hypervigilance, exaggerated startle response, sleep disturbance, impaired concentration, and irritability or outbursts of anger. A PTSD diagnosis requires that the symptoms are present for at least a month and that they cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The efficacy of PAXIL in longer-term treatment of PTSD, i.e., for more than 12 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to prescribe PAXIL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).
CONTRAINDICATIONS

The use of MAOIs intended to treat psychiatric disorders with PAXIL or within 14 days of stopping treatment with PAXIL is contraindicated because of an increased risk of serotonin syndrome. The use of PAXIL within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated (see WARNINGS and DOSAGE AND ADMINISTRATION).

Starting PAXIL in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome (see WARNINGS and DOSAGE AND ADMINISTRATION).

Concomitant use with thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

PAXIL is contraindicated in patients with a hypersensitivity to paroxetine or any of the inactive ingredients in PAXIL.

WARNINGS

Clinical Worsening and Suicide Risk: Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.
### Table 1

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>14 additional cases</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional cases</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer case</td>
</tr>
<tr>
<td>≥65</td>
<td>6 fewer cases</td>
</tr>
</tbody>
</table>

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

**All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.**

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION: Discontinuation of Treatment With PAXIL, for a description of the risks of discontinuation of PAXIL).

**Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability,
unusual changes in behavior, and the other symptoms described above, as well as the
emergence of suicidality, and to report such symptoms immediately to healthcare
providers. Such monitoring should include daily observation by families and caregivers.
Prescriptions for PAXIL should be written for the smallest quantity of tablets consistent with
good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial
presentation of bipolar disorder. It is generally believed (though not established in controlled
trials) that treating such an episode with an antidepressant alone may increase the likelihood of
precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the
symptoms described above represent such a conversion is unknown. However, prior to initiating
treatment with an antidepressant, patients with depressive symptoms should be adequately
screened to determine if they are at risk for bipolar disorder; such screening should include a
detailed psychiatric history, including a family history of suicide, bipolar disorder, and
depression. It should be noted that PAXIL is not approved for use in treating bipolar depression.

Serotonin Syndrome: The development of a potentially life-threatening serotonin syndrome
has been reported with SNRIs and SSRIs, including PAXIL, alone but particularly with
concomitant use of other serotonergic drugs (including triptans, tricyclic antidepressants,
fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John’s Wort) and with drugs that
impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric
disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation,
hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood
pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor,
rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms
(e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin
syndrome.

The concomitant use of PAXIL with MAOIs intended to treat psychiatric disorders is
contraindicated. PAXIL should also not be started in a patient who is being treated with MAOIs
such as linezolid or intravenous methylene blue. All reports with methylene blue that provided
information on the route of administration involved intravenous administration in the dose range
of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes
(such as oral tablets or local tissue injection) or at lower doses. There may be circumstances
when it is necessary to initiate treatment with an MAOI such as linezolid or intravenous
methylene blue in a patient taking PAXIL. PAXIL should be discontinued before initiating
treatment with the MAOI (see CONTRAINDICATIONS and DOSAGE AND
ADMINISTRATION).

If concomitant use of PAXIL with certain other serotonergic drugs, i.e., triptans, tricyclic
antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John’s Wort is
clinically warranted, be aware of a potential increased risk for serotonin syndrome, particularly
during treatment initiation and dose increases.
Treatment with PAXIL and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Potential Interaction With Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as torsade de pointes–type arrhythmias, and sudden death. This effect appears to be dose related.

An in vivo study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

Usage in Pregnancy: Teratogenic Effects: Epidemiological studies have shown that infants exposed to paroxetine in the first trimester of pregnancy have an increased risk of congenital malformations, particularly cardiovascular malformations. The findings from these studies are summarized below:

- A study based on Swedish national registry data demonstrated that infants exposed to paroxetine during pregnancy (n = 815) had an increased risk of cardiovascular malformations (2% risk in paroxetine-exposed infants) compared to the entire registry population (1% risk), for an odds ratio (OR) of 1.8 (95% confidence interval 1.1 to 2.8). No increase in the risk of overall congenital malformations was seen in the paroxetine-exposed infants. The cardiac malformations in the paroxetine-exposed infants were primarily ventricular septal defects (VSDs) and atrial septal defects (ASDs). Septal defects range in severity from those that resolve spontaneously to those which require surgery.

- A separate retrospective cohort study from the United States (United Healthcare data) evaluated 5,956 infants of mothers dispensed antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine (risk of 1.5%) compared to other antidepressants (risk of 1%), for an OR of 1.5 (95% confidence interval 0.8 to 2.9). Of the 12 paroxetine-exposed infants with cardiovascular malformations, 9 had VSDs. This study also suggested an increased risk of overall major congenital malformations including cardiovascular defects for paroxetine (4% risk) compared to other (2% risk) antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8).

- Two large case-control studies using separate databases, each with >9,000 birth defect cases and >4,000 controls, found that maternal use of paroxetine during the first trimester of pregnancy was associated with a 2- to 3-fold increased risk of right ventricular outflow tract obstructions. In one study the odds ratio was 2.5 (95% confidence interval, 1.0 to 6.0, 7 exposed infants) and in the other study the odds ratio was 3.3 (95% confidence interval, 1.3 to 8.8, 6 exposed infants).

Other studies have found varying results as to whether there was an increased risk of overall, cardiovascular, or specific congenital malformations. A meta-analysis of epidemiological data over a 16-year period (1992 to 2008) on first trimester paroxetine use in pregnancy and
congenital malformations included the above-noted studies in addition to others (n = 17 studies that included overall malformations and n = 14 studies that included cardiovascular malformations; n = 20 distinct studies). While subject to limitations, this meta-analysis suggested an increased occurrence of cardiovascular malformations (prevalence odds ratio [POR] 1.5; 95% confidence interval 1.2 to 1.9) and overall malformations (POR 1.2; 95% confidence interval 1.1 to 1.4) with paroxetine use during the first trimester. It was not possible in this meta-analysis to determine the extent to which the observed prevalence of cardiovascular malformations might have contributed to that of overall malformations, nor was it possible to determine whether any specific types of cardiovascular malformations might have contributed to the observed prevalence of all cardiovascular malformations.

If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS: Discontinuation of Treatment With PAXIL). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

**Animal Findings:** Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no-effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

**Nonteratogenic Effects:** Neonates exposed to PAXIL and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS: Serotonin Syndrome).

Infants exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 – 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRi use (including PAXIL) in pregnancy and PPHN. Other studies do not show a significant statistical association.

Physicians should also note the results of a prospective longitudinal study of 201 pregnant women with a history of major depression, who were either on antidepressants or had received...
antidepressants less than 12 weeks prior to their last menstrual period, and were in remission.
Women who discontinued antidepressant medication during pregnancy showed a significant
increase in relapse of their major depression compared to those women who remained on
antidepressant medication throughout pregnancy.
When treating a pregnant woman with PAXIL, the physician should carefully consider both
the potential risks of taking an SSRI, along with the established benefits of treating depression
with an antidepressant. This decision can only be made on a case by case basis (see DOSAGE
AND ADMINISTRATION and ADVERSE REACTIONS: Postmarketing Reports).

PRECAUTIONS

General: Activation of Mania/Hypomania: During premarketing testing, hypomania or
mania occurred in approximately 1.0% of unipolar patients treated with PAXIL compared to
1.1% of active-control and 0.3% of placebo-treated unipolar patients. In a subset of patients
classified as bipolar, the rate of manic episodes was 2.2% for PAXIL and 11.6% for the
combined active-control groups. As with all drugs effective in the treatment of major depressive
disorder, PAXIL should be used cautiously in patients with a history of mania.
Seizures: During premarketing testing, seizures occurred in 0.1% of patients treated with
PAXIL, a rate similar to that associated with other drugs effective in the treatment of major
depressive disorder. PAXIL should be used cautiously in patients with a history of seizures. It
should be discontinued in any patient who develops seizures.
Discontinuation of Treatment With PAXIL: Recent clinical trials supporting the various
approved indications for PAXIL employed a taper-phase regimen, rather than an abrupt
discontinuation of treatment. The taper-phase regimen used in GAD and PTSD clinical trials
involved an incremental decrease in the daily dose by 10 mg/day at weekly intervals. When a
daily dose of 20 mg/day was reached, patients were continued on this dose for 1 week before
treatment was stopped.
With this regimen in those studies, the following adverse events were reported at an incidence
of 2% or greater for PAXIL and were at least twice that reported for placebo: Abnormal dreams,
paresthesia, and dizziness. In the majority of patients, these events were mild to moderate and
were self-limiting and did not require medical intervention.
During marketing of PAXIL and other SSRIs and SNRIs, there have been spontaneous reports
of adverse events occurring upon the discontinuation of these drugs (particularly when abrupt),
including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances
(e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache,
lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-
limiting, there have been reports of serious discontinuation symptoms.
Patients should be monitored for these symptoms when discontinuing treatment with PAXIL.
A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible.
If intolerable symptoms occur following a decrease in the dose or upon discontinuation of
treatment, then resuming the previously prescribed dose may be considered. Subsequently, the
physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND
ADMINISTRATION).

See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of
treatment with PAXIL in pediatric patients.

**Tamoxifen:** Some studies have shown that the efficacy of tamoxifen, as measured by the risk
of breast cancer relapse/mortality, may be reduced when co-prescribed with paroxetine as a
result of paroxetine’s irreversible inhibition of CYP2D6 (see Drug Interactions). However, other
studies have failed to demonstrate such a risk. It is uncertain whether the coadministration of
paroxetine and tamoxifen has a significant adverse effect on the efficacy of tamoxifen. One study
suggests that the risk may increase with longer duration of coadministration. When tamoxifen is
used for the treatment or prevention of breast cancer, prescribers should consider using an
alternative antidepressant with little or no CYP2D6 inhibition.

**Akathisia:** The use of paroxetine or other SSRIs has been associated with the development
of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation
such as an inability to sit or stand still usually associated with subjective distress. This is most
likely to occur within the first few weeks of treatment.

**Hyponatremia:** Hyponatremia may occur as a result of treatment with SSRIs and SNRIs,
including PAXIL. In many cases, this hyponatremia appears to be the result of the syndrome of
inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than
110 mmol/L have been reported. Elderly patients may be at greater risk of developing
hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise
volume depleted may be at greater risk (see PRECAUTIONS: Geriatric Use). Discontinuation of
PAXIL should be considered in patients with symptomatic hyponatremia and appropriate
medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory
impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and
symptoms associated with more severe and/or acute cases have included hallucination, syncope,
seizure, coma, respiratory arrest, and death.

**Abnormal Bleeding:** SSRIs and SNRIs, including paroxetine, may increase the risk of
bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and
other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control
and cohort design) have demonstrated an association between use of drugs that interfere with
serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to
SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to
life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated
with the concomitant use of paroxetine and NSAIDs, aspirin, or other drugs that affect
cohagulation.

**Bone Fracture:** Epidemiological studies on bone fracture risk following exposure to some
antidepressants, including SSRIs, have reported an association between antidepressant treatment
and fractures. There are multiple possible causes for this observation and it is unknown to what
extent fracture risk is directly attributable to SSRI treatment. The possibility of a pathological fracture, that is, a fracture produced by minimal trauma in a patient with decreased bone mineral density, should be considered in patients treated with paroxetine who present with unexplained bone pain, point tenderness, swelling, or bruising.

**Use in Patients With Concomitant Illness:** Clinical experience with PAXIL in patients with certain concomitant systemic illness is limited. Caution is advisable in using PAXIL in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with PAXIL. A few cases of acute angle closure glaucoma associated with paroxetine therapy have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when PAXIL is prescribed for patients with narrow angle glaucoma.

PAXIL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product’s premarket testing. Evaluation of electrocardiograms of 682 patients who received PAXIL in double-blind, placebo-controlled trials, however, did not indicate that PAXIL is associated with the development of significant ECG abnormalities. Similarly, PAXIL does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance <30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

**Information for Patients:** PAXIL should not be chewed or crushed, and should be swallowed whole.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of PAXIL and triptans, tramadol, or other serotonergic agents.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with PAXIL and should counsel them in its appropriate use. A patient Medication Guide is available for PAXIL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking PAXIL.

**Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal
ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

**Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin):**

Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation since combined use of psychotrophic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

**Interference With Cognitive and Motor Performance:** Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies PAXIL has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with PAXIL does not affect their ability to engage in such activities.

**Completing Course of Therapy:** While patients may notice improvement with treatment with PAXIL in 1 to 4 weeks, they should be advised to continue therapy as directed.

**Concomitant Medication:** Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

**Alcohol:** Although PAXIL has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PAXIL.

**Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see WARNINGS: Usage in Pregnancy: Teratogenic Effects and Nonteratogenic Effects).

**Nursing:** Patients should be advised to notify their physician if they are breastfeeding an infant (see PRECAUTIONS: Nursing Mothers).

**Laboratory Tests:** There are no specific laboratory tests recommended.

**Drug Interactions: Tryptophan:** As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking PAXIL. Consequently, concomitant use of PAXIL with tryptophan is not recommended (see WARNINGS: Serotonin Syndrome).

**Monoamine Oxidase Inhibitors:** See CONTRAINDICATIONS and WARNINGS.

**Pimozide:** In a controlled study of healthy volunteers, after PAXIL was titrated to 60 mg daily, co-administration of a single dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_max of 62%, compared to pimozide administered alone. The
increase in pimozide AUC and $C_{\text{max}}$ is due to the CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and PAXIL is contraindicated (see CONTRAINDICATIONS).

**Serotonergic Drugs:** Based on the mechanism of action of SNRIs and SSRIs, including paroxetine hydrochloride, and the potential for serotonin syndrome, caution is advised when PAXIL is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, lithium, fentanyl, tramadol, or St. John's Wort (see WARNINGS: Serotonin Syndrome).

The concomitant use of PAXIL with MAOIs (including linezolid and intravenous methylene blue) is contraindicated (see CONTRAINDICATIONS). The concomitant use of PAXIL with other SSRIs, SNRIs or tryptophan is not recommended (see PRECAUTIONS: Drug Interactions: Tryptophan).

**Thioridazine:** See CONTRAINDICATIONS and WARNINGS.

**Warfarin:** Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of PAXIL and warfarin should be undertaken with caution (see PRECAUTIONS: Drugs That Interfere With Hemostasis).

**Triptans:** There have been rare postmarketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of PAXIL with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS: Serotonin Syndrome).

**Drugs Affecting Hepatic Metabolism:** The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

**Cimetidine:** Cimetidine inhibits many cytochrome $P_{450}$ (oxidative) enzymes. In a study where PAXIL (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of PAXIL after the 20-mg starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine’s pharmacokinetics was not studied.

**Phenobarbital:** Phenobarbital induces many cytochrome $P_{450}$ (oxidative) enzymes. When a single oral 30-mg dose of PAXIL was administered at phenobarbital steady state (100 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since PAXIL exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment of PAXIL is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical
Phenytoin: When a single oral 30-mg dose of PAXIL was administered at phenytoin steady state (300 mg once daily for 14 days), paroxetine AUC and T½ were reduced (by an average of 50% and 35%, respectively) compared to PAXIL administered alone. In a separate study, when a single oral 300-mg dose of phenytoin was administered at paroxetine steady state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when these drugs are coadministered; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS: Postmarketing Reports).

Drugs Metabolized by CYP2D6: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P450 isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (>90%), this CYP2D6 isozyme is saturated early during dosing with PAXIL. In 1 study, daily dosing of PAXIL (20 mg once daily) under steady-state conditions increased single dose desipramine (100 mg) Cmax, AUC, and T½ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In 1 study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine Cmax values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine.

Concomitant use of PAXIL with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either PAXIL or the other drug.

Therefore, coadministration of PAXIL with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be
Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite (endoxifen) and hence reduced efficacy of tamoxifen (see PRECAUTIONS).

At steady state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P_{450} isozymes that, unlike CYP2D6, show no evidence of saturation (see PRECAUTIONS: Tricyclic Antidepressants [TCAs]).

**Drugs Metabolized by Cytochrome CYP3A4:** An in vivo interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for cytochrome CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine’s in vitro K_i and its lack of effect on terfenadine’s in vivo clearance predicts its effect on other CYP3A4 substrates, paroxetine’s extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

**Tricyclic Antidepressants (TCAs):** Caution is indicated in the coadministration of tricyclic antidepressants (TCAs) with PAXIL, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with PAXIL (see PRECAUTIONS: Drugs Metabolized by Cytochrome CYP2D6).

**Drugs Highly Bound to Plasma Protein:** Because paroxetine is highly bound to plasma protein, administration of PAXIL to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

**Drugs That Interfere With Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin):**
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

**Alcohol:** Although PAXIL does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking PAXIL.

**Lithium:** A multiple-dose study has shown that there is no pharmacokinetic interaction between PAXIL and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when PAXIL is coadministered with lithium.
Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady state. Mean digoxin AUC at steady state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of PAXIL (30 mg once daily) increased steady-state AUC₀­­₀⁻²₄, C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with PAXIL (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS: Postmarketing Reports).

Theophylline: Reports of elevated theophylline levels associated with treatment with PAXIL have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Fosamprenavir/Ritonavir: Co-administration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and PAXIL.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Two-year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to 2.4 (mouse) and 3.9 (rat) times the MRHD for major depressive disorder, social anxiety disorder, GAD, and PTSD on a mg/m² basis. Because the MRHD for major depressive disorder is slightly less than that for OCD (50 mg versus 60 mg), the doses used in these carcinogenicity studies were only 2.0 (mouse) and 3.2 (rat) times the MRHD for OCD. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose-related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of 5 in vitro and 2 in vivo assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations in vivo in mouse
bone marrow and in vitro in human lymphocytes and in a dominant lethal test in rats.

**Impairment of Fertility:** Some clinical studies have shown that SSRIs (including paroxetine) may affect sperm quality during SSRI treatment, which may affect fertility in some men.

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is 2.9 times the MRHD for major depressive disorder, social anxiety disorder, GAD, and PTSD or 2.4 times the MRHD for OCD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (9.8 and 4.9 times the MRHD for major depressive disorder, social anxiety disorder, and GAD; 8.2 and 4.1 times the MRHD for OCD and PD on a mg/m² basis).

**Pregnancy:** Pregnancy Category D. See WARNINGS: Usage in Pregnancy: *Teratogenic Effects* and *Nonteratogenic Effects*.

**Labor and Delivery:** The effect of paroxetine on labor and delivery in humans is unknown.

**Nursing Mothers:** Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when PAXIL is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with PAXIL, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of PAXIL in a child or adolescent must balance the potential risks with the clinical need. Decreased appetite and weight loss have been observed in association with the use of SSRIs. Consequently, regular monitoring of weight and growth should be performed in children and adolescents treated with an SSRI such as PAXIL.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with PAXIL and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self-harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with PAXIL in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received PAXIL and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see DOSAGE AND ADMINISTRATION: Discontinuation of Treatment With PAXIL).

**Geriatric Use:** SSRIs and SNRIs, including PAXIL, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS: Hyponatremia).
In worldwide premarketing clinical trials with PAXIL, 17% of patients treated with PAXIL (approximately 700) were 65 years of age or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

**ADVERSE REACTIONS**

**Associated With Discontinuation of Treatment:** Twenty percent (1,199/6,145) of patients treated with PAXIL in worldwide clinical trials in major depressive disorder and 16.1% (84/522), 11.8% (64/542), 9.4% (44/469), 10.7% (79/735), and 11.7% (79/676) of patients treated with PAXIL in worldwide trials in social anxiety disorder, OCD, panic disorder, GAD, and PTSD, respectively, discontinued treatment due to an adverse event. The most common events (≥1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate approximately twice or greater for PAXIL compared to placebo) included the following:
### Commonly Observed Adverse Events: Major Depressive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 2) were: Asthenia, sweating, nausea, decreased appetite, somnolence, dizziness, insomnia, tremor, nervousness, ejaculatory disturbance, and other male genital disorders.

### Obsessive Compulsive Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 3) were: Nausea, dry mouth, constipation, dizziness, somnolence, tremor, sweating, impotence, and abnormal ejaculation.

### Panic Disorder

The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 3) were: Asthenia, sweating, decreased appetite, libido decreased, tremor,}

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**Table: Commonly Observed Adverse Events**

<table>
<thead>
<tr>
<th></th>
<th>Major Depressive Disorder</th>
<th>OCD</th>
<th>Panic Disorder</th>
<th>Social Anxiety Disorder</th>
<th>Generalized Anxiety Disorder</th>
<th>PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>PAXIL Placebo</td>
<td>PAXIL Placebo</td>
<td>PAXIL Placebo</td>
<td>PAXIL Placebo</td>
<td>PAXIL Placebo</td>
<td>PAXIL Placebo</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.3% 0.7%</td>
<td></td>
<td>1.9% 0.3%</td>
<td>3.4% 0.3%</td>
<td>2.0% 0.2%</td>
<td>2.8% 0.6%</td>
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<tr>
<td>Insomnia</td>
<td>— —</td>
<td></td>
<td>1.7% 0%</td>
<td>1.3% 0.3%</td>
<td>3.1% 0%</td>
<td>—</td>
</tr>
<tr>
<td>Agitation</td>
<td>1.1% 0.5%</td>
<td>—</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>Tremor</td>
<td>1.1% 0.3%</td>
<td></td>
<td>1.7% 0%</td>
<td></td>
<td>1.0% 0.2%</td>
<td>—</td>
</tr>
<tr>
<td>Anxiety</td>
<td>— —</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>—</td>
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<tr>
<td>Dizziness</td>
<td>— —</td>
<td>1.5% 0%</td>
<td></td>
<td></td>
<td>1.9% 0%</td>
<td>1.0% 0.2%</td>
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**Gastrointestinal**

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<tbody>
<tr>
<td>Constipation</td>
<td>—</td>
<td>1.1%</td>
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<tr>
<td>Nausea</td>
<td>3.2%</td>
<td>1.1%</td>
<td>1.9%</td>
<td>0%</td>
<td>3.2%</td>
<td>1.2%</td>
<td>4.0%</td>
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<tr>
<td>Diarrhea</td>
<td>1.0%</td>
<td>0.3%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1.0%</td>
<td>0.3%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>1.0%</td>
<td>0.3%</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Flatulence</td>
<td>1.0%</td>
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**Other**

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<tbody>
<tr>
<td>Asthenia</td>
<td>1.6%</td>
<td>0.4%</td>
<td>1.9%</td>
<td>0.4%</td>
<td>—</td>
<td>2.5%</td>
<td>0.6%</td>
</tr>
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<td>Abnormal</td>
<td>—</td>
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<td>—</td>
<td>—</td>
<td>1.8%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Ejaculation a</td>
<td>1.6%</td>
<td>0%</td>
<td>2.1%</td>
<td>0%</td>
<td>—</td>
<td>4.9%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Sweating</td>
<td>1.0%</td>
<td>0.3%</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.1%</td>
<td>0%</td>
</tr>
<tr>
<td>Impotence a</td>
<td>—</td>
<td>1.5%</td>
<td>0%</td>
<td>—</td>
<td>—</td>
<td>1.1%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Libido Decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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Where numbers are not provided the incidence of the adverse events in patients treated with PAXIL was not >1% or was not greater than or equal to 2 times the incidence of placebo.

a. Incidence corrected for gender.

Reference ID: 3231319
abnormal ejaculation, female genital disorders, and impotence.

**Social Anxiety Disorder:** The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 3) were: Sweating, nausea, dry mouth, constipation, decreased appetite, somnolence, tremor, libido decreased, yawn, abnormal ejaculation, female genital disorders, and impotence.

**Generalized Anxiety Disorder:** The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 4) were: Asthenia, infection, constipation, decreased appetite, dry mouth, nausea, libido decreased, somnolence, tremor, sweating, and abnormal ejaculation.

**Posttraumatic Stress Disorder:** The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence for PAXIL at least twice that for placebo, derived from Table 4) were: Asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence.

**Incidence in Controlled Clinical Trials:** The prescriber should be aware that the figures in the tables following cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the populations studied.

**Major Depressive Disorder:** Table 2 enumerates adverse events that occurred at an incidence of 1% or more among paroxetine-treated patients who participated in short-term (6-week) placebo-controlled trials in which patients were dosed in a range of 20 mg to 50 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.
Table 2. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Major Depressive Disorder\(^a\)

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>PAXIL (n = 421)</th>
<th>Placebo (n = 421)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body as a Whole</td>
<td>Headache</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Palpitation</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Vasodilation</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Sweating</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>26%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Dry Mouth</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Decreased Appetite</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Oropharynx Disorder(^b)</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Myopathy</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Myasthenia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Somnolence</td>
<td>23%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Nervousness</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Libido Decreased</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Drugged Feeling</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Respiration</td>
<td>Yawn</td>
<td>4%</td>
<td>0%</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Blurred Vision</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Taste Perversion</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>Ejaculatory Disturbance(^c,d)</td>
<td>13%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Other Male Genital Disorders(^c,e)</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Urinary Frequency</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Urination Disorder(^f)</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Female Genital Disorders(^c,g)</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(^a\) Events reported by at least 1% of patients treated with PAXIL are included, except the following events which had an incidence on placebo ≥ PAXIL: Abdominal pain, agitation, back pain, chest pain, CNS stimulation, fever, increased appetite, myoclonus, pharyngitis, postural hypotension, respiratory disorder (includes mostly “cold symptoms” or “URI”), trauma, and vomiting.

\(^b\) Includes mostly “lump in throat” and “tightness in throat.”
c. Percentage corrected for gender.
d. Mostly “ejaculatory delay.”
e. Includes “anorgasmia,” “erectile difficulties,” “delayed ejaculation/orgasm,” and “sexual
dysfunction,” and “impotence.”
f. Includes mostly “difficulty with micturition” and “urinary hesitancy.”
g. Includes mostly “anorgasmia” and “difficulty reaching climax/orgasm.”

**Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder:**

Table 3 enumerates adverse events that occurred at a frequency of 2% or more among OCD patients on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 60 mg/day or among patients with panic disorder on PAXIL who participated in placebo-controlled trials of 10- to 12-weeks duration in which patients were dosed in a range of 10 mg to 60 mg/day or among patients with social anxiety disorder on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg to 50 mg/day.

**Table 3. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Obsessive Compulsive Disorder, Panic Disorder, and Social Anxiety Disorder**

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>Obsessive Compulsive Disorder</th>
<th>Panic Disorder</th>
<th>Social Anxiety Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PAXIL (n = 542)</td>
<td>Placebo (n = 265)</td>
<td>PAXIL (n = 469)</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Asthenia</td>
<td>22%</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain</td>
<td>—</td>
<td>—</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Chest Pain</td>
<td>3%</td>
<td>2%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Back Pain</td>
<td>—</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Vasodilation</td>
<td>4%</td>
<td>1%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Palpitation</td>
<td>2%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Sweating</td>
<td>9%</td>
<td>3%</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>3%</td>
<td>2%</td>
<td>—</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>23%</td>
<td>10%</td>
<td>23%</td>
</tr>
<tr>
<td></td>
<td>Dry Mouth</td>
<td>18%</td>
<td>9%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>16%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>10%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Decreased</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Appetite</td>
<td>9%</td>
<td>3%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Increased</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
A. Events reported by at least 2% of OCD, panic disorder, and social anxiety disorder in patients treated with PAXIL are included, except the following events which had an incidence on placebo ≥PAXIL: [OCD]: Abdominal pain, agitation, anxiety, back pain, cough increased, depression, headache, hyperkinesia, infection, paresthesia, pharyngitis, respiratory disorder, rhinitis, and sinusitis. [panic disorder]: Abnormal dreams, abnormal vision, chest pain, cough increased, depersonalization, depression, dysmenorrhea, dyspepsia, flu syndrome, headache,
infection, myalgia, nervousness, palpitation, paresthesia, pharyngitis, rash, respiratory disorder, sinusitis, taste perversion, trauma, urination impaired, and vasodilation. [social anxiety disorder]: Abdominal pain, depression, headache, infection, respiratory disorder, and sinusitis.

b. Percentage corrected for gender.

**Generalized Anxiety Disorder and Posttraumatic Stress Disorder:** Table 4 enumerates adverse events that occurred at a frequency of 2% or more among GAD patients on PAXIL who participated in placebo-controlled trials of 8-weeks duration in which patients were dosed in a range of 10 mg/day to 50 mg/day or among PTSD patients on PAXIL who participated in placebo-controlled trials of 12-weeks duration in which patients were dosed in a range of 20 mg/day to 50 mg/day.
Table 4. Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder and Posttraumatic Stress Disorder

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>Generalized Anxiety Disorder</th>
<th>Placebo (n = 529)</th>
<th>Posttraumatic Stress Disorder</th>
<th>Placebo (n = 504)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PAXIL (n = 735)</td>
<td></td>
<td>PAXIL (n = 676)</td>
<td></td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>Asthenia</td>
<td>14%</td>
<td>6%</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>17%</td>
<td>14%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>6%</td>
<td>3%</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain</td>
<td>4%</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Trauma</td>
<td>6%</td>
<td>5%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Vasodilation</td>
<td>3%</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Sweating</td>
<td>6%</td>
<td>2%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea</td>
<td>20%</td>
<td>5%</td>
<td>19%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Dry Mouth</td>
<td>11%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>10%</td>
<td>2%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>9%</td>
<td>7%</td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Decreased Appetite</td>
<td>5%</td>
<td>1%</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>—</td>
<td>—</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>Insomnia</td>
<td>11%</td>
<td>8%</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>15%</td>
<td>5%</td>
<td>16%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>6%</td>
<td>5%</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>5%</td>
<td>1%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Nervousness</td>
<td>4%</td>
<td>3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Libido Decreased</td>
<td>9%</td>
<td>2%</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Abnormal Dreams</td>
<td>—</td>
<td>—</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory System</td>
<td>Respiratory Disorder</td>
<td>7%</td>
<td>5%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>4%</td>
<td>3%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Yawn</td>
<td>4%</td>
<td>—</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Abnormal Vision</td>
<td>2%</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>Abnormal Ejaculation</td>
<td>25%</td>
<td>2%</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td></td>
<td>Female Genital Disorder</td>
<td>4%</td>
<td>1%</td>
<td>5%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Impotence</td>
<td>4%</td>
<td>3%</td>
<td>9%</td>
<td>1%</td>
</tr>
</tbody>
</table>

a. Events reported by at least 2% of GAD and PTSD in patients treated with PAXIL are included, except the following events which had an incidence on placebo ≥PAXIL [GAD]: Abdominal pain, back pain, trauma, dyspepsia, myalgia, and pharyngitis. [PTSD]: Back pain, headache, anxiety, depression, nervousness, respiratory disorder, pharyngitis, and sinusitis.

b. Percentage corrected for gender.

**Dose Dependency of Adverse Events:** A comparison of adverse event rates in a fixed-dose study comparing 10, 20, 30, and 40 mg/day of PAXIL with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with use of PAXIL, as shown in Table 5:
<table>
<thead>
<tr>
<th>Body System/Preferred Term</th>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
<th>30 mg</th>
<th>40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body as a Whole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>0.0%</td>
<td>2.9%</td>
<td>10.6%</td>
<td>13.9%</td>
<td>12.7%</td>
</tr>
<tr>
<td><strong>Dermatology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>2.0%</td>
<td>1.0%</td>
<td>6.7%</td>
<td>8.9%</td>
<td>11.8%</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>5.9%</td>
<td>4.9%</td>
<td>7.7%</td>
<td>9.9%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>2.0%</td>
<td>2.0%</td>
<td>5.8%</td>
<td>4.0%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.8%</td>
<td>9.8%</td>
<td>19.2%</td>
<td>7.9%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>2.0%</td>
<td>10.8%</td>
<td>18.3%</td>
<td>15.8%</td>
<td>20.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13.7%</td>
<td>14.7%</td>
<td>26.9%</td>
<td>34.7%</td>
<td>36.3%</td>
</tr>
<tr>
<td><strong>Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.0%</td>
<td>2.0%</td>
<td>5.8%</td>
<td>5.9%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.9%</td>
<td>6.9%</td>
<td>6.7%</td>
<td>8.9%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Nervousness</td>
<td>0.0%</td>
<td>5.9%</td>
<td>5.8%</td>
<td>4.0%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0.0%</td>
<td>2.9%</td>
<td>1.0%</td>
<td>5.0%</td>
<td>5.9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>7.8%</td>
<td>12.7%</td>
<td>18.3%</td>
<td>20.8%</td>
<td>21.6%</td>
</tr>
<tr>
<td>Tremor</td>
<td>0.0%</td>
<td>0.0%</td>
<td>7.7%</td>
<td>7.9%</td>
<td>14.7%</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>2.0%</td>
<td>2.9%</td>
<td>2.9%</td>
<td>2.0%</td>
<td>7.8%</td>
</tr>
<tr>
<td><strong>Urogenital System</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal Ejaculation</td>
<td>0.0%</td>
<td>5.8%</td>
<td>6.5%</td>
<td>10.6%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Impotence</td>
<td>0.0%</td>
<td>1.9%</td>
<td>4.3%</td>
<td>6.4%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Male Genital Disorders</td>
<td>0.0%</td>
<td>3.8%</td>
<td>8.7%</td>
<td>6.4%</td>
<td>3.7%</td>
</tr>
</tbody>
</table>

**Table 5. Treatment-Emergent Adverse Experience Incidence in a Dose-Comparison Trial in the Treatment of Major Depressive Disorder**

*Rule for including adverse events in table: Incidence at least 5% for 1 of paroxetine groups and ≥ twice the placebo incidence for at least 1 paroxetine group.*

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of OCD, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned. No new adverse events were observed in the group treated with 60 mg of PAXIL compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 10, 20, and 40 mg of PAXIL in the treatment of panic disorder, there was no clear relationship between adverse events and the dose of PAXIL to which patients were assigned, except for asthenia, dry mouth, anxiety, libido decreased, tremor, and abnormal ejaculation. In flexible-dose studies, no new adverse events were observed in patients receiving 60 mg of PAXIL compared to any of the other treatment groups.

In a fixed-dose study comparing placebo and 20, 40, and 60 mg of PAXIL in the treatment of social anxiety disorder, for most of the adverse events, there was no clear relationship between...
adverse events and the dose of PAXIL to which patients were assigned.
In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
generalized anxiety disorder, for most of the adverse events, there was no clear relationship
between adverse events and the dose of PAXIL to which patients were assigned, except for the
following adverse events: Asthenia, constipation, and abnormal ejaculation.
In a fixed-dose study comparing placebo and 20 and 40 mg of PAXIL in the treatment of
posttraumatic stress disorder, for most of the adverse events, there was no clear relationship
between adverse events and the dose of PAXIL to which patients were assigned, except for
impotence and abnormal ejaculation.

Adaptation to Certain Adverse Events: Over a 4- to 6-week period, there was evidence
of adaptation to some adverse events with continued therapy (e.g., nausea and dizziness), but less
to other effects (e.g., dry mouth, somnolence, and asthenia).

Male and Female Sexual Dysfunction With SSRIs: Although changes in sexual desire,
sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric
disorder, they may also be a consequence of pharmacologic treatment. In particular, some
evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can cause such untoward
sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual
desire, performance, and satisfaction are difficult to obtain, however, in part because patients and
physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of
untoward sexual experience and performance cited in product labeling, are likely to
underestimate their actual incidence.
In placebo-controlled clinical trials involving more than 3,200 patients, the ranges for the
reported incidence of sexual side effects in males and females with major depressive disorder,
OCD, panic disorder, social anxiety disorder, GAD, and PTSD are displayed in Table 6.

Table 6. Incidence of Sexual Adverse Events in Controlled Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>PAXIL</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (males)</td>
<td>1446</td>
<td>1042</td>
</tr>
<tr>
<td>Decreased Libido</td>
<td>6-15%</td>
<td>0-5%</td>
</tr>
<tr>
<td>Ejaculatory Disturbance</td>
<td>13-28%</td>
<td>0-2%</td>
</tr>
<tr>
<td>Impotence</td>
<td>2-9%</td>
<td>0-3%</td>
</tr>
<tr>
<td>n (females)</td>
<td>1822</td>
<td>1340</td>
</tr>
<tr>
<td>Decreased Libido</td>
<td>0-9%</td>
<td>0-2%</td>
</tr>
<tr>
<td>Orgasmic Disturbance</td>
<td>2-9%</td>
<td>0-1%</td>
</tr>
</tbody>
</table>

There are no adequate and well-controlled studies examining sexual dysfunction with
paroxetine treatment.
Paroxetine treatment has been associated with several cases of priapism. In those cases with a
known outcome, patients recovered without sequelae.
While it is difficult to know the precise risk of sexual dysfunction associated with the use of
SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with PAXIL for some patients but, on average, patients in controlled trials had minimal (about 1 pound) weight loss versus smaller changes on placebo and active control. No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with PAXIL in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with PAXIL and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In placebo-controlled clinical trials, patients treated with PAXIL exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients. In particular, the PAXIL-versus-placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9089 patients receiving drug and 4 of 3187 patients receiving placebo.

Other Events Observed During the Premarketing Evaluation of PAXIL: During its premarketing assessment in major depressive disorder, multiple doses of PAXIL were administered to 6,145 patients in phase 2 and 3 studies. The conditions and duration of exposure to PAXIL varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed-dose, and titration studies. During premarketing clinical trials in OCD, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder, 542, 469, 522, 735, and 676 patients, respectively, received multiple doses of PAXIL. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based Dictionary terminology. The frequencies presented, therefore, represent the proportion of the 9,089 patients exposed to multiple doses of PAXIL who experienced an event of the type cited on at least 1 occasion while receiving PAXIL. All reported events are included except those already listed in Tables 2 to 5, those reported in terms so general as to be uninformative and those events where a drug cause was remote. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from
placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients. Events of major clinical importance are also described in the PRECAUTIONS section.

**Body as a Whole:** Infrequent: Allergic reaction, chills, face edema, malaise, neck pain; rare: Adrenergic syndrome, cellulitis, moniliasis, neck rigidity, pelvic pain, peritonitis, sepsis, ulcer.

**Cardiovascular System:** Frequent: Hypertension, tachycardia; infrequent: Bradycardia, hematoma, hypotension, migraine, postural hypotension, syncope; rare: Angina pectoris, arrhythmia nodal, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, heart block, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, varicose vein, vascular headache, ventricular extrasystoles.

**Digestive System:** Infrequent: Bruxism, colitis, dysphagia, eructation, gastritis, gastroenteritis, gingivitis, glossitis, increased salivation, liver function tests abnormal, rectal hemorrhage, ulcerative stomatitis; rare: Aphthous stomatitis, bloody diarrhea, bulimia, cardiomyopathy, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, intestinal obstruction, jaundice, melena, mouth ulceration, peptic ulcer, salivary gland enlargement, sialadenitis, stomach ulcer, stomatitis, tongue discoloration, tongue edema, tooth caries.

**Endocrine System:** Rare: Diabetes mellitus, goiter, hyperthyroidism, hypothyroidism, thyroiditis.

**Hemic and Lymphatic Systems:** Infrequent: Anemia, leukopenia, lymphadenopathy, purpura; rare: Abnormal erythrocytes, basophilia, bleeding time increased, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, lymphedema, abnormal lymphocytes, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia, thrombocytopenia, thrombocytosis.

**Metabolic and Nutritional:** Frequent: Weight gain; infrequent: Edema, peripheral edema, SGOT increased, SGPT increased, thirst, weight loss; rare: Alkaline phosphatase increased, bilirubinemia, BUN increased, creatinine phosphokinase increased, dehydration, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, ketosis, lactic dehydrogenase increased, non-protein nitrogen (NPN) increased.

**Musculoskeletal System:** Frequent: Arthralgia; infrequent: Arthritis, arthrosis; rare: Bursitis, myositis, osteoporosis, generalized spasm, tenosynovitis, tetany.

**Nervous System:** Frequent: Emotional lability, vertigo; infrequent: Abnormal thinking, alcohol abuse, ataxia, dystonia, dyskinesia, euphoria, hallucinations, hostility, hypertonia, hypesthesia, hypokinesia, incoordination, lack of emotion, libido increased, manic reaction, neurosis, paralysis, paranoid reaction; rare: Abnormal gait, akinesia, antisocial reaction, aphasia, choreothetosis, circumoral paresthesias, convulsion, delirium, delusions, diplopia, drug dependence, dysarthria, extrapyramidal syndrome, fasciculations, grand mal convulsion,
hyperalgesia, hysteria, manic-depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, peripheral neuritis, psychotic depression, psychosis, reflexes decreased, reflexes increased, stupor, torticollis, trismus, withdrawal syndrome.

**Respiratory System:** *Infrequent:* Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu; *rare:* Emphysema, hemoptysis, hiccups, lung fibrosis, pulmonary edema, sputum increased, stridor, voice alteration.

**Skin and Appendages:** *Frequent:* Pruritus; *infrequent:* Acne, alopecia, contact dermatitis, dry skin, ecchymosis, eczema, herpes simplex, photosensitivity, urticaria; *rare:* Angioedema, erythema nodosum, erythema multiforme, exfoliative dermatitis, fungal dermatitis, furunculosis; herpes zoster, hirsutism, maculopapular rash, seborrhea, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

**Special Senses:** *Frequent:* Tinnitus; *infrequent:* Abnormality of accommodation, conjunctivitis, ear pain, eye pain, keratoconjunctivitis, mydriasis, otitis media; *rare:* Amblyopia, anisocoria, blepharitis, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, night blindness, otitis externa, parosmia, photophobia, ptosis, retinal hemorrhage, taste loss, visual field defect.

**Urogenital System:** *Infrequent:* Amenorrhea, breast pain, cystitis, dysuria, hematuria, menorrhagia, nocturia, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginitis; *rare:* Abortion, breast atrophy, breast enlargement, endometrial disorder, epididymitis, female lactation, fibrocystic breast, kidney calculus, kidney pain, leukorrhea, mastitis, metrorrhagia, nephritis, oliguria, salpingitis, urethritis, urinary casts, uterine spasm, urolith, vaginal hemorrhage, vaginal moniliasis.

**Postmarketing Reports:** Voluntary reports of adverse events in patients taking PAXIL that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, restless legs syndrome (RLS), ventricular fibrillation, ventricular tachycardia (including torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), vasculitic syndromes (such as Henoch-Schönlein purpura), and premature births in pregnant women. There has been a case report of an elevated phenytoin level after 4 weeks of PAXIL and phenytoin coadministration. There has been a case report of severe hypotension when PAXIL was added to chronic metoprolol treatment.
DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: PAXIL is not a controlled substance.

Physical and Psychologic Dependence: PAXIL has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of PAXIL (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience: Since the introduction of PAXIL in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 non-fatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2,000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: No specific antidotes for paroxetine are known. Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, or exchange transfusion are unlikely to be of benefit.

A specific caution involves patients who are taking or have recently taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS: Drugs...
Metabolized by Cytochrome CYP2D6).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference (PDR).

**DOSAGE AND ADMINISTRATION**

**Major Depressive Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose with or without food, usually in the morning. The recommended initial dose is 20 mg/day. Patients were dosed in a range of 20 to 50 mg/day in the clinical trials demonstrating the effectiveness of PAXIL in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 20-mg dose may benefit from dose increases, in 10-mg/day increments, up to a maximum of 50 mg/day. Dose changes should occur at intervals of at least 1 week.

**Maintenance Therapy:** There is no body of evidence available to answer the question of how long the patient treated with PAXIL should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of PAXIL has shown that efficacy is maintained for periods of up to 1 year with doses that averaged about 30 mg.

**Obsessive Compulsive Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose with or without food, usually in the morning. The recommended dose of PAXIL in the treatment of OCD is 40 mg daily. Patients should be started on 20 mg/day and the dose can be increased in 10-mg/day increments. Dose changes should occur at intervals of at least 1 week. Patients were dosed in a range of 20 to 60 mg/day in the clinical trials demonstrating the effectiveness of PAXIL in the treatment of OCD. The maximum dosage should not exceed 60 mg/day.

**Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 6-month relapse prevention trial. In this trial, patients with OCD assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). OCD is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

**Panic Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose with or without food, usually in the morning. The target dose of PAXIL in the treatment of panic disorder is 40 mg/day. Patients should be started on 10 mg/day. Dose changes should occur in 10-mg/day increments and at intervals of at least 1 week. Patients were dosed in a range of 10 to
60 mg/day in the clinical trials demonstrating the effectiveness of PAXIL. The maximum dosage should not exceed 60 mg/day.

**Maintenance Therapy:** Long-term maintenance of efficacy was demonstrated in a 3-month relapse prevention trial. In this trial, patients with panic disorder assigned to paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). Panic disorder is a chronic condition, and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

**Social Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose with or without food, usually in the morning. The recommended and initial dosage is 20 mg/day. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a range of 20 to 60 mg/day. While the safety of PAXIL has been evaluated in patients with social anxiety disorder at doses up to 60 mg/day, available information does not suggest any additional benefit for doses above 20 mg/day (see CLINICAL PHARMACOLOGY: Clinical Trials).

**Maintenance Therapy:** There is no body of evidence available to answer the question of how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

**Generalized Anxiety Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose with or without food, usually in the morning. In clinical trials the effectiveness of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. The recommended starting dosage and the established effective dosage is 20 mg/day. There is not sufficient evidence to suggest a greater benefit to doses higher than 20 mg/day. Dose changes should occur in 10 mg/day increments and at intervals of at least 1 week.

**Maintenance Therapy:** Systematic evaluation of continuing PAXIL for periods of up to 24 weeks in patients with Generalized Anxiety Disorder who had responded while taking PAXIL during an 8-week acute treatment phase has demonstrated a benefit of such maintenance (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

**Posttraumatic Stress Disorder: Usual Initial Dosage:** PAXIL should be administered as a single daily dose with or without food, usually in the morning. The recommended starting dosage and the established effective dosage is 20 mg/day. In 1 clinical trial, the effectiveness of PAXIL was demonstrated in patients dosed in a range of 20 to 50 mg/day. However, in a fixed dose study, there was not sufficient evidence to suggest a greater benefit for a dose of 40 mg/day compared to 20 mg/day. Dose changes, if indicated, should occur in 10 mg/day increments and at intervals of at least 1 week.
**Maintenance Therapy:** There is no body of evidence available to answer the question of how long the patient treated with PAXIL should remain on it. Although the efficacy of PAXIL beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, PTSD is recognized as a chronic condition, and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for continued treatment.

**Special Populations: Treatment of Pregnant Women During the Third Trimester:** Neonates exposed to PAXIL and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS: Usage in Pregnancy). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

**Dosage for Elderly or Debilitated Patients, and Patients With Severe Renal or Hepatic Impairment:** The recommended initial dose is 10 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 40 mg/day.

**Switching a Patient to or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders:** At least 14 days should elapse between discontinuation of an MAOI intended to treat psychiatric disorders and initiation of therapy with PAXIL. Conversely, at least 14 days should be allowed after stopping PAXIL before starting an MAOI intended to treat psychiatric disorders (see CONTRAINDICATIONS).

**Use of PAXIL With Other MAOIs, Such as Linezolid or Methylene Blue:** Do not start PAXIL in a patient who is being treated with linezolid or intravenous methylene blue because there is increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered (see CONTRAINDICATIONS).

In some cases, a patient already receiving therapy with PAXIL may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, PAXIL should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 2 weeks or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with PAXIL may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue (see WARNINGS).

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with PAXIL is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use (see WARNINGS).
Discontinuation of Treatment With PAXIL: Symptoms associated with discontinuation of PAXIL have been reported (see PRECAUTIONS: Discontinuation of Treatment With PAXIL). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which PAXIL is being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

NOTE: SHAKE SUSPENSION WELL BEFORE USING.

HOW SUPPLIED

Tablets: Film-coated, modified-oval as follows:

- 10-mg yellow, scored tablets engraved on the front with PAXIL and on the back with 10.
- NDC 0029-3210-13 Bottles of 30
- 20-mg pink, scored tablets engraved on the front with PAXIL and on the back with 20.
- NDC 0029-3211-13 Bottles of 30
- 30-mg blue tablets engraved on the front with PAXIL and on the back with 30.
- NDC 0029-3212-13 Bottles of 30
- 40-mg green tablets engraved on the front with PAXIL and on the back with 40.
- NDC 0029-3213-13 Bottles of 30

Store tablets between 15° and 30°C (59° and 86°F).

Oral Suspension: Orange-colored, orange-flavored, 10 mg/5 mL, in white bottles containing 250 mL.

NDC 0029-3215-48

Store suspension at or below 25°C (77°F).

PAXIL is a registered trademark of GlaxoSmithKline.
Medication Guide
PAXIL® (PAX-il)
(paroxetine hydrochloride)
Tablets and Oral Suspension

Read the Medication Guide that comes with PAXIL before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment. Talk with your healthcare provider if there is something you do not understand or want to learn more about.

What is the most important information I should know about PAXIL?

PAXIL and other antidepressant medicines may cause serious side effects, including:

1. Suicidal thoughts or actions:
   - PAXIL and other antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment or when the dose is changed.
   - Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.
   - Watch for these changes and call your healthcare provider right away if you notice:
     - New or sudden changes in mood, behavior, actions, thoughts, or feelings, especially if severe.
     - Pay particular attention to such changes when PAXIL is started or when the dose is changed.

Keep all follow-up visits with your healthcare provider and call between visits if you are worried about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety or panic attacks
- feeling agitated, restless, angry, or irritable
- trouble sleeping
- an increase in activity or talking more than what is normal for you
- other unusual changes in behavior or mood

Call your healthcare provider right away if you have any of the following symptoms, or call 911 if an emergency.
911 if an emergency. PAXIL may be associated with these serious side effects:

2. Serotonin Syndrome or Neuroleptic Malignant Syndrome-like reactions. This condition can be life-threatening and may include:
   - agitation, hallucinations, coma, or other changes in mental status
   - coordination problems or muscle twitching (overactive reflexes)
   - racing heartbeat, high or low blood pressure
   - sweating or fever
   - nausea, vomiting, or diarrhea
   - muscle rigidity

3. Severe allergic reactions:
   - trouble breathing
   - swelling of the face, tongue, eyes, or mouth
   - rash, itchy welts (hives), or blisters, alone or with fever or joint pain

4. Abnormal bleeding: PAXIL and other antidepressant medicines may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAIDs, like ibuprofen or naproxen), or aspirin.

5. Seizures or convulsions

6. Manic episodes:
   - greatly increased energy
   - severe trouble sleeping
   - racing thoughts
   - reckless behavior
   - unusually grand ideas
   - excessive happiness or irritability
   - talking more or faster than usual

7. Changes in appetite or weight. Children and adolescents should have height and weight monitored during treatment.

8. Low salt (sodium) levels in the blood. Elderly people may be at greater risk for this.
   - Symptoms may include:
     - headache
     - weakness or feeling unsteady
     - confusion, problems concentrating or thinking, or memory problems

Do not stop PAXIL without first talking to your healthcare provider. Stopping PAXIL too quickly may cause serious symptoms including:
   - anxiety, irritability, high or low mood, feeling restless, or changes in sleep habits
   - headache, sweating, nausea, dizziness
   - electric shock-like sensations, shaking, confusion

What is PAXIL?
PAXIL is a prescription medicine used to treat depression. It is important to talk with your healthcare provider about the risks of treating depression and also the risks of not treating it. You should discuss all treatment choices with your healthcare provider. PAXIL is also used to treat:

- Major Depressive Disorder (MDD)
- Obsessive Compulsive Disorder (OCD)
- Panic Disorder
- Social Anxiety Disorder
- Generalized Anxiety Disorder (GAD)
- Posttraumatic Stress Disorder (PTSD)

Talk to your healthcare provider if you do not think that your condition is getting better with treatment using PAXIL.

Who should not take PAXIL?

Do not take PAXIL if you:

- are allergic to paroxetine or any of the ingredients in PAXIL. See the end of this Medication Guide for a complete list of ingredients in PAXIL.
- take a monoamine oxidase inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI within 2 weeks of stopping PAXIL unless directed to do so by your physician.
- Do not start PAXIL if you stopped taking an MAOI in the last 2 weeks unless directed to do so by your physician.
- People who take PAXIL close in time to an MAOI may have serious or even life-threatening side effects. Get medical help right away if you have any of these symptoms:
  - high fever
  - uncontrolled muscle spasms
  - stiff muscles
  - rapid changes in heart rate or blood pressure
  - confusion
  - loss of consciousness (pass out)
- take MELLARIL® (thioridazine). Do not take MELLARIL® together with PAXIL because this can cause serious heart rhythm problems or sudden death.
- take the antipsychotic medicine pimozide (ORAP®) because this can cause serious heart problems.

What should I tell my healthcare provider before taking PAXIL? Ask if you are not sure.

Before starting PAXIL, tell your healthcare provider if you:
are pregnant, may be pregnant, or plan to become pregnant. There is a possibility that
PAXIL may harm your unborn baby, including an increased risk of birth defects, particularly
heart defects. Other risks may include a serious condition in which there is not enough
oxygen in the baby’s blood. Your baby may also have certain other symptoms shortly after
birth. Premature births have also been reported in some women who used PAXIL during
pregnancy.
• are breastfeeding. PAXIL passes into your milk. Talk to your healthcare provider about the
best way to feed your baby while taking PAXIL.
• are taking certain drugs such as:
  • triptans used to treat migraine headache
  • other antidepressants (SSRIs, SNRIs, tricyclics, or lithium) or antipsychotics
  • drugs that affect serotonin, such as lithium, tramadol, tryptophan, St. John’s wort
  • certain drugs used to treat irregular heart beats
  • certain drugs used to treat schizophrenia
  • certain drugs used to treat HIV infection
  • certain drugs that affect the blood, such as warfarin, aspirin, and ibuprofen
  • certain drugs used to treat epilepsy
  • atomoxetine
  • cimetidine
  • fentanyl
  • metoprolol
  • pimozide
  • procyclidine
  • tamoxifen
• have liver problems
• have kidney problems
• have heart problems
• have or had seizures or convulsions
• have bipolar disorder or mania
• have low sodium levels in your blood
• have a history of a stroke
• have high blood pressure
• have or had bleeding problems
• have glaucoma (high pressure in the eye)
• have or had miscarriages

Tell your healthcare provider about all the medicines you take, including prescription and
non-prescription medicines, vitamins, and herbal supplements. PAXIL and some medicines may
interact with each other, may not work as well, or may cause serious side effects.
Your healthcare provider or pharmacist can tell you if it is safe to take PAXIL with your other medicines. Do not start or stop any medicine while taking PAXIL without talking to your healthcare provider first.

If you take PAXIL, you should not take any other medicines that contain paroxetine, including PAXIL CR and PEXEVA® (paroxetine mesylate).

How should I take PAXIL?

- Take PAXIL exactly as prescribed. Your healthcare provider may need to change the dose of PAXIL until it is the right dose for you.
- PAXIL may be taken with or without food.
- If you are taking PAXIL Oral Suspension, shake the suspension well before use.
- If you miss a dose of PAXIL, take the missed dose as soon as you remember. If it is almost time for the next dose, skip the missed dose and take your next dose at the regular time. Do not take two doses of PAXIL at the same time.
- If you take too much PAXIL, call your healthcare provider or poison control center right away, or get emergency treatment.
- Do not stop taking PAXIL suddenly without talking to your doctor (unless you have symptoms of a severe allergic reaction). If you need to stop taking PAXIL, your healthcare provider can tell you how to safely stop taking it.

What should I avoid while taking PAXIL?

PAXIL can cause sleepiness or may affect your ability to make decisions, think clearly, or react quickly. You should not drive, operate heavy machinery, or do other dangerous activities until you know how PAXIL affects you. Do not drink alcohol while using PAXIL.

What are possible side effects of PAXIL?

PAXIL may cause serious side effects, including all of those described in the section entitled “What is the most important information I should know about PAXIL?”

Common possible side effects in people who take PAXIL include:

- nausea
- sleepiness
- weakness
- dizziness
- feeling anxious or trouble sleeping
- sexual problems
- sweating
- shaking
- not feeling hungry
Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of PAXIL. For more information, ask your healthcare provider or pharmacist.

CALL YOUR DOCTOR FOR MEDICAL ADVICE ABOUT SIDE EFFECTS. YOU MAY REPORT SIDE EFFECTS TO THE FDA AT 1-800-FDA-1088 or 1-800-332-1088.

How should I store PAXIL?

- Store PAXIL Tablets at room temperature between 59º and 86ºF (15º and 30ºC).
- Store PAXIL Oral Suspension at or below 77ºF (25ºC).
- Keep PAXIL away from light.
- Keep bottle of PAXIL closed tightly.

Keep PAXIL and all medicines out of the reach of children.

General information about PAXIL

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use PAXIL for a condition for which it was not prescribed. Do not give PAXIL to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about PAXIL. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about PAXIL that is written for healthcare professionals.

For more information about PAXIL call 1-888-825-5249 or go to www.us.gsk.com.

What are the ingredients in PAXIL?

Active ingredient: paroxetine hydrochloride

Inactive ingredients in tablets: dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and 1 or more of the following: D&C Red No. 30 aluminum lake, D&C Yellow No. 10 aluminum lake, FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake.

Inactive ingredients in suspension for oral administration: polacrilin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methylparaben, propylparaben, sodium citrate dihydrate, citric acid anhydrous, sodium saccharin, flavorings, FD&C Yellow No. 6 aluminum lake, and simethicone emulsion, USP.
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This Medication Guide has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709

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December 2012
XANAX®
alprazolam tablets, USP

CIV

DESCRIPTION

XANAX Tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-α] [1,4] benzodiazepine.

The structural formula is represented to the right:

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  8-Chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-α] [1,4] benzodiazepine
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Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each XANAX Tablet, for oral administration, contains 0.25, 0.5, 1 or 2 mg of alprazolam.

XANAX Tablets, 2 mg, are multi-scored and may be divided as shown below:

![Diagram of tablet scoring]

Inactive ingredients: Cellulose, corn starch, docusate sodium, lactose, magnesium stearate, silicon dioxide and sodium benzoate. In addition, the 0.5 mg tablet contains FD&C Yellow No. 6 and the 1 mg tablet contains FD&C Blue No. 2.
CLINICAL PHARMACOLOGY

Pharmacodynamics

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereo specific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Pharmacokinetics

Absorption
Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in 1 to 2 hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3-26.9 hours) in healthy adults.

Distribution
In vitro, alprazolam is bound (80 percent) to human serum protein. Serum albumin accounts for the majority of the binding.

Metabolism/Elimination
Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam relative to unchanged alprazolam concentration were always less than 4%. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α-hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α-hydroxyalprazolam suggest that they are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Alprazolam and its metabolites are excreted primarily in the urine.

Special Populations
Changes in the absorption, distribution, metabolism and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0-26.9 hours, n=16) compared to 11.0 hours (range: 6.3-15.8 hours, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the half-life
of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours, n=12) as compared to between 6.3 and 15.8 hours (mean=10.6 hours, n=12) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

Race — Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Pediatrics — The pharmacokinetics of alprazolam in pediatric patients have not been studied. Gender — Gender has no effect on the pharmacokinetics of alprazolam.

Cigarette Smoking — Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

Drug-Drug Interactions
Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied in vivo, along with their effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.70 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS–Drug Interactions).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed in vivo. The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90±0.21 mL/min/kg to 2.13±0.54 mL/min/kg and the elimination t1/2 was shortened (from 17.1±4.9 to 7.7 ±1.7 h) following administration of 300 mg/day carbamazepine for 10 days (see PRECAUTIONS–Drug Interactions). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000-1200 mg/day); the effect at usual carbamazepine doses is unknown.

The ability of alprazolam to induce human hepatic enzyme systems has not yet been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

CLINICAL STUDIES

Anxiety Disorders
XANAX Tablets were compared to placebo in double blind clinical studies (doses up to 4 mg/day) in patients with a diagnosis of anxiety or anxiety with associated depressive symptomatology. XANAX was significantly better than placebo at each of the evaluation periods of these 4-week studies as judged by the following psychometric instruments:

**Panic Disorder**
Support for the effectiveness of XANAX in the treatment of panic disorder came from three short-term, placebo-controlled studies (up to 10 weeks) in patients with diagnoses closely corresponding to DSM-III-R criteria for panic disorder.

The average dose of XANAX was 5-6 mg/day in two of the studies, and the doses of XANAX were fixed at 2 and 6 mg/day in the third study. In all three studies, XANAX was superior to placebo on a variable defined as "the number of patients with zero panic attacks" (range, 37-83% met this criterion), as well as on a global improvement score. In two of the three studies, XANAX was superior to placebo on a variable defined as "change from baseline on the number of panic attacks per week" (range, 3.3-5.2), and also on a phobia rating scale. A subgroup of patients who were improved on XANAX during short-term treatment in one of these trials was continued on an open basis up to 8 months, without apparent loss of benefit.

**INDICATIONS AND USAGE**

**Anxiety Disorders**
XANAX Tablets (alprazolam) are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

Generalized anxiety disorder is characterized by unrealistic or excessive anxiety and worry (apprehensive expectation) about two or more life circumstances, for a period of 6 months or longer, during which the person has been bothered more days than not by these concerns. At least 6 of the following 18 symptoms are often present in these patients: **Motor Tension** (trembling, twitching, or feeling shaky; muscle tension, aches, or soreness; restlessness; easy fatigability); **Autonomic Hyperactivity** (shortness of breath or smothering sensations; palpitations or accelerated heart rate; sweating, or cold clammy hands; dry mouth; dizziness or light-headedness; nausea, diarrhea, or other abdominal distress; flushes or chills; frequent urination; trouble swallowing or 'lump in throat’); **Vigilance and Scanning** (feeling keyed up or on edge; exaggerated startle response; difficulty concentrating or 'mind going blank’ because of anxiety; trouble falling or staying asleep; irritability). These symptoms must not be secondary to another psychiatric disorder or caused by some organic factor.

Anxiety associated with depression is responsive to XANAX.

**Panic Disorder**
XANAX is also indicated for the treatment of panic disorder, with or without agoraphobia.

Studies supporting this claim were conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL STUDIES).
Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Demonstrations of the effectiveness of XANAX by systematic clinical study are limited to 4 months duration for anxiety disorder and 4 to 10 weeks duration for panic disorder; however, patients with panic disorder have been treated on an open basis for up to 8 months without apparent loss of benefit. The physician should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

XANAX Tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines. XANAX may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

XANAX is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see WARNINGS and PRECAUTIONS–Drug Interactions).

WARNINGS

Dependence and Withdrawal Reactions, Including Seizures
Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to XANAX. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at the doses recommended for the treatment of transient anxiety and anxiety disorder (i.e., 0.75 to 4.0 mg per day), there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

The importance of dose and the risks of XANAX as a treatment for panic disorder: Because the management of panic disorder often requires the use of average daily doses of XANAX above 4 mg, the risk of dependence among panic disorder patients may be higher than that
among those treated for less severe anxiety. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder showed a high rate of rebound and withdrawal symptoms in patients treated with XANAX compared to placebo-treated patients.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

In a controlled clinical trial in which 63 patients were randomized to XANAX and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal.

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71%-93% of patients treated with XANAX tapered completely off therapy compared to 89%-96% of placebo-treated patients. In a controlled postmarketing discontinuation study of panic disorder patients, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures attributable to XANAX were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of XANAX greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every 3 days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from XANAX. The risk of seizure seems to be greatest 24-72 hours after discontinuation (see DOSAGE AND ADMINISTRATION for recommended tapering and discontinuation schedule).

**Status Epilepticus and its Treatment**

The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of XANAX. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

**Interdose Symptoms**
Early morning anxiety and emergence of anxiety symptoms between doses of XANAX have been reported in patients with panic disorder taking prescribed maintenance doses of XANAX. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound or withdrawal symptoms over the entire course of the interdosing interval. In these situations, it is recommended that the same total daily dose be given divided as more frequent administrations (see DOSAGE AND ADMINISTRATION).

**Risk of Dose Reduction**
Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (e.g., the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of XANAX should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

**CNS Depression and Impaired Performance**
Because of its CNS depressant effects, patients receiving XANAX should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with XANAX.

**Risk of Fetal Harm**
Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If XANAX is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, XANAX is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

**Alprazolam Interaction with Drugs that Inhibit Metabolism via Cytochrome P4503A**
The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A. With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from in vitro data and/or experience with similar drugs in the same pharmacologic class.
The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

**Potent CYP3A Inhibitors**

Azole antifungal agents—Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

*Drugs demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs)*

Nefazodone—Coadministration of nefazodone increased alprazolam concentration two-fold.

Fluvoxamine—Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine—Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

*Other drugs possibly affecting alprazolam metabolism*

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

**PRECAUTIONS**

**General**

**Suicide**

As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

**Mania**

Episodes of hypomania and mania have been reported in association with the use of XANAX in patients with depression.

**Uricosuric Effect**

Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with XANAX.
Use in Patients with Concomitant Illness
It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients. (See DOSAGE AND ADMINISTRATION.) The usual precautions in treating patients with impaired renal, hepatic or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with XANAX. A decreased systemic alprazolam elimination rate (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving XANAX (see CLINICAL PHARMACOLOGY).

Information for Patients
For all users of XANAX:
To assure safe and effective use of benzodiazepines, all patients prescribed XANAX should be provided with the following guidance.
1. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.
2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.
3. Inform your physician if you are nursing.
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
5. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.
6. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

Additional advice for panic disorder patients:
The use of XANAX at doses greater than 4 mg/day, often necessary to treat panic disorder, is accompanied by risks that you need to carefully consider. When used at doses greater than 4 mg/day, which may or may not be required for your treatment, XANAX has the potential to cause severe emotional and physical dependence in some patients and these patients may find it exceedingly difficult to terminate treatment. In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 7 to 29% of patients treated with XANAX did not completely taper off therapy. In a controlled postmarketing discontinuation study of panic disorder patients, the patients treated with doses of XANAX greater than 4 mg/day had more difficulty tapering to zero dose than patients treated with less than 4 mg/day. In all cases, it is important that your physician help you discontinue this medication in a careful and safe manner to avoid overly extended use of XANAX.

In addition, the extended use at doses greater than 4 mg/day appears to increase the incidence and severity of withdrawal reactions when XANAX is discontinued. These are generally
minor but seizure can occur, especially if you reduce the dose too rapidly or discontinue the medication abruptly. Seizure can be life-threatening.

**Laboratory Tests**
Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

**Drug Interactions**

**Use with Other CNS Depressants**
If XANAX Tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when co-administered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

**Use with Imipramine and Desipramine**
The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of XANAX Tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

**Drugs that inhibit alprazolam metabolism via cytochrome P450 3A**
The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

**Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam)**
 Fluoxetine—Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene—Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives—Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP 3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of in
vitro studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam)

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from an in vivo drug interaction study involving a single dose of alprazolam 1 mg and steady state dose of sertraline (50 to 150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from in vitro studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

Drugs demonstrated to be inducers of CYP3A

Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

Drug/Laboratory Test Interactions

Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic in vitro in the DNA Damage/Alkaline Elution Assay or the Ames Assay.

Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

Pregnancy

Teratogenic Effects: Pregnancy Category D: (See WARNINGS section).
Nonteratogenic Effects: It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

Labor and Delivery

XANAX has no established use in labor or delivery.
**Nursing Mothers**
Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use XANAX.

**Pediatric Use**
Safety and effectiveness of XANAX in individuals below 18 years of age have not been established.

**Geriatric Use**
The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of XANAX should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

**ADVERSE REACTIONS**
Side effects to XANAX Tablets, if they occur, are generally observed at the beginning of therapy and usually disappear upon continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of alprazolam, eg, drowsiness or light-headedness.

The data cited in the two tables below are estimates of untoward clinical event incidence among patients who participated under the following clinical conditions: relatively short duration (ie, four weeks) placebo-controlled clinical studies with dosages up to 4 mg/day of XANAX (for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety) and short-term (up to ten weeks) placebo-controlled clinical studies with dosages up to 10 mg/day of XANAX in patients with panic disorder, with or without agoraphobia.

These data cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics, and other factors often differ from those in clinical trials. These figures cannot be compared with those obtained from other clinical studies involving related drug products and placebo as each group of drug trials are conducted under a different set of conditions.

Comparison of the cited figures, however, can provide the prescriber with some basis for estimating the relative contributions of drug and non-drug factors to the untoward event incidence in the population studied. Even this use must be approached cautiously, as a drug may relieve a symptom in one patient but induce it in others. (For example, an anxiolytic drug may relieve dry mouth [a symptom of anxiety] in some subjects but induce it [an untoward event] in others.)
Additionally, for anxiety disorders the cited figures can provide the prescriber with an indication as to the frequency with which physician intervention (e.g., increased surveillance, decreased dosage or discontinuation of drug therapy) may be necessary because of the untoward clinical event.
Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Anxiety Disorders

<table>
<thead>
<tr>
<th>Symptom</th>
<th>XANAX % of Patients</th>
<th>PLACEBO % of Patients</th>
<th>XANAX % of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central Nervous System</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>41.0</td>
<td>21.6</td>
<td>15.1</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>20.8</td>
<td>19.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Depression</td>
<td>13.9</td>
<td>18.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Headache</td>
<td>12.9</td>
<td>19.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Confusion</td>
<td>9.9</td>
<td>10.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>8.9</td>
<td>18.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Nervousness</td>
<td>4.1</td>
<td>10.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Syncope</td>
<td>3.1</td>
<td>4.0</td>
<td>*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.8</td>
<td>0.8</td>
<td>2.5</td>
</tr>
<tr>
<td>Akathisia</td>
<td>1.6</td>
<td>1.2</td>
<td>*</td>
</tr>
<tr>
<td>Tiredness/Sleepiness</td>
<td>*</td>
<td>*</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>14.7</td>
<td>13.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Constipation</td>
<td>10.4</td>
<td>11.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.1</td>
<td>10.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>9.6</td>
<td>12.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Increased Salivation</td>
<td>4.2</td>
<td>2.4</td>
<td>*</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia/Palpitations</td>
<td>7.7</td>
<td>15.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.7</td>
<td>2.2</td>
<td>*</td>
</tr>
<tr>
<td><strong>Sensory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>6.2</td>
<td>6.2</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R rigidity</td>
<td>4.2</td>
<td>5.3</td>
<td>*</td>
</tr>
<tr>
<td>Tremor</td>
<td>4.0</td>
<td>8.8</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis/Allergy</td>
<td>3.8</td>
<td>3.1</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>7.3</td>
<td>9.3</td>
<td>*</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>2.7</td>
<td>2.7</td>
<td>*</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>2.3</td>
<td>3.0</td>
<td>*</td>
</tr>
</tbody>
</table>

*No reported

†Events reported by 1% or more of XANAX patients are included.

In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.
# Treatment-Emergent Adverse Events Reported in Placebo-Controlled Trials of Panic Disorder

## PANIC DISORDER

### Treatment-Emergent Symptom Incidence*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>XANAX</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>1388</td>
<td>1231</td>
</tr>
<tr>
<td>% of Patients Reporting:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td>76.8</td>
<td>42.7</td>
</tr>
<tr>
<td>Fatigue and Tiredness</td>
<td>48.6</td>
<td>42.3</td>
</tr>
<tr>
<td>Impaired Coordination</td>
<td>40.1</td>
<td>17.9</td>
</tr>
<tr>
<td>Irritability</td>
<td>33.1</td>
<td>30.1</td>
</tr>
<tr>
<td>Memory Impairment</td>
<td>33.1</td>
<td>22.1</td>
</tr>
<tr>
<td>Light-headedness/Dizziness</td>
<td>29.8</td>
<td>36.9</td>
</tr>
<tr>
<td>Insomnia</td>
<td>29.4</td>
<td>41.8</td>
</tr>
<tr>
<td>Headache</td>
<td>29.2</td>
<td>35.6</td>
</tr>
<tr>
<td>Cognitive Disorder</td>
<td>28.8</td>
<td>20.5</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>23.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16.6</td>
<td>24.9</td>
</tr>
<tr>
<td>Abnormal Involuntary Movement</td>
<td>14.8</td>
<td>21.0</td>
</tr>
<tr>
<td>Decreased Libido</td>
<td>14.4</td>
<td>8.0</td>
</tr>
<tr>
<td>Depression</td>
<td>13.8</td>
<td>14.0</td>
</tr>
<tr>
<td>Confusional State</td>
<td>10.4</td>
<td>8.2</td>
</tr>
<tr>
<td>Muscular Twitching</td>
<td>7.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Increased Libido</td>
<td>7.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Change in Libido (Not Specified)</td>
<td>7.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Weakness</td>
<td>7.1</td>
<td>8.4</td>
</tr>
<tr>
<td>Muscle Tone Disorders</td>
<td>6.3</td>
<td>7.5</td>
</tr>
<tr>
<td>Syncope</td>
<td>3.8</td>
<td>4.8</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Agitation</td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>2.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Taltativeness</td>
<td>2.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Vasomotor Disturbances</td>
<td>2.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Derealization</td>
<td>1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Dream Abnormalities</td>
<td>1.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Fear</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Feeling Warm</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Salivation</td>
<td>32.8</td>
<td>34.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>26.2</td>
<td>15.4</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>22.0</td>
<td>31.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20.6</td>
<td>22.8</td>
</tr>
<tr>
<td>Abdominal Distress</td>
<td>18.3</td>
<td>21.5</td>
</tr>
<tr>
<td>Increased Salivation</td>
<td>5.6</td>
<td>4.4</td>
</tr>
<tr>
<td>Cardio-Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>17.4</td>
<td>16.5</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>15.4</td>
<td>26.8</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>10.6</td>
<td>18.1</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>9.7</td>
<td>14.5</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>4.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Sensory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>21.0</td>
<td>21.4</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>6.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular Cramps</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Muscle Stiffness</td>
<td>2.2</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Reference ID: 3004871
In addition to the relatively common (ie, greater than 1%) untoward events enumerated in the table above, the following adverse events have been reported in association with the use of XANAX: seizures, hallucinations, depersonalization, taste alterations, diplopia, elevated bilirubin, elevated hepatic enzymes, and jaundice.

Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients (see PRECAUTIONS, General).

Adverse Events Reported as Reasons for Discontinuation in Treatment of Panic Disorder in Placebo-Controlled Trials

In a larger database comprised of both controlled and uncontrolled studies in which 641 patients received XANAX, discontinuation-emergent symptoms which occurred at a rate of over 5% in patients treated with XANAX and at a greater rate than the placebo treated group were as follows:

**DISCONTINUATION-EMERGENT SYMPTOM INCIDENCE**

<table>
<thead>
<tr>
<th>Body System/Event</th>
<th>Percentage of 641 XANAX-Treated Panic Disorder Patients Reporting Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurologic</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>29.5</td>
</tr>
<tr>
<td>Light-headedness</td>
<td>19.3</td>
</tr>
<tr>
<td>Abnormal involuntary movement</td>
<td>17.3</td>
</tr>
<tr>
<td>Headache</td>
<td>17.0</td>
</tr>
<tr>
<td>Muscular twitching</td>
<td>6.9</td>
</tr>
<tr>
<td>Impaired coordination</td>
<td>6.6</td>
</tr>
<tr>
<td>Muscle tone disorders</td>
<td>5.9</td>
</tr>
<tr>
<td>Weakness</td>
<td>5.8</td>
</tr>
<tr>
<td><strong>Psychiatric</strong></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>19.2</td>
</tr>
<tr>
<td>Fatigue and Tiredness</td>
<td>18.4</td>
</tr>
<tr>
<td>Irritability</td>
<td>10.5</td>
</tr>
<tr>
<td>Cognitive disorder</td>
<td>10.3</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>5.5</td>
</tr>
<tr>
<td>Depression</td>
<td>5.1</td>
</tr>
<tr>
<td>Confusional state</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>16.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.6</td>
</tr>
<tr>
<td><strong>Metabolic-Nutritional</strong></td>
<td></td>
</tr>
<tr>
<td>Decreased salivation</td>
<td>10.6</td>
</tr>
<tr>
<td>Weight loss</td>
<td>13.3</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12.8</td>
</tr>
<tr>
<td><strong>Dermatological</strong></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>14.4</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>12.2</td>
</tr>
<tr>
<td><strong>Special Senses</strong></td>
<td></td>
</tr>
<tr>
<td>Blurred vision</td>
<td>10.0</td>
</tr>
</tbody>
</table>
From the studies cited, it has not been determined whether these symptoms are clearly related to the dose and duration of therapy with XANAX in patients with panic disorder. There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of XANAX Tablets (see WARNINGS).

To discontinue treatment in patients taking XANAX, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

Post Introduction Reports: Various adverse drug reactions have been reported in association with the use of XANAX since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of XANAX cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, angioedema, peripheral edema, hyperprolactinemia, gynecomastia, and galactorrhea (see PRECAUTIONS).

DRUG ABUSE AND DEPENDENCE

Physical and Psychological Dependence
Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including XANAX. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors and convulsions. Distinguishing between withdrawal emergent signs and symptoms and the recurrence of illness is often difficult in patients undergoing dose reduction. The long term strategy for treatment of these phenomena will vary with their cause and the therapeutic goal. When necessary, immediate
management of withdrawal symptoms requires re-institution of treatment at doses of XANAX sufficient to suppress symptoms. There have been reports of failure of other benzodiazepines to fully suppress these withdrawal symptoms. These failures have been attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing regimen of the substituted benzodiazepine or the effects of concomitant medications.

While it is difficult to distinguish withdrawal and recurrence for certain patients, the time course and the nature of the symptoms may be helpful. A withdrawal syndrome typically includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly after discontinuation, and will decrease with time. In recurring panic disorder, symptoms similar to those observed before treatment may recur either early or late, and they will persist.

While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with XANAX at doses within the recommended range for the treatment of anxiety (eg, 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day (see WARNINGS).

Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly discontinued from any CNS depressant agent, including XANAX. It is recommended that all patients on XANAX who require a dosage reduction be gradually tapered under close supervision (see WARNINGS and DOSAGE AND ADMINISTRATION).

Psychological dependence is a risk with all benzodiazepines, including XANAX. The risk of psychological dependence may also be increased at doses greater than 4 mg/day and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. Some patients have experienced considerable difficulty in tapering and discontinuing from XANAX, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving XANAX. As with all anxiolytics, repeat prescriptions should be limited to those who are under medical supervision.

**Controlled Substance Class**
Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration and XANAX Tablets have been assigned to Schedule IV.

**OVERDOSAGE**

**Clinical Experience**
Manifestations of alprazolam overdosage include somnolence, confusion, impaired coordination, diminished reflexes and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.
The acute oral LD$_{50}$ in rats is 331-2171 mg/kg. Other experiments in animals have indicated that cardiopulmonary collapse can occur following massive intravenous doses of alprazolam (over 195 mg/kg; 975 times the maximum recommended daily human dose of 10 mg/day). Animals could be resuscitated with positive mechanical ventilation and the intravenous infusion of norepinephrine bitartrate.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

**General Treatment of Overdose**
Overdosage reports with XANAX Tablets are limited. As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS should be consulted prior to use.

**DOSAGE AND ADMINISTRATION**

Dosage should be individualized for maximum beneficial effect. While the usual daily dosages given below will meet the needs of most patients, there will be some who require doses greater than 4 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

**Anxiety Disorders and Transient Symptoms of Anxiety**
Treatment for patients with anxiety should be initiated with a dose of 0.25 to 0.5 mg given three times daily. The dose may be increased to achieve a maximum therapeutic effect, at intervals of 3 to 4 days, to a maximum daily dose of 4 mg, given in divided doses. The lowest possible effective dose should be employed and the need for continued treatment reassessed frequently. The risk of dependence may increase with dose and duration of treatment.
In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every 3 days. Some patients may require an even slower dosage reduction.

**Panic Disorder**

The successful treatment of many panic disorder patients has required the use of XANAX at doses greater than 4 mg daily. In controlled trials conducted to establish the efficacy of XANAX in panic disorder, doses in the range of 1 to 10 mg daily were used. The mean dosage employed was approximately 5 to 6 mg daily. Among the approximately 1700 patients participating in the panic disorder development program, about 300 received XANAX in dosages of greater than 7 mg/day, including approximately 100 patients who received maximum dosages of greater than 9 mg/day. Occasional patients required as much as 10 mg a day to achieve a successful response.

**Dose Titration**

Treatment may be initiated with a dose of 0.5 mg three times daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg per day. Slower titration to the dose levels greater than 4 mg/day may be advisable to allow full expression of the pharmacodynamic effect of XANAX. To lessen the possibility of interdose symptoms, the times of administration should be distributed as evenly as possible throughout the waking hours, that is, on a three or four times per day schedule.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (ie, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

**Dose Maintenance**

For patients receiving doses greater than 4 mg/day, periodic reassessment and consideration of dosage reduction is advised. In a controlled postmarketing dose-response study, patients treated with doses of XANAX greater than 4 mg/day for 3 months were able to taper to 50% of their total maintenance dose without apparent loss of clinical benefit. Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided. (See WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE.)

The necessary duration of treatment for panic disorder patients responding to XANAX is unknown. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

**Dose Reduction**
Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every 3 days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

**Dosing in Special Populations**
In elderly patients, in patients with advanced liver disease or in patients with debilitating disease, the usual starting dose is 0.25 mg, given two or three times daily. This may be gradually increased if needed and tolerated. The elderly may be especially sensitive to the effects of benzodiazepines. If side effects occur at the recommended starting dose, the dose may be lowered.

**HOW SUPPLIED**

XANAX Tablets are available as follows:

**0.25 mg** (white, oval, scored, imprinted “XANAX 0.25”)
- Bottles of 100 NDC 0009-0029-01
- Reverse Numbered Unit dose (100) NDC 0009-0029-46
- Bottles of 500 NDC 0009-0029-02
- Bottles of 1000 NDC 0009-0029-14

**0.5 mg** (peach, oval, scored, imprinted “XANAX 0.5”)
- Bottles of 100 NDC 0009-0055-01
- Reverse Numbered Unit Dose (100) NDC 0009-0055-46
- Bottles of 500 NDC 0009-0055-03
- Bottles of 1000 NDC 0009-0055-15

**1 mg** (blue, oval, scored, imprinted “XANAX 1.0”)
- Bottles of 100 NDC 0009-0090-01
- Bottles of 500 NDC 0009-0090-04
- Bottles of 1000 NDC 0009-0090-13
2 mg (white, oblong, multi-scored, imprinted “XANAX” on one side and “2” on the reverse side)

- Bottles of 100 NDC 0009-0094-01
- Bottles of 500 NDC 0009-0094-03

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Rx only

ANIMAL STUDIES
When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

Distributed by

Pfizer
Pharmacia & Upjohn Co
Division of Pfizer Inc, NY, NY 10017

LAB-0004-6.0
Revised June 2011
XANAX® XR CIV
(alprazolam) extended-release tablets

DESCRIPTION

XANAX XR Tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds.

The chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4\text-H-s-triazolo [4,3-\text{a}] [1,4] benzodiazepine. The molecular formula is $C_{17}H_{13}ClN_4$ which corresponds to a molecular weight of 308.76.

The structural formula is represented below:

Alprazolam is a white crystalline powder, which is soluble in methanol or ethanol but which has no appreciable solubility in water at physiological pH.

Each XANAX XR extended-release tablet, for oral administration, contains 0.5 mg, 1 mg, 2 mg, or 3 mg of alprazolam. The inactive ingredients are lactose, magnesium stearate, colloidal silicon dioxide, and hypromellose. In addition, the 1 mg and 3 mg tablets contain D & C yellow No. 10 and the 2 mg and 3 mg tablets contain FD&C blue No. 2.

CLINICAL PHARMACOLOGY

Pharmacodynamics

CNS agents of the 1,4 benzodiazepine class presumably exert their effects by binding at stereospecific receptors at several sites within the central nervous system. Their exact mechanism of action is unknown. Clinically, all benzodiazepines cause a dose-related central nervous system depressant activity varying from mild impairment of task performance to hypnosis.

Pharmacokinetics

Absorption

Following oral administration of XANAX (immediate-release) Tablets, alprazolam is readily absorbed. Peak concentrations in the plasma occur in one to two hours following administration. Plasma levels are proportional to the dose given; over the dose range of 0.5
to 3.0 mg, peak levels of 8.0 to 37 ng/mL were observed. Using a specific assay methodology, the mean plasma elimination half-life of alprazolam has been found to be about 11.2 hours (range: 6.3–26.9 hours) in healthy adults.

The mean absolute bioavailability of alprazolam from XANAX XR Tablets is approximately 90%, and the relative bioavailability compared to XANAX Tablets is 100%. The bioavailability and pharmacokinetics of alprazolam following administration of XANAX XR Tablets are similar to that for XANAX Tablets, with the exception of a slower rate of absorption. The slower absorption rate results in a relatively constant concentration that is maintained between 5 and 11 hours after the dosing. The pharmacokinetics of alprazolam and two of its major active metabolites (4-hydroxyalprazolam and α-hydroxyalprazolam) are linear, and concentrations are proportional up to the recommended maximum daily dose of 10 mg given once daily. Multiple dose studies indicate that the metabolism and elimination of alprazolam are similar for the immediate-release and the extended-release products.

Food has a significant influence on the bioavailability of XANAX XR Tablets. A high-fat meal given up to 2 hours before dosing with XANAX XR Tablets increased the mean $C_{max}$ by about 25%. The effect of this meal on $T_{max}$ depended on the timing of the meal, with a reduction in $T_{max}$ by about 1/3 for subjects eating immediately before dosing and an increase in $T_{max}$ by about 1/3 for subjects eating 1 hour or more after dosing. The extent of exposure (AUC) and elimination half-life ($t_{1/2}$) were not affected by eating.

There were significant differences in absorption rate for the XANAX XR Tablet, depending on the time of day administered, with the $C_{max}$ increased by 30% and the $T_{max}$ decreased by an hour following dosing at night, compared to morning dosing.

**Distribution**

The apparent volume of distribution of alprazolam is similar for XANAX XR and XANAX Tablets. In vitro, alprazolam is bound (80%) to human serum protein. Serum albumin accounts for the majority of the binding.

**Metabolism**

Alprazolam is extensively metabolized in humans, primarily by cytochrome P450 3A4 (CYP3A4), to two major metabolites in the plasma: 4-hydroxyalprazolam and α-hydroxyalprazolam. A benzophenone derived from alprazolam is also found in humans. Their half-lives appear to be similar to that of alprazolam. The pharmacokinetic parameters at steady-state for the two hydroxylated metabolites of alprazolam (4-hydroxyalprazolam and α-hydroxyalprazolam) were similar for XANAX and XANAX XR Tablets, indicating that the metabolism of alprazolam is not affected by absorption rate. The plasma concentrations of 4-hydroxyalprazolam and α-hydroxyalprazolam relative to unchanged alprazolam concentration after both XANAX XR and XANAX Tablets were always less than 10% and 4%, respectively. The reported relative potencies in benzodiazepine receptor binding experiments and in animal models of induced seizure inhibition are 0.20 and 0.66, respectively, for 4-hydroxyalprazolam and α-hydroxyalprazolam. Such low concentrations and the lesser potencies of 4-hydroxyalprazolam and α-hydroxyalprazolam suggest that they
are unlikely to contribute much to the pharmacological effects of alprazolam. The benzophenone metabolite is essentially inactive.

Elimination
Alprazolam and its metabolites are excreted primarily in the urine. The mean plasma elimination half-life of alprazolam following administration of XANAX XR Tablet ranges from 10.7–15.8 hours in healthy adults.

Special Populations
While pharmacokinetic studies have not been performed in special populations with XANAX XR Tablets, the factors (such as age, gender, hepatic or renal impairment) that would affect the pharmacokinetics of alprazolam after the administration of XANAX Tablets would not be expected to be different with the administration of XANAX XR Tablets.

Changes in the absorption, distribution, metabolism, and excretion of benzodiazepines have been reported in a variety of disease states including alcoholism, impaired hepatic function, and impaired renal function. Changes have also been demonstrated in geriatric patients. A mean half-life of alprazolam of 16.3 hours has been observed in healthy elderly subjects (range: 9.0–26.9 hours, n=16) compared to 11.0 hours (range: 6.3–15.8 hours, n=16) in healthy adult subjects. In patients with alcoholic liver disease the half-life of alprazolam ranged between 5.8 and 65.3 hours (mean: 19.7 hours, n=17) as compared to between 6.3 and 26.9 hours (mean=11.4 hours, n=17) in healthy subjects. In an obese group of subjects the half-life of alprazolam ranged between 9.9 and 40.4 hours (mean=21.8 hours, n=12) as compared to between 6.3 and 15.8 hours (mean=10.6 hours, n=12) in healthy subjects.

Because of its similarity to other benzodiazepines, it is assumed that alprazolam undergoes transplacental passage and that it is excreted in human milk.

Race — Maximal concentrations and half-life of alprazolam are approximately 15% and 25% higher in Asians compared to Caucasians.

Pediatrics — The pharmacokinetics of alprazolam after administration of the XANAX XR Tablet in pediatric patients have not been studied.

Gender — Gender has no effect on the pharmacokinetics of alprazolam.

Cigarette Smoking — Alprazolam concentrations may be reduced by up to 50% in smokers compared to non-smokers.

Drug-Drug Interactions
Alprazolam is primarily eliminated by metabolism via cytochrome P450 3A (CYP3A). Most of the interactions that have been documented with alprazolam are with drugs that inhibit or induce CYP3A4.

Compounds that are potent inhibitors of CYP3A would be expected to increase plasma alprazolam concentrations. Drug products that have been studied in vivo, along with their
effect on increasing alprazolam AUC, are as follows: ketoconazole, 3.98 fold; itraconazole, 2.70 fold; nefazodone, 1.98 fold; fluvoxamine, 1.96 fold; and erythromycin, 1.61 fold (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS–Drug Interactions).

CYP3A inducers would be expected to decrease alprazolam concentrations and this has been observed in vivo. The oral clearance of alprazolam (given in a 0.8 mg single dose) was increased from 0.90±0.21 mL/min/kg to 2.13±0.54 mL/min/kg and the elimination t1/2 was shortened (from 17.1±4.9 to 7.7±1.7 h) following administration of 300 mg/day carbamazepine for 10 days (see PRECAUTIONS–Drug Interactions). However, the carbamazepine dose used in this study was fairly low compared to the recommended doses (1000–1200 mg/day); the effect at usual carbamazepine doses is unknown.

The ability of alprazolam to induce or inhibit human hepatic enzyme systems has not been determined. However, this is not a property of benzodiazepines in general. Further, alprazolam did not affect the prothrombin or plasma warfarin levels in male volunteers administered sodium warfarin orally.

CLINICAL EFFICACY TRIALS
The efficacy of XANAX XR Tablets in the treatment of panic disorder was established in two 6-week, placebo-controlled studies of XANAX XR in patients with panic disorder.

In two 6-week, flexible-dose, placebo-controlled studies in patients meeting DSM-III criteria for panic disorder, patients were treated with XANAX XR in a dose range of 1 to 10 mg/day, on a once-a-day basis. The effectiveness of XANAX XR was assessed on the basis of changes in various measures of panic attack frequency, on various measures of the Clinical Global Impression, and on the Overall Phobia Scale. In all, there were seven primary efficacy measures in these studies, and XANAX XR was superior to placebo on all seven outcomes in both studies. The mean dose of XANAX XR at the last treatment visit was 4.2 mg/day in the first study and 4.6 mg/day in the second.

In addition, there were two 8-week, fixed-dose, placebo-controlled studies of XANAX XR in patients with panic disorder, involving fixed XANAX XR doses of 4 and 6 mg/day, on a once-a-day basis, that did not show a benefit for either dose of XANAX XR.

The longer-term efficacy of XANAX XR in panic disorder has not been systematically evaluated.

Analyses of the relationship between treatment outcome and gender did not suggest any differential responsiveness on the basis of gender.

INDICATIONS AND USAGE
XANAX XR Tablets are indicated for the treatment of panic disorder, with or without agoraphobia.
This claim is supported on the basis of two positive studies with XANAX XR conducted in patients whose diagnoses corresponded closely to the DSM-III-R/IV criteria for panic disorder (see CLINICAL EFFICACY TRIALS).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, ie, a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart, or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded, or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

The longer-term efficacy of XANAX XR has not been systematically evaluated. Thus, the physician who elects to use this drug for periods longer than 8 weeks should periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS

XANAX XR Tablets are contraindicated in patients with known sensitivity to this drug or other benzodiazepines. XANAX XR may be used in patients with open angle glaucoma who are receiving appropriate therapy, but is contraindicated in patients with acute narrow angle glaucoma.

XANAX XR is contraindicated with ketoconazole and itraconazole, since these medications significantly impair the oxidative metabolism mediated by cytochrome P450 3A (CYP3A) (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS–Drug Interactions).

WARNINGS

Dependence and Withdrawal Reactions, Including Seizures
Certain adverse clinical events, some life-threatening, are a direct consequence of physical dependence to alprazolam. These include a spectrum of withdrawal symptoms; the most important is seizure (see DRUG ABUSE AND DEPENDENCE). Even after relatively short-term use at doses of ≤ 4 mg/day, there is some risk of dependence. Spontaneous reporting system data suggest that the risk of dependence and its severity appear to be greater in patients treated with doses greater than 4 mg/day and for long periods (more than 12 weeks). However, in a controlled postmarketing discontinuation study of panic disorder patients who received XANAX Tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose. In contrast, patients treated with
doses of XANAX Tablets greater than 4 mg/day had more difficulty tapering to zero dose than those treated with less than 4 mg/day.

Relapse or return of illness was defined as a return of symptoms characteristic of panic disorder (primarily panic attacks) to levels approximately equal to those seen at baseline before active treatment was initiated. Rebound refers to a return of symptoms of panic disorder to a level substantially greater in frequency, or more severe in intensity than seen at baseline. Withdrawal symptoms were identified as those which were generally not characteristic of panic disorder and which occurred for the first time more frequently during discontinuation than at baseline.

The rate of relapse, rebound, and withdrawal in patients with panic disorder who received XANAX XR Tablets has not been systematically studied. Experience in randomized placebo-controlled discontinuation studies of patients with panic disorder who received XANAX Tablets showed a high rate of rebound and withdrawal symptoms compared to placebo treated patients.

In a controlled clinical trial in which 63 patients were randomized to XANAX Tablets and where withdrawal symptoms were specifically sought, the following were identified as symptoms of withdrawal: heightened sensory perception, impaired concentration, dysosmia, clouded sensorium, paresthesias, muscle cramps, muscle twitch, diarrhea, blurred vision, appetite decrease, and weight loss. Other symptoms, such as anxiety and insomnia, were frequently seen during discontinuation, but it could not be determined if they were due to return of illness, rebound, or withdrawal.

In two controlled trials of 6 to 8 weeks duration where the ability of patients to discontinue medication was measured, 71%–93% of patients treated with XANAX Tablets tapered completely off therapy compared to 89%–96% of placebo treated patients. In a controlled postmarketing discontinuation study of panic disorder patients treated with XANAX Tablets, the duration of treatment (3 months compared to 6 months) had no effect on the ability of patients to taper to zero dose.

Seizures were reported for three patients in panic disorder clinical trials with XANAX XR. In two cases, the patients had completed 6 weeks of treatment with XANAX XR 6 mg/day before experiencing a single seizure. In one case, the patient abruptly discontinued XANAX XR, and in both cases, alcohol intake was implicated. The third case involved multiple seizures after the patient completed treatment with XANAX XR 4 mg/day and missed taking the medication on the first day of taper. All three patients recovered without sequelae.

Seizures have also been observed in association with dose reduction or discontinuation of XANAX Tablets, the immediate release form of alprazolam. Seizures attributable to XANAX were seen after drug discontinuance or dose reduction in 8 of 1980 patients with panic disorder or in patients participating in clinical trials where doses of XANAX greater than 4 mg/day for over 3 months were permitted. Five of these cases clearly occurred during abrupt dose reduction, or discontinuation from daily doses of 2 to 10 mg. Three cases occurred in situations where there was not a clear relationship to abrupt dose reduction or
discontinuation. In one instance, seizure occurred after discontinuation from a single dose of 1 mg after tapering at a rate of 1 mg every three days from 6 mg daily. In two other instances, the relationship to taper is indeterminate; in both of these cases the patients had been receiving doses of 3 mg daily prior to seizure. The duration of use in the above 8 cases ranged from 4 to 22 weeks. There have been occasional voluntary reports of patients developing seizures while apparently tapering gradually from XANAX. The risk of seizure seems to be greatest 24–72 hours after discontinuation (see DOSAGE AND ADMINISTRATION for recommended tapering and discontinuation schedule).

**Status Epilepticus**
The medical event voluntary reporting system shows that withdrawal seizures have been reported in association with the discontinuation of XANAX Tablets. In most cases, only a single seizure was reported; however, multiple seizures and status epilepticus were reported as well.

**Interdose Symptoms**
Early morning anxiety and emergence of anxiety symptoms between doses of XANAX Tablets have been reported in patients with panic disorder taking prescribed maintenance doses. These symptoms may reflect the development of tolerance or a time interval between doses which is longer than the duration of clinical action of the administered dose. In either case, it is presumed that the prescribed dose is not sufficient to maintain plasma levels above those needed to prevent relapse, rebound, or withdrawal symptoms over the entire course of the interdosing interval.

**Risk of Dose Reduction**
Withdrawal reactions may occur when dosage reduction occurs for any reason. This includes purposeful tapering, but also inadvertent reduction of dose (eg, the patient forgets, the patient is admitted to a hospital). Therefore, the dosage of XANAX XR should be reduced or discontinued gradually (see DOSAGE AND ADMINISTRATION).

**CNS Depression and Impaired Performance**
Because of its CNS depressant effects, patients receiving XANAX XR should be cautioned against engaging in hazardous occupations or activities requiring complete mental alertness such as operating machinery or driving a motor vehicle. For the same reason, patients should be cautioned about the simultaneous ingestion of alcohol and other CNS depressant drugs during treatment with XANAX XR.

**Risk of Fetal Harm**
Benzodiazepines can potentially cause fetal harm when administered to pregnant women. If alprazolam is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Because of experience with other members of the benzodiazepine class, alprazolam is assumed to be capable of causing an increased risk of congenital abnormalities when administered to a pregnant woman during the first trimester. Because use of these drugs is rarely a matter of urgency, their use during the first trimester should almost always be avoided. The possibility that a woman of childbearing potential may be pregnant at the time of institution of therapy
should be considered. Patients should be advised that if they become pregnant during therapy or intend to become pregnant they should communicate with their physicians about the desirability of discontinuing the drug.

**Alprazolam Interaction With Drugs That Inhibit Metabolism Via Cytochrome P450 3A**

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs that inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam. Consequently, alprazolam should be avoided in patients receiving very potent inhibitors of CYP3A. With drugs inhibiting CYP3A to a lesser but still significant degree, alprazolam should be used only with caution and consideration of appropriate dosage reduction. For some drugs, an interaction with alprazolam has been quantified with clinical data; for other drugs, interactions are predicted from in vitro data and/or experience with similar drugs in the same pharmacologic class.

The following are examples of drugs known to inhibit the metabolism of alprazolam and/or related benzodiazepines, presumably through inhibition of CYP3A.

**Potent CYP3A Inhibitors**

Azole antifungal agents — Ketoconazole and itraconazole are potent CYP3A inhibitors and have been shown in vivo to increase plasma alprazolam concentrations 3.98 fold and 2.70 fold, respectively. The coadministration of alprazolam with these agents is not recommended. Other azole-type antifungal agents should also be considered potent CYP3A inhibitors and the coadministration of alprazolam with them is not recommended (see CONTRAINDICATIONS).

Drugs demonstrated to be CYP3A inhibitors on the basis of clinical studies involving alprazolam (caution and consideration of appropriate alprazolam dose reduction are recommended during coadministration with the following drugs)

Nefazodone — Coadministration of nefazodone increased alprazolam concentration two-fold.

Fluvoxamine — Coadministration of fluvoxamine approximately doubled the maximum plasma concentration of alprazolam, decreased clearance by 49%, increased half-life by 71%, and decreased measured psychomotor performance.

Cimetidine — Coadministration of cimetidine increased the maximum plasma concentration of alprazolam by 86%, decreased clearance by 42%, and increased half-life by 16%.

**Other Drugs Possibly Affecting Alprazolam Metabolism**

Other drugs possibly affecting alprazolam metabolism by inhibition of CYP3A are discussed in the PRECAUTIONS section (see PRECAUTIONS–Drug Interactions).

**PRECAUTIONS**

**General**
Suicide
As with other psychotropic medications, the usual precautions with respect to administration of the drug and size of the prescription are indicated for severely depressed patients or those in whom there is reason to expect concealed suicidal ideation or plans. Panic disorder has been associated with primary and secondary major depressive disorders and increased reports of suicide among untreated patients.

Mania
Episodes of hypomania and mania have been reported in association with the use of XANAX Tablets in patients with depression.

Uricosuric Effect
Alprazolam has a weak uricosuric effect. Although other medications with weak uricosuric effect have been reported to cause acute renal failure, there have been no reported instances of acute renal failure attributable to therapy with alprazolam.

Use in Patients with Concomitant Illness
It is recommended that the dosage be limited to the smallest effective dose to preclude the development of ataxia or oversedation which may be a particular problem in elderly or debilitated patients (see DOSAGE AND ADMINISTRATION). The usual precautions in treating patients with impaired renal, hepatic, or pulmonary function should be observed. There have been rare reports of death in patients with severe pulmonary disease shortly after the initiation of treatment with XANAX Tablets. A decreased systemic alprazolam elimination rate (eg, increased plasma half-life) has been observed in both alcoholic liver disease patients and obese patients receiving XANAX Tablets (see CLINICAL PHARMACOLOGY).

Information for Patients
To assure safe and effective use of XANAX XR, the physician should provide the patient with the following guidance.

1. Inform your physician about any alcohol consumption and medicine you are taking now, including medication you may buy without a prescription. Alcohol should generally not be used during treatment with benzodiazepines.

2. Not recommended for use in pregnancy. Therefore, inform your physician if you are pregnant, if you are planning to have a child, or if you become pregnant while you are taking this medication.

3. Inform your physician if you are nursing.

4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery, etc.
5. Do not increase the dose even if you think the medication "does not work anymore" without consulting your physician. Benzodiazepines, even when used as recommended, may produce emotional and/or physical dependence.

6. Do not stop taking this medication abruptly or decrease the dose without consulting your physician, since withdrawal symptoms can occur.

7. Some patients may find it very difficult to discontinue treatment with XANAX XR due to severe emotional and physical dependence. Discontinuation symptoms, including possible seizures, may occur following discontinuation from any dose, but the risk may be increased with extended use at doses greater than 4 mg/day, especially if discontinuation is too abrupt. It is important that you seek advice from your physician to discontinue treatment in a careful and safe manner. Proper discontinuation will help to decrease the possibility of withdrawal reactions that can range from mild reactions to severe reactions such as seizure.

**Laboratory Tests**

Laboratory tests are not ordinarily required in otherwise healthy patients. However, when treatment is protracted, periodic blood counts, urinalysis, and blood chemistry analyses are advisable in keeping with good medical practice.

**Drug Interactions**

**Use with Other CNS Depressants**

If XANAX XR Tablets are to be combined with other psychotropic agents or anticonvulsant drugs, careful consideration should be given to the pharmacology of the agents to be employed, particularly with compounds which might potentiate the action of benzodiazepines. The benzodiazepines, including alprazolam, produce additive CNS depressant effects when coadministered with other psychotropic medications, anticonvulsants, antihistaminics, ethanol and other drugs which themselves produce CNS depression.

**Use with Imipramine and Desipramine**

The steady state plasma concentrations of imipramine and desipramine have been reported to be increased an average of 31% and 20%, respectively, by the concomitant administration of XANAX Tablets in doses up to 4 mg/day. The clinical significance of these changes is unknown.

**Drugs that inhibit alprazolam metabolism via cytochrome P450 3A**

The initial step in alprazolam metabolism is hydroxylation catalyzed by cytochrome P450 3A (CYP3A). Drugs which inhibit this metabolic pathway may have a profound effect on the clearance of alprazolam (see CONTRAINDICATIONS and WARNINGS for additional drugs of this type).

**Drugs demonstrated to be CYP3A inhibitors of possible clinical significance on the basis of clinical studies involving alprazolam (caution is recommended during coadministration with alprazolam)**
Fluoxetine — Coadministration of fluoxetine with alprazolam increased the maximum plasma concentration of alprazolam by 46%, decreased clearance by 21%, increased half-life by 17%, and decreased measured psychomotor performance.

Propoxyphene — Coadministration of propoxyphene decreased the maximum plasma concentration of alprazolam by 6%, decreased clearance by 38%, and increased half-life by 58%.

Oral Contraceptives — Coadministration of oral contraceptives increased the maximum plasma concentration of alprazolam by 18%, decreased clearance by 22%, and increased half-life by 29%.

Drugs and other substances demonstrated to be CYP3A inhibitors on the basis of clinical studies involving benzodiazepines metabolized similarly to alprazolam or on the basis of in vitro studies with alprazolam or other benzodiazepines (caution is recommended during coadministration with alprazolam)

Available data from clinical studies of benzodiazepines other than alprazolam suggest a possible drug interaction with alprazolam for the following: diltiazem, isoniazid, macrolide antibiotics such as erythromycin and clarithromycin, and grapefruit juice. Data from in vitro studies of alprazolam suggest a possible drug interaction with alprazolam for the following: sertraline and paroxetine. However, data from an in vivo drug interaction study involving a single dose of alprazolam 1 mg and steady state doses of sertraline (50 to 150 mg/day) did not reveal any clinically significant changes in the pharmacokinetics of alprazolam. Data from in vitro studies of benzodiazepines other than alprazolam suggest a possible drug interaction for the following: ergotamine, cyclosporine, amiodarone, nicardipine, and nifedipine. Caution is recommended during the coadministration of any of these with alprazolam (see WARNINGS).

Drugs demonstrated to be inducers of CYP3A
Carbamazepine can increase alprazolam metabolism and therefore can decrease plasma levels of alprazolam.

Drug/Laboratory Test Interactions
Although interactions between benzodiazepines and commonly employed clinical laboratory tests have occasionally been reported, there is no consistent pattern for a specific drug or specific test.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of carcinogenic potential was observed during 2-year bioassay studies of alprazolam in rats at doses up to 30 mg/kg/day (150 times the maximum recommended daily human dose of 10 mg/day) and in mice at doses up to 10 mg/kg/day (50 times the maximum recommended daily human dose).

Alprazolam was not mutagenic in the rat micronucleus test at doses up to 100 mg/kg, which is 500 times the maximum recommended daily human dose of 10 mg/day. Alprazolam also was not mutagenic in vitro in the DNA Damage/Alkaline Elution Assay or the Ames Assay.
Alprazolam produced no impairment of fertility in rats at doses up to 5 mg/kg/day, which is 25 times the maximum recommended daily human dose of 10 mg/day.

**Pregnancy**

*Teratogenic Effects: Pregnancy Category D:* (see WARNINGS section).

Nonteratogenic Effects: It should be considered that the child born of a mother who is receiving benzodiazepines may be at some risk for withdrawal symptoms from the drug during the postnatal period. Also, neonatal flaccidity and respiratory problems have been reported in children born of mothers who have been receiving benzodiazepines.

**Labor and Delivery**

Alprazolam has no established use in labor or delivery.

**Nursing Mothers**

Benzodiazepines are known to be excreted in human milk. It should be assumed that alprazolam is as well. Chronic administration of diazepam to nursing mothers has been reported to cause their infants to become lethargic and to lose weight. As a general rule, nursing should not be undertaken by mothers who must use alprazolam.

**Pediatric Use**

Safety and effectiveness of alprazolam in individuals below 18 years of age have not been established.

**Geriatric Use**

The elderly may be more sensitive to the effects of benzodiazepines. They exhibit higher plasma alprazolam concentrations due to reduced clearance of the drug as compared with a younger population receiving the same doses. The smallest effective dose of alprazolam should be used in the elderly to preclude the development of ataxia and oversedation (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

**ADVERSE REACTIONS**

The information included in the subsection on Adverse Events Observed in Short-Term, Placebo-Controlled Trials with XANAX XR Tablets is based on pooled data of five 6- and 8-week placebo-controlled clinical studies in panic disorder.

Adverse event reports were elicited either by general inquiry or by checklist, and were recorded by clinical investigators using terminology of their own choosing. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened during therapy following baseline evaluation. In the tables and tabulations that follow, standard MedDRA terminology (version 4.0) was used to classify reported adverse events.
Adverse Events Observed in Short-Term, Placebo-Controlled Trials of XANAX XR

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials

Approximately 17% of the 531 patients who received XANAX XR in placebo-controlled clinical trials for panic disorder had at least one adverse event that led to discontinuation compared to 8% of 349 placebo-treated patients. The most common events leading to discontinuation and considered to be drug-related (ie, leading to discontinuation in at least 1% of the patients treated with XANAX XR at a rate at least twice that of placebo) are shown in the following table.

| Common Adverse Events Leading to Discontinuation of Treatment in Placebo-Controlled Trials |
|-----------------------------------------|---------------------------------------------|
| System Organ Class/Adverse Event          | Percentage of Patients Discontinuing Due to Adverse Events |
|                                         | XANAX XR (n=531) | Placebo (n=349) |
| Nervous system disorders                   |                       |
| Sedation                                | 7.5                     | 0.6                  |
| Somnolence                              | 3.2                     | 0.3                  |
| Dysarthria                              | 2.1                     | 0                    |
| Coordination abnormal                    | 1.9                     | 0.3                  |
| Memory impairment                        | 1.5                     | 0.3                  |
| General disorders/administration site conditions | | |
| Fatigue                                 | 1.7                     | 0.6                  |
| Psychiatric disorders                    |                       |
| Depression                              | 2.5                     | 1.2                  |

Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated with XANAX XR

The prescriber should be aware that adverse event incidence cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with event incidence obtained from other clinical investigations involving different treatments, uses, and investigators. The cited values, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The following table shows the incidence of treatment-emergent adverse events that occurred during 6- to 8-week placebo-controlled trials in 1% or more of patients treated with XANAX XR where the incidence in patients treated with XANAX XR was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in panic disorder patients treated with XANAX XR (incidence of 5% or greater and at least twice the incidence in placebo patients) were: sedation, somnolence, memory impairment, dysarthria, coordination abnormal, ataxia, libido decreased (see table).
### Treatment-Emergent Adverse Events: Incidence in Short-Term, Placebo-Controlled Clinical Trials with XANAX XR

<table>
<thead>
<tr>
<th>System Organ Class/Adverse Event</th>
<th>Percentage of Patients Reporting Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XANAX XR (n=531)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=349)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>45.2</td>
</tr>
<tr>
<td>Somnolence</td>
<td>23.0</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>15.4</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>10.9</td>
</tr>
<tr>
<td>Coordination abnormal</td>
<td>9.4</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>7.2</td>
</tr>
<tr>
<td>Ataxia</td>
<td>7.2</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>3.2</td>
</tr>
<tr>
<td>Balance impaired</td>
<td>3.2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2.4</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>1.7</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>1.3</td>
</tr>
<tr>
<td>General disorders/administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13.9</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1.7</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>2.4</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>1.9</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>12.1</td>
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<tr>
<td>Libido decreased</td>
<td>6.0</td>
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<tr>
<td>Disorientation</td>
<td>1.5</td>
</tr>
<tr>
<td>Confusion</td>
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<tr>
<td>Depressed mood</td>
<td>1.3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.1</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>7.3</td>
</tr>
<tr>
<td>Appetite increased</td>
<td>7.0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.5</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.1</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.0</td>
</tr>
<tr>
<td>Pharyngolaryngeal pain</td>
<td>3.2</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
</tr>
<tr>
<td>Weight increased</td>
<td>5.1</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4.3</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural complications</td>
<td></td>
</tr>
<tr>
<td>Road traffic accident</td>
<td>1.5</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3004871
Other Adverse Events Observed During the Premarketing Evaluation of XANAX XR Tablets

Following is a list of MedDRA terms that reflect treatment-emergent adverse events reported by 531 patients with panic disorder treated with XANAX XR. All potentially important reported events are included except those already listed in the above table or elsewhere in labeling, those events for which a drug cause was remote, those event terms that were so general as to be uninformative, and those events that occurred at rates similar to background rates in the general population. It is important to emphasize that, although the events reported occurred during treatment with XANAX XR, they were not necessarily caused by the drug. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

**Cardiac disorders:** Frequent: palpitation; Infrequent: sinus tachycardia

**Ear and Labyrinth disorders:** Frequent: Vertigo; Infrequent: tinnitus, ear pain

**Eye disorders:** Frequent: blurred vision; Infrequent: mydriasis, photophobia

**Gastrointestinal disorders:** Frequent: diarrhea, vomiting, dyspepsia, abdominal pain; Infrequent: dysphagia, salivary hypersecretion

**General disorders and administration site conditions:** Frequent: malaise, weakness, chest pains; Infrequent: fall, pyrexia, thirst, feeling hot and cold, edema, feeling jittery, sluggishness, asthenia, feeling drunk, chest tightness, increased energy, feeling of relaxation, hangover, loss of control of legs, rigors

**Musculoskeletal and connective tissue disorders:** Frequent: back pain, muscle cramps, muscle twitching

**Nervous system disorders:** Frequent: headache, dizziness, tremor; Infrequent: amnesia, clumsiness, syncope, hypotonia, seizures, depressed level of consciousness, sleep apnea syndrome, sleep talking, stupor
**Psychiatric system disorders:** Frequent: irritability, insomnia, nervousness, derealization, libido increased, restlessness, agitation, depersonalization, nightmare; *Infrequent:* abnormal dreams, apathy, aggression, anger, bradyphrenia, euphoric mood, logorrhea, mood swings, dysphonia, hallucination, homicidal ideation, mania, hypomania, impulse control, psychomotor retardation, suicidal ideation

**Renal and urinary disorders:** Frequent: difficulty in micturition; *Infrequent:* urinary frequency, urinary incontinence

**Respiratory, thoracic, and mediastinal disorders:** Frequent: nasal congestion, hyperventilation; *Infrequent:* choking sensation, epistaxis, rhinorrhea

**Skin and subcutaneous tissue disorders:** Frequent: sweating increased; *Infrequent:* clamminess, rash, urticaria

**Vascular disorders:** *Infrequent:* hypotension

The categories of adverse events reported in the clinical development program for XANAX Tablets in the treatment of panic disorder differ somewhat from those reported for XANAX XR Tablets because the clinical trials with XANAX Tablets and XANAX XR Tablets used different standard medical nomenclature for reporting the adverse events. Nevertheless, the types of adverse events reported in the clinical trials with XANAX Tablets were generally the same as those reported in the clinical trials with XANAX XR Tablets.

Discontinuation-Emergent Adverse Events Occurring at an Incidence of 5% or More Among Patients Treated with XANAX XR

The following table shows the incidence of discontinuation-emergent adverse events that occurred during short-term, placebo-controlled trials in 5% or more of patients treated with XANAX XR where the incidence in patients treated with XANAX XR was two times greater than the incidence in placebo-treated patients.

<table>
<thead>
<tr>
<th>System Organ Class/AdverseEvent</th>
<th>Percentage of Patients Reporting Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XANAX XR (n=422)</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>28.2</td>
</tr>
<tr>
<td>Headache</td>
<td>26.5</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>7.8</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>7.1</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>24.2</td>
</tr>
<tr>
<td>Nervousness</td>
<td>21.8</td>
</tr>
<tr>
<td>Depression</td>
<td>10.9</td>
</tr>
<tr>
<td>Derealization</td>
<td>8.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>7.8</td>
</tr>
<tr>
<td>Depersonalization</td>
<td>5.7</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12.1</td>
</tr>
<tr>
<td>Disorder Type</td>
<td>Symptom</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>disorders</td>
<td>Metabolism and</td>
</tr>
<tr>
<td></td>
<td>nutrition disorders</td>
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<tr>
<td></td>
<td>Appetite decreased</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>Muscle twitching</td>
</tr>
<tr>
<td>disorders</td>
<td>Vascular disorders</td>
</tr>
<tr>
<td></td>
<td>Hot flushes</td>
</tr>
</tbody>
</table>

There have also been reports of withdrawal seizures upon rapid decrease or abrupt discontinuation of alprazolam (see WARNINGS).

To discontinue treatment in patients taking XANAX XR Tablets, the dosage should be reduced slowly in keeping with good medical practice. It is suggested that the daily dosage of XANAX XR Tablets be decreased by no more than 0.5 mg every three days (see DOSAGE AND ADMINISTRATION). Some patients may benefit from an even slower dosage reduction. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome.

As with all benzodiazepines, paradoxical reactions such as stimulation, increased muscle spasticity, sleep disturbances, hallucinations, and other adverse behavioral effects such as agitation, rage, irritability, and aggressive or hostile behavior have been reported rarely. In many of the spontaneous case reports of adverse behavioral effects, patients were receiving other CNS drugs concomitantly and/or were described as having underlying psychiatric conditions. Should any of the above events occur, alprazolam should be discontinued. Isolated published reports involving small numbers of patients have suggested that patients who have borderline personality disorder, a prior history of violent or aggressive behavior, or alcohol or substance abuse may be at risk for such events. Instances of irritability, hostility, and intrusive thoughts have been reported during discontinuation of alprazolam in patients with posttraumatic stress disorder.

**Post Introduction Reports**

Various adverse drug reactions have been reported in association with the use of XANAX Tablets since market introduction. The majority of these reactions were reported through the medical event voluntary reporting system. Because of the spontaneous nature of the reporting of medical events and the lack of controls, a causal relationship to the use of XANAX Tablets cannot be readily determined. Reported events include: gastrointestinal disorder, hypomania, mania, liver enzyme elevations, hepatitis, hepatic failure, Stevens-Johnson syndrome, angioedema, peripheral edema, hyperprolactinemia, gynecomastia, and galactorrhea (see PRECAUTIONS).
Physical and Psychological Dependence

Withdrawal symptoms similar in character to those noted with sedative/hypnotics and alcohol have occurred following discontinuance of benzodiazepines, including alprazolam. The symptoms can range from mild dysphoria and insomnia to a major syndrome that may include abdominal and muscle cramps, vomiting, sweating, tremors, and convulsions. Distinguishing between withdrawal emergent signs and symptoms and the recurrence of illness is often difficult in patients undergoing dose reduction. The long-term strategy for treatment of these phenomena will vary with their cause and the therapeutic goal. When necessary, immediate management of withdrawal symptoms requires re-institution of treatment at doses of alprazolam sufficient to suppress symptoms. There have been reports of failure of other benzodiazepines to fully suppress these withdrawal symptoms. These failures have been attributed to incomplete cross-tolerance but may also reflect the use of an inadequate dosing regimen of the substituted benzodiazepine or the effects of concomitant medications.

While it is difficult to distinguish withdrawal and recurrence for certain patients, the time course and the nature of the symptoms may be helpful. A withdrawal syndrome typically includes the occurrence of new symptoms, tends to appear toward the end of taper or shortly after discontinuation, and will decrease with time. In recurring panic disorder, symptoms similar to those observed before treatment may recur either early or late, and they will persist.

While the severity and incidence of withdrawal phenomena appear to be related to dose and duration of treatment, withdrawal symptoms, including seizures, have been reported after only brief therapy with alprazolam at doses within the recommended range for the treatment of anxiety (eg, 0.75 to 4 mg/day). Signs and symptoms of withdrawal are often more prominent after rapid decrease of dosage or abrupt discontinuance. The risk of withdrawal seizures may be increased at doses above 4 mg/day (see WARNINGS).

Patients, especially individuals with a history of seizures or epilepsy, should not be abruptly discontinued from any CNS depressant agent, including alprazolam. It is recommended that all patients on alprazolam who require a dosage reduction be gradually tapered under close supervision (see WARNINGS and DOSAGE AND ADMINISTRATION).

Psychological dependence is a risk with all benzodiazepines, including alprazolam. The risk of psychological dependence may also be increased at doses greater than 4 mg/day and with longer term use, and this risk is further increased in patients with a history of alcohol or drug abuse. Some patients have experienced considerable difficulty in tapering and discontinuing from alprazolam, especially those receiving higher doses for extended periods. Addiction-prone individuals should be under careful surveillance when receiving alprazolam. As with
all anxiolytics, repeat prescriptions should be limited to those who are under medical supervision.

**Controlled Substance Class**

Alprazolam is a controlled substance under the Controlled Substance Act by the Drug Enforcement Administration and XANAX XR Tablets have been assigned to Schedule IV.

**OVERDOSAGE**

**Clinical Experience**

Overdosage reports with XANAX Tablets are limited. Manifestations of alprazolam overdose include somnolence, confusion, impaired coordination, diminished reflexes, and coma. Death has been reported in association with overdoses of alprazolam by itself, as it has with other benzodiazepines. In addition, fatalities have been reported in patients who have overdosed with a combination of a single benzodiazepine, including alprazolam, and alcohol; alcohol levels seen in some of these patients have been lower than those usually associated with alcohol-induced fatality.

Animal experiments have suggested that forced diuresis or hemodialysis are probably of little value in treating overdosage.

**General Treatment of Overdose**

As in all cases of drug overdosage, respiration, pulse rate, and blood pressure should be monitored. General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered and an adequate airway maintained. If hypotension occurs, it may be combated by the use of vasopressors. Dialysis is of limited value. As with the management of intentional overdosing with any drug, it should be borne in mind that multiple agents may have been ingested.

Flumazenil, a specific benzodiazepine receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with a benzodiazepine is known or suspected. Prior to the administration of flumazenil, necessary measures should be instituted to secure airway, ventilation, and intravenous access. Flumazenil is intended as an adjunct to, not as a substitute for, proper management of benzodiazepine overdose. Patients treated with flumazenil should be monitored for re-sedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. **The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users and in cyclic antidepressant overdose.** The complete flumazenil package insert including CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS should be consulted prior to use.
DOSAGE AND ADMINISTRATION
XANAX XR Tablets may be administered once daily, preferably in the morning. The tablets should be taken intact; they should not be chewed, crushed, or broken.

The suggested total daily dose ranges between 3 to 6 mg/day. Dosage should be individualized for maximum beneficial effect. While the suggested total daily dosages given will meet the needs of most patients, there will be some patients who require doses greater than 6 mg/day. In such cases, dosage should be increased cautiously to avoid adverse effects.

Dosing in Special Populations
In elderly patients, in patients with advanced liver disease, or in patients with debilitating disease, the usual starting dose of XANAX XR is 0.5 mg once daily. This may be gradually increased if needed and tolerated (see Dose Titration). The elderly may be especially sensitive to the effects of benzodiazepines.

Dose Titration
Treatment with XANAX XR may be initiated with a dose of 0.5 mg to 1 mg once daily. Depending on the response, the dose may be increased at intervals of 3 to 4 days in increments of no more than 1 mg/day. Slower titration to the dose levels may be advisable to allow full expression of the pharmacodynamic effect of XANAX XR.

Generally, therapy should be initiated at a low dose to minimize the risk of adverse responses in patients especially sensitive to the drug. Dose should be advanced until an acceptable therapeutic response (ie, a substantial reduction in or total elimination of panic attacks) is achieved, intolerance occurs, or the maximum recommended dose is attained.

Dose Maintenance
In controlled trials conducted to establish the efficacy of XANAX XR Tablets in panic disorder, doses in the range of 1 to 10 mg/day were used. Most patients showed efficacy in the dose range of 3 to 6 mg/day. Occasional patients required as much as 10 mg/day to achieve a successful response.

The necessary duration of treatment for panic disorder patients responding to XANAX XR is unknown. However, periodic reassessment is advised. After a period of extended freedom from attacks, a carefully supervised tapered discontinuation may be attempted, but there is evidence that this may often be difficult to accomplish without recurrence of symptoms and/or the manifestation of withdrawal phenomena.

Dose Reduction
Because of the danger of withdrawal, abrupt discontinuation of treatment should be avoided (see WARNINGS, PRECAUTIONS, DRUG ABUSE AND DEPENDENCE).

In all patients, dosage should be reduced gradually when discontinuing therapy or when decreasing the daily dosage. Although there are no systematically collected data to support a specific discontinuation schedule, it is suggested that the daily dosage be decreased by no
more than 0.5 mg every three days. Some patients may require an even slower dosage reduction.

In any case, reduction of dose must be undertaken under close supervision and must be gradual. If significant withdrawal symptoms develop, the previous dosing schedule should be reinstituted and, only after stabilization, should a less rapid schedule of discontinuation be attempted. In a controlled postmarketing discontinuation study of panic disorder patients which compared this recommended taper schedule with a slower taper schedule, no difference was observed between the groups in the proportion of patients who tapered to zero dose; however, the slower schedule was associated with a reduction in symptoms associated with a withdrawal syndrome. It is suggested that the dose be reduced by no more than 0.5 mg every three days, with the understanding that some patients may benefit from an even more gradual discontinuation. Some patients may prove resistant to all discontinuation regimens.

**Switch from XANAX (immediate-release) Tablets to XANAX XR (extended-release) Tablets**

Patients who are currently being treated with divided doses of XANAX (immediate-release) Tablets, for example 3 to 4 times a day, may be switched to XANAX XR Tablets at the same total daily dose taken once daily. If the therapeutic response after switching is inadequate, the dosage may be titrated as outlined above.

**HOW SUPPLIED**

XANAX XR (extended-release) Tablets are available as follows:

- **0.5 mg** (white, pentagonal-shaped tablets debossed with an "X" on one side and "0.5" on the other side)
  - Bottles of 60   NDC 0009-0057-07

- **1 mg** (yellow, square-shaped tablets debossed with an "X" on one side and "1" on the other side)
  - Bottles of 60   NDC 0009-0059-07

- **2 mg** (blue, round-shaped tablets debossed with an "X" on one side and "2" on the other side)
  - Bottles of 60   NDC 0009-0066-07

- **3 mg** (green, triangular-shaped tablets debossed with an "X" on one side and "3" on the other side)
  - Bottles of 60   NDC 0009-0068-07

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature].

**ANIMAL STUDIES**
When rats were treated with alprazolam at 3, 10, and 30 mg/kg/day (15 to 150 times the maximum recommended human dose) orally for 2 years, a tendency for a dose related increase in the number of cataracts was observed in females and a tendency for a dose related increase in corneal vascularization was observed in males. These lesions did not appear until after 11 months of treatment.

Rx only

Distributed by
Pfizer
Pharmacia & Upjohn Co
Division of Pfizer Inc, NY, NY 10017

LAB-0006-5.0
Revised June 2011
# COMMONWEALTH OF PENNSWOODS

## Driver’s Accident Report

FORWARD THIS REPORT WITHIN 5 DAYS TO THE P DEPARTMENT OF TRANSPORTATION, BUREAU OF HIGHWAY SAFETY AND TRAFFIC ENGINEERING, P.O. Box 2047, Steelton, PW 17105-2047

**Pennwoods Vehicle Code, Section 3747 states:** All reports are confidential, not available as trial evidence

**Date of Accident (Month - Day - Year):** September 4, 2017

**County:** Steelton

**Day of Week:** Monday

**Hour (AM - PM):** 1819

**Check if Hit-Run:** ☐

**Severities:**
- **Was Towing Required?**
  - UNIT 1: ☑ YES ☐ NO
  - UNIT 2: ☑ YES ☐ NO

**Number of Vehicles Involved:** 2

**Number Injured:** 1

**Number Killed:** 0

**Location:**
- **City - Borough - Township:** Webster Street
- **On:** (Street Name or Highway Number)
- **At Intersection With:** no intersection

**Operator’s Name (First, Middle, Last):** Carson Gray

**Date of Birth:** 1/8/1988

**Operator’s License Number and State:** Steelton

**Vehicle License Number and State:** 5064 Yoh Avenue, Steelton

**Owner’s Name (First, Middle, Last):** Same

**Year:** 2016

**Make:** Edison

**Model:** Road Master

**Description of damaged property:**

**Insurance Information:**
- **Company:**
- **Policy No.:**

**Other:**

**Operator’s Name (First, Middle, Last):** Mr. Mrs. Miss

**Date of Birth:** --

**Operator’s License Number and State:** --

**Vehicle License Number and State:** 269 Lyber Road

**Address (Street, City, State, Zip Code):** 269 Lyber Road

**Owner’s Name (First, Middle, Last):** Mr. Mrs. Miss

**Year:** 2016

**Make:** Hurley

**Model:** Road Master

**Address (Street, City, State, Zip Code):** 5064 Yoh Avenue, Steelton

**Description of damaged property:**

**Insurance Information:**
- **Company:**
- **Policy No.:**

**IF MORE VEHICLES/PEDESTRIANS/OCCUPANTS ARE INVOLVED USE ADDITIONAL REPORTS.**

**Persons Involved:**

<table>
<thead>
<tr>
<th>NAME</th>
<th>AGE</th>
<th>SEX</th>
<th>VEH.NO.</th>
<th>INJURY CLASS</th>
<th>ACTIVE RESTRAINT</th>
<th>PASSIVE RESTRAINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CarsonGray</td>
<td>29</td>
<td>2</td>
<td>1</td>
<td>0 - NO INJURY</td>
<td>2</td>
<td>9</td>
</tr>
</tbody>
</table>

**Position:**
- 1 - DRIVER
- 2 - PASSENGER
- 3 - PEDESTRIAN
- 4 - Other

**Passive Restraint:**
- 0 - None
- 1 - Airbag (Deployed)
- 2 - Airbag (Not Deployed)
- 3 - Automatic Seat Belt
- 4 - Child Restraint
- 5 - Motorcycle Helmet
- 6 - Other
- 9 - Unknown

**Active Restraint:**
- 0 - None
- 1 - Shoulder Harness Only
- 2 - Seat Belt Only
- 3 - Combination (Harness & Belt)
- 4 - Child Restraint
- 5 - Motorcycle Helmet
- 6 - Other
- 9 - Unknown

**Insurance Information:**
- **Company:**
- **Policy No.:** STAC 180
<table>
<thead>
<tr>
<th>WEATHER:</th>
<th>ROADWAY:</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Rain</td>
<td>□ Wet</td>
</tr>
<tr>
<td>□ Snow</td>
<td>□ Snowy</td>
</tr>
<tr>
<td>☑ Clear</td>
<td>☑ Dry</td>
</tr>
<tr>
<td>☑ Foggy</td>
<td>☑ Icy</td>
</tr>
<tr>
<td>☑ Other</td>
<td>☑ Rain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VEHICLE NUMBER 1:</th>
<th>VEHICLE NUMBER 2:</th>
</tr>
</thead>
<tbody>
<tr>
<td>INITIAL IMPACT POINT</td>
<td>INITIAL IMPACT POINT</td>
</tr>
<tr>
<td>1-2</td>
<td>7-8</td>
</tr>
<tr>
<td>LEGAL SPEED</td>
<td>LEGAL SPEED</td>
</tr>
<tr>
<td>25 MPH</td>
<td>25 MPH</td>
</tr>
<tr>
<td>ESTIMATED SPEED</td>
<td>ESTIMATED SPEED</td>
</tr>
<tr>
<td>5-10 MPH</td>
<td>0-5 MPH</td>
</tr>
</tbody>
</table>

**INSTRUCTIONS:**
1. Draw Diagram As Clearly As You Can.
2. Show Your Vehicle As Number 1.
3. Label All Streets, Highways, and Landmarks.
4. Draw An Arrow In Circle Below So It Points North.
5. Complete Narrative.

See attached diagram

GIVE A DETAILED DESCRIPTION OF THE ACCIDENT IMMEDIATELY PRIOR TO IMPACT, AT IMPACT, AND IMMEDIATELY AFTER IMPACT, REFER TO VEHICLES BY NUMBERS

Unit 1 was heading west bound on Webster. Unit 1 is an autonomous vehicle. Unit 1 was apparently pulling into a designated Lyber pick up space when the accident occurred. Unit 2 was parked directly in front of said Lyber pick up space. Operator of Unit 2 was seated on vehicle when struck from behind.

Speed of Unit 2 was undetermined, however, this officer discovered that the engine for Unit 2 was engaged at the time of this officer’s arrival. This officer turned Unit 2 off and removed keys. Said keys were placed into an evidence bag for safekeeping.

SIGNATURE

DATE

POLICE INVESTIGATED: ☑ YES ☑ NO

If Yes, Name of Police Department:

STAC 181
JURY INSTRUCTIONS

BELIEVABILITY OF WITNESSES GENERALLY

As judges of the facts, you decide the believability of the witnesses’ testimony. This means that you decide the truthfulness and accuracy of each witness’ testimony and decide whether to believe all, or part, or none of that witness’ testimony. The following are some of the factors that you may and should consider when determining the believability of the witnesses and their testimony:

a. How well could each witness see, hear or know the things about which he or she testified?

b. How well could the witness remember and describe those things?

c. Was the ability of the witness to see, hear, know, remember, or describe those things affected by age or by any physical, mental or intellectual deficiency?

d. Did the witness testify in a convincing manner? How did the witness look, act and speak while testifying?

e. Was the testimony uncertain, confused, self-contradictory or presented in an evasive manner?

f. Did the witness have any interest in the outcome of the case, or any bias, or any prejudice, or any other motive that might have affected his or her testimony?
g. Was a witness’ testimony contradicted or supported by other witnesses’ testimony or other evidence?

h. Does the testimony make sense to you?

i. If you believe some part of the testimony of a witness to be inaccurate, consider whether that inaccuracy cast doubt upon the rest of that same witness’ testimony. This may depend on whether the inaccuracy is in an important matter or in a minor detail.

j. You should also consider any possible explanation for the inaccuracy. Did the witness make an honest mistake or simply forget, or was there a deliberate attempt to present false testimony?

k. If you find that a witness intentionally lied about a significant fact that may affect the outcome of the trial, you may, for that reason alone, choose to disbelieve the rest of that witness’ testimony. But, you are not required to do so.

l. As you decide the believability of each witness’ testimony, you will at the same time decide the believability of other witnesses and other evidence in the case.

m. If there is a conflict in the testimony, you must decide which, if any, testimony you believe is true.

As the only judges of believability and facts in this case, you, the jurors, are responsible to give the testimony of every witness, and all the other evidence, whatever credibility and weight you think it is entitled to receive.

**EXPERT TESTIMONY**

During the trial you have heard testimony from both fact witnesses and expert witnesses. To assist juries in deciding cases such as this one, involving scientific, technical or other specialized knowledge beyond that possessed by a layperson, the law allows an expert witness with special education and experience to present opinion testimony.

An expert witness gives his or her opinion, to a reasonable degree of professional
certainty, based upon the assumption of certain facts. You do not have to accept an expert’s opinion just because he or she is considered an expert in his or her field.

In evaluating an expert witness’ testimony and in resolving any conflicting expert witness’ testimony, you should consider the following:

a. The witness’ knowledge, skill, experience, training and education;

b. Whether you find that the facts the witness relied upon in reaching his or her opinion are accurate; and,

c. All the believability factors I have given to you.

EXPERT OPINION – BASIS FOR OPINION GENERALLY

In general, the opinion of an expert has value only when you accept the facts upon which it is based. This is true whether the facts are assumed hypothetically by the expert, or they come from the expert’s personal knowledge, from some other proper source, or from some combination of these.

WEIGHING CONFLICTING EXPERT TESTIMONY

In resolving any conflict that may exist in the testimony of expert witnesses, you are entitled to weigh the opinion of one expert against that of another. In doing this, you should consider the relative qualifications and reliability of the expert witnesses, as well as the reasons for each opinion and the facts and other matters upon which it was based.

CONFLICTING TESTIMONY

You may find inconsistencies within the testimony of a single witness, or conflicts between the testimony of several witnesses. Conflicts or inconsistencies do not necessarily mean that a witness intentionally lied. Sometimes two or more persons witnessing the same incident see, hear or remember it differently. Sometimes a witness remembers
incorrectly or forgets. If the testimony of a witness seems inconsistent within itself, or if the testimony given by several witnesses conflicts, you should try to reconcile the differences. If you cannot reconcile the differences, you must then decide which testimony, if any, you believe.

**DIRECT AND CIRCUMSTANTIAL EVIDENCE**

The evidence presented to you may be either *direct* or *circumstantial evidence*. Direct evidence is testimony about what a witness personally saw, heard or did. Circumstantial evidence is testimony about one or more facts that logically lead you to believe the truth of another fact. You should consider both *direct* and *circumstantial* evidence in reaching your verdict. You may decide the facts in this case based upon circumstantial evidence alone.

**NEGLIGENCE – DEFINITION**

In this case you must decide whether the Defendant was negligent. I will now explain what negligence is. A person must act in a reasonably careful manner to avoid injuring others. The care required varies according to the circumstances and the degree of danger at a particular time. You must decide how a reasonably careful person would act under the circumstances established by the evidence in this case. A person who does something a reasonably careful person would not do under the circumstances is negligent. A person also can be negligent by failing to act. A person who fails to do something a reasonably careful person would do under the circumstances is negligent.

**BURDEN OF PROOF**

In civil cases, the Plaintiff has the burden of proving his or her claims.

The Plaintiff must prove his or her claims by a legal standard called “a
preponderance of the evidence.” Preponderance of the evidence means the claim is more likely true than not.

If, after considering all the evidence, you find the Plaintiff’s claims are more likely true than not, you must find for the Plaintiff.

Think about an ordinary balance scale with a pan on each side to hold objects. Imagine using the scale as you deliberate in the jury room. Place all the evidence favorable to the Plaintiff in one pan. Place all evidence favorable to the Defendant in the other. If the scales tip, even slightly, to the Plaintiff’s side, then, you must find for the Plaintiff. If, however, the scales tip even slightly on the Defendant’s side, or if the two sides balance, then you must find for the Defendant.

In this case, the Plaintiff has the burden of proving the following claims:

a. The Defendant was negligent;

b. The Defendant’s negligence was a factual cause in bringing about the harms/damages; and,

c. The extent of damages caused by the Defendant’s negligence.

FACTUAL CAUSE

In order for Plaintiff to recover in this case, Defendant's negligent conduct must have been a factual cause in bringing about harm. Conduct is a factual cause of harm when the harm would not have occurred absent the conduct. To be a factual cause, the conduct must have been an actual, real factor in causing the harm, even if the result is unusual or unexpected. A factual cause cannot be an imaginary or fanciful factor having no connection or only an insignificant connection with the harm.

To be a factual cause, Defendant’s conduct need not be the only factual cause. The fact that some other causes concur with the negligence of the Defendant in producing
an injury does not relieve the defendant from liability as long as his or her own negligence is a factual cause of the injury.

CONCURRING CAUSES

Sometimes a person’s negligent conduct combines with other people’s conduct to cause harm.

When a defendant’s negligent conduct combines with the conduct of other persons, the defendant is legally responsible if his or her negligent conduct was one of the factual causes of the harm.

In such a case, Defendant is fully responsible for the harm suffered by Plaintiff regardless of the extent to which Defendant’s conduct contributed to the harm.

COMPARATIVE NEGLIGENCE

Defendant claims that Plaintiff was negligent and Plaintiff’s negligence was a factual cause of Plaintiff’s injury. Defendant has the burden of proving by a fair preponderance of the evidence that Plaintiff was negligent and that the Plaintiff’s negligence was a factual cause of the plaintiff's harm. Plaintiff does not have the burden to prove he was not negligent. The burden is not on Plaintiff to prove his or her freedom from negligence. You must determine whether Defendant has proven that Plaintiff, under all the circumstances, failed to use reasonable care for his or her own protection.

ASSUMPTION OF THE RISK

Assumption of the risk arises when a plaintiff consciously decides to tempt fate and face an appreciated danger. In order to prove the affirmative defense of assumption of the risk, the defense must demonstrate that the plaintiff saw, understood, and voluntarily faced the risk that caused injury. Assumption of the risk may be express or implied.
DEPOSITION TESTIMONY

The testimony of a witness, who for some proper reason cannot be present to testify in person, may be presented in this form. Such testimony is given under oath and in the presence of attorneys for the parties, who question the witness. A court reporter takes down everything that is said and then transcribes the testimony. The use of videotape permits you to see and hear the witness as he appeared and testified under questioning by counsel. This form of testimony is entitled to neither more nor less consideration by the jury because of the manner of its submission.
IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF STEELTON

CARSON GRAY;

Plaintiff,

v.

EDISON AUTOMOBILE COMPANY;

Defendant.

VERDICT SLIP

You must decide whether Edison Automobile Company’s negligence on September 4, 2017 was a factual cause of harm.

I will now read you the questions on the verdict form that you must answer to arrive at a proper verdict:

**Question 1:**

Was Edison Automobile Company negligent?

Yes ___ No ___

**Question 2:**

Was the negligence of Edison Automobile Company a factual cause of any harm to Carson Gray?

Yes ___No ___

If you answer Question 2 “Yes,” go to Question 3.

If you answer Question 2 “No,” do not answer any more questions.
Question 3:
Was Carson Gray negligent?
Yes ___ No ___
If you answer Question 3 “Yes,” go to Question 4.
If you answer Question 3 “No,” do not answer any more questions.

Question 4:
Was the negligence of Carson Gray a factual cause of any harm to Carson Gray?
Yes ___ No ___
If you answer Question 4 “Yes,” go to Question 5.
If you answer Question 4 “No,” do not answer any more questions.

Question 5:
If you find that Carson Gray was negligent, taking the combined negligence that was a factual cause of harm to Carson Gray as 100%, what percentage of that negligence do you attribute to Carson Gray and what percentage do you attribute to Edison Automobile Company?

Percentage of negligence attributable to Carson Gray _____%
Percentage of negligence attributable to Edison Automobile Company _____%  
Total 100%

Advise the court officer that you have reached a verdict.