Date: October 1, 2020 Time: 10:30 a.m.

EMERGENCY ORDER OF SUSPENSION AND SHOW CAUSE:

Thomas Harold Tvedten, M.D.

BEFORE THE ARKANSAS STATE MEDICAL BOARD

IN THE MATTER OF: THOMAS HAROLD TVEDTEN, M.D.

EMERGENCY ORDER OF SUSPENSION AND NOTICE OF HEARING

Pursuant to ACA §25-15-201, and ACA §25-15-211(c), *et seq.*, of the Administrative Procedure Act, and ACA §17-95-410 of the Medical Practices Act, the Arkansas State Medical Board issues the following Emergency Order of Suspension and Notice of Hearing charging Thomas Harold Tvedten, M.D., with alleged violations of the Medical Practices Act, more specifically, A.C.A. § 17-95-409(a)(2)(g) that is, he exhibited gross negligence and ignorant malpractice in this care of a patient identified as TS.

I.

Thomas Harold Tvedten, M.D., is a licensed physician in the State of Arkansas under the provisions of the Medical Practices Act.

II.

Thomas Harold Tvedten, M.D., exhibited gross negligence and ignorant malpractice in the manner in which he failed to properly evaluate a patient identified as TS.

III.

Thomas Harold Tvedten, M.D., exhibited gross negligence and ignorant malpractice in the evaluation, diagnosing of the patient identified as TS, a minor, and for certifying the minor child for a medical marijuana card.

IV.

Thomas Harold Tvedten, M.D., exhibited gross negligence and ignorant malpractice in his care and treatment of a patient identified as TS.

V.

Pursuant to the Administrative Procedure Act, A.C.A. 25-15-211(c) upon an affirmative vote of the majority of the Arkansas State Medical Board, the Board finds that the acts of Thomas Harold Tvedten, M.D., described herein above, exhibits a danger to the public and his continued practice of medicine. Therefore, the license to practice medicine in the State of Arkansas of Thomas Harold Tvedten, M.D., is suspended on an emergency basis, pending a disciplinary hearing in this matter or further Orders of the Board.

WHEREFORE, IT IS CONSIDERED, ORDERED AND ADJUDGED, by the Arkansas State Medical Board that the license to practice medicine in the State of Arkansas of Thomas Harold Tvedten, M.D., is suspended on an emergency basis, pending a disciplinary hearing in this matter or further Orders of the Board.

IT IS FURTHER CONSIDERED, ORDERED, AND ADJUDGED, by the Arkansas State Medical Board, that a hearing should be conducted to determine whether Thomas Harold Tvedten, M.D., has violated the Medical Practices Act. If it is found that he has, in fact, violated the Medical Practices Act, then the Board should determine whether the license of Thomas Harold Tvedten, M.D., to practice medicine in the State of Arkansas, should be revoked or suspended, or whether other sanctions should be imposed pursuant to the authority granted the Board in ACA § 17-95-410 and ACA§17-95-704(c)(1). Said hearing will be conducted on the 1 day of October, 2020, at 10:30 o'clock A.m. at a meeting of the Arkansas State Medical Board at the offices of the Board, 1401 W. Capitol, Suite 340, Little Rock, Pulaski County, Arkansas.

Thomas Harold Tvedten, M.D., is hereby advised that he may be represented by counsel at the hearing, and that she will be given the opportunity to examine all of the evidence offered to the Board, cross-examine witnesses, and offer evidence and witnesses in her own behalf. **Thomas Harold Tvedten, M.D., is further advised that any additional records and/or exhibits that you as a Respondent wish to present to the Board at your hearing MUST be supplied to the Board no later than 20 days prior to the hearing date. Failure to do so can result in the Board refusal to allow the information or documentation to be presented by the Respondent. Any and all documents submitted after the 20 day deadline are subject to the Chairman's discretion regarding admission of those documents to the Board. Further, any submission of documents after the 20 day deadline are provided with the knowledge of the respondent that the Board and/or its expert may not have time to review those documents prior to or during the hearing.**

IT IS SO ORDERED.

ARKANSAS STATE MEDICAL BOARD

BY: Sylvia Simon MD
Sylvia D. Simon, M.D.

DATE: 8/13/2020

APPROVED AS TO FORM:

Kevin M. O'Dwyer
Attorney for Arkansas State Medical Board

Expert Reviewer's Report

Expert File Review RE: Dr. Thomas Harold Tvedten, M.D. and care of minor patient T.S.

The board has asked for review of Dr. Tvedten and his issue of a medical marijuana physician written certification for a minor, age 12, after receiving complaint from two child and adolescent psychiatrists who claim this is a violation of the Medical Practice Act.

In order to meet criteria for a medical marijuana certification, a patient must meet criteria for specific diagnoses of which THREE may be considered to fall under the category of psychiatric in nature—PTSD, Tourette's syndrome, and Alzheimer's disease. Of these three diagnosis, Dr. Tvedten is claiming to have made a diagnosis of for the minor, T.S., on the date February 25, 2020. He is basing this diagnosis on a SCREENING tool for PTSD, which is also a self-administered tool meant for adults. It is not intended for use in child and adolescent populations, and if Dr. Tvedten worked in the area of psychiatry, it is likely he would have realized this. Screening tools are meant to be used along with a diagnostic evaluation performed by a clinician. They are not to replace a psychiatric evaluation. The claim by patient and her step mother is that the patient is traumatized by abuse that occurred at the hands of her biological mother 6 years ago. It is worth noting that on review of the medical records, the patient's family reports that the patient has not had any significant interaction of any kind with biological mother since the age of 4 when she went into custody with father, step mother, and siblings. The family also consistently denies any history of abuse of any kind. The patient was 12 at the time of evaluation which would have put her at age of 6 for the reported abuse. These are inconsistent facts that could have potentially been uncovered during a true psychiatric diagnostic evaluation.

It is also clearly stated that the department shall not issue a registry card to anyone under 18 unless physician issuing certificate has explained risks and benefits to guardian and the guardian consents IN WRITING to allowing the minor to use it, assisting the minor, and controlling the acquisition and dosing of the marijuana.

On review of Dr. Tvedten's records, it does not appear that this last requirement was met. There is no WRITTEN documentation of the guardian agreeing to assist the minor in use of cannabis product, and agreeing to control the acquisition and dosing of the cannabis product. The absence of this documentation would put him in violation of certification criteria for a minor. He does mention this as though a conversation occurred verbally in his response to the complaint, but again, it is not documented in his medical records.

With regards to determining whether or not Dr. Tvedten violated the Medical Practice Act by acting in gross negligence, I would concur with doctors Hogan's and Thomas' concern that this certification for marijuana use in a 12-year-old child is a significant deviation from the standard of care in the field of child and adolescent psychiatry. Dr. Tvedten's claim that millions of Americans use marijuana products on a daily basis may in fact be true, however, the current population of children and adolescents with severe mental illnesses are considered to be at *significant* risk of worsening symptoms with exposure to marijuana/cannabis. This is in no way a political or opinion driven comment, but rather, based entirely on sound data in the field

of psychiatry. The psychiatrists reference a specific peer reviewed and published study in their complaints that supports this, though there are hundreds of similar ones available for review if so inclined.

In addition, it needs to be pointed out that Dr. Tvedten notes on average spending 20 minutes with patients who are seeking approval for medical marijuana certification and his visit with T.S. and her mom (which is actually her step mother) was "somewhat longer". I spent nearly 3 hours reviewing the multiple medical records of the patient for this file review. To consider that he spent maybe 20-30 minutes reviewing medical records (which also show NO history or suggestion of diagnosis o ppears cursory and inadequate. In day to day practice I can also report that an initial psychiatric evaluation performed in an outpatient setting generally takes anywhere from 45-60 minutes by professionals trained in this specific area of medicine.

Sometimes during the practice of medicine, it may occur for a physician to try something that is not completely "mainstream", however, these are rarities and certainly are not taken lightly, often consulting other physicians in that area of specialty. If Dr. Tvedten had in fact communicated with any of the psychiatrists who have previously taken care of this patient, he may have been able to more fully appreciate the complexity and difficulty in treating this chronically suicidal and homicidal child. His assumption that multiple child and adolescent psychiatrists had somehow misdiagnosed and inappropriately treated a vulnerable child is off mark and short sighted. In addition to his desire to try something "out of the box" given her lack of reported responses to other interventions, Dr. Tvedten made no mention as to any kind of follow up with the patient, outside of potentially recertifying her in another 12 months. This would be an egregious level of negligence for a psychiatrist to prescribe a controlled substance that significant alters brain neurotransmitters without some kind of timely follow-up. (think 2-6 weeks, not 12 months.)

He also makes reference that trileptal
is an anticonvulsant and marijuana has been shown to be effective in managing pediatric seizures disorders. The child has no diagnosis of a seizure disorder (by him or a neurologist) and exposes his lack of psychopharmacology knowledge given its use in psychiatry as a mood stabilizer—not as an anticonvulsant.

His claim that he does not prescribe the marijuana makes little difference in his role in this child's use of cannabis products. He knows the step-mother uses marijuana and wants the patient to use it as well. His certification letter is an absolute endorsement for his approval for the child to use cannabis products.

In closing, it is with absolute certainty that I can say Dr. Tvedten has acted in a grossly negligent manner in attempting to care for this young child by making a diagnosis o as, per his own words, a doctor with a "primary medical practice as an abortion provider" and medical marijuana certifier. Neither of these areas of medicine focus on the diagnosis and management of child and adolescent psychiatric disorders.

Sincerely,

Kristi Kindrick, M.D.
Board Certified Psychiatrist
Fort Smith, AR

7/21/20

Exhibits Submitted by Dr. Tvedten's Attorney

AFFIDAVIT OF JANET RILEY CATHEY M.D.

I, Janet Cathey M.D., being duly Sworn, depose and state:

To the Members of the Arkansas State medical Board:

I am writing on behalf of Dr. Tom Tvedten regarding his upcoming appearance before the Arkansas State medical Board.

I have been licensed in the practice of medicine in the state of Arkansas without restriction since February 1982. I am Board certified in Obstetrics and Gynecology and a fellow in ACOG. I was in private practice in Little Rock for 23 years. I served on the faculty in the Dept of Obstetrics-Gynecology at UAMS from 2013-2018. I now limit my practice to Reproductive Health and Transgender Health and Education through Planned Parenthood Great Plains in Little Rock.

Through each of these areas of practice and teaching, I have had the many opportunities to interact with Dr. Tvedten in a variety of situations. Never in any actions with Dr. Tvedten have I not found him to be anything short of fully competent and never anything but professional.

I now refer to Dr. Tvedten on a regular basis and do so knowing he will provide my patients with quality and compassionate medical care. He is always current in his practice standards and uses good judgment in patient management. He is very good at what he does not only technically but more importantly, he is good at evaluation and education of patients in a reproductive health setting. I always receive positive feedback from patients he has cared for.

In summary, I have known Dr. Tvedten for many years and interacted in many situations and from several different perspectives. He has very high medical practice standards and delivers a high quality of medical care.

Sincerely,

Janet Riley Cathey, M.D.

Janet Riley Cathey, MD
Planned Parenthood Great Plains
1501 Aldersgate Road, Little Rock AR, 72205
Janet.Cathey@PPgreatplains.org 501 350-2250

VERIFICATION

STATE OF **ARKANSAS**)
)
COUNTY OF **CLEBURNE**)

I, **JANET CATHEY M.D**, after first being duly sworn upon oath state that the facts contained in the above and foregoing Affidavit are true and correct to the best of my knowledge and belief.

Janet Cathey, M.D.
JANET CATHEY M.D

Subscribed and sworn to before me this **10** day of **September** 2020.

William Z. White
Notary Public

My commission expires: **03-10-2024**

[SEAL]

WILLIAM Z. WHITE
Notary Public-Arkansas
Cleburne County
My Commission Expires 03-10-2024
Commission # 12398224

Arkansas Medical Marijuana Amendment of 2016

As revised through 2017 General and First Extraordinary Sessions

§ 1. Short title.

This amendment shall be known and cited as the "Arkansas Medical Marijuana Amendment of 2016".

[As added by Const. Amend. 98.]

§ 2. Definitions.

As used in this amendment:

(1) "Acquire" or "acquisition" means coming to possess marijuana by means of any legal source herein authorized, not from an unauthorized source, and in accordance with this amendment and any rules promulgated under this amendment;

(2) "Assist" or "assisting" means helping a qualifying patient make medical use of marijuana by enabling the medical use by any means authorized under this amendment;

(3) "Cardholder" means a qualifying patient, a dispensary agent, a cultivation facility agent, or a designated caregiver;

(4) "Cultivation facility" means an entity that:

(A) Has been licensed by the Medical Marijuana Commission under § 8 of this amendment; and

(B) Cultivates, prepares, manufactures, processes, packages, sells to and delivers usable marijuana to a dispensary;

(5) "Cultivation facility agent" means an employee, supervisor, or agent of a cultivation facility who:

(A) Is twenty-one (21) years of age or older;

(B) Works at the cultivation facility; and

(C) Has registered with the Alcoholic Beverage Control Division under § 9 of this amendment;

(6) (A) "Designated caregiver" means a person who is at least twenty-one (21) years of age, has not been convicted of an excluded felony offense, has agreed to assist a physically disabled qualifying patient with the medical use of marijuana, and who has registered with the Department of Health under § 5 of this amendment.

(B) "Designated caregiver" includes without limitation a parent:

(i) Of a qualifying patient who is under the age of eighteen (18); and

(ii) Required to register as a designated caregiver under this amendment.

(C) "Designated caregiver" shall not include a member of the Arkansas National Guard or the United States military;

(7) "Dispensary" means an entity that has been licensed by the Medical Marijuana Commission under § 8 of this amendment;

(8) "Dispensary agent" means:

(A) An employee, supervisor, volunteer, or agent of a dispensary who:

(i) Is twenty-one (21) years of age or older;

(ii) Works at the dispensary; and

(iii) Has registered with the division under § 9 of this amendment; and

(B) An owner, officer, or board member of a dispensary who has registered with the division under § 8 of this amendment;

(9) "Enclosed, locked facility" means a room, greenhouse, or other enclosed area equipped with locks or other security devices that permit access only by an authorized individual;

(10) "Excluded felony offense" means:

(A) (i) (a) A felony offense as determined by the jurisdiction where the felony offense occured.

(b) The Medical Marijuana Commission, the Department of Health, or the Alcoholic Beverage Control Division shall determine whether an offense is a felony offense based upon a review of the relevant court records concerning the conviction for the offense.

(ii) An offense that has been sealed by a court or for which a pardon has been granted is not considered an excluded felony offense; or

(B) A violation of a state or federal controlled-substance law that was classified as a felony in the jurisdiction where the person was convicted, but not including:

(i) An offense for which the sentence, including any term of probation, incarceration, or supervised release, was completed ten (10) or more years earlier; or

(ii) An offense that has been sealed by a court or for which a pardon has been granted;

(11) "Medical use" means the acquisition, possession, use, delivery, transfer, or

transportation of marijuana or paraphernalia relating to the administration of marijuana to treat or alleviate a qualifying patient's qualifying medical condition or symptoms associated with the qualifying patient's qualifying medical condition;

(12) "Physician" means a doctor of medicine or doctor of osteopathic medicine who holds a valid, unrestricted, and existing license to practice in the state of Arkansas and has been issued a registration from the United States Drug Enforcement Administration to prescribe controlled substances;

(13) "Qualifying medical condition" means one (1) or more of the following:

(A) Cancer, glaucoma, positive status for human immunodeficiency virus/acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Tourette's syndrome, Crohn's disease, ulcerative colitis, post-traumatic stress disorder, severe arthritis, fibromyalgia, Alzheimer's disease, or the treatment of these conditions;

(B) A chronic or debilitating disease or medical condition or its treatment that produces one (1) or more of the following: cachexia or wasting syndrome; peripheral neuropathy; intractable pain, which is pain that has not responded to ordinary medications, treatment, or surgical measures for more than six (6) months; severe nausea; seizures, including without limitation those characteristic of epilepsy; or severe and persistent muscle spasms, including without limitation those characteristic of multiple sclerosis; and

(C) Any other medical condition or its treatment approved by the Department of Health under § 4 of this amendment;

(14) (A) "Qualifying patient" means a person who has been diagnosed by a physician as having a qualifying medical condition and who has registered with the department under § 5 of this amendment.

(B) "Qualifying patient" shall not include a member of the Arkansas National Guard or the United States military;

(15) "Registry identification card" means a document issued by the department or the division that identifies a person as a qualifying patient, a dispensary agent, a cultivation facility agent, or a designated caregiver;

(16) "Sealed" means to expunge, remove, sequester, and treat as confidential the record or records of a felony offense;

(17) (A) "Usable marijuana" means the stalks, seeds, roots, dried leaves, flowers, oils, vapors, waxes, and other portions of the marijuana plant and any mixture or preparation thereof.

(B) "Usable marijuana" does not include the weight of any ingredients other than marijuana that are combined with marijuana and prepared for consumption as food or drink;

(18) "Visiting qualifying patient" means a patient with a qualifying medical condition who

is not a resident of Arkansas or who has been a resident of Arkansas for less than thirty (30) days and who is in actual possession of a registry identification card or its equivalent that is issued under the laws of another state, district, territory, commonwealth, or insular possession of the United States and pertains to a qualifying medical condition under this section;

(19) (A) "Written certification" means a document signed by a physician stating that in the physician's professional opinion, after having completed an assessment of the qualifying patient's medical history and current medical condition made in the course of a physician-patient relationship, the qualifying patient has a qualifying medical condition.

(B) A written certification shall specify the qualifying patient's qualifying medical condition, which also shall be noted in the physician's records.

(C) A physician shall not issue a written certificate to a patient based on an assessment performed through telemedicine.

(D) A written certification is not a medical prescription.

(20) (A) "Current use of marijuana" means use of marijuana that justifies the good faith belief of an employer that an applicant or employee is engaging in the use of marijuana.

(B) "Current use of marijuana" is presumed when a positive test result for marijuana occurs;

(21) "Employee" means an individual employed by an employer, but does not include:

(A) An individual employed by his or her parents, spouse, or child;

(B) An individual participating in a specialized employment training program conducted by a nonprofit sheltered workshop or rehabilitation facility;

(C) An individual employed outside the State of Arkansas; or

(D) An independent contractor;

(22) "Employer" means an entity that who employs nine (9) or more employees in the State of Arkansas in twenty (20) or more calendar weeks in the current or preceding calendar year;

(23) (A) "Good faith belief" means reasonable reliance on a fact, or that which is held out to be factual, without intent to deceive or be deceived and without reckless or malicious disregard for the truth.

(B) "Good faith belief" does not include a belief formed with gross negligence.

(C) "Good faith belief" may be based on any of the following:

(i) Observed conduct, behavior, or appearance;

(ii) Information reported by a person believed to be reliable, including without limitation a report by a person who witnessed the use or possession of marijuana or marijuana paraphernalia by an applicant or employee in the workplace;

(iii) Written, electronic, or verbal statements from the employee or other persons;

(iv) Lawful video surveillance;

(v) A record of government agencies, law enforcement agencies, or courts;

(vi) A positive test result for marijuana;

(vii) A warning label, usage standard, or other printed material that accompany instructions for usable marijuana;

(viii) Information from a physician, medical review officer, or a dispensary;

(ix) Information from reputable reference sources in print or on the internet;

(x) Other information reasonably believed to be reliable or accurate; or

(xi) Any combination of the items listed in subdivisions (23)(C)(i)-(x) of this section;

(24) "Positive test result for marijuana" means a result that is at or above the cutoff concentration level established by the United States Department of Transportation or the Arkansas laws regarding being under the influence, whichever is lower;

(25) (A) "Safety sensitive position" means any position involving a safety sensitive function pursuant to federal regulations governing drug and alcohol testing adopted by the United States Department of Transportation or any other rules, guidelines, or regulations adopted by any other federal or state agency.

(B) "Safety sensitive position" also means any position designated in writing by an employer as a safety sensitive position in which a person performing the position while under the influence of marijuana may constitute a threat to health or safety, including without limitation a position:

(i) That requires any of the following activities:

(a) Carrying a firearm;

(b) Performing life-threatening procedures;

(c) Working with confidential information or documents pertaining to criminal investigations; or

(d) Working with hazardous or flammable materials, controlled substances, food, or medicine; or

(ii) In which a lapse of attention could result in injury, illness, or death, including without limitation a position that includes the operating, repairing, maintaining, or monitoring of heavy equipment, machinery, aircraft, motorized watercraft, or motor vehicles as part of the job duties; and

(26) (A) "Under the influence" means symptoms of the current use of marijuana that may negatively impact the performance of the job duties or tasks or constitute a threat to health or safety.

(B) "Under the influence" includes without limitation:

(i) Symptoms of the applicant's or employee's speech, walking, standing, physical dexterity, agility, coordination, actions, movement, demeanor, appearance, clothing, odor,

or other irrational or unusual behavior that are inconsistent with the usual conduct of the applicant or employee;

(ii) Negligence or carelessness in operating equipment, machinery, or production or manufacturing processes;

(iii) Disregard for safety;

(iv) Involvement in an accident that results in:

(a) Damage to equipment, machinery, or property;

(b) Disruption of a production or manufacturing process; or

(c) An injury; or

(v) Other symptoms causing a reasonable suspicion that the current use of marijuana may negatively impact the performance of the job duties or tasks or constitute a threat to health or safety.

[As added by Const. Amend. 98; as amended by Acts 2017, No. 5, § 1, No. 438, § 1, No. 479, §§ 1 & 2, No. 544, § 1, No. 593, §§ 1 & 2.]

§ 3. Protections for the medical use of marijuana.

(a) A qualifying patient or designated caregiver in actual possession of a registry identification card shall not be subject to arrest, prosecution, or penalty in any manner or denied any right or privilege, including without limitation a civil penalty or disciplinary action by a business, occupational, or professional licensing board or bureau, for the medical use of marijuana in accordance with this amendment if the qualifying patient or designated caregiver possesses not more than two and one-half ounces (2 1/2 oz.) of usable marijuana.

(b) (1) A qualifying patient or designated caregiver is presumed to be lawfully engaged in the medical use of marijuana in accordance with this amendment if the qualifying patient or designated caregiver is in actual possession of a registry identification card and possesses an amount of usable marijuana that does not exceed the amount allowed under this amendment.

(2) The presumption made in subdivision (b)(1) of this section may be rebutted by evidence that conduct related to marijuana was not for the purpose of treating or alleviating the qualifying patient's qualifying medical condition or symptoms associated with the qualifying medical condition in accordance with this amendment.

(c) A qualifying patient or designated caregiver shall not be subject to arrest, prosecution, or penalty in any manner or denied any right or privilege, including without limitation a civil penalty or disciplinary action by a business, occupational, or professional licensing board or bureau, for giving, or offering to give, up to two and one-half ounces (2 1/2 oz.) of usable marijuana to a qualifying patient or designated caregiver for the qualifying patient's medical use when nothing of value is transferred in return.

(d) A designated caregiver is not prohibited from receiving compensation or reimbursement

of expenses from a qualifying patient for assisting a qualifying patient with the medical use of marijuana.

(e) A dispensary may:

(1) Accept marijuana seedlings, plants, or usable marijuana from:

(A) Cultivation facilities;

(B) Other dispensaries in Arkansas; and

(C) If permissible under federal law, out-of-state dispensaries;

(2) Transfer or sell marijuana seedlings, plants, or usable marijuana to:

(A) Cultivation facilities;

(B) Other dispensaries in Arkansas; and

(C) If permissible under federal law, out-of-state dispensaries; and

(3) Accept marijuana seeds from any individual lawfully entitled to possess marijuana seeds, seedlings, or plants under the laws of the state in which the individual resides.

(f) (1) A school or landlord shall not refuse to enroll, refuse to lease to, or otherwise penalize an individual solely for his or her status as a qualifying patient or designated caregiver unless doing so would put the school or landlord in violation of federal law or regulations.

(2) For the purposes of medical care, including without limitation organ transplants, a qualifying patient's authorized use of marijuana in accordance with this amendment is considered the equivalent of the authorized use of any other medication used at the direction of a physician and does not constitute the use of an illicit substance.

(3) (A) An employer shall not discriminate against an applicant or employee in hiring, termination, or any term or condition of employment, or otherwise penalize an applicant or employee, based upon the applicant's or employee's past or present status as a qualifying patient or designated caregiver.

(B) A cause of action shall not be established against an employer based upon, and an employer is not prohibited from, any of the following actions:

(i) Establishing and implementing a substance abuse or drug-free workplace policy that may include a drug testing program that complies with state or federal law and taking action with respect to an applicant or employee under the policy;

(ii) Acting on the employer's good faith belief that a qualifying patient;

(a) Possessed, smoked, ingested, or otherwise engaged in the use of marijuana while on the premises of the employer or during the hours of employment; or

(b) Was under the influence of marijuana while on the premises of the employer or during the hours of employment, provided that a positive test result for marijuana cannot provide the sole basis for the employer's good faith belief; or

(iii) Acting to exclude a qualifying patient from being employed in or performing a safety sensitive position based on the employer's good faith belief that the qualifying patient was engaged in the current use of marijuana.

(C) The authorized or protected actions of an employer under this subdivision (f)(3) include without limitation:

(i) Implementing, monitoring, or taking measures to assess, supervise, or control the job performance of an employee;

(ii) Reassigning an employee to a different position or job duties;

(iii) Placing an employee on paid or unpaid leave; (iv) Suspending or terminating an employee;

(v) Requiring an employee to successfully complete a substance abuse program before returning to work;

(vi) Refusing to hire an applicant; or

(vii) Any combination of the actions listed in subdivisions (f)(3)(C)(i) - (f)(3)(C)(vi) of this section.

(D) (i) Damages established for an employment discrimination claim based on an applicant's or employee's past or present status as a qualifying patient or designated caregiver in violation of this amendment shall be limited to the damages available for an employment discrimination claim under § 16-123-107(c) of the Arkansas Civil Rights Act of 1993, § 16-123-101 et seq., including the statutory limits provided under § 16-123-107(c)(2)(A)(i)-(v).

(ii) Liability for back pay shall not accrue from a date more than two (2) years prior to the filing of an action.

(iii) Damages under this subdivision (f)(3) shall not duplicate or increase an award for damages over the statutory limit allowed by state law or federal law existing on January 1, 2017, whichever is lower.

(E) An action based on employment discrimination in violation of this subdivision (f)(3) shall be brought within one (1) year of the occurrence of the alleged discrimination.

(F) An individual employee, agent of the employer, or employee of the agent of the employer is not liable for any violation of this subdivision (f)(3) that the employer is found to have committed.

(G) This amendment does not waive the sovereign immunity of the State of Arkansas.

(g) A person otherwise entitled to custody of, or visitation or parenting time with, a minor shall not be denied custody, visitation, or parenting time solely for conduct allowed under this amendment, nor shall there be:

(1) A finding of abuse solely for conduct allowed under this amendment; or

(2) A presumption of neglect or child endangerment for conduct allowed under this amendment.

(h) (1) A physician shall not be subject to arrest, prosecution, or penalty in any manner or denied any right or privilege, including without limitation a civil penalty or disciplinary action by the Arkansas State Medical Board or by any other business, occupational, or professional licensing board or bureau, solely for providing a written certification.

(2) Subdivision (g)(1) of this section does not prevent a professional licensing board from sanctioning a physician for failing to properly evaluate a patient's medical condition or for otherwise violating the applicable physician-patient standard of care.

(i) A person shall not be subject to arrest, prosecution, or penalty in any manner or denied any right or privilege, including without limitation a civil penalty or disciplinary action by a business, occupational, or professional licensing board or bureau, for providing a qualifying patient or designated caregiver with marijuana paraphernalia for purposes of facilitating the qualifying patient's medical use of marijuana.

(j) Any marijuana, marijuana paraphernalia, licit property, or interest in licit property, that is possessed, owned, or used exclusively in connection with the medical use of marijuana as allowed under this amendment, or property incidental to such use, shall not be seized or forfeited.

(k) A person shall not be subject to arrest, prosecution, or penalty in any manner or denied any right or privilege, including without limitation a civil penalty or disciplinary action by a business, occupational, or professional licensing board or bureau, simply for being in the presence or vicinity of the medical use of marijuana as allowed under this amendment or for directly assisting a physically disabled qualifying patient with the medical use of marijuana.

(l) (1) A registry identification card or its equivalent that is issued under the laws of another state, district, territory, commonwealth, or insular possession of the United States that allows a visiting qualifying patient to possess or use marijuana for medical use in the jurisdiction of issuance has the same force and effect when held by a visiting qualifying patient as a registry identification card issued by the Department of Health if the same qualifying medical condition exists.

(2) (A) A visiting qualifying patient may obtain marijuana from a dispensary upon producing evidence of his or her registry identification card or its equivalent that is issued under the laws of another state, district, territory, commonwealth, or insular possession of the United States.

(B) The department shall promulgate necessary rules concerning a visiting qualifying patient obtaining marijuana from a dispensary.

(m) A pharmacist shall not be subject to arrest, prosecution, or penalty in any manner or denied any right or privilege, including without limitation a civil penalty or disciplinary action by the Arkansas State Board of Pharmacy or by any other business, occupational, or

professional licensing board or bureau, solely for performing his or her duties as a pharmacist consultant for a registered dispensary.

[As added by Const. Amend. 98; Acts 2017, No. 593, § 3, No. 1024, § 1.]

§ 4. Qualifying patient -- Administration and enforcement -- Rules.

(a) (1) The Department of Health shall administer and enforce the provisions of this amendment concerning qualifying patients, qualifying medical conditions, and designated caregivers, including without limitation the issuance of a registry identification card to a qualifying patient and designated caregiver.

(2) The department shall adopt rules necessary to:

(A) Carry out the purposes of this amendment; and

(B) Perform its duties under this amendment.

(3) Rules adopted under this section are rules as defined in the Arkansas Administrative Procedure Act, § 25-15-201 et seq.

(4) (A) The Department of Health shall require each applicant for a designated caregiver registry identification card to apply for or authorize the Department of Health to obtain state and national criminal background checks to be conducted by the Identification Bureau of the Department of Arkansas State Police and the Federal Bureau of Investigation.

(B) The criminal background checks shall conform to the applicable federal standards and shall include the taking of fingerprints.

(C) The applicant shall authorize the release of the criminal background checks to the Department of Health and shall be responsible for the payment of any fee associated with the criminal background checks.

(D) Upon completion of the criminal background checks, the Identification Bureau of the Department of Arkansas State Police shall forward to the Department of Health all information obtained concerning the applicant.

(b) Not later than one hundred eighty (180) days after the effective date of this amendment, the department shall adopt rules governing:

(1) The manner in which the department considers applications for and renewals of registry identification cards;

(2) Labeling and testing standards for marijuana distributed to qualifying patients, including a warning label on all marijuana for medical use that is processed or sold for smoking that communicates the health and safety risks associated with smoking and a list of places and conditions in which smoking marijuana for medical use is illegal in the State of Arkansas; and

(3) Any other matters necessary for the department's fair, impartial, stringent, and comprehensive administration of this amendment.

(2) One (1) dispensary.

(m) (1) (A) A dispensary licensed under this section may acquire, possess, manufacture, process, prepare, deliver, transfer, transport, supply, and dispense marijuana, marijuana paraphernalia, and related supplies and educational materials to a qualifying patient or designated caregiver, but shall not supply, possess, manufacture, deliver, transfer, or sell marijuana paraphernalia that requires the combustion of marijuana to be properly utilized, including pipes, water pipers, bongs, chillums, rolling papers, and roach clips.

(B) A dispensary licensed under this section shall:

(i) Make marijuana vaporizers available for sale to qualifying patients; and

(ii) Provide educational materials about medical marijuana methods of ingestion to qualifying patients and designated caregivers, including without limitation:

(a) Warnings on the potential health risks of smoking or combusting marijuana; and

(b) Information on potential health benefits of vaporizing marijuana compared to smoking or combusting.

(2) (A) A dispensary may receive compensation for providing the goods and services allowed by this section.

(B) A dispensary may contract with a transporter, distributer, or processer to extent of the license of the transporter, 1 distributer, or processer.

(3) (A) A dispensary may grow or possess:

(i) Fifty (50) mature marijuana plants at any one (1) time plus seedlings; and

(ii) All usable marijuana derived from the plants under subdivision (m)(3)(A)(i) of this section or predecessor plants.

(B) A dispensary may contract with a cultivation facility to cultivate one (1) or more mature marijuana plants the dispensary is permitted to grow.

(4) (A) (i) A cultivation facility may cultivate and possess usable marijuana in an amount reasonably necessary to meet the demand for and needs of qualifying patients as determined by the commission with the assistance of the Department of Health.

(ii) However, a cultivation facility shall not sell marijuana in any form except to a dispensary or other cultivation facility.

(B) A cultivation facility may also possess marijuana seeds.

(C) The commission with the assistance of the Department of Health shall promulgate rules determining the amount of marijuana reasonably necessary under subdivision (m)(4)(A) of this section.

(5) (A) A cultivation facility may receive compensation for providing the goods and services allowed by this section.

(B) A cultivation facility may contract with a transporter, distributer, or processer to extent of the license of the transporter, distributer, or processer.

(n) (1) A dispensary license and cultivation facility license shall expire on June 30 of each calendar 7 year and are renewable on or before June 30 of each calendar year for the 8 fiscal year beginning July 1.

(2) The commission shall issue a renewal dispensary license or a renewal cultivation facility license within ten (10) days to any entity who complies with the requirements contained in this amendment, including without limitation the payment of a renewal fee.

(o) The commission may charge a reasonable fee as established by rule for the issuance of a renewal license.

(p) The commission and the division may collect fines or fees for any violation of a rule adopted under this section.

(q) (1) A license for a dispensary or cultivation facility shall only be issued to a natural person.

(2) A license issued for a dispensary or cultivation facility shall be transferable only to a natural person upon approval of the commission.

(r) Data or records submitted to the division or commission under rules adopted under this amendment may be shared with the Department of Health and the State Insurance Department for purposes of the Arkansas all-payer claims database established under § 23-61-901 et seq.

(s) (1) A dispensary shall appoint a pharmacist consultant who is a pharmacist licensed with the Arkansas State Board of Pharmacy.

(2) A pharmacist consultant shall:

(A) Register as a dispensary agent under this amendment and follow all procedures;

(B) Develop and provide training to other dispensary agents at least one (1) time every twelve (12) months from the initial date of the opening of the dispensary on the following subjects:

(i) Guidelines for providing information to qualifying patients related to risks, benefits, and side effects associated with medical marijuana;

(ii) Recognizing the signs and symptoms of substance abuse; and

(iii) Guidelines for refusing to provide medical marijuana to an individual who appears to be impaired or abusing medical marijuana;

(A) Assist in the development and implementation of review and improvement processes for patient education and support provided by the dispensary;

(B) Provide oversight for the development and dissemination of:

(i) Education materials for qualifying patients and designated caregivers that include:

(a) Information about possible side effects and contraindications of medical marijuana;

(b) Guidelines for notifying the physician who provided the written certification for medical marijuana if side effects or contraindications occur;

(c) A description of the potential effects of differing strengths of medical marijuana strains and products;

(d) Information about potential drug-to-drug interactions, including interactions with alcohol, prescription drugs, nonprescription drugs, and supplements;

(e) Techniques for the use of medical marijuana and marijuana paraphernalia; and

(f) Information about different methods, forms, and routes of medical marijuana administration;

(i) Systems for documentation by a qualifying patient or designated caregiver of the symptoms of a qualifying patient that includes a logbook, rating scale for pain and symptoms, and guidelines for a patient's self-assessment; and

(ii) Policies and procedures for refusing to provide medical marijuana to an individual who appears to be impaired or abusing medical marijuana; and

(A) Be accessible by the dispensary or dispensary agent through:

(i) Telephonic means at all times during operating hours; and

(ii) Telephone or video conference for a patient consultation during operating hours.

(t) (1) A cultivation facility shall meet the following security requirements:

(A)(i) The physical security controls set forth in 21 C.F.R. § 1301.72 — 1301.74, as existing on January 1, 2017.

(ii) The Alcoholic Beverage Control Division of the Department of Finance and Administration shall adopt rules to implement subdivision (p)(1)(A)(i) of this section;

(B) All cultivation of marijuana occurs within a building, greenhouse, or other structure that:

(i) Has a complete roof enclosure supported by connecting walls that are constructed of solid material extending from the ground to the roof;

(ii) Is secure against unauthorized entry;

(iii) Has a foundation, slab, or equivalent base to which the floor is securely attached;

(iv) Meets performance standards ensuring that cultivation and processing activities cannot be and are not perceptible from the structure in terms of:

(a) Common visual observation;

(b) Odors, smell, fragrances, or other olfactory stimulus;

(c) Light pollution, glare, or brightness;

(d) Adequate ventilation to prevent mold; and

(e) Noise;

(v) Provides complete visual screening; and

(vi) Is accessible only through one (1) or more lockable doors;

(C) Current detailed plans and elevation drawings of all operational areas involved with the production of medical marijuana are maintained on the premises of the cultivation facility, including:

(i) All storage areas, ventilation systems, and equipment used for production;

(ii) All entrances and exits to the cultivation facility;

(iii) All windows, skylights, and retractable mechanisms built into the roof;

(iv) The location of all required security cameras;

(v) The location of all alarm inputs, detectors, and sirens;

(vi) All video and alarm system surveillance areas;

(vii) All production areas labeled according to the specific activity occurring within the area;

(viii) All restricted and limited access areas identified; and

(ix) All nonproduction areas labeled according to purpose;

(D) Access to areas where marijuana is grown, harvested, processed, and stored is limited to authorized personnel and:

(i) Designated by clearly marked signage; and

(ii) Locked and accessible only by authorized personnel on a current roster of authorized personnel;

(E)(i) Written policies regarding any nonregistered agent who may visit the premises and a log of all visitors to the premises are developed and maintained.

(ii) The log shall consist of the visitor's name, purpose of visit, time of arrival, and time of departure.

(iii) Visitors to a cultivation facility shall be:

(a) Issued a visitor identification tag containing the visitor's name that shall be worn for the duration of the visit on the premises; and

(b) Escorted by a cultivation facility agent at all times while present on the premises.

(iv)(a) However, contractors conducting repairs, maintenance, or other specific duties may be escorted to their work site and left unaccompanied while completing a job.

(b) Cultivation facility agents shall ensure that the contractor and area under repair are under video surveillance for the duration of the time spent on the premises by the contractor; and

(F) (i) An alarm system is equipped that upon attempted unauthorized entry, transmits a signal directly to a central protection company for a local or state police agency and a designated cultivation facility agent.

(ii) The alarm system shall:

(a) Provide coverage for all points of ingress and egress to the cultivation facility, including without limitation doorways, windows, loading bays, skylights, and retractable roof mechanisms;

(b) Provide coverage of any room with an exterior wall, any room containing a safe, and any room used to grow or store medical marijuana;

(c) Be equipped with a panic drive that upon activation will not only sound any audible alarm components but will also notify law enforcement;

(d) Have duress and hold up features to enable a cultivation facility agent to activate a silent alarm notifying law enforcement of an emergency;

(e) Be equipped with failure notification systems to notify cultivation facilities and law enforcement of any failure in the alarm system; and

(f) Have the ability to remain operational during a power outage.

(2) A cultivation facility shall maintain compliance with applicable city or county building or structure rules, regulations, or ordinances and any other applicable state laws or rules regarding buildings or structures.

[As added by Const. Amend. 98; as amended by Acts 2017, No. 4, §§ 4-6, No. 545, § 2, No. 587, § 1, No. 594, §§ 1-2, No. 639, § 2, No. 640, § 1, No. 641, § 1, No. 642, § 1, No. 948, § 2, No. 1023, § 3, No. 1024, §§ 2-3, No. 1100, § 1.]

§ 9. Registration and certification of cultivation facility agents and dispensary agents.

(a) (1) Cultivation facility agents and dispensary agents shall register with the Alcoholic Beverage Control Division.

(2) The division shall administer and enforce the provisions of this amendment concerning cultivation facility agents and dispensary agents, including without limitation the

(2) (A) (i) The department shall maintain a confidential list of the persons to whom the department has issued registry identification cards.

(ii) (a) The department may share information from the confidential list under this subsection with the Alcoholic Beverage Control Division and the Medical Marijuana Commission as necessary and the State Insurance Department for the purposes of the Arkansas all-payer claims database established under § 23-61-901 et seq.

(b) Confidential information shared with the division or commission shall remain confidential while in the division's or commission's possession.

(B) Individual names and other identifying information on the confidential list are confidential, exempt from the Freedom of Information Act of 1967, § 25-19-101 et seq., and not subject to disclosure except to authorized employees of the department, division, and commission as necessary to perform official duties of the department, division, and commission.

(3) The department shall verify to law enforcement personnel whether a registry identification card is valid without disclosing more information than is reasonably necessary to verify the authenticity of the registry identification card.

(4) A person, including without limitation an employee or official of the department, division, commission, or another state agency or local government, who knowingly breaches the confidentiality of information obtained under this amendment commits a Class A misdemeanor.

(g) (1) Except as provided in § 3 of this amendment, a cardholder who transfers marijuana to a person who is not a qualifying patient or designated caregiver under this amendment shall have his or her registry identification card revoked and shall be subject to any other penalties established by law.

(2) The department may revoke the registry identification card of any cardholder who knowingly violates any provision of this amendment, and the cardholder is subject to any other penalties established by law.

(3) This subsection does not prohibit:

(A) A qualifying patient or designated caregiver from giving up to two and one-half ounces (2 1/2 oz.) of usable marijuana to another qualifying patient or designated caregiver as set forth in § 3 of this amendment; or

(B) The transfer of marijuana seedlings, plants, or usable marijuana as set forth in § 3 of this amendment.

(h) The department, division, and commission shall submit to the General Assembly an annual report that does not disclose any identifying information about cardholders or physicians but contains at a minimum:

(1) The number of applications and renewals filed for registry identification cards;

(2) The nature of the qualifying medical conditions of the qualifying patients;

(C) Inside a motor vehicle, aircraft, motorized watercraft, or any vehicle drawn by power other than muscle power;

(D) Knowingly in the presence of a pregnant woman; or

(E) In a place where the smoking of marijuana for medical use is likely to cause another person not authorized to use marijuana to be under the influence of marijuana; or

(5) Smoke marijuana for medical use if the person is under twenty-one (21) years of age.

(b) This amendment does not require:

(1) A government medical assistance program or private health insurer to reimburse a person for costs associated with the medical use of marijuana unless federal law requires reimbursement;

(2) An employer to accommodate the ingestion of marijuana in a workplace or an employee working while under the influence of marijuana;

(3) An individual or establishment in lawful possession of property to allow a guest, client, customer, or other visitor to use marijuana on or in that property;

(4) An individual or establishment in lawful possession of property to admit a guest, client, customer, or other visitor who is inebriated as a result of his or her medical used of marijuana;

(5) A landlord to permit a qualifying patient to smoke marijuana on or in leased property, except that a landlord may not prohibit the medical use of marijuana through means other than smoking on leased property by a qualifying patient; or

(6) A public school to permit a qualifying patient who is a student to be present on school grounds, to attend a school event, or to participate in extracurricular activities in violation of the public school's student discipline policies when a school office has a good faith belief that the behavior of the qualifying patient is impaired.

[As added by Const. Amend. 98; as amended by Acts 2017, No. 479, § 3, No. 740, § 1, No. 1099, § 1.]

§ 7. Affirmative defense and dismissal for medical use of marijuana.

(a) Except as provided in § 6 of this amendment and this section, an individual may assert a medical purpose for using marijuana as an affirmative defense to prosecution for an offense involving marijuana intended for the individual's medical use, and this defense shall be presumed valid and the prosecution shall be dismissed where the evidence demonstrates that the individual is:

(1) A qualifying patient or a designated caregiver; and

(2) In compliance with the conditions set forth in § 3 of this amendment.

(b) The defense and motion to dismiss shall not prevail if either of the following are proven:

(1) The individual's registry identification card had been revoked at the time of the

alleged offense; or

(2) The purposes for the possession of marijuana were not solely for medical use.

(c) An individual is not required to be in actual physical possession of a registry identification card to raise the affirmative defense set forth in this section.

(d) If an individual demonstrates a medical use of marijuana under this section, except as provided in § 6 of this amendment, the individual shall not be subject to the following:

(1) Disciplinary action by a business, occupational, or professional licensing board or bureau; or

(2) Forfeiture of any interest in or right to nonmarijuana, licit property. [As added by Const. Amend. 98.]

§ 8. Licensing of dispensaries and cultivation facilities.

(a) (1) Dispensaries and cultivation facilities shall be licensed by the Medical Marijuana Commission.

(2) The commission shall administer and regulate the licensing of dispensaries and cultivation facilities, including the issuance of a:

(i) License to operate a dispensary; and

(ii) License to operate a cultivation facility.

(3) The Alcoholic Beverage Control Division shall administer and enforce the provisions of this amendment concerning dispensaries and cultivation facilities.

(b) (1) The commission and division shall each adopt rules necessary to:

(A) Carry out the purposes of this amendment; and

(B) Perform its duties under this amendment.

(2) Rules adopted under this section are rules as defined in the Arkansas Administrative Procedure Act, § 25-15-201 et seq.

(c) The following individuals associated with a dispensary or cultivation facility shall be current residents of Arkansas who have resided in the state for the previous seven (7) consecutive years:

(1) The individual(s) submitting an application to license a dispensary or cultivation facility; and,

(2) Sixty percent (60%) of the individuals owning an interest in a dispensary or cultivation facility.

(d) Not later than one hundred eighty (180) days after the effective date of this amendment, the commission shall adopt rules governing:

(1) The manner in which the commission considers applications for and renewals of licenses for dispensaries and cultivation facilities;

(2) The form and content of registration and renewal applications for dispensaries and cultivation facilities; and

(3) Any other matters necessary for the commission's fair, impartial, stringent, and comprehensive administration of its duties under this amendment.

(e) Not later than one hundred eighty (180) days after the effective date of this amendment, the division shall adopt rules governing:

(1) Oversight requirements for dispensaries and cultivation facilities;

(2) Recordkeeping requirements for dispensaries and cultivation facilities;

(3) Security requirements for dispensaries and cultivation facilities;

(4) Personnel requirements for dispensaries and cultivation facilities;

(5) The manufacture, processing, packaging, labeling, and dispensing of usable marijuana to qualifying patients and designated caregivers, including without limitation;

(A) Before sale, food or drink that has been combined with usable marijuana shall not exceed ten milligrams (10 mg) of active tetrahydrocannabinol per portion and shall be physically demarked; and

(B) If portions cannot be physically determined, the entirety of the food or drink that has been combined with usable marijuana shall not contain more than ten milligrams (10 mg) of active 31 tetrahydrocannabinol;

(6) Procedures for suspending or terminating the licenses of dispensaries and cultivation facilities that violate the provisions of this amendment or the rules adopted under this amendment, procedures for appealing penalties, and a schedule of penalties;

(7) Procedures for inspections and investigations of dispensaries and cultivation facilities;

(8) Advertising restrictions for dispensaries and cultivation facilities, including without limitation the advertising, marketing, packaging, and promotion of dispensaries and cultivation facilities with the purpose to avoid making the product of a dispensary or a cultivation facility appealing to children, including without limitation:

(A) Artwork;

(B) Building signage;

(C) Product design, including without limitation shapes and flavors;

(D) Child-proof packaging that cannot be opened by a child or that prevents ready access to toxic or harmful amount of the product, and that meets the testing

requirements in accordance with the method described in 16 C.F.R. § 1700.20, as existing on January 1, 2017;

(E) Indoor displays that can be seen from outside the dispensary or cultivation facility; and

(F) Other forms of marketing related to medical marijuana;

(9) Procedures for the disposal or other use of marijuana not dispensed to a qualifying patient; and

(10) Any other matters necessary for the division's fair, impartial, stringent, and comprehensive administration of its duties under this amendment.

(f) (1) Not later than one hundred eighty (180) days after the effective date of this amendment, the commission shall adopt rules establishing license application and license renewal fees for dispensary and cultivation facility licenses.

(2) (A) The initial dispensary application fee shall be a maximum of seven thousand five hundred dollars ($7,500).

(B) The initial cultivation facility application fee shall be a maximum of fifteen thousand dollars ($15,000).

(C) A license that is initially issued between January 1 and July 1 may have the licensing fees up to fifty percent (50%) prorated and refunded as determined by the commission.

(g) (1) Not later than July 1, 2017, the commission shall begin accepting applications for licenses to operate a dispensary and cultivation facility.

(2) The application shall include without limitation the following:

(A) The application fee;

(B) The legal name of the dispensary or cultivation facility;

(C) The physical address of the:

(i) Dispensary, the location of which may not be within one thousand five hundred feet (1,500') of a public or private school, church, or daycare center existing before the date of the dispensary application, which shall be calculated from the primary entrance of the dispensary to the nearest property boundary of a public or private school, church, or daycare center; or

(ii) Cultivation facility, the location of which may not be within three thousand feet (3,000') of a public or private school, church, or daycare center existing before the date of the cultivation facility application, which shall be calculated from the primary entrance of the cultivation facility to the nearest property boundary of a public or private school, church, or daycare center;

(D) The name, address, and date of birth of each dispensary agent or cultivation facility

agent; and

(E) If the city, town, or county in which the dispensary or cultivation facility would be located has enacted zoning restrictions, a sworn statement certifying that the dispensary or cultivation facility will operate in compliance with the restrictions.

(3) None of the owners, board members, or officers of the dispensary or cultivation facility:

(A) Shall have been convicted of an excluded felony offense;

(B) Shall have previously been an owner of a dispensary or cultivation facility that has had its license revoked; and

(C) Shall be under twenty-one (21) years of age.

(4) (A) The commission may issue a temporary license to a another natural person in conjunction with a dispensary or a cultivation facility when the natural person whose name is on the license for the dispensary or cultivation facility ceases to be in actual control of the dispensary or cultivation facility.

(B) The commission shall adopt rules as necessary to provide temporary licenses.

(h) The commission shall issue at least twenty (20) but no more than forty (40) dispensary licenses.

(i) There shall be no more than four (4) dispensaries in any one (1) county.

(j) The commission shall issue at least four (4) but no more than eight (8) cultivation facility licenses.

(k) (1) The commission shall conduct a criminal background check in order to carry out this section.

(2) The commission shall require each applicant for a dispensary license or cultivation facility license to apply for or authorize the commission to obtain state and national criminal background checks to be conducted by the Identification Bureau of the Department of Arkansas State Police and the Federal Bureau of Investigation.

(3) The criminal background checks shall conform to the applicable federal standards and shall include the taking of fingerprints.

(4) The applicant shall authorize the release of the criminal background checks to the commission and shall be responsible for the payment of any fee associated with the criminal background checks.

(5) Upon completion of the criminal background checks, the Identification Bureau of the Department of Arkansas State Police shall forward to the commission all information obtained concerning the applicant.

(l) (1) No individual shall own an interest in more than:

(1) One (1) cultivation facility; and,

(2) One (1) dispensary.

(m) (1) (A) A dispensary licensed under this section may acquire, possess, manufacture, process, prepare, deliver, transfer, transport, supply, and dispense marijuana, marijuana paraphernalia, and related supplies and educational materials to a qualifying patient or designated caregiver, but shall not supply, possess, manufacture, deliver, transfer, or sell marijuana paraphernalia that requires the combustion of marijuana to be properly utilized, including pipes, water pipers, bongs, chillums, rolling papers, and roach clips.

(B) A dispensary licensed under this section shall:

(i) Make marijuana vaporizers available for sale to qualifying patients; and

(ii) Provide educational materials about medical marijuana methods of ingestion to qualifying patients and designated caregivers, including without limitation:

(a) Warnings on the potential health risks of smoking or combusting marijuana; and

(b) Information on potential health benefits of vaporizing marijuana compared to smoking or combusting.

(2) (A) A dispensary may receive compensation for providing the goods and services allowed by this section.

(B) A dispensary may contract with a transporter, distributer, or processer to extent of the license of the transporter, 1 distributer, or processer.

(3) (A) A dispensary may grow or possess:

(i) Fifty (50) mature marijuana plants at any one (1) time plus seedlings; and

(ii) All usable marijuana derived from the plants under subdivision (m)(3)(A)(i) of this section or predecessor plants.

(B) A dispensary may contract with a cultivation facility to cultivate one (1) or more mature marijuana plants the dispensary is permitted to grow.

(4) (A) (i) A cultivation facility may cultivate and possess usable marijuana in an amount reasonably necessary to meet the demand for and needs of qualifying patients as determined by the commission with the assistance of the Department of Health.

(ii) However, a cultivation facility shall not sell marijuana in any form except to a dispensary or other cultivation facility.

(B) A cultivation facility may also possess marijuana seeds.

(C) The commission with the assistance of the Department of Health shall promulgate rules determining the amount of marijuana reasonably necessary under subdivision (m)(4)(A) of this section.

(5) (A) A cultivation facility may receive compensation for providing the goods and services allowed by this section.

(B) A cultivation facility may contract with a transporter, distributer, or processer to extent of the license of the transporter, distributer, or processer.

(n) (1) A dispensary license and cultivation facility license shall expire on June 30 of each calendar 7 year and are renewable on or before June 30 of each calendar year for the 8 fiscal year beginning July 1.

(2) The commission shall issue a renewal dispensary license or a renewal cultivation facility license within ten (10) days to any entity who complies with the requirements contained in this amendment, including without limitation the payment of a renewal fee.

(o) The commission may charge a reasonable fee as established by rule for the issuance of a renewal license.

(p) The commission and the division may collect fines or fees for any violation of a rule adopted under this section.

(q) (1) A license for a dispensary or cultivation facility shall only be issued to a natural person.

(2) A license issued for a dispensary or cultivation facility shall be transferable only to a natural person upon approval of the commission.

(r) Data or records submitted to the division or commission under rules adopted under this amendment may be shared with the Department of Health and the State Insurance Department for purposes of the Arkansas all-payer claims database established under § 23-61-901 et seq.

(s) (1) A dispensary shall appoint a pharmacist consultant who is a pharmacist licensed with the Arkansas State Board of Pharmacy.

(2) A pharmacist consultant shall:

(A) Register as a dispensary agent under this amendment and follow all procedures;

(B) Develop and provide training to other dispensary agents at least one (1) time every twelve (12) months from the initial date of the opening of the dispensary on the following subjects:

(i) Guidelines for providing information to qualifying patients related to risks, benefits, and side effects associated with medical marijuana;

(ii) Recognizing the signs and symptoms of substance abuse; and

(iii) Guidelines for refusing to provide medical marijuana to an individual who appears to be impaired or abusing medical marijuana;

(A) Assist in the development and implementation of review and improvement processes for patient education and support provided by the dispensary;

(B) Provide oversight for the development and dissemination of:

(i) Education materials for qualifying patients and designated caregivers that include:

(a) Information about possible side effects and contraindications of medical marijuana;

(b) Guidelines for notifying the physician who provided the written certification for medical marijuana if side effects or contraindications occur;

(c) A description of the potential effects of differing strengths of medical marijuana strains and products;

(d) Information about potential drug-to-drug interactions, including interactions with alcohol, prescription drugs, nonprescription drugs, and supplements;

(e) Techniques for the use of medical marijuana and marijuana paraphernalia; and

(f) Information about different methods, forms, and routes of medical marijuana administration;

(i) Systems for documentation by a qualifying patient or designated caregiver of the symptoms of a qualifying patient that includes a logbook, rating scale for pain and symptoms, and guidelines for a patient's self-assessment; and

(ii) Policies and procedures for refusing to provide medical marijuana to an individual who appears to be impaired or abusing medical marijuana; and

(A) Be accessible by the dispensary or dispensary agent through:

(i) Telephonic means at all times during operating hours; and

(ii) Telephone or video conference for a patient consultation during operating hours.

(t) (1) A cultivation facility shall meet the following security requirements:

(A)(i) The physical security controls set forth in 21 C.F.R. § 1301.72 — 1301.74, as existing on January 1, 2017.

(ii) The Alcoholic Beverage Control Division of the Department of Finance and Administration shall adopt rules to implement subdivision (p)(1)(A)(i) of this section;

(B) All cultivation of marijuana occurs within a building, greenhouse, or other structure that:

(i) Has a complete roof enclosure supported by connecting walls that are constructed of solid material extending from the ground to the roof;

(ii) Is secure against unauthorized entry;

(iii) Has a foundation, slab, or equivalent base to which the floor is securely attached;

(iv) Meets performance standards ensuring that cultivation and processing activities cannot be and are not perceptible from the structure in terms of:

(a) Common visual observation;

(b) Odors, smell, fragrances, or other olfactory stimulus;

(c) Light pollution, glare, or brightness;

(d) Adequate ventilation to prevent mold; and

(e) Noise;

(v) Provides complete visual screening; and

(vi) Is accessible only through one (1) or more lockable doors;

(C) Current detailed plans and elevation drawings of all operational areas involved with the production of medical marijuana are maintained on the premises of the cultivation facility, including:

(i) All storage areas, ventilation systems, and equipment used for production;

(ii) All entrances and exits to the cultivation facility;

(iii) All windows, skylights, and retractable mechanisms built into the roof;

(iv) The location of all required security cameras;

(v) The location of all alarm inputs, detectors, and sirens;

(vi) All video and alarm system surveillance areas;

(vii) All production areas labeled according to the specific activity occurring within the area;

(viii) All restricted and limited access areas identified; and

(ix) All nonproduction areas labeled according to purpose;

(D) Access to areas where marijuana is grown, harvested, processed, and stored is limited to authorized personnel and:

(i) Designated by clearly marked signage; and

(ii) Locked and accessible only by authorized personnel on a current roster of authorized personnel;

(E)(i) Written policies regarding any nonregistered agent who may visit the premises and a log of all visitors to the premises are developed and maintained.

(ii) The log shall consist of the visitor's name, purpose of visit, time of arrival, and time of departure.

(iii) Visitors to a cultivation facility shall be:

issuance of a:

(A) Registry identification card to a dispensary agent; and

(B) Registry identification card to a cultivation facility agent.

(b) (1) The division shall adopt rules necessary to:

(A) Carry out the purposes of this amendment; and

(B) Perform its duties under this amendment.

(2) Rules adopted under this section are rules as defined in the Arkansas Administrative Procedure Act, § 25-15-201 et seq.

(c) Not later than one hundred eighty (180) days after the effective date of this amendment, the division shall adopt rules governing:

(1) The manner in which the division considers applications for and renewals of registry identification cards for dispensary agents and cultivation facility agents;

(2) The form and content of registration and renewal applications for dispensary agents and cultivation facility agents;

(3) Procedures for suspending or terminating the registration of dispensary agents and cultivation facility agents who violate the provisions of this amendment or the rules adopted under this amendment, procedures for appealing penalties, and a schedule of penalties; and

(4) Any other matters necessary for the division's fair, impartial, stringent, and comprehensive administration of its duties under this amendment.

(d) (1) The division shall conduct criminal background checks in order to carry out this section.

(2) The division shall require each applicant for a dispensary agent license or cultivation facility agent license to apply for or authorize the division to obtain state and national criminal background checks to be conducted by the Identification Bureau of the Department of Arkansas State Police and the Federal Bureau of Investigation.

(3) The criminal background checks shall conform to the applicable federal standards and shall include the taking of fingerprints.

(4) The applicant shall authorize the release of the criminal background checks to the division and shall be responsible for the payment of any fee associated with the criminal background checks.

(5) Upon completion of the criminal background checks, the Identification Bureau of the Department of Arkansas State Police shall forward to the division all information obtained concerning the applicant.

(e) Except as provided herein, the division shall issue each dispensary agent and cultivation facility agent a registry identification card within ten (10) days of receipt of:

(1) The person's name, address, and date of birth under this amendment; and

(2) A reasonable fee in an amount established by rule of the division.

(f) (1) The division shall not issue a registry identification card to a dispensary agent or cultivation facility agent who has been convicted of an excluded felony offense.

(2) The division shall conduct a criminal background check as described in subsection (d) of this section of each dispensary agent or cultivation facility agent in order to carry out this provision.

(3) The division shall notify the dispensary or cultivation facility in writing of the reason for denying the registry identification card.

(g) (1) A registry identification card for a dispensary agent or cultivation facility agent shall expire on June 30 of each calendar year and is renewable on or before June 30 of each calendar year for the fiscal year beginning July 1.

(2) A registry identification card of a dispensary agent or cultivation facility agent expires upon notification to the division by a dispensary or cultivation facility that the person ceases to work at the dispensary or cultivation facility.

(h) The division may charge a reasonable fee as established by rule for the issuance of a new, renewal or replacement registry identification card.

(i) (1) The division may revoke the registry identification card of a dispensary agent or cultivation facility agent who knowingly violates any provision of this amendment, and the cardholder is subject to any other penalties established by law for the violation.

(2) The division may revoke or suspend the dispensary license or cultivation facility license of a dispensary or cultivation facility that the division determines knowingly aided or facilitated a violation of any provision of this amendment, and the licenseholder is subject to any other penalties established in law for the violation.

(j) The division may collect fines or fees for any violation of a rule adopted under this section.

[As added by Const. Amend. 98; as amended by Acts 2017, No. 4, § 7, No. 545, §§ 3-4, No. 594, § 3, No. 639, § 3.]

§ 10. Dispensary and cultivation facility inspections and requirements.

(a) Dispensaries and cultivation facilities are highly regulated by the state, and a dispensary and cultivation facility is therefore subject to reasonable inspection by the Alcoholic Beverage Control Division.

(b) (1) This subsection governs the operations of dispensaries and cultivation facilities.

(2) A dispensary and a cultivation facility shall be an entity incorporated in the State of Arkansas.

(3) A dispensary and cultivation facility shall implement appropriate security measures to deter and prevent unauthorized entrance into areas containing marijuana and the theft of

marijuana.

(4) A dispensary and cultivation facility shall have procedures in place to ensure accurate recordkeeping.

(5) Each dispensary shall keep the following records, dating back at least three (3) years:

(A) Records of the disposal of marijuana that is not distributed by the dispensary to qualifying patients; and

(B) A record of each transaction, including the amount of marijuana dispensed, the amount of compensation, and the registry identification number of the qualifying patient or designated caregiver.

(6) Each dispensary and cultivation facility shall:

(A) Conduct an initial comprehensive inventory of all marijuana, including without limitation usable marijuana available for dispensing, mature marijuana plants, and seedlings at each authorized location on the date the dispensary first dispenses usable marijuana or the cultivation facility first cultivates, prepares, manufactures, processes, or packages usable marijuana; and

(B) Conduct a biannual comprehensive inventory of all marijuana, including without limitation usable marijuana available for dispensing, mature marijuana plants, and seedlings at each authorized location.

(7) All cultivation of marijuana shall take place in an enclosed, locked facility.

(8) (A) A qualifying patient or designated caregiver acting on behalf of a qualifying patient shall not be dispensed more than a total of two and one-half ounces (2 1/2 oz.) of usable marijuana during a fourteen-day period.

(B) A dispensary or a dispensary agent may not dispense more than a total of two and one-half ounces (2 1/2 oz.) of usable marijuana to either a qualifying patient or designated caregiver acting on behalf of a qualifying patient during a fourteen-day period.

(C) Each time a dispensary agent dispenses usable marijuana to a qualifying patient or designated caregiver, he or she shall verify that the dispensing of usable marijuana would not cause the qualifying patient or designated caregiver to receive more usable marijuana than is permitted in a fourteen-day period.

(D) Each time usable marijuana is dispensed, the dispensary agent shall:

(i) Record the date the usable marijuana was dispensed and the amount dispensed; and

(ii) Notify the Department of Health in the manner required by the department.

(E) The department shall maintain a database that enables a dispensary to verify that dispensing usable marijuana to a qualifying patient or designated caregiver will not cause the qualifying patient or designated caregiver to exceed the amount allowed by law.

(F) All records shall be kept according to the registry identification number of the

qualifying patient or designated caregiver.

(G) It is the specific intent of this Amendment that no qualifying patient or designated caregiver acting on behalf of a qualifying patient be dispensed more than a total of two and one-half ounces (2 1/2 oz.) of usable marijuana during a fourteen-day period whether the usable marijuana is dispensed from one or any combination of dispensaries.

(9) The dispensary records with patient information shall be treated as confidential records that are exempt from the Freedom of Information Act of 1967, § 25-19-101 et seq.

[As added by Const. Amend. 98; as amended by Acts 2017, No. 5, § 3.]

§ 11. Immunity for dispensaries and cultivation facilities.

(a) A dispensary, cultivation facility, transporter, distributer, or processor is not subject to the following:

(1) Prosecution for the acquisition, possession, cultivation, processing, preparation, manufacture, delivery, transfer, transport, sale, supply, or dispensing of marijuana and related supplies in accordance with the provisions of this amendment and any rule adopted under this amendment;

(2) Inspection, except under § 10 of this amendment or upon a search warrant issued by a court or judicial officer;

(3) Seizure of marijuana, except upon any order issued by a court or judicial officer and with due process of law; or

(4) Imposition of a penalty or denial of a right or privilege, including without limitation imposition of a civil penalty or disciplinary action by a business, occupational, or professional licensing board or entity, solely for acting in accordance with this amendment.

(b) (1) A dispensary agent, cultivation facility agent, transporter agent, distributer agent, or processor agent shall not be subject to arrest, prosecution, search, seizure, or penalty in any manner or denied any right or privilege, including without limitation civil penalty or disciplinary action by a business, occupational, or professional licensing board or entity, solely for working for or with a dispensary, cultivation facility, transporter, distributer, or processor to engage in acts permitted by this amendment.

(2) (A) A dispensary agent, cultivation facility agent, or processor agent may possess and manufacture marijuana at the dispensary, cultivation facility location, or processor location or locations for which the dispensary agent, cultivation facility agent, or processor agent is registered or when transferring marijuana under this section.

(B) (i) A dispensary agent who is a volunteer may possess and manufacture marijuana at a dispensary location.

(ii) A dispensary agent who is a volunteer may not dispense or transport marijuana.

(3) A cultivation facility and processor shall label the marijuana that is moved between the cultivation facility or processor and a dispensary, other cultivation facility, or processor with a trip ticket that identifies the cultivation facility by identification number, the time,

date, origin, and destination of the marijuana being transported, and the amount and form of marijuana that is being transported.

(4) A transporter agent or distributer agent may possess marijuana at any location while the transporter agent or distributor agent is transferring marijuana from a dispensary, cultivation facility, or processer to another dispensary, cultivation facility, or processor.

(c) Importation of seeds, cuttings, clones, or plants by a dispensary 29 or cultivation facility shall not be prosecuted in the courts of this state.

[As added by Const. Amend. 98; Acts 2017, No. 642, § 2. No. 1022, § 1.]

§ 12. Prohibitions for dispensaries.

(a) (1) Except as provided in § 3 of this amendment and subdivision (a)(2) of this section, a dispensary may not dispense, deliver, or otherwise transfer marijuana to a person other than a qualifying patient or designated caregiver.

(2) A dispensary may transfer marijuana to a transporter, distributer, or processer to operate to extent of the license of the transporter, distributer, or processer.

(b) (1) Except as provided in § 3 of this amendment, the Alcoholic Beverage Control Division shall immediately revoke the registry identification card of a dispensary agent who has dispensed, delivered, or otherwise transferred marijuana to a person other than a qualifying patient or designated caregiver, and that dispensary agent shall be disqualified from serving as a dispensary agent.

(2) A dispensary employing a dispensary agent found to violate subdivision (b)(1) of this section is not subject to penalties, including without limitation the revocation of its license, for the actions of a dispensary agent unless the dispensary knowingly aided or facilitated the violation.

[As added by Const. Amend. 98; Acts 2017, No. 642, § 2.]

§ 13. Prohibitions for cultivation facilities.

(a) A cultivation facility may sell marijuana plants, seeds, and usable marijuana only to a dispensary, other cultivation facility, or processor.

(b) A cultivation facility may employ a transporter or a distributor to transfer marijuana from the cultivation facility to a dispensary, other cultivation facility, or processer.

[As added by Const. Amend. 98; Acts 2017, No. 642, § 2.]

§ 14. Local regulation.

(a) This amendment does not prohibit a city, incorporated town, or county of this state from enacting reasonable zoning regulations applicable to dispensaries or cultivation facilities, provided that those zoning regulations are the same as those for a licensed retail pharmacy.

(b) This section does not allow a city, incorporated town, or county to prohibit the operation

of any dispensaries or cultivation facilities in the city, incorporated town, or county unless such a prohibition is approved at an election under Article 5, § 1, of this constitution.

[As added by Const. Amend. 98.]

§ 15. Prohibited conduct for physicians.

A physician shall not:

(1) Accept, solicit, or offer any form of pecuniary remuneration from or to a dispensary or cultivation facility provided however, that this does not prohibit a physician who is also a qualifying patient from purchasing usable marijuana from a dispensary;

(2) Offer a discount or other thing of value to a qualifying patient who uses or agrees to use a particular dispensary;

(3) Examine a patient for purposes of diagnosing a qualifying medical condition at a dispensary; or

(4) Hold an economic interest in a dispensary or cultivation facility if the physician certifies the qualifying medical condition of a patient for medical use of marijuana.

[As added by Const. Amend. 98.]

§ 16. Failure to adopt rules or issue registry identification cards or licenses.

If the Department of Health, Alcoholic Beverage Control Division, or Medical Marijuana Commission fails to adopt rules to implement this amendment within the time prescribed or fails to issue the minimum number of dispensary licenses or cultivation facility licenses, any person who would be a qualifying patient under this amendment may commence a mandamus action in Pulaski County Circuit Court to compel the department, division, or commission to perform the actions mandated under the provisions of this amendment.

[As added by Const. Amend. 98.]

§ 17. Taxation and distribution of proceeds.

(a) (1) The sale of usable marijuana is subject to all state and local sales taxes at the same rate as other tangible personal property.

(2) The sale of usable marijuana is also subject to the Arkansas Medical Marijuana Special Privilege Tax Act of 2017, Ark. Code § 26-57-1501 et seq., or its successor.

(b) The state sales and special privilege tax revenues received by the Department of Finance and Administration from the sale of usable marijuana under this amendment shall be distributed as follows:

(1) All moneys received as part of this amendment are designated as special revenue and the funds collected shall be deposited in the State Treasury and credited to the Arkansas Medical Marijuana Implementation and Operations Fund;

(2) All moneys received as part of this amendment prior to the effective date of this section shall be immediately transferred to the Arkansas Medical Marijuana Implementation and Operations Fund upon the effective date of this section;

(3) In order for the Chief Fiscal Officer of the State to determine the expenses that state agencies incurred due to the passage of this amendment, the following state entities shall submit a report to the Chief Fiscal Officer of the State no later than May 1 of each year of the projected expenses for the next fiscal year, including without limitation expenses as set out in subdivision (b)(4) of this section:

(A) The Alcoholic Beverage Control Division of the Department of Finance and Administration;

(B) The Department of Health;

(C) The Medical Marijuana Commission; and

(D) Any other state agency that incurs implementation, administration, or enforcement expenses related to this amendment; and

(4) (A) From time to time, the Chief Fiscal Officer of the State shall transfer on his or her books and those of the Treasurer of State and the Auditor of State the amounts as set out in subdivision (b)(3) of this section or so much as is available in proportion to the amount identified by each agency in subdivision (b)(3) of this section from the Arkansas Medical Marijuana Implementation and Operations Fund to the Miscellaneous Agencies Fund Account for the Alcoholic Beverage Control Division of the Department of Finance and Administration, the paying account as determined by the Chief Fiscal Officer for the Department of Health, the Medical Marijuana Commission Fund, and any other fund necessary to the implementation, administration, or enforcement of this amendment to pay for or reimburse personal services, operating expenses, professional fees, equipment, monitoring, auditing, and other miscellaneous expenses of this amendment.

(B) At the end of each fiscal year, any unobligated balances of the amounts transferred shall be deducted from the amount transferred in the next fiscal year as authorized in subdivision (b)(4)(A) of this section.

(C) Any unanticipated expenses or expenses over the amount transferred may be added from time to time to the transfer amount authorized in subdivision (b)(4)(A) of this section.

(D) The Department of Finance and Administration shall report at the end of the fiscal year to the Legislative Council or the Joint Budget Committee if during a legislative session the following information:

(i) The total annual amount received as a result of this amendment;

(ii) The amount transferred to each agency; and

(iii) Copies of the report submitted to the Chief Fiscal Officer of the State identifying estimated expenses as set out in subdivision (b)(3) of this section.

(c) After the transfer described in subsection (b) of this section, the amounts remaining in the Arkansas Medical Marijuana Implementation and Operations Fund shall be distributed

one hundred percent (100%) to the General Revenue Fund Account.

(d) An entity receiving a grant of state sales tax revenue under subsection (b) of this section may make one (1) or more successive grant applications for the same project or projects.

[As added by Const. Amend. 98; Acts 2017, No. 670, § 1, No. 1098, § 1.]

§ 18. Costs of administration and regulation of amendment.

(a) The following funds shall be used by the Department of Health to perform its duties under this amendment:

(1) State sales tax revenues received under § 17 of this amendment;

(2) (A) The revenue generated from fees, penalties, and other assessments of the department provided for by this amendment, including without limitation:

(i) Registry identification card application and renewal fees; and

(ii) Fees for replacement registry identification cards.

(B) Revenue generated from fees, penalties, and other assessments under this amendment shall be used solely for the performance of the department's duties under this amendment and shall be used for no other purpose;

(3) Private donations, if such funds are available; and

(4) Other appropriations by the General Assembly, if such funds are available.

(b) The following funds shall be used by the Alcoholic Beverage Control Division to perform its duties under this amendment:

(1) State sales tax revenues received under § 17 of this amendment;

(2) (A) The revenue generated from fees, penalties, and other assessments of the division provided for by this amendment.

(B) Revenue generated from fees, penalties, and other assessments of the division under this amendment shall be used solely for the performance of the division's duties under this amendment and shall be used for no other purpose;

(3) Private donations, if such funds are available; and

(4) Other appropriations by the General Assembly, if such funds are available.

(c) The following funds shall be used by the Medical Marijuana Commission to perform its duties under this amendment:

(1) State sales tax revenues received under § 17 of this amendment;

(2) The revenue generated from fees, penalties, and other assessments of the commission provided for by this amendment, including without limitation dispensary and

cultivation facility application fees, licensing fees, and renewal fees;

(3) Private donations, if such funds are available; and

(4) Other appropriations by the General Assembly, if such funds are available.

[As added by Const. Amend. 98.]

§ 19. Medical Marijuana Commission -- Creation.

(a) (1) There is created a Medical Marijuana Commission within the Department of Finance and Administration to determine the qualifications for receiving a license to operate a dispensary or a license to operate a cultivation facility and the awarding of licenses.

(2) Each member of the commission shall serve a term of four (4) years.

(3) The commission shall consist of five (5) members as follows:

(A) Two (2) members appointed by the President Pro Tempore of the Senate;

(B) Two (2) members appointed by the Speaker of the House of Representatives; and

(C) One (1) member appointed by the Governor.

(4) Vacancies on the commission shall be filled in the manner of the original appointment.

(5) The commission shall select one (1) of its members as chair.

(6) An affirmative vote of a majority of a quorum present shall be necessary to transact business.

(b) (1) (A) One (1) of the initial members appointed by the President Pro Tempore of the Senate shall serve a term of two (2) years and one (1) of the initial members appointed by the President Pro Tempore of the Senate shall serve a term of four (4) years.

(B) The initial members appointed by the President Pro Tempore of the Senate shall draw lots to determine which member shall serve a term of two (2) years.

(2) (A) One (1) of the initial members appointed by the Speaker of the House of Representatives shall serve a term of two (2) years and one (1) of the initial members appointed by the Speaker of the House of Representatives shall serve a term of four (4) years.

(B) The initial members appointed by the Speaker of the House of Representatives shall draw lots to determine which member shall serve a term of two (2) years.

(3) The initial member appointed by the Governor shall serve a term of four (4) years.

(4) All subsequent persons appointed to the commission shall serve a term of four (4) years.

(c) A member of the commission shall be:

(1) A citizen of the United States;

(2) A resident of the State of Arkansas for at least ten (10) years preceding his or her appointment;

(3) A qualified elector;

(4) At least twenty-five (25) years of age; and

(5) Have no economic interest in a dispensary or cultivation facility.

(d) (1) The commission, by a majority vote of the total membership of the commission cast during its first regularly scheduled meeting of each calendar year, may authorize payment to its members of a stipend not to exceed eighty-five dollars ($85.00) per day for each meeting attended or for any day while performing any proper business of the commission.

(2) Members of the commission shall receive no other compensation, expense reimbursement, or in-lieu-of payments.

(e) (1) The commission may employ staff necessary to assist in the performance of its duties under this amendment.

(2) The Alcoholic Beverage Control Division shall provide staff for the commission if the commission does not have employees available for that purpose.

(f) (1) Initial members of the commission shall be appointed within thirty (30) days of the effective date of this section.

(2) The President Pro Tempore of the Senate shall call the first meeting of the commission, which shall occur within forty-five (45) days of the effective date of this section.

[As added by Const. Amend. 98 Acts 2017, No. 638, § 1.]

§ 20. No implied repeal.

(a) By adoption of this amendment, there is no implied repeal of the existing Arkansas laws criminalizing possession of marijuana for purposes not specified in this amendment.

(b) This amendment acknowledges that marijuana use, possession, and distribution for any purpose remains illegal under federal law.

[As added by Const. Amend. 98.]

§ 21. Limitation on growing.

This amendment:

(1) Authorizes the growing of marijuana at a dispensary or cultivation facility that is properly licensed with the state; and

(2) Does not authorize a qualifying patient, designated caregiver, or other person to grow marijuana.

[As added by Const. Amend. 98.]

§ 22. Severabillty.

If any provision or section of this amendment or the application thereof to any person or circumstance is held invalid, such invalidity shall not affect any other provisions or application of the amendment that can be given effect without the invalid provisions or applications, and to this end the provisions of this amendment are declared to be severable.

[As added by Const. Amend. 98.]

§ 23. Amendment by General Assembly.

(a) Except as provided in subsection (b) of this section, the General Assembly, in the same manner as required for amendment of laws initiated by the people, may amend the sections of this amendment so long as the amendments are germane to this section and consistent with its policy and purposes.

(b) The General Assembly shall not amend the following provisions of this amendment:

(1) Subsections (a), (b), and (c) of § 3;

(2) Subsection (h), (i), and (j) of § 8; and

(3) Section 23.

[As added by Const. Amend. 98.]

§ 24. Licensure for transporters, distributers, and processers.

(a) (1) The Medical Marijuana Commission shall license transporters, distributors, and processers.

(2) The Alcoholic Beverage Control Division shall administer and enforce the provisions of this section concerning transporters, distributers, and processors.

(b) The owners, board members, or officers of a transporter, distributor, or processor shall not:

(1) Have been convicted of an excluded felony offense;

(2) Have previously been an owner of a dispensary, cultivation facility, transporter, distributor, or processor that has had a license revoked; and

(3) Be under twenty-one (21) years of age.

(c) The commission may conduct a criminal records check in order to carry out this section.

(d) (1) A transporter license, distributor license, and processor license shall expire one (1) year after the date of issuance.

(2) The commission shall issue a renewal license within ten (10) days to any entity who complies with the requirements contained in this amendment, including without limitation the payment of a renewal fee.

(e) The commission may charge a reasonable fee as established by rule for the issuance of an initial license and a renewal license.

(f) (1) (A) A transporter or distributer licensed under this section may:

(i) Acquire, possess, deliver, transfer, transport, or distribute marijuana to a dispensary, cultivation facility, or processor; and

(ii) Receive compensation for providing services allowed by this section.

(B) A transporter or distributor licensed under this section shall not grow, manufacture, process, prepare, supply, or dispense marijuana.

(2) (A) A processer licensed under this section may:

(i) Acquire, possess, manufacture, process, prepare, deliver, transport, and supply marijuana to a dispensary or cultivation facility; and

(ii) Receive compensation for providing services allowed by this section.

(B) A processer licensed under this section shall not grow or dispense marijuana.

(g) The division may make reasonable inspections on a transporter, distributer, and processor to ensure that the transporter, distributor, and processer:

(1) Is an entity incorporated in the State of Arkansas;

(2) Has implemented appropriate security measures to deter and prevent unauthorized entrance into areas containing marijuana and the theft of marijuana;

(3) Conducts an initial comprehensive inventory of all marijuana and a biannual comprehensive inventory of all marijuana; and

(4) Records each transaction between the transporter, distributer, or processer and a dispensary, cultivation facility, or another processer and maintains the records for three (3) years;

(5) Has adopted procedures to ensure accurate recordkeeping.

(h) (1) The commission shall adopt rules governing the applications for a transporter license, distributor license, or processer license.

(2) The division shall adopt rules governing:

(A) Oversight requirements for transporters, distributers, and processers;

(B) Recordkeeping requirements for transporters, distributers, and processers;

(C) Security requirements for transporters, distributers, and processers;

(D) Personnel requirements for transporters, distributers, and processers;

(E) The manufacture, processing, packaging, and dispensing of usable marijuana to qualifying patients and designated caregivers;

(F) Procedures for suspending or terminating the licenses of transporters, distributers, and processers that violate the provisions of this amendment or the rules adopted under this amendment, procedures for appealing penalties, and a schedule of penalties;

(G) Procedures for inspections and investigations of transporters, distributers, and processers;

(H) Advertising restrictions for transporters, distributers, and processers; and

(J) Any other matters necessary to the fair, impartial, stringent, and comprehensive administration of the duties of the division under this section.

[As added by Acts 2017; No. 642, § 2.]

§ 25. Registration and certification of transporter agents, distributer agents, and processor agents.

(a) The Alcoholic Beverage Control Division shall:

(1) License transporter agents, distributor agents, and processer agents; and

(2) Administer and enforce the provisions of this section concerning transporter agents, distributer agents, and processor agents.

(b) The division may conduct criminal records checks in order to carry out this section.

(c) Except as prohibited by subdivision (d)(1) of this section, the division shall issue each transporter agent, distributer agent, and processor agent a registry identification card within ten (10) days of receipt of:

(1) The person's name, address, and date of birth under this amendment; and

(2) A reasonable fee in an amount established by rule for the division.

(d) (1) The division shall not issue a registry identification card to a transporter agent, distributer agent, or processor agent who has been convicted of an excluded felony offense.

(2) The division may conduct a criminal background check of each transporter agent, distributer agent, and processor agent in order to carry out this provision.

(3) The division shall notify the transporter, distributer, or processer in writing of the reason for denying the registry identification card.

(e) (1) A registry identification card for a transporter agent, distributer agent, or processor agent shall expire one (1) year after the date of issuance.

(2) A registry identification card of a transporter agent, distributer agent, or processor agent expires upon notification to the division by a dispensary or cultivation facility that the person ceases to work at the transporter, distributer, or processer.

(f) The division may charge a reasonable fee as established by rule for the issuance of a new, renewal, or replacement registry identification card.

(g) (1) The division may revoke the registry identification card of a transporter agent, distributer agent, or processor agent who knowingly violates any provision of this amendment, and the cardholder is subject to any other penalties established by law for the violation.

(2) The division may revoke or suspend the transporter license, distributor license, or processer license of a transporter, distributer, or processer that the division determines knowingly aided or facilitated a violation of any provision of this amendment, and the cardholder is subject to any other penalties established in law for the violation.

(h) The division shall adopt rules governing:

(1) The manner in which the division considers applications for and renewals of registry identification cards for transporter agents, distributor agents, and processer agents;

(2) The form and content of registration and renewal applications for transporter agents, distributor agents, and processer agents;

(3) Procedures for suspending or terminating the registration of transporter agents, distributor agents, and processer agents who violate the provisions of this section or the rules adopted under this section, procedures for appealing penalties, and a schedule of penalties; and

(4) Any other matters necessary for the fair, impartial, stringent, and comprehensive administration of the duties of the division under this section.

[As added by Acts 2017; No. 642, § 2.]

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Celexa (citalopram hydrobromide) Tablets/Oral Solution
NDA 20-822/NDA 21-046
Proposed Labeling Text

Celexa®
(citalopram hydrobromide)
Tablets/Oral Solution

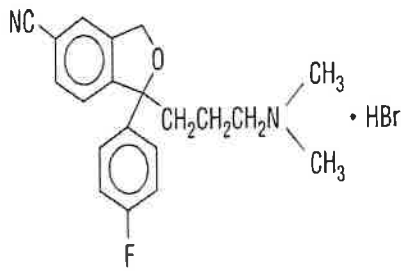
Rx Only

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 Celexa 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. Celexa is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients, and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

Celexa® (citalopram HBr) is an orally administered selective serotonin reuptake inhibitor (SSRI) with a chemical structure unrelated to that of other SSRIs or of tricyclic, tetracyclic, or other available antidepressant agents. Citalopram HBr is a racemic bicyclic phthalane derivative designated (±)-1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, HBr with the following structural formula:



The molecular formula is $C_{20}H_{22}BrFN_2O$ and its molecular weight is 405.35.

Citalopram HBr occurs as a fine, white to off-white powder. Citalopram HBr is sparingly soluble in water and soluble in ethanol.

Celexa (citalopram hydrobromide) is available as tablets or as an oral solution.

Celexa 10 mg tablets are film-coated, oval tablets containing citalopram HBr in strengths equivalent to 10 mg citalopram base. Celexa 20 mg and 40 mg tablets are film-coated, oval, scored tablets containing citalopram HBr in strengths equivalent to 20 mg or 40 mg citalopram base. The tablets also contain the following inactive ingredients: copolyvidone, corn starch, crosscarmellose sodium, glycerin, lactose monohydrate, magnesium stearate, hypromellose, microcrystalline cellulose, polyethylene glycol, and titanium dioxide. Iron oxides are used as coloring agents in the beige (10 mg) and pink (20 mg) tablets.

Celexa oral solution contains citalopram HBr equivalent to 2 mg/mL citalopram base. It also contains the following inactive ingredients: sorbitol, purified water, propylene glycol, methylparaben, natural peppermint flavor, and propylparaben.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of action of citalopram HBr as an antidepressant is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that citalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine (NE) and dopamine (DA) neuronal reuptake. Tolerance to the inhibition of 5-HT uptake is not induced by long-term (14-day) treatment of rats with citalopram. Citalopram is a racemic mixture (50/50), and the inhibition of 5-HT reuptake by citalopram is primarily due to the (S)-enantiomer.

Citalopram has no or very low affinity for 5-HT_{1A}, 5-HT_{2A}, dopamine D_1 and D_2, α_1-, α_2-, and β-adrenergic, histamine H_1, gamma aminobutyric acid (GABA), muscarinic cholinergic, and benzodiazepine receptors. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of other psychotropic drugs.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of citalopram are linear and dose-proportional in a dose range of 10-60 mg/day. Biotransformation of citalopram is mainly hepatic, with a mean terminal half-life of about 35 hours. With once daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of citalopram in plasma, based on the half-life, is expected to be 2.5 times the plasma concentrations observed after a single dose. The tablet and oral solution dosage forms of citalopram HBr are bioequivalent.

Absorption and Distribution

Following a single oral dose (40 mg tablet) of citalopram, peak blood levels occur at about 4 hours. The absolute bioavailability of citalopram was about 80% relative to an intravenous dose, and absorption is not affected by food. The volume of distribution of citalopram is about 12 L/kg and the binding of citalopram (CT), demethylcitalopram (DCT) and didemethylcitalopram (DDCT) to human plasma proteins is about 80%.

Metabolism and Elimination

Following intravenous administrations of citalopram, the fraction of drug recovered in the urine as citalopram and DCT was about 10% and 5%, respectively. The systemic clearance of citalopram was 330 mL/min, with approximately 20% of that due to renal clearance.

Citalopram is metabolized to demethylcitalopram (DCT), didemethylcitalopram (DDCT), citalopram-N-oxide, and a deaminated propionic acid derivative. In humans, unchanged citalopram is the predominant compound in plasma. At steady state, the concentrations of citalopram's metabolites, DCT and DDCT, in plasma are approximately one-half and one-tenth, respectively, that of the parent drug. *In vitro* studies show that citalopram is at least 8 times more potent than its metabolites in the inhibition of serotonin reuptake, suggesting that the metabolites evaluated do not likely contribute significantly to the antidepressant actions of citalopram.

In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of citalopram.

Population Subgroups

Age - Citalopram pharmacokinetics in subjects ≥ 60 years of age were compared to younger subjects in two normal volunteer studies. In a single-dose study, citalopram AUC and half-life were increased in the elderly subjects by 30% and 50%, respectively, whereas in a multiple-dose study they were increased by 23% and 30%, respectively. 20 mg is the recommended dose for most elderly patients (see **DOSAGE AND ADMINISTRATION**).

Gender - In three pharmacokinetic studies (total N=32), citalopram AUC in women was one and a half to two times that in men. This difference was not observed in five other pharmacokinetic studies (total N=114). In clinical studies, no differences in steady state serum citalopram levels were seen between men (N=237) and women (N=388). There were no gender differences in the pharmacokinetics of DCT and DDCT. No adjustment of dosage on the basis of gender is recommended.

Reduced hepatic function - Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 20 mg is the recommended dose for most hepatically impaired patients (see **DOSAGE AND ADMINISTRATION**).

Reduced renal function - In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of citalopram in patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of citalopram on CYP3A4, -2C9, or -2E1, but did suggest that it is a weak inhibitor of CYP1A2, -2D6, and -2C19. Citalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. However, *in vivo* data to address this question are limited.

Since CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram, it is expected that potent inhibitors of 3A4 (e.g., ketoconazole, itraconazole, and macrolide antibiotics) and potent inhibitors of CYP2C19 (e.g., omeprazole) might decrease the clearance of citalopram. However, coadministration of citalopram and the potent 3A4 inhibitor ketoconazole did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Citalopram steady state levels were not significantly different in poor metabolizers and extensive 2D6 metabolizers after multiple-dose administration of Celexa, suggesting that coadministration, with Celexa, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on citalopram metabolism. See **Drug Interactions** under **PRECAUTIONS** for more detailed information on available drug interaction data.

Clinical Efficacy Trials

The efficacy of Celexa as a treatment for depression was established in two placebo-controlled

studies (of 4 to 6 weeks in duration) in adult outpatients (ages 18-66) meeting DSM-III or DSM-III-R criteria for major depression. Study 1, a 6-week trial in which patients received fixed Celexa doses of 10, 20, 40, and 60 mg/day, showed that Celexa at doses of 40 and 60 mg/day was effective as measured by the Hamilton Depression Rating Scale (HAMD) total score, the HAMD depressed mood item (Item 1), the Montgomery Asberg Depression Rating Scale, and the Clinical Global Impression (CGI) Severity scale. This study showed no clear effect of the 10 and 20 mg/day doses, and the 60 mg/day dose was not more effective than the 40 mg/day dose. In study 2, a 4-week, placebo-controlled trial in depressed patients, of whom 85% met criteria for melancholia, the initial dose was 20 mg/day, followed by titration to the maximum tolerated dose or a maximum dose of 80 mg/day. Patients treated with Celexa showed significantly greater improvement than placebo patients on the HAMD total score, HAMD item 1, and the CGI Severity score. In three additional placebo-controlled depression trials, the difference in response to treatment between patients receiving Celexa and patients receiving placebo was not statistically significant, possibly due to high spontaneous response rate, smaller sample size, or, in the case of one study, too low a dose.

In two long-term studies, depressed patients who had responded to Celexa during an initial 6 or 8 weeks of acute treatment (fixed doses of 20 or 40 mg/day in one study and flexible doses of 20-60 mg/day in the second study) were randomized to continuation of Celexa or to placebo. In both studies, patients receiving continued Celexa treatment experienced significantly lower relapse rates over the subsequent 6 months compared to those receiving placebo. In the fixed-dose study, the decreased rate of depression relapse was similar in patients receiving 20 or 40 mg/day of Celexa.

Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.

Comparison of Clinical Trial Results

Highly variable results have been seen in the clinical development of all antidepressant drugs. Furthermore, in those circumstances when the drugs have not been studied in the same controlled clinical trial(s), comparisons among the results of studies evaluating the effectiveness of different antidepressant drug products are inherently unreliable. Because conditions of testing (e.g., patient samples, investigators, doses of the treatments administered and compared, outcome measures, etc.) vary among trials, it is virtually impossible to distinguish a difference in drug effect from a difference due to one of the confounding factors just enumerated.

INDICATIONS AND USAGE

Celexa (citalopram HBr) is indicated for the treatment of depression.

The efficacy of Celexa in the treatment of depression was established in 4-6 week, controlled trials of outpatients whose diagnosis corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder (see **CLINICAL PHARMACOLOGY**).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. The antidepressant action of Celexa in hospitalized depressed patients has not been adequately studied.

The efficacy of Celexa in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials (see **CLINICAL PHARMACOLOGY**). Nevertheless, the physician who elects to use Celexa for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**).

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

Celexa is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in Celexa.

WARNINGS

WARNINGS-Clinical Worsening and Suicide Risk

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 4400 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 1000 patients treated) are provided in **Table 1**.

TABLE 1

Age Range	**Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated**
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

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 Celexa**, for a description of the risks of discontinuation of Celexa).

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 health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Celexa 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 Celexa is not approved for use in treating bipolar depression.

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Celexa should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Celexa before starting an MAOI.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions

The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Celexa treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of Celexa with MAOIs intended to treat depression is contraindicated. If concomitant treatment of Celexa with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of Celexa with serotonin precursors (such as tryptophan) is not recommended. Treatment with Celexa and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

PRECAUTIONS

General

Discontinuation of Treatment with Celexa

During marketing of Celexa and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon 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), 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 Celexa. 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**).

Abnormal Bleeding

SSRIs and SNRIs, including Celexa, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the 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 Celexa and NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Celexa. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Celexa was discontinued. 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 **Geriatric Use**). Discontinuation of Celexa 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.

Activation of Mania/Hypomania

In placebo-controlled trials of Celexa, some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with Celexa and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants. As with all antidepressants, Celexa should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of citalopram have been observed in animal studies, Celexa has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Celexa, seizures occurred in 0.3% of patients treated with Celexa (a rate of one patient per 98 years of exposure) and 0.5% of patients treated with placebo (a rate of one patient per 50 years of exposure). Like other antidepressants, Celexa should be introduced with care in patients with a history of seizure disorder.

Interference with Cognitive and Motor Performance

In studies in normal volunteers, Celexa in doses of 40 mg/day did not produce impairment of

intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities.

Use in Patients with Concomitant Illness

Clinical experience with Celexa in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Celexa in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

Celexa has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 1116 patients who received Celexa in clinical trials were evaluated and the data indicate that Celexa is not associated with the development of clinically significant ECG abnormalities.

In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Celexa in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended (see **DOSAGE AND ADMINISTRATION**).

Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Celexa, however, it should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Celexa.

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

Although in controlled studies Celexa has not been shown to impair psychomotor performance, any psychoactive drug may impair judgment, thinking, or motor skills, so patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities.

Patients should be told that, although Celexa has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of Celexa and alcohol in depressed patients is not advised.

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

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

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breastfeeding an infant.

While patients may notice improvement with Celexa therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with Celexa and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for Celexa. 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 Celexa.

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.

Laboratory Tests
There are no specific laboratory tests recommended.

Drug Interactions
Serotonergic Drugs: Based on the mechanism of action of SNRIs and SSRIs including Celexa, and the potential for serotonin syndrome, caution is advised when Celexa is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort (see **WARNINGS-Serotonin Syndrome**). The concomitant use of **Celexa** with other SSRIs, SNRIs or tryptophan is not recommended (see **PRECAUTIONS - Drug Interactions**).

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

CNS Drugs - Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs.

Alcohol - Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking Celexa is not recommended.

Monoamine Oxidase Inhibitors (MAOIs) - See **CONTRAINDICATIONS** and **WARNINGS**.

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.) - 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 the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored

when Celexa is initiated or discontinued.

Cimetidine - In subjects who had received 21 days of 40 mg/day Celexa, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.

Digoxin - In subjects who had received 21 days of 40 mg/day Celexa, combined administration of Celexa and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.

Lithium - Coadministration of Celexa (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalopram, caution should be exercised when Celexa and lithium are coadministered.

Pimozide - In a controlled study, a single dose of pimozide 2 mg co-administered with citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.

Theophylline - Combined administration of Celexa (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.

Sumatriptan - There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised.

Warfarin - Administration of 40 mg/day Celexa for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.

Carbamazepine - Combined administration of Celexa (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the

pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered.

Triazolam - Combined administration of Celexa (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.

Ketoconazole - Combined administration of Celexa (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.

CYP3A4 and 2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and 2C19 are the primary enzymes involved in the metabolism of citalopram. However, coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance.

Metoprolol - Administration of 40 mg/day Celexa for 22 days resulted in a two-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Celexa and metoprolol had no clinically significant effects on blood pressure or heart rate.

Imipramine and Other Tricyclic Antidepressants (TCAs) - *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of Celexa (40 mg/day for 10 days) with the TCA imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCAs with Celexa.

Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and Celexa.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for

18 and 24 months, respectively. There was no evidence for carcinogenicity of citalopram in mice receiving up to 240 mg/kg/day, which is equivalent to 20 times the maximum recommended human daily dose (MRHD) of 60 mg on a surface area (mg/m^2) basis. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day, doses which are approximately 1.3 and 4 times the MRHD, respectively, on a mg/m^2 basis. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

Citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Impairment of Fertility

When citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day, approximately 5 times the MRHD of 60 mg/day on a body surface area (mg/m^2) basis. Gestation duration was increased at 48 mg/kg/day, approximately 8 times the MRHD.

Pregnancy

Pregnancy Category C

In animal reproduction studies, citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose, which is approximately 18 times the MRHD of 60 mg/day on a body surface area (mg/m^2) basis. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental, no-effect dose of 56 mg/kg/day is approximately 9 times the MRHD on a mg/m^2 basis. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of up to 16 mg/kg/day, or

approximately 5 times the MRHD on a mg/m^2 basis. Thus, teratogenic effects were observed at a maternally toxic dose in the rat and were not observed in the rabbit.

When female rats were treated with citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose, which is approximately 5 times the MRHD on a mg/m^2 basis. The no-effect dose of 12.8 mg/kg/day is approximately 2 times the MRHD on a mg/m^2 basis. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day, approximately 4 times the MRHD on a mg/m^2 basis. A no-effect dose was not determined in that study.

There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects
Neonates exposed to Celexa and other SSRIs or 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**).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1—2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

When treating a pregnant woman with Celexa during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Labor and Delivery
The effect of Celexa on labor and delivery in humans is unknown.

Nursing Mothers
As has been found to occur with many other drugs, citalopram is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or Celexa therapy should take into account the risks of citalopram exposure for the infant and the benefits of Celexa treatment for the mother.

Pediatric Use
Safety and effectiveness in the pediatric population have not been established (see **BOX WARNING and WARNINGS—Clinical Worsening and Suicide Risk**). Two placebo-controlled trials in 407 pediatric patients with MDD have been conducted with Celexa, and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of Celexa in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use
Of 4422 patients in clinical studies of Celexa, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with Celexa in clinical trials received daily doses between 20 and 40 mg (see **DOSAGE AND ADMINISTRATION**).

SSRIs and SNRIs, including Celexa, 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 two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively (see **CLINICAL PHARMACOLOGY**).

20 mg/day is the recommended dose for most elderly patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The premarketing development program for Celexa included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient-exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Celexa varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained primarily by general inquiry 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, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.

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

Among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in

placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (i.e., associated with discontinuation in at least 1% of Celexa-treated patients at a rate at least twice that of placebo) are shown in **TABLE 2**. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in this table.

TABLE 2

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled, Depression Trials		
	Percentage of Patients Discontinuing Due to Adverse Event	
	Citalopram (N=1063)	**Placebo (N=446)**
Body System/Adverse Event		
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomiting	1%	0%
Central and Peripheral		
Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Adverse Events Occurring at an Incidence of 2% or More Among Celexa-Treated Patients

Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with Celexa and for which the incidence in patients treated with Celexa was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures 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 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 non-drug factors to the adverse event incidence rate in the population studied.

The only commonly observed adverse event that occurred in Celexa patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see **TABLE 3**).

TABLE 3

Treatment-Emergent Adverse Events:		
Incidence in Placebo-Controlled Clinical Trials*		
	(Percentage of Patients Reporting Event)	
Body System/Adverse Event	**Celexa**	**Placebo**
	(N=1063)	**(N=446)**
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central & Peripheral Nervous System Disorders		
Tremor	8%	6%
Gastrointestinal Disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%
Vomiting	4%	3%
Abdominal Pain	3%	2%
General		
Fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%

Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea[1]	3%	2%
Libido Decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation Disorder[2,3]	6%	1%
Impotence[3]	3%	<1%

*Events reported by at least 2% of patients treated with Celexa are reported, except for the following events which had an incidence on placebo ≥ Celexa: headache, asthenia, dizziness, constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain.

[1]Denominator used was for females only (N=638 Celexa; N=252 placebo).

[2]Primarily ejaculatory delay.

[3]Denominator used was for males only (N=425 Celexa; N=194 placebo).

Dose Dependency of Adverse Events

The potential relationship between the dose of Celexa administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or Celexa 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response ($p<0.05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning.

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 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.

The table below displays the incidence of sexual side effects reported by at least 2% of patients taking Celexa in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	Celexa (425 males)	Placebo (194 males)
Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
Libido Decreased	3.8% (males only)	<1% (males only)
Impotence	2.8% (males only)	<1% (males only)

In female depressed patients receiving Celexa, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively.

There are no adequately designed studies examining sexual dysfunction with citalopram treatment.

Priapism has been reported with all SSRIs.

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.

Vital Sign Changes

Celexa and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Celexa treatment. In addition, a comparison of supine and standing vital sign measures for Celexa and placebo treatments indicated that Celexa treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with Celexa in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients.

Laboratory Changes

Celexa and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Celexa treatment.

ECG Changes

Electrocardiograms from Celexa (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals.

Other Events Observed During the Premarketing Evaluation of Celexa (citalopram HBr)

Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by patients treated with Celexa at multiple doses in a range of 10 to 80 mg/day during any phase of a trial within the premarketing database of 4422 patients. 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 those occurring in only one patient. It is important to emphasize that, although the events reported occurred during treatment with Celexa, 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 one 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.

Cardiovascular - *Frequent:* tachycardia, postural hypotension, hypotension. *Infrequent:* hypertension, bradycardia, edema (extremities), angina pec toris, extrasystoles, cardiac failure,

flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. *Rare:* transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block.

Central and Peripheral Nervous System Disorders - *Frequent:* paresthesia, migraine. *Infrequent:* hyperkinesia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. *Rare:* abnormal coordination, hyperesthesia, ptosis, stupor.

Endocrine Disorders - *Rare:* hypothyroidism, goiter, gynecomastia.

Gastrointestinal Disorders - *Frequent:* saliva increased, flatulence. *Infrequent:* gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. *Rare:* colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups.

General - *Infrequent:* hot flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms. *Rare:* hayfever.

Hemic and Lymphatic Disorders - *Infrequent:* purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. *Rare:* pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding.

Metabolic and Nutritional Disorders - *Frequent:* decreased weight, increased weight. *Infrequent:* increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. *Rare:* bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration.

Musculoskeletal System Disorders - *Infrequent:* arthritis, muscle weakness, skeletal pain. *Rare:* bursitis, osteoporosis.

Psychiatric Disorders - *Frequent:* impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. *Infrequent:* increased libido, aggressive reaction, paroniria, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. *Rare:* catatonic reaction, melancholia.

Reproductive Disorders/Female* - *Frequent:* amenorrhea. *Infrequent:* galactorrhea, breast pain, breast enlargement, vaginal hemorrhage.

*% based on female subjects only: 2955

Respiratory System Disorders - *Frequent:* coughing. *Infrequent:* bronchitis, dyspnea, pneumonia. *Rare:* asthma, laryngitis, bronchospasm, pneumonitis, sputum increased.

Skin and Appendages Disorders - *Frequent:* rash, pruritus. *Infrequent:* photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. *Rare:* hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani.

Special Senses - *Frequent:* accommodation abnormal, taste perversion. *Infrequent:* tinnitus, conjunctivitis, eye pain. *Rare:* mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss.

Urinary System Disorders - *Frequent:* polyuria. *Infrequent:* micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare:* facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain.

Other Events Observed During the Postmarketing Evaluation of Celexa (citalopram HBr)
It is estimated that over 30 million patients have been treated with Celexa since market introduction. Although no causal relationship to Celexa treatment has been found, the following adverse events have been reported to be temporally associated with Celexa treatment, and have not been described elsewhere in labeling: acute renal failure, akathisia, allergic reaction, anaphylaxis, angioedema, choreoathetosis, chest pain, delirium, dyskinesia, ecchymosis, epidermal necrolysis, erythema multiforme, gastrointestinal hemorrhage, glaucoma, grand mal convulsions, hemolytic anemia, hepatic necrosis, myoclonus, nystagmus, pancreatitis, priapism, prolactinemia, prothrombin decreased, QT prolonged, rhabdomyolysis, spontaneous abortion, thrombocytopenia, thrombosis, ventricular arrhythmia, torsade de pointes, and withdrawal syndrome.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Celexa (citalopram HBr) is not a controlled substance.

Physical and Psychological Dependence

Animal studies suggest that the abuse liability of Celexa is low. Celexa has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Celexa did not reveal any drug-seeking behavior. However, 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, physicians should carefully evaluate Celexa patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

In clinical trials of citalopram, there were reports of citalopram overdose, including overdoses of up to 2000mg, with no associated fatalities. During the postmarketing evaluation of citalopram, Celexa overdoses, including overdoses of up to 6000 mg, have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely reported.

Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, and sinus tachycardia. In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose.

Management of Overdose

Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of citalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Celexa.

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.

DOSAGE AND ADMINISTRATION

Initial Treatment

Celexa (citalopram HBr) should be administered at an initial dose of 20 mg once daily, generally with an increase to a dose of 40 mg/day. Dose increases should usually occur in increments of 20 mg at intervals of no less than one week. Although certain patients may require a dose of 60

mg/day, the only study pertinent to dose response for effectiveness did not demonstrate an advantage for the 60 mg/day dose over the 40 mg/day dose; doses above 40 mg are therefore not ordinarily recommended.

Celexa should be administered once daily, in the morning or evening, with or without food.

Special Populations
20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients.

No dosage adjustment is necessary for patients with mild or moderate renal impairment. Celexa should be used with caution in patients with severe renal impairment.

Treatment of Pregnant Women During the Third Trimester
Neonates exposed to Celexa and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with Celexa during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Celexa in the third trimester.

Maintenance Treatment
It is generally agreed that acute episodes of depression require several months or longer of sustained pharmacologic therapy. Systematic evaluation of Celexa in two studies has shown that its antidepressant efficacy is maintained for periods of up to 24 weeks following 6 or 8 weeks of initial treatment (32 weeks total). In one study, patients were assigned randomly to placebo or to the same dose of Celexa (20-60 mg/day) during maintenance treatment as they had received during the acute stabilization phase, while in the other study, patients were assigned randomly to continuation of Celexa 20 or 40 mg/day, or placebo, for maintenance treatment. In the latter study, the rates of relapse to depression were similar for the two dose groups (see **Clinical Trials** under **CLINICAL PHARMACOLOGY**). Based on these limited data, it is not known whether the dose of citalopram needed to maintain euthymia is identical to the dose needed to induce remission. If adverse reactions are bothersome, a decrease in dose to 20 mg/day can be considered.

Discontinuation of Treatment with Celexa
Symptoms associated with discontinuation of Celexa and other SSRIs and SNRIs have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. 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.

Switching Patients To or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of Celexa therapy. Similarly, at least 14 days should be allowed after stopping Celexa before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED

Tablets:

10 mg Bottle of 100 NDC # 0456-4010-01
Beige, oval, film-coated.
Imprint on one side with "FP". Imprint on the other side with "10 mg".

20 mg Bottle of 100 NDC # 0456-4020-01
10 x 10 Unit Dose NDC # 0456-4020-63
Pink, oval, scored, film-coated.
Imprint on scored side with "F" on the left side and "P" on the right side.
Imprint on the non-scored side with "20 mg".

40 mg Bottle of 100 NDC # 0456-4040-01
10 x 10 Unit Dose NDC # 0456-4040-63
White, oval, scored, film-coated.
Imprint on scored side with "F" on the left side and "P" on the right side.
Imprint on the non-scored side with "40 mg".

Oral Solution:
10 mg/5 mL, peppermint flavor (240 mL) NDC 0456-4130-08

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

ANIMAL TOXICOLOGY

Retinal Changes in Rats

Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day (13 times the

maximum recommended daily human dose of 60 mg on a mg/m^2 basis). Similar findings were not present in rats receiving 24 mg/kg/day for two years, in mice treated for 18 months at doses up to 240 mg/kg/day, or in dogs treated for one year at doses up to 20 mg/kg/day (4, 20, and 10 times, respectively, the maximum recommended daily human dose on a mg/m^2 basis).

Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

Cardiovascular Changes in Dogs

In a one-year toxicology study, 5 of 10 beagle dogs receiving oral doses of 8 mg/kg/day (4 times the maximum recommended daily human dose of 60 mg on a mg/m^2 basis) died suddenly between weeks 17 and 31 following initiation of treatment. Although appropriate data from that study are not available to directly compare plasma levels of citalopram (CT) and its metabolites, demethylcitalopram (DCT) and didemethylcitalopram (DDCT), to levels that have been achieved in humans, pharmacokinetic data indicate that the relative dog-to-human exposure was greater for the metabolites than for citalopram. Sudden deaths were not observed in rats at doses up to 120 mg/kg/day, which produced plasma levels of CT, DCT, and DDCT similar to those observed in dogs at doses of 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs. This effect occurred in dogs at doses producing peak DDCT plasma levels of 810 to 3250 nM (39-155 times the mean steady state DDCT plasma level measured at the maximum recommended human daily dose of 60 mg). In dogs, peak DDCT plasma concentrations are approximately equal to peak CT plasma concentrations, whereas in humans, steady state DDCT plasma concentrations are less than 10% of steady state CT plasma concentrations. Assays of DDCT plasma concentrations in 2020 citalopram-treated individuals demonstrated that DDCT levels rarely exceeded 70 nM; the highest measured level of DDCT in human overdose was 138 nM. While DDCT is ordinarily present in humans at lower levels than in dogs, it is unknown whether there are individuals who may achieve higher DDCT levels. The possibility that DCT, a principal metabolite in humans, may prolong the QT interval in dogs has not been directly examined because DCT is rapidly converted to DDCT in that species.

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Medication Guide
Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions

Read the Medication Guide that comes with you or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
2. **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
   - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very 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

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

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.
Rev. 01/09

Dr. Scott M Hogan, MD - Reviews Is this you? Claim your profile

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[illegible] [illegible] [illegible]

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1.8

★★★★★

- Excellent
- Great
- Good
- Poor
- Bad

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Most Recent

★★★★★ Five Stars

Self-verified patient of Dr. Scott M Hogan - Posted on January 27th, 2017

★★★★★ One Star

Self-verified patient of Dr. Scott M Hogan - Posted on March 2nd, 2016

He is very arrogant and negligent. Though he is very bright, he is not interested in truly helping people.

Hide Full Review ^

Accurate Diagnosis ★★★★★

★★★★★ *DO NOT USE* POOR Doctor

Self-verified patient of Dr. Scott M Hogan - Posted on September 23rd, 2015

Mr. Hogan miss diagnosed my son which led to severe problems. I urge anyone considering seeing him not too.

Hide Full Review ^

Wait time 30 min

Easy Appointment ★★★★★

Promptness	★★★★★
Friendly Staff	★★★★★
Accurate Diagnosis	★★★★★
Bedside Manner	★★★★★
Appropriate Follow-up	★★★★★
Spends Time with Me	★★★★★

★★½★★ Parent of patient

Self-verified patient of Dr. Scott M Hogan - Posted on April 9th, 2013

A horrible example of "health" care. Dr. Hogan demonstrated a lack of interest in the relevant medical history of the patient, also in working collaboratively with the child's treating Neurologist or other providers overseeing the child's therapies or medication. When asked to discuss alternative medications used to treat the symptoms or explain the discontinuation of certain medications and use of others, the Dr. refused to provide answers to the questions. I work in the medical field and understand patient rights and the difference between unreasonable and reasonable requests. I would not recommend this physician for any population, but not pediatrics, the elderly and or those with special needs.

Hide Full Review ^

Wait time	5 min
Easy Appointment	★★★★★
Promptness	★★★★★
Friendly Staff	★★★★★
Accurate Diagnosis	★★★★★
Bedside Manner	★★★★★
Appropriate Follow-up	★★★★★
Spends Time with Me	★★★★★

★★★★★ One Star

Self-verified patient of Dr. Scott M Hogan - Posted on April 19th, 2009

Hide Rating Breakdown ^

Easy Appointment	★★★★★
Promptness	★★★★★
Friendly Staff	★★★★★
Accurate Diagnosis	★★★★★
Bedside Manner	★★★★★
Spends Time with Me	★★★★★

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Dr. Scott M Hogan is similar to the following 3 Doctors near Little Rock, AR

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use INTUNIV® safely and effectively. See full prescribing information for INTUNIV®.

INTUNIV® (guanfacine) extended-release tablets, for oral use
Initial U.S. Approval: 1986

----------RECENT MAJOR CHANGES----------

Dosage and Administration, Dose Selection (2.2), 02/2013

----------INDICATIONS AND USAGE----------

INTUNIV® is a central alpha$_{2A}$-adrenergic receptor agonist indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications (1).

----------DOSAGE AND ADMINISTRATION----------

- Recommended dose: 1 to 4 mg once daily in the morning or evening (2.2).
- Begin at a dose of 1 mg once daily and adjust in increments of no more than 1 mg/week (2.2).
- Do not crush, chew or break tablets before swallowing (2.1).
- Do not administer with high-fat meals, because of increased exposure (2.1).
- Do not substitute for immediate-release guanfacine tablets on a mg-per-mg basis, because of differing pharmacokinetic profiles (2.3).
- If switching from immediate-release guanfacine, discontinue that treatment and titrate with INTUNIV® as directed (2.3).
- Consider dosing on a mg/kg basis. Improvements observed starting at doses of 0.05-0.08 mg/kg once daily. Doses up to 0.12 mg/kg once daily may provide additional benefit (2.2).
- When discontinuing, taper the dose in decrements of no more than 1 mg every 3 to 7 days (2.5).

----------DOSAGE FORMS AND STRENGTHS----------

Extended-release tablets: 1 mg, 2 mg, 3 mg and 4 mg (3)

----------CONTRAINDICATIONS----------

History of hypersensitivity to INTUNIV®, its inactive ingredients, or other products containing guanfacine (4).

----------WARNINGS AND PRECAUTIONS----------

- Hypotension, bradycardia, and syncope: Use INTUNIV® with caution in patients at risk for hypotension, bradycardia, heart block, or syncope (e.g., those taking antihypertensives). Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Advise patients to avoid becoming dehydrated or overheated (5.1).
- Sedation and somnolence: Occur commonly with INTUNIV®. Consider the potential for additive sedative effects with CNS depressant drugs. Caution patients against operating heavy equipment or driving until they know how they respond to INTUNIV® (5.2).

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥5% and at least twice placebo rate) in the monotherapy trials: somnolence, fatigue, nausea, lethargy, and hypotension (6). Most common adverse reactions (≥5% and at least twice placebo rate) in the adjunctive trial: somnolence, fatigue, insomnia, dizziness, and abdominal pain (6).

To report SUSPECTED ADVERSE REACTIONS, contact Shire US Inc. at 1-800-828-2088 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong CYP3A4 inhibitors (e.g., ketoconazole): Coadministration increases guanfacine exposure. Guanfacine dose should be limited to no more than 2 mg/day. When discontinuing CYP3A4 inhibitors, guanfacine dose should be doubled based on patient tolerability. The maximum dose should not exceed 4 mg/day (2.7 and 7).
- Strong CYP3A4 inducers (e.g., rifampin): Coadministration decreases guanfacine exposure. Guanfacine dose may be titrated up to 8 mg/day. When discontinuing CYP3A4 inducers, guanfacine dose should be decreased by half in 1-2 weeks based on patient tolerability. The maximum dose should not exceed 4 mg/day (2.7 and 7).

----------USE IN SPECIFIC POPULATIONS----------

Hepatic or Renal Impairment: dose reduction may be required in patients with clinically significant impairment of hepatic or renal function (8.6).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

INTUNIV® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications. The efficacy of INTUNIV® was studied for the treatment of ADHD in three controlled monotherapy clinical trials (up to 8 weeks in duration) and one controlled adjunctive trial with psychostimulants (8 weeks in duration) in children and adolescents ages 6-17 who met DSM-IV® criteria for ADHD [*see Clinical Studies (14)*]. The effectiveness of INTUNIV® for longer-term use (more than 8 weeks) has not been systematically evaluated in controlled trials.

2 DOSAGE AND ADMINISTRATION

2.1 General Instruction for Use

Swallow tablets whole. Do not crush, chew, or break tablets because this will increase the rate of guanfacine release. Do not administer with high fat meals, due to increased exposure.

2.2 Dose Selection

INTUNIV should be taken once daily, either in the morning or evening, at approximately same time each day. Begin at a dose of 1 mg/day, and adjust in increments of no more than 1 mg/week. Maintain the dose within the range of 1 mg to 4 mg once daily, depending on clinical response and tolerability, for both monotherapy and adjunctive therapy to a psychostimulant. Doses above 4 mg/day have not been systematically studied in controlled clinical studies *[see Clinical Studies (14.1)]*.

Clinically relevant improvements were observed beginning at doses in the range 0.05-0.08 mg/kg once daily in both mono- and adjunctive therapy. Efficacy increased with increasing weight-adjusted dose (mg/kg). If well tolerated, doses up to 0.12 mg/kg once daily may provide additional benefit.

In clinical trials, there were dose-related and exposure-related risks for several clinically significant adverse reactions (hypotension, bradycardia, sedative events). Thus, consideration should be given to dosing INTUNIV® on a mg/kg basis, in order to balance the exposure-related potential benefits and risks of treatment.

2.3 Switching from Immediate-Release Guanfacine to INTUNIV

If switching from immediate-release guanfacine, discontinue that treatment, and titrate with INTUNIV® following above recommended schedule.

Do not substitute for immediate-release guanfacine tablets on a milligram-per-milligram basis, because of differing pharmacokinetic profiles. INTUNIV® has a delayed T_{max}, reduced C_{max} and lower bioavailability compared to those of the same dose of immediate-release guanfacine *[see Clinical Pharmacology (12.3)]*.

2.4 Maintenance Treatment

It is generally agreed that pharmacological treatment of ADHD may be needed for extended period. The effectiveness of INTUNIV® for longer-term use (more than 9 weeks) has not been systematically evaluated in controlled trials. Therefore the physician electing to use INTUNIV® for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

2.5 Discontinuation

Infrequent, transient elevations in blood pressure above original baseline (i.e., rebound) have been reported to occur upon abrupt discontinuation of guanfacine. To minimize these effects, the dose should generally be tapered in decrements of no more than 1 mg every 3 to 7 days.

2.6 Missed Doses

When reinitiating patients to the previous maintenance dose after two or more missed consecutive doses, physicians should consider titration based on patient tolerability.

2.7 Dose Adjustment with Concomitant Use of Strong CYP3A4 Inhibitors or Inducers

Dosage adjustments for INTUNIV ® are recommended with concomitant use of strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole), or CYP3A4 inducers (e.g., avasimibe, carbamazepine, phenytoin, rifampin, and St.John's wort) (Table 1) *[see Drug Interactions (7)]*.

Table 1: Dose Adjustments in Patients Taking Concomitant CYP3A4 Inhibitors or Inducers

Comedications	Scenarios		
	Initiate INTUNIV ® when taking comedications	Continue INTUNIV ® when adding a comedication	Stop a comedication when continuing INTUNIV ®
Strong CYP3A4 Inhibitors	INTUNIV ® dose should be limited to 2 mg/day	INTUNIV ® dose should be decreased by half.	INTUNIV ® dose should be doubled based on patient tolerability. The maximum dose should not exceed 4 mg/day
Strong CYP3A4 Inducers	INTUNIV ® dose may be titrated up to 8 mg/day. Consider faster titration (e.g. in increments of 2 mg/week)	Consider increase INTUNIV ® dose gradually in 1-2 weeks to 2 fold of the original dose based on patient tolerability.	INTUNIV ® dose should be decreased by half in 1-2 weeks based on patient tolerability. The maximum dose should not exceed 4 mg/day

3 DOSAGE FORMS AND STRENGTHS

1 mg, 2 mg, 3 mg and 4 mg extended-release tablets

4 CONTRAINDICATIONS

Patients with a history of hypersensitivity to INTUNIV®, its inactive ingredients *[see Description (11)]* or other products containing guanfacine should not take INTUNIV®.

5 WARNINGS AND PRECAUTIONS

5.1 Hypotension, Bradycardia, and Syncope

Treatment with INTUNIV® can cause dose-dependent decreases in blood pressure and heart rate. Decreases were less pronounced over time of treatment. Orthostatic hypotension and syncope have been reported *[see Adverse Reactions (6.1)]*.

Measure heart rate and blood pressure prior to initiation of therapy, following dose increases, and periodically while on therapy. Use INTUNIV® with caution in patients with a history of hypotension, heart block, bradycardia, cardiovascular disease, or who have a history of syncope or may have a condition that predisposes them to syncope, such as hypotension, orthostatic hypotension, bradycardia, or dehydration. Use INTUNIV® with caution in patients treated concomitantly with antihypertensives or other drugs that can reduce blood pressure or heart rate or increase the risk of syncope. Advise patients to avoid becoming dehydrated or overheated.

5.2 Sedation and Somnolence

Somnolence and sedation were commonly reported adverse reactions in clinical studies [*see Adverse Reactions (6.1)]*. Before using INTUNIV® with other centrally active depressants (such as phenothiazines, barbiturates, or benzodiazepines), consider the potential for additive sedative effects. Caution patients against operating heavy equipment or driving until they know how they respond to treatment with INTUNIV®. Advise patients to avoid use with alcohol.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labelling:

- Hypotension, bradycardia, and syncope *[see Warnings and Precautions (5.1)]*
- Sedation and somnolence *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

A total of 2,028 subjects have been exposed to INTUNIV® while participating in clinical trials. This includes 1,533 patients from completed studies in children and adolescents, and 495 subjects in completed studies in adult healthy volunteers.
The mean duration of exposure of 446 patients that previously participated in two 2-year, open-label long-term studies was approximately 10 months.

Monotherapy Trials

Most Common Adverse Reactions - The most commonly observed adverse reactions (incidence ≥ 5% and at least twice the rate for placebo) in the monotherapy trials (Studies 1 and 2) with INTUNIV® were: somnolence, fatigue, nausea, lethargy, and hypotension.

Adverse Reactions Leading to Discontinuation - Twelve percent (12%) of patients receiving INTUNIV® discontinued from the monotherapy clinical studies (Studies 1 and 2) due to adverse reactions, compared to 4% in the placebo group. The most common adverse reactions leading to discontinuation of INTUNIV®-treated patients from the studies were somnolence/sedation (6%) and fatigue (2%). Less common adverse reactions leading to discontinuation (occurring in approximately 1% of patients) included: hypotension, headache, and dizziness.

Adjunctive Trial

Most Common Adverse Reactions - The most commonly observed adverse reactions (incidence ≥ 5% and at least twice the rate for placebo) in the adjunctive trial with INTUNIV® were: somnolence, fatigue, insomnia, dizziness, and abdominal pain.

Adverse Reactions Leading to Discontinuation – In the adjunctive clinical study, 3% of patients receiving INTUNIV® discontinued due to adverse reactions, compared to 1% in the placebo group. Each adverse reaction leading to discontinuation occurred in less than 1% of INTUNIV®-treated patients.

Short Term Monotherapy Clinical Studies

Common Adverse Reactions - Two short-term, placebo-controlled, double-blind pivotal studies (Studies 1 and 2) were conducted in children and adolescents with ADHD, using fixed doses of INTUNIV® (1 mg, 2 mg, 3 mg, and 4 mg/day). The most commonly reported adverse reactions (occurring in ≥ 2% of patients) that were considered drug-related and reported in a greater percentage of patients taking INTUNIV® compared to patients taking placebo are shown in Table 1. Adverse reactions that were dose-related include: somnolence/sedation, abdominal pain, dizziness, hypotension, dry mouth and constipation.

Table 1: Percentage of Patients Experiencing Common (≥ 2%) Adverse Reactions in Short-Term Monotherapy Studies 1 and 2		
Adverse Reaction Term	**All Doses of INTUNIV® (N=513)**	**Placebo (N=149)**
Somnolence[a]	38%	12%
Headache	24%	19%
Fatigue	14%	3%
Abdominal pain[b]	11%	9%
Hypotension[c]	7%	3%
Nausea	6%	2%
Lethargy	6%	3%
Dizziness	6%	4%
Irritability	6%	4%
Decreased appetite	5%	3%
Dry mouth	4%	1%
Constipation	3%	1%
a: The somnolence term includes somnolence, sedation, and hypersomnia. b: The abdominal pain term includes abdominal pain, abdominal pain upper, and abdominal pain lower c: The hypotension term includes hypotension, orthostatic hypotension, and decreased blood pressure.		

In an 8-week, placebo-controlled study in children 6-12 years of age with ADHD in which INTUNIV® was dosed once (1-4 mg/day) in the morning or evening (Study 4), the safety profile was consistent with the once daily morning dosing of INTUNIV®.

Short Term Adjunctive Clinical Study

Common Adverse Reactions - A 8-week, placebo-controlled, double-blind, dose-optimized pivotal study (Study 3) was conducted in children and adolescents aged 6-17 years with a diagnosis of ADHD who were identified as having a sub-optimal response to psychostimulants. Patients received INTUNIV® (1 mg, 2 mg, 3 mg, and 4 mg/day) or placebo, dosed in the morning or in the evening, in combination with their morning dose of psychostimulant. The most commonly reported adverse reactions (occurring in ≥ 2%

of patients in the overall INTUNIV® group) that were reported in a greater percentage of patients taking INTUNIV® compared to patients taking placebo are shown in Table 2.

Table 2: Percentage of Patients Experiencing Common (≥ 2%) Adverse Reactions in Short-Term Adjunctive Study 3

Adverse Reaction Term	All Doses of INTUNIV® (N=302)[a]	Placebo (N=153)
Headache	21%	13%
Somnolence[b]	18%	7%
Insomnia[c]	12%	6%
Fatigue	10%	3%
Abdominal pain[d]	10%	3%
Dizziness	8%	4%
Decreased appetite	7%	4%
Nausea	5%	3%
Diarrhea	4%	1%
Hypotension[e]	3%	0%
Affect lability	2%	1%
Bradycardia	2%	0%
Constipation	2%	0%
Dry mouth	2%	0%

a: The morning and evening dose groups of INTUNIV® are combined.
b: The somnolence term includes somnolence, sedation, and hypersomnia.
c: The insomnia term includes insomnia, initial insomnia, and middle insomnia.
d: The abdominal pain term includes abdominal pain, abdominal pain upper, and abdominal pain lower
e: The hypotension term includes hypotension, orthostatic hypotension, and decreased blood pressure.

Effects on Blood Pressure and Heart Rate

In the monotherapy pediatric, short-term, controlled trials (Studies 1 and 2), the maximum mean changes from baseline in systolic blood pressure, diastolic blood pressure, and pulse were −5 mmHg, −3 mmHg, and −6 bpm, respectively, for all dose groups combined (generally one week after reaching target doses of 1 mg/day, 2 mg/day, 3 mg/day or 4 mg/day). These changes were dose dependent. Decreases in blood pressure and heart rate were usually modest and asymptomatic; however, hypotension and bradycardia can occur. Hypotension was reported as an adverse reaction for 7% of the INTUNIV® group and 3% of the placebo group. This includes orthostatic hypotension, which was reported for 1% of the INTUNIV® group and none in the placebo group. In the adjunctive trial, hypotension (3%) and bradycardia (2%) were observed in patients treated with INTUNIV® as compared to none in the placebo group. In long-term, open label studies, (mean exposure of approximately 10 months), maximum decreases in systolic and diastolic blood pressure occurred in the first month

of therapy. Decreases were less pronounced over time. Syncope occurred in 1% of pediatric subjects in the clinical program. The majority of these cases occurred in the long-term, open-label studies.

Other Adverse Reactions Observed in Clinical Studies

Table 3 includes additional adverse reactions observed in short-term, placebo-controlled and long-term, open-label clinical studies not included elsewhere in section 6.1, listed by organ system.

Table 3: Other adverse reactions observed in clinical studies

Body System	**Adverse Reaction**
Cardiac	Atrioventricular block, sinus arrhythmia
Gastrointestinal	Dyspepsia, stomach discomfort, vomiting
General	Asthenia, chest pain
Immune System Disorders	Hypersensitivity
Investigations	Increased alanine amino transferase, increased weight
Nervous system	Convulsion,
Psychiatric	Agitation, anxiety, depression, nightmare
Renal	Increased urinary frequency, enuresis
Respiratory	Asthma
Vascular	Hypertension, pallor

6.2 Post-marketing Experience

The following adverse reactions have been identified during post-approval use of guanfacine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

An open-label post-marketing study involving 21,718 patients was conducted to assess the safety of guanfacine (as the hydrochloride) 1 mg/day given at bedtime for 28 days. Guanfacine was administered with or without other antihypertensive agents. Adverse events reported in the post-marketing study at an incidence greater than 1% included dry mouth, dizziness, somnolence, fatigue, headache and nausea. The most commonly

reported adverse events in this study were the same as those observed in controlled clinical trials.

Less frequent, possibly guanfacine-related events observed in the post-marketing study and/or reported spontaneously, not included in section 6.1, include:

General: edema, malaise, tremor

Cardiovascular: palpitations, tachycardia

Central Nervous System: paresthesias, vertigo

Eye Disorders: blurred vision

Musculo-Skeletal System: arthralgia, leg cramps, leg pain, myalgia

Psychiatric: confusion, hallucinations

Reproductive System, Male: impotence

Respiratory System: dyspnea

Skin and Appendages: alopecia, dermatitis, exfoliative dermatitis, pruritus, rash

Special Senses: alterations in taste

7 DRUG INTERACTIONS

Guanfacine is primarily metabolized by CYP3A4 and its plasma concentrations can be affected significantly by CYP3A4 inhibitors or inducers (Figure 1). Dose adjustments are recommended *[see Dosage and Administration (2.7)]*. Guanfacine does not significantly affect exposures of methylphenidate and lisdexamfetamine when coadministered (Figure 2). Therefore, no dose adjustments in methylphenidate or lisdexamfetamine are necessary.

Figure 1: Impact of Other Drugs on the Pharmacokinetics (PK) of Intuniv

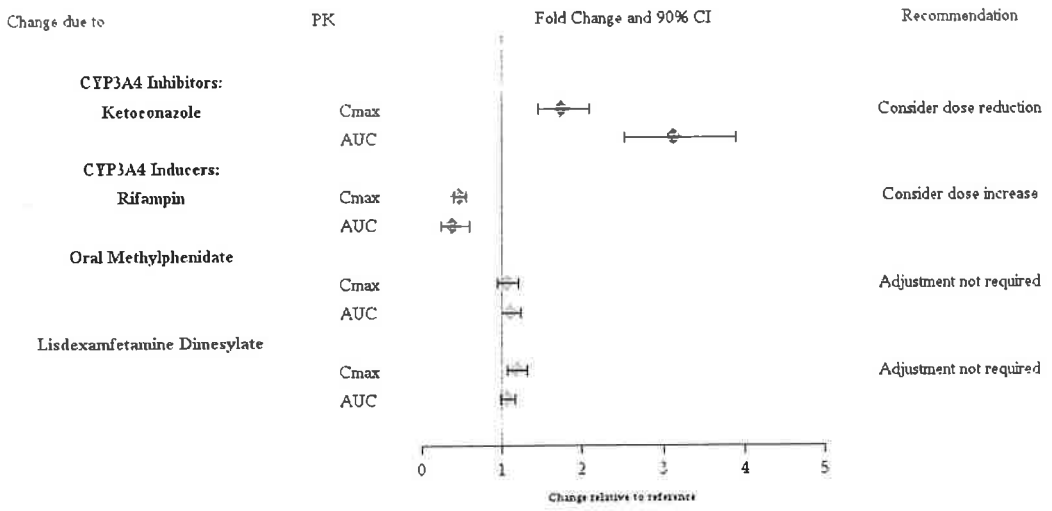
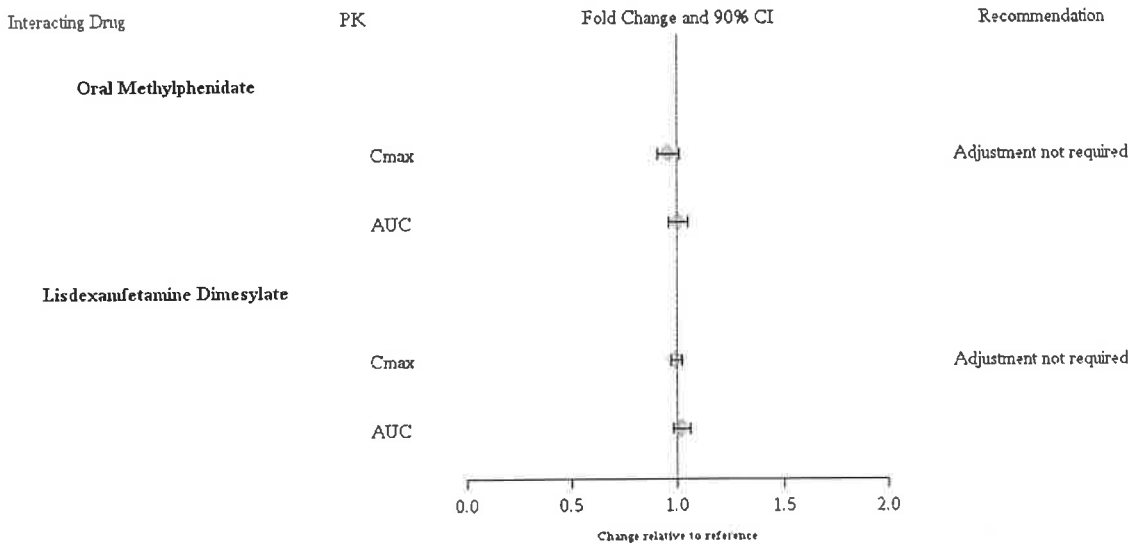


Figure 2: Impact of Intuniv on the Pharmacokinetics (PK) of Other Drugs



8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well-controlled studies of INTUNIV in pregnant women. No fetal harm was observed in rats and rabbits with administration of guanfacine at 6 and 4 times, respectively, the maximum recommended human dose. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Animal data

Reproduction studies conducted in rats have shown that guanfacine crosses the placenta. However, administration of guanfacine to rats and rabbits at 6 and 4 times, respectively, the maximum recommended human dose of 4 mg/day on a mg/m^2 basis resulted in no evidence of harm to the fetus. Higher doses (20 times the maximum recommended human dose in both rabbits and rats) were associated with reduced fetal survival and maternal toxicity.

8.3 Nursing Mothers

It is not known whether guanfacine is excreted in human milk; however, guanfacine is excreted in rat milk. Because many drugs are excreted in human milk, caution should be exercised when INTUNIV® is administered to a nursing woman. Observe human milk-fed infants for sedation and somnolence.

8.4 Pediatric Use

Safety and efficacy of INTUNIV® in pediatric patients less than 6 years of age have not been established

Animal Data

In studies in juvenile rats, guanfacine alone produced a slight delay in sexual maturation in males and females at 2-3 times the maximum recommended human dose (MRHD). Guanfacine in combination with methylphenidate produced a slight delay in sexual maturation and decreased growth as measured by a decrease in bone length in males at a dose of guanfacine comparable to the MRHD and a dose of methylphenidate approximately 4 times the MRHD.

In a study where juvenile rats were treated with guanfacine alone from 7 to 59 days of age, development was delayed as indicated by a slight delay in sexual maturation and decreased body weight gain in males at 2 mg/kg/day and in females at 3 mg/kg/day. The No Adverse Effect Level (NOAEL) for delayed sexual maturation was 1 mg/kg/day, which is equivalent to the MRHD of 4 mg/day, on a mg/m^2 basis. The effects on fertility were not evaluated in this study.

In a study where juvenile rats were treated with guanfacine in combination with methylphenidate from 7 to 59 days of age, a decrease in ulna bone length and a slight delay in sexual maturation were observed in males given 1 mg/kg/day of guanfacine in combination with 50 mg/kg/day of methylphenidate. The NOAELs for these findings were 0.3 mg/kg of guanfacine in combination with 16 mg/kg/day of methylphenidate, which are equivalent to 0.3 and 1.4 times the MRHD of 4 mg/day and 54 mg/day for guanfacine and methylphenidate, respectively, on a mg/m^2 basis. These findings were not observed with guanfacine alone at 1 mg/kg/day or methylphenidate alone at 50 mg/kg/day.

8.5 Geriatric Use

The safety and efficacy of INTUNIV® in geriatric patients have not been established.

8.6 Use in Patients with Renal or Hepatic Impairment

Renal Impairment

The impact of renal impairment on the pharmacokinetics of guanfacine in children was not assessed. In adult patients with impaired renal function, the cumulative urinary excretion of guanfacine and the renal clearance diminished as renal function decreased. In patients on hemodialysis, the dialysis clearance was about 15% of the total clearance. The low dialysis clearance suggests that the hepatic elimination (metabolism) increases as renal function decreases. It may be necessary to adjust the dose in patients with significant impairment of renal function.

Hepatic Impairment

The impact of hepatic impairment on PK of guanfacine in children was not assessed. Guanfacine in adults is cleared both by the liver and the kidney, and approximately 50% of the clearance of guanfacine is hepatic. It may be necessary to adjust the dose in patients with significant impairment of hepatic function.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

INTUNIV® is not a controlled substance and has no known potential for abuse or dependence.

10 OVERDOSAGE

Symptoms

Post-marketing reports of guanfacine overdosage indicate that hypotension, drowsiness, lethargy, and bradycardia have been observed following overdose. Initial hypertension may develop early and may be followed by hypotension. Similar symptoms have been described in voluntary reports to the American Association of Poison Control Center's National Poison Data System. Miosis of the pupils may be noted on examination. No fatal overdoses of guanfacine have been reported in published literature.

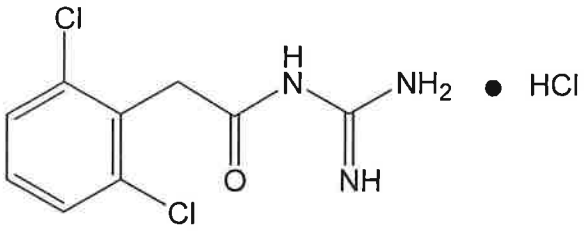
Treatment

Consult a Certified Poison Control Center by calling 1-800-222-1222 for up to date guidance and advice.

Management of INTUNIV® overdose should include monitoring for and the treatment of initial hypertension, if that occurs, as well as hypotension, bradycardia, lethargy and respiratory depression. Children and adolescents who develop lethargy should be observed for the development of more serious toxicity including coma, bradycardia and hypotension for up to 24 hours, due to the possibility of delayed onset hypotension.

11 DESCRIPTION

INTUNIV® is a once-daily, extended-release formulation of guanfacine hydrochloride (HCl) in a matrix tablet formulation for oral administration only. The chemical designation is N-amidino-2-(2,6-dichlorophenyl) acetamide monohydrochloride. The molecular formula is $C_9H_9Cl_2N_3O \cdot HCl$ corresponding to a molecular weight of 282.55. The chemical structure is:



Guanfacine HCl is a white to off-white crystalline powder, sparingly soluble in water (approximately 1 mg/mL) and alcohol and slightly soluble in acetone. The only organic solvent in which it has relatively high solubility is methanol (>30 mg/mL). Each tablet contains guanfacine HCl equivalent to 1 mg, 2 mg, 3 mg, or 4 mg of guanfacine base. The tablets also contain hypromellose, methacrylic acid copolymer, lactose, povidone, crospovidone, microcrystalline cellulose, fumaric acid, and glyceryl behenate. In addition, the 3mg and 4mg tablets also contain green pigment blend PB-1763.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Guanfacine is a central $alpha_{2A}$-adrenergic receptor agonist. Guanfacine is not a central nervous system (CNS) stimulant. The mechanism of action of guanfacine in ADHD is not known.

12.2 Pharmacodynamics

Guanfacine is a selective central $alpha_{2A}$-adrenergic receptor agonist in that it has a 15-20 times higher affinity for this receptor subtype than for the $alpha_{2B}$ or $alpha_{2C}$ subtypes.

Guanfacine is a known antihypertensive agent. By stimulating central $alpha_{2A}$-adrenergic receptors, guanfacine reduces sympathetic nerve impulses from the vasomotor center to

the heart and blood vessels. This results in a decrease in peripheral vascular resistance and a reduction in heart rate.

Effects on Height, Weight, and Body Mass Index (BMI)

Patients taking INTUNIV® demonstrated similar growth compared to normative data. Patients taking INTUNIV® had a mean increase in weight of 0.5 kg (1 lb) compared to those receiving placebo over a comparative treatment period. Patients receiving INTUNIV® for at least 12 months in open-label studies gained an average of 8 kg (17 lbs) in weight and 8 cm (3 in) in height. The height, weight, and BMI percentile remained stable in patients at 12 months in the long-term studies compared to when they began receiving INTUNIV®.

Effect on ECG

The effect of two dose levels of immediate-release guanfacine (4 mg and 8 mg) on the QT interval was evaluated in a double-blind, randomized, placebo- and active-controlled, cross-over study in healthy adults. A dose-dependent decrease in heart rate was observed during the first 12 hours, at time of maximal concentrations. The mean change in heart rate was -13 bpm at 4 mg and -22 bpm at 8 mg. An apparent increase in mean QTc was observed for both doses. However, guanfacine does not appear to interfere with cardiac repolarization of the form associated with pro-arrhythmic drugs. This finding has no known clinical relevance.

12.3 Pharmacokinetics

Absorption and Distribution

Guanfacine is readily absorbed and approximately 70% bound to plasma proteins independent of drug concentration. After oral administration of INTUNIV® the time to peak plasma concentration is approximately 5 hours in children and adolescents with ADHD.

Immediate-release guanfacine and INTUNIV® have different pharmacokinetic characteristics; dose substitution on a milligram for milligram basis will result in differences in exposure.

A comparison across studies suggests that the C_{max} is 60% lower and $AUC_{0-\infty}$ 43% lower, respectively, for INTUNIV® compared to immediate-release guanfacine. Therefore, the relative bioavailability of INTUNIV® to immediate-release guanfacine is 58%. The mean pharmacokinetic parameters in adults following the administration of INTUNIV® 1 mg once daily and immediate-release guanfacine 1mg once daily are summarized in Table 4.

Table 4: Pharmacokinetic Parameters in Adults		
Parameter	**INTUNIV® 1 mg once daily (n=52)**	**Immediate-release guanfacine 1 mg once daily (n=12)**
C_{max} (ng/mL)	1.0 ± 0.3	2.5 ± 0.6
$AUC_{0-\infty}$ (ng.h/mL)	32 ± 9	56 ± 15
t_{max} (h)	6.0 (4.0 – 8.0)	3.0 (1.5-4.0)
$t_{½}$ (h)	18 ± 4	16 ± 3

Note: Values are mean +/- SD, except for t_{max} which is median (range)

Exposure to guanfacine was higher in children (ages 6-12) compared to adolescents (ages 13-17) and adults. After oral administration of multiple doses of INTUNIV® 4 mg, the C_{max} was 10 ng/mL compared to 7 ng/mL and the AUC was 162 ng h/mL compared to 116 ng h/mL in children (ages 6-12) and adolescents (ages 13-17), respectively. These differences are probably attributable to the lower body weight of children compared to adolescents and adults.

The pharmacokinetics were affected by intake of food when a single dose of INTUNIV® 4 mg was administered with a high-fat breakfast. The mean exposure increased (C_{max} ~75% and AUC ~40%) compared to dosing in a fasted state.

Dose Proportionality

Following administration of INTUNIV® in single doses of 1 mg, 2 mg, 3 mg, and 4 mg to adults, C_{max} and $AUC_{0-\infty}$ of guanfacine were proportional to dose.

Metabolism and Elimination

In vitro studies with human liver microsomes and recombinant CYP's demonstrated that guanfacine was primarily metabolized by CYP3A4. In pooled human hepatic microsomes, guanfacine did not inhibit the activities of the major cytochrome P450 isoenzymes (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5). Guanfacine is a substrate of CYP3A4/5 and exposure is affected by CYP3A4/5 inducers/inhibitors.

Renal and Hepatic Impairment

The impact of renal impairment on PK of guanfacine in children was not assessed *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
No carcinogenic effect of guanfacine was observed in studies of 78 weeks in mice or 102 weeks in rats at doses up to 6-7 times the maximum recommended human dose of 4 mg/day on a mg/ m^2 basis.

Mutagenesis
Guanfacine was not genotoxic in a variety of test models, including the Ames test and an *in vitro* chromosomal aberration test; however, a marginal increase in numerical aberrations (polyploidy) was observed in the latter study.

Impairment of Fertility
No adverse effects were observed in fertility studies in male and female rats at doses up to 30 times the maximum recommended human dose on a mg/ m^2 basis.

14 CLINICAL STUDIES

14.1 Safety and Efficacy Studies

The efficacy of INTUNIV® in the treatment of ADHD was established in 3 placebo-controlled monotherapy trials (Studies 1, 2 and 4) and in 1 placebo-controlled adjunctive trial with psychostimulants (Study 3) in pediatric population. Studies 1, 2, and 3 were conducted in children and adolescents ages 6-17 and Study 4 was conducted in children ages 6-12 years.

Studies 1 and 2: Fixed-dose INTUNIV® Monotherapy

Study 1 was a double-blind, placebo-controlled, parallel-group, fixed dose study, in which efficacy of once daily dosing with INTUNIV® (2 mg, 3 mg and 4 mg) was evaluated for 5 weeks (n=345). Study 2 was a double-blind, placebo-controlled, parallel-group, fixed-dose study, in which efficacy of once daily dosing with INTUNIV® (1 mg, 2 mg, 3 mg and 4 mg) was evaluated for 6 weeks (n=324). In both studies, randomized subjects in 2 mg, 3 mg and 4 mg dose groups were titrated to their target fixed dose, and continued on the same dose until a dose tapering phase started The lowest dose of 1 mg used in Study 2 was assigned only to patients less than 50 kg (110 lbs). Patients who weighed less than 25 kg (55 lbs) were not included in either study.

Signs and symptoms of ADHD were evaluated on a once weekly basis using the clinician administered and scored ADHD Rating Scale (ADHD-RS-IV), which includes both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the change from baseline to endpoint in ADHD-RS-IV total scores. Endpoint was defined as the last post-randomization treatment week for which a valid score was obtained prior to dose tapering (up to Week 5 in Study 1 and up to Week 6 in Study 2).

The mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for INTUNIV® compared to placebo for Studies 1 and 2. Placebo-adjusted changes from baseline were statistically significant for each of the 2 mg, 3 mg, and 4 mg INTUNIV® randomized treatment groups in both studies, as well as the 1 mg

INTUNIV® treatment group (for patients 55-110 lbs) that was included only in Study 2 (see Table 5).

Dose-responsive efficacy was evident, particularly when data were examined on a weight-adjusted (mg/kg) basis. When evaluated over the dose range of 0.01-0.17 mg/kg/day, clinically relevant improvements were observed beginning at doses in the range 0.05-0.08 mg/kg/day. Doses up to 0.12 mg/kg/day were shown to provide additional benefit.

Controlled, monotherapy long-term efficacy studies (>9 weeks) have not been conducted.

In the monotherapy trials (Studies 1 and 2), subgroup analyses were performed to identify any differences in response based on gender or age (6-12 vs. 13-17). Analyses of the primary outcome did not suggest any differential responsiveness on the basis of gender. Analyses by age revealed a statistically significant treatment effect only in the 6-12 age subgroup. Due to the relatively small proportion of adolescent patients (ages 13-17) enrolled into these studies (approximately 25%), these data may not be sufficient to demonstrate efficacy in the adolescent patients. In these studies, patients were randomized to a fixed dose of INTUNIV® rather than optimized by body weight. Therefore, some adolescent patients were randomized to a dose that might have resulted in relatively lower plasma guanfacine concentrations compared to the younger patients. Over half (55%) of the adolescent patients received doses of 0.01-0.04mg/kg. In studies in which systematic pharmacokinetic data were obtained, there was a strong inverse correlation between body weight and plasma guanfacine concentrations.

Table 5: Fixed dose Studies

Study (Age Range)	Primary Efficacy Measure	Treatment Group				
		Placebo	Intuniv® 1mg	Intuniv® 2mg	Intuniv® 3mg	Intuniv® 4mg
1 (6 – 17 years)	Mean Baseline (SD)	38.1 (9.34)	--	36.1 (9.99)	36.8 (8.72)	38.4 (9.21)
	LS Mean Change from Baseline (SE)	-8.5 (1.42)	--	-15.9 (1.37)	-16.0 (1.38)	-18.5 (1.39)
	LS Mean Difference from Placebo (95% CI)	--	--	-7.4[a] (-11.3, -3.5)	-7.5[a] (-11.4, -3.6)	-10.0[a] (-13.9, -6.1)

	Mean Baseline (SD)	39.3 (8.85)	41.7 (7.81)	39.9 (8.74)	39.1 (9.22)	40.6 (8.57)
2 (6 – 17 years)	LS Mean Change from Baseline (SE)	-12.7 (1.60)	-19.4 (1.69)	-18.1 (1.60)	-20.0 (1.64)	-20.6 (1.60)
	LS Mean Difference from Placebo (95% CI)	--	-6.8[a] (-11.3, -2.2)	-5.4[a] (-9.9, -0.9)	-7.3[a] (-11.8, -2.8)	-7.9[a] (-12.3, -3.4)

LS Mean: least-square mean; SD: standard deviation; SE: standard error; 95% CI (unadjusted)

[a] Doses were shown to be statistically significantly superior to placebo.

Study 3: Flexible-dose INTUNIV® as Adjunctive Therapy to Psychostimulants

Study 3 was a double-blind, randomized, placebo-controlled, dose-optimization study, in which efficacy of once daily optimized dosing (morning or evening) with INTUNIV® (1mg, 2mg, 3mg and 4mg), when co-administered with psychostimulants, was evaluated for 8 weeks, in children and adolescents aged 6-17 years with a diagnosis of ADHD, with a sub-optimal response to stimulants (n=455). Subjects were started at the 1 mg INTUNIV® dose level and were titrated weekly over a 5-week dose-optimization period to an optimal INTUNIV® dose not to exceed 4 mg/day based on tolerability and clinical response. The dose was then maintained for a 3-week dose maintenance period before entry to 1 week of dose tapering. Subjects took INTUNIV® either in the morning or the evening while maintaining their current dose of psychostimulant treatment given each morning. Allowable psychostimulants in the study were ADDERALL XR®, VYVANSE®, CONCERTA®, FOCALIN XR®, RITALIN LA®, METADATE CD® or FDA-approved generic equivalents.

Symptoms of ADHD were evaluated on a weekly basis by clinicians using the ADHD Rating Scale (ADHD-RS-IV), which includes both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the change from baseline to endpoint in ADHD-RS-IV total scores. Endpoint was defined as the last post-randomization treatment week prior to dose tapering for which a valid score was obtained (up to Week 8).

Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for INTUNIV® given in combination with a psychostimulant compared to placebo given with a psychostimulant for Study 3, for both morning and evening INTUNIV® dosing (see Table 6). Nearly two-thirds (64.2%) of subjects reached optimal doses in the 0.05-0.12 mg/kg/day range.

Study 4: Flexible-dose INTUNIV® Monotherapy

Study 4 was a double-blind, randomized, placebo-controlled, dose-optimization study, in which efficacy of once daily dosing (morning or evening) with INTUNIV® (1mg, 2mg, 3mg, and 4mg) was evaluated for 8 weeks in children aged 6-12 years (n=340).

Signs and symptoms of ADHD were evaluated on a once weekly basis using the clinician administered and scored ADHD Rating Scale (ADHD-RS-IV), which includes both hyperactive/impulsive and inattentive subscales. The primary efficacy outcome was the change from baseline score at endpoint on the ADHD-RS-IV total scores. Endpoint was defined as the last post-randomization treatment week for which a valid score was obtained prior to dose tapering (up to Week 8).

Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for INTUNIV® compared to placebo in both AM and PM dosing groups of INTUNIV® (see Table 6).

Table 6: Flexible-Dose studies

Study (Age Range)		Treatment Group		
		Placebo	Intuniv® 1mg – 4mg	
			AM	PM
3[a] (6 – 17 years)	Mean Baseline (SD)	37.7 (7.75)	37.6 (8.13)	37.0 (7.65)
	LS Mean Change from Baseline (SE)	-15.9 (0.96)	-20.3 (0.97)	-21.2 (0.97)
	LS Mean Difference from Placebo (95% CI)	--	-4.5[b] (-7.5, -1.4)	-5.3[b] (-8.3, -2.3)
4 (6 – 12 years)	Mean Baseline (SD)	42.9 (6.21)	41.7 (6.39)	41.6 (6.66)
	LS Mean Change from Baseline (SE)	-10.6 (1.20)	-20.0 (1.23)	-20.4 (1.19)
	LS Mean Difference from Placebo	--	-9.4[b] (-12.8, -6.0)	-9.8[b] (-13.1, -6.4)

	(95% CI)

LS Mean: least-square mean; SD: standard deviation; SE: standard error; 95% CI (unadjusted)

[a] Treatment was given in combination with a psychostimulant.

[b] Doses were shown to be statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

INTUNIV® is supplied in 1 mg, 2 mg, 3 mg, and 4 mg strength extended-release tablets in 100 count bottles.

	1 mg	2 mg	3 mg	4 mg
Color	White/off-white	White/off-white	Green	Green
Shape	Round	Caplet	Round	Caplet
Debossment (top/bottom)	503 / 1mg	503 / 2mg	503 / 3mg	503 / 4mg
NDC number	54092-513-02	54092-515-02	54092-517-02	54092-519-02

Storage - Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

Dosing and Administration

Instruct patients to swallow INTUNIV® whole with water, milk or other liquid. Tablets should not be crushed, chewed or broken prior to administration because this may increase the rate of release of the active drug. Patients should not take INTUNIV® together with a high-fat meal, since this can raise blood levels of INTUNIV®. Instruct the parent or caregiver to supervise the child or adolescent taking INTUNIV® and to keep the bottle of tablets out of reach of children.

Instruct patients on how to properly taper the medication, if the physician decides to discontinue treatment. *[see Dosage and Administration (2.5)].*

Adverse Reactions

Advise patients that sedation can occur, particularly early in treatment or with dose increases. Caution against operating heavy equipment or driving until they know how they respond to treatment with INTUNIV® *[see Warnings and Precautions (5.2)].* Headache and abdominal pain can also occur. If any of these symptoms persist, or other symptoms occur, the patient should be advised to discuss the symptoms with the physician.

Advise patients to avoid becoming dehydrated or overheated which may potentially increase the risks of hypotension and syncope.*[see Warnings and Precautions (5.1)]*, Advise patients to avoid use with alcohol.

Patient Information

INTUNIV® (in-TOO-niv)

(guanfacine)

Extended-Release Tablets

Read the Patient Information that comes with INTUNIV® before you start taking it and each time you get a refill. There may be new information. **This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.**

What is INTUNIV®?

INTUNIV® is a prescription medicine used to treat the symptoms of attention deficit/hyperactivity disorder (ADHD).

INTUNIV® is not a central nervous system (CNS) stimulant.

What should I tell my doctor before taking INTUNIV®?

Before you take INTUNIV®, tell your doctor if you:

- have heart problems or a low heart rate
- have fainted
- have low blood pressure
- have liver or kidney problems
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if INTUNIV® will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. It is not known if INTUNIV® passes into your breast milk. Talk to your doctor about the best way to feed your baby while taking INTUNIV®.

Tell your doctor about all of the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

INTUNIV® may affect the way other medicines work, and other medicines may affect how INTUNIV® works.

Especially tell your doctor if you take:

- ketoconazole
- medicines that can affect enzyme metabolism
- high blood pressure medicine
- sedatives
- benzodiazepines
- barbiturates
- antipsychotics

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

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

How should I take INTUNIV®?

- Take INTUNIV® exactly as your doctor tells you.
- Your doctor may change your dose. Do not change your dose of INTUNIV® without talking to your doctor.
- Do not stop taking INTUNIV® without talking to your doctor.
- INTUNIV® should be taken 1 time a day in the morning or in the evening, either alone or in combination with an ADHD stimulant medication that your doctor may prescribe. Your doctor will tell you when to take INTUNIV® and when to take your ADHD stimulant medication.
- INTUNIV® should be swallowed whole with a small amount of water, milk, or other liquid.
- Do not crush, chew, or break INTUNIV®. Tell your doctor if you can not swallow INTUNIV® whole.
- Do not take INTUNIV® with a high-fat meal.
- Your doctor will check your blood pressure and heart rate while you take INTUNIV®.
- If you take too much INTUNIV®, call your local Poison Control Center or go to the nearest emergency room right away.

What should I avoid while taking INTUNIV®?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how INTUNIV® affects you. INTUNIV® can slow your thinking and motor skills.

- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking INTUNIV® until you talk with your doctor. INTUNIV® taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

What are the possible side effects of INTUNIV®?

INTUNIV® may cause serious side effects including:

- low blood pressure
- low heart rate
- fainting
- sleepiness

Get medical help right away, if you have any of the symptoms listed above.

The most common side effects of INTUNIV® include:

- sleepiness
- tiredness
- trouble sleeping
- low blood pressure
- nausea
- stomach pain
- dizziness

Tell the doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of INTUNIV®. For more information, ask your doctor or pharmacist.

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 INTUNIV®?

- Store INTUNIV® between 59^0F to 86^0F (15°C to 30°C)

Keep INTUNIV® and all medicines out of the reach of children.

General Information about INTUNIV®

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

This leaflet summarizes the most important information about INTUNIV®. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for

information about INTUNIV® that is written for health professionals.

For more information, go to **www.INTUNIV.com or call 1-800-828-2088.**

What are the ingredients in INTUNIV®?

Active ingredient: guanfacine hydrochloride

Inactive ingredients: hypromellose, methacrylic acid copolymer, lactose, povidone, crospovidone, microcrystalline cellulose, fumaric acid, and glycerol behenate. In addition, the 3mg and 4mg tablets also contain green pigment blend PB-1763.

Manufactured for Shire US Inc., Wayne, PA 19087.

INTUNIV® is a registered trademark of Shire LLC.

This product is covered by US patents including 6,287,599; 6,811,794.
Version: 0X XXXX

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRILEPTAL safely and effectively. See full prescribing information for TRILEPTAL.

TRILEPTAL® (oxcarbazepine) film-coated tablets, for oral use
TRILEPTAL® (oxcarbazepine) oral suspension
Initial U.S. Approval: 2000

RECENT MAJOR CHANGES

Contraindications (4)	3/2017
Warnings and Precautions (5.1, 5.3, 5.6, 5.7, 5.8, 5.11)	3/2017

INDICATIONS AND USAGE

TRILEPTAL is indicated for:

- Adults: Monotherapy or adjunctive therapy in the treatment of partial seizures
- Pediatrics:
  - Monotherapy in the treatment of partial seizures in children 4–16 years
  - Adjunctive therapy in the treatment of partial seizures in children 2–16 years (1)

DOSAGE AND ADMINISTRATION

Adults: initiate with a dose of 600 mg/day, given twice-a-day

- Adjunctive Therapy: Maximum increment of 600 mg/day at approximately weekly intervals. The recommended daily dose is 1200 mg/day (2.1)
- Conversion to Monotherapy: withdrawal concomitant over 3 to 6 weeks;reach maximum dose of TRILEPTAL in 2 to 4 weeks with increments of 600 mg/day at weekly intervals to a recommended daily dose of 2400 mg/day (2.2)
- Initiation of Monotherapy: Increments of 300 mg/day every third day to a dose of 1200 mg/day. (2.3)
- Initiate at one-half the usual starting dose and increase slowly in patients with a creatinine clearance <30 mL/min, (2.7)

Pediatrics: initiation with 8 to 10 mg/kg/day, given twice-a-day. For patients aged 2 to <4 years and under 20 kg, a starting dose of 16 to 20 mg/kg/day may be considered. Recommended daily dose is dependent upon patient weight.

- Adjunctive Patients (Aged 2–16 Years): For patients aged 4 to 16 years, target maintenance dose should be achieved over 2 weeks (2.4). For patients aged 2 to <4 years, maximum maintenance dose should be achieved over 2 to 4 weeks and should not to exceed 60 mg/kg/day (2.4)
- Conversion to Monotherapy for Patients (Aged 4–16 Years) Maximum increment of 10 mg/kg/day at weekly intervals, concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks (2.5)
- Initiation of Monotherapy for Patients (Aged 4–16 Years) Increments of 5 mg/kg/day every third day (2.6)

DOSAGE FORMS AND STRENGTHS

- Film-coated tablets: 150 mg, 300 mg and 600 mg (3)
- Oral suspension a 300 mg/5 mL (60 mg/mL) (3)

CONTRAINDICATIONS

Known hypersensitivity to oxcarbazepine or to any of its components, or to eslicarbazepine acetate (4, 5.2)

WARNINGS AND PRECAUTIONS

- Hyponatremia: Monitor serum sodium levels. (5.1)
- Cross Hypersensitivity Reaction to Carbamazepine: Discontinue immediately if hypersensitivity occurs. (5.3)
- Serious Dermatological Reactions: If occurs consider discontinuation. (5.4)
- Suicidal Behavior and Ideation: Monitor for suicidal thoughts/ behavior. (5.5)
- Withdrawal of AEDs: Withdraw TRILEPTAL gradually. (5.6)
- Cognitive/Neuropsychiatric Adverse Reactions: May cause cognitive dysfunction, somnolence, coordination abnormalities. Use caution when operating machinery. (5.7)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity: Monitor and discontinue if another cause cannot be established. (5.8)
- Hematologic Events: Consider discontinuing. (5.9)
- Seizure Control During Pregnancy: Active metabolite may decrease. (5.10)
- Risk of Seizure Aggravation: Discontinue if occurs. (5.11)

ADVERSE REACTIONS

The most common (≥10% more than placebo fpr adjunctive or low dose for monotherapy) adverse reactions in adults and pediatrics were: dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision,headache, nystagmus, tremor,and abnormal gait. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Phenytoin: Increased phenytoin levels. Reduced dose of phenytoin may be required. (7.1)
- Carbamazepine, Phenytoin, Phenobarbital: Decreased plasma levels of MHD (the active metabolite). Dose adjustments may be necessary. (7.1)
- Oral Contraceptive: TRILEPTAL may decrease the effectiveness of hormonal contraceptives. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: May cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TRILEPTAL is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as monotherapy in the treatment of partial seizures in pediatric patients aged 4 years and above with epilepsy, and as adjunctive therapy in pediatric patients aged 2 years and above with partial seizures.

2 DOSAGE AND ADMINISTRATION

2.1 Adjunctive Therapy for Adults

Initiate TRILEPTAL with a dose of 600 mg/day, given twice-a-day. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals; the maximum recommended daily dose is 1200 mg/day. Daily doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate the 2400 mg/day dose, primarily because of CNS effects. It is recommended that the patient be observed closely and plasma levels of the concomitant AEDs be monitored during the period of TRILEPTAL titration, as these plasma levels may be altered, especially at TRILEPTAL doses greater than 1200 mg/day [*see Drug Interactions (7.1)*].

2.2 Conversion to Monotherapy for Adults

Patients receiving concomitant AEDs may be converted to monotherapy by initiating treatment with TRILEPTAL at 600 mg/day (given in a twice-a-day regimen) while simultaneously initiating the reduction of the dose of the concomitant AEDs. The concomitant AEDs should be completely withdrawn over 3 to 6 weeks, while the maximum dose of TRILEPTAL should be reached in about 2 to 4 weeks. TRILEPTAL may be increased as clinically indicated by a maximum increment of 600 mg/day at approximately weekly intervals to achieve the maximum recommended daily dose of 2400 mg/day. A daily dose of 1200 mg/day has been shown in one study to be effective in patients in whom monotherapy has been initiated with TRILEPTAL. Patients should be observed closely during this transition phase.

2.3 Initiation of Monotherapy for Adults

Patients not currently being treated with AEDs may have monotherapy initiated with TRILEPTAL. In these patients, initiate TRILEPTAL at a dose of 600 mg/day (given a twice-a-day); the dose should be increased by 300 mg/day every third day to a dose of 1200 mg/day. Controlled trials in these patients examined the effectiveness of a 1200 mg/day dose; a dose of 2400 mg/day has been shown to be effective in patients converted from other AEDs to TRILEPTAL monotherapy (see above).

2.4 Adjunctive Therapy for Pediatric Patients (Aged 2–16 Years)

In pediatric patients aged 4–16 years, initiate TRILETPAL at a daily dose of 8 to 10 mg/kg generally not to exceed 600 mg/day, given twice-a-day. The target maintenance dose of TRILEPTAL should be achieved over 2 weeks, and is dependent upon patient weight, according to the following chart:

20 to 29 kg – 900 mg/day

29.1 to 39 kg – 1200 mg/day

>39 kg – 1800 mg/day

In the clinical trial, in which the intention was to reach these target doses, the median daily dose was 31 mg/kg with a range of 6 to 51 mg/kg.

In pediatric patients aged 2 to <4 years, initiate TRILEPTAL at a daily dose of 8 to 10 mg/kg generally not to exceed 600 mg/day, given twice-a-day. For patients less than 20 kg, a starting dose of 16 to 20 mg/kg may be considered [*see Clinical Pharmacology (12.3)*]. The maximum maintenance dose of TRILEPTAL should be achieved over 2 to 4 weeks and should not exceed 60 mg/kg/day in a twice-a-day regimen.

In the clinical trial in pediatric patients (2 to 4 years of age) in which the intention was to reach the target dose of 60 mg/kg/day, 50% of patients reached a final dose of at least 55 mg/kg/day.

Under adjunctive therapy (with and without enzyme-inducing AEDs), when normalized by body weight, apparent clearance (L/hr/kg) decreased when age increased such that children 2 to <4 years of age may require up to twice the oxcarbazepine dose per body weight compared to adults; and children 4 to ≤12 years of age may require a 50% higher oxcarbazepine dose per body weight compared to adults.

2.5 Conversion to Monotherapy for Pediatric Patients (Aged 4–16 Years)

Patients receiving concomitant antiepileptic drugs may be converted to monotherapy by initiating treatment with TRILEPTAL at approximately 8 to 10 mg/kg/day given twice-a-day, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks while TRILEPTAL may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended daily dose. Patients should be observed closely during this transition phase.

The recommended total daily dose of TRILEPTAL is shown in Table 1.

2.6 Initiation of Monotherapy for Pediatric Patients (Aged 4–16 Years)

Patients not currently being treated with antiepileptic drugs may have monotherapy initiated with TRILEPTAL. In these patients, initiate TRILEPTAL at a dose of 8 to 10 mg/kg/day given twice-a-day. The dose should be increased by 5 mg/kg/day every third day to the recommended daily dose shown in the table below.

Table 1 Range of Maintenance Doses of TRILEPTAL for Pediatrics by Weight During Monotherapy

	From	To
Weight in kg	**Dose (mg/day)**	**Dose (mg/day)**
20	600	900
25	900	1200
30	900	1200
35	900	1500
40	900	1500
45	1200	1500
50	1200	1800
55	1200	1800
60	1200	2100
65	1200	2100
70	1500	2100

2.7 Dosage Modification for Patients with Renal Impairment

In patients with impaired renal function (creatinine clearance <30 mL/min) initiate TRILEPTAL at one-half the usual starting dose (300 mg/day, given twice-a-day) and increase slowly to achieve the desired clinical response [*see Clinical Pharmacology (12.3)*].

2.8 Administration Information

TRILEPTAL can be taken with or without food [*see Clinical Pharmacology (12.3)*].

Before using TRILEPTAL oral suspension, shake the bottle well and prepare the dose immediately afterwards. The prescribed amount of oral suspension should be withdrawn from the bottle using the oral dosing syringe supplied. TRILEPTAL oral suspension can be mixed in a small glass of water just prior to administration or, alternatively, may be swallowed directly from the syringe. After each use, close the bottle and rinse the syringe with warm water and allow it to dry thoroughly.

TRILEPTAL oral suspension and TRILEPTAL film-coated tablets may be interchanged at equal doses.

3 DOSAGE FORMS AND STRENGTHS

Film-coated Tablets:

- 150 mg: pale grey-green, ovaloid, slightly biconvex, scored on both sides. Imprinted with T/D on one side and C/G on the other side.
- 300 mg: yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with TE/TE on one side and CG/CG on the other side.
- 600 mg: light pink, ovaloid, slightly biconvex, scored on both sides. Imprinted with TF/TF on one side and CG/CG on the other side.

Oral Suspension:

- 300 mg/5 mL (60 mg/mL): off-white to slightly brown or slightly red suspension.

4 CONTRAINDICATIONS

TRILEPTAL is contraindicated in patients with a known hypersensitivity to oxcarbazepine or to any of its components, or to eslicarbazepine acetate [*see Warnings and Precautions (5.2, 5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hyponatremia

Clinically significant hyponatremia (sodium <125 mmol/L) can develop during TRILEPTAL use. In the 14 controlled epilepsy studies 2.5% of TRILEPTAL-treated patients (38/1,524) had a sodium of less than 125 mmol/L at some point during treatment, compared to no such patients assigned placebo or active control (carbamazepine and phenobarbital for adjunctive and monotherapy substitution studies, and phenytoin and valproate for the monotherapy initiation studies). Clinically significant hyponatremia generally occurred during the first 3 months of treatment with TRILEPTAL, although there were patients who first developed a serum sodium <125 mmol/L more than 1 year after initiation of therapy. Most patients who developed hyponatremia were asymptomatic but patients in the clinical trials were frequently monitored and some had their TRILEPTAL dose reduced, discontinued, or had their fluid intake restricted for hyponatremia. Whether or not these maneuvers prevented the occurrence of more severe events is unknown. Cases of symptomatic hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported during postmarketing use. In clinical trials, patients whose treatment with TRILEPTAL was discontinued due to hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment.

Measurement of serum sodium levels should be considered for patients during maintenance treatment with TRILEPTAL, particularly if the patient is receiving other medications known to decrease serum sodium levels (e.g., drugs associated with inappropriate ADH secretion) or if symptoms possibly indicating hyponatremia develop (e.g., nausea, malaise, headache, lethargy, confusion, obtundation, or increase in seizure frequency or severity).

5.2 Anaphylactic Reactions and Angioedema

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of TRILEPTAL. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with TRILEPTAL, the drug should be discontinued and an alternative treatment started. These patients should not be rechallenged with the drug [*see Warnings and Precautions (5.3)*].

5.3 Cross Hypersensitivity Reaction to Carbamazepine

Approximately 25% to 30% of patients who have had hypersensitivity reactions to carbamazepine will experience hypersensitivity reactions with TRILEPTAL. For this reason patients should be specifically questioned about any prior experience with carbamazepine, and patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with TRILEPTAL only if the potential benefit justifies the potential risk. If signs or symptoms of hypersensitivity develop, TRILEPTAL should be discontinued immediately [*see Warnings and Precautions (5.2, 5.8)*].

5.4 Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults in association with TRILEPTAL use. Such serious skin reactions may be life threatening, and some patients have required hospitalization with very rare reports of fatal outcome. The median time of onset for reported cases was 19 days after treatment initiation. Recurrence of the serious skin reactions following rechallenge with TRILEPTAL has also been reported.

The reporting rate of TEN and SJS associated with TRILEPTAL use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate estimates by a factor of 3- to 10-fold. Estimates of the background incidence rate for these serious skin reactions in the general population range between 0.5 to 6 cases per million-person years. Therefore, if a patient develops a skin reaction while taking TRILEPTAL, consideration should be given to discontinuing TRILEPTAL use and prescribing another antiepileptic medication.

Association with HLA-B*1502

Patients carrying the HLA-B*1502 allele may be at increased risk for SJS/TEN with TRILEPTAL treatment.

Human Leukocyte Antigen (HLA) allele B*1502 increases the risk for developing SJS/TEN in patients treated with carbamazepine. The chemical structure of TRILEPTAL is similar to that of carbamazepine. Available clinical evidence, and

data from nonclinical studies showing a direct interaction between Trileptal and HLA-B*1502 protein, suggest that the HLA-B*1502 allele may also increase the risk for SJS/TEN with TRILEPTAL.

The frequency of HLA-B*1502 allele ranges from 2 to 12% in Han Chinese populations, is about 8% in Thai populations, and above 15% in the Philippines and in some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in people from European descent, several African populations, indigenous peoples of the Americas, Hispanic populations, and in Japanese (< 1%).

Testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with TRILEPTAL. The use of TRILEPTAL should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Consideration should also be given to avoid the use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLAB* 1502 is low, or in current TRILEPTAL users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA B*1502 status.

The use of HLA-B*1502 genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been well characterized.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including TRILEPTAL, 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 4 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 to 100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2 Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1,000 Patients	Drug Patients with Events Per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

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 TRILEPTAL 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.

5.6 Withdrawal of AEDs

As with most antiepileptic drugs, TRILEPTAL should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus [*see Dosage and Administration (2.4) and Clinical Studies (14)*]. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

5.7 Cognitive/Neuropsychiatric Adverse Reactions

Use of TRILEPTAL has been associated with central nervous system-related adverse reactions. The most significant of these can be classified into 3 general categories: 1) cognitive symptoms including psychomotor slowing, difficulty with concentration, and speech or language problems, 2) somnolence or fatigue, and 3) coordination abnormalities, including ataxia and gait disturbances.

Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on TRILEPTAL to gauge whether it adversely affects their ability to drive or operate machinery.

Adult Patients

In one large, fixed-dose study, TRILEPTAL was added to existing AED therapy (up to three concomitant AEDs). By protocol, the dosage of the concomitant AEDs could not be reduced as TRILEPTAL was added, reduction in TRILEPTAL dosage was not allowed if intolerance developed, and patients were discontinued if unable to tolerate their highest target maintenance doses. In this trial, 65% of patients were discontinued because they could not tolerate the 2400 mg/day dose of TRILEPTAL on top of existing AEDs. The adverse events seen in this study were primarily CNS related and the risk for discontinuation was dose related.

In this trial, 7.1% of oxcarbazepine-treated patients and 4% of placebo-treated patients experienced a cognitive adverse reaction. The risk of discontinuation for these events was about 6.5 times greater on oxcarbazepine than on placebo. In addition, 26% of oxcarbazepine-treated patients and 12% of placebo-treated patients experienced somnolence. The risk of discontinuation for somnolence was about 10 times greater on oxcarbazepine than on placebo. Finally, 28.7% of oxcarbazepine-treated patients and 6.4% of placebo-treated patients experienced ataxia or gait disturbances. The risk for discontinuation for these events was about 7 times greater on oxcarbazepine than on placebo.

In a single placebo-controlled monotherapy trial evaluating 2400 mg/day of TRILEPTAL, no patients in either treatment group discontinued double-blind treatment because of cognitive adverse events, somnolence, ataxia, or gait disturbance.

In the 2 dose-controlled conversion to monotherapy trials comparing 2400 mg/day and 300 mg/day TRILEPTAL, 1.1% of patients in the 2400 mg/day group discontinued double-blind treatment because of somnolence or cognitive adverse reactions compared to 0% in the 300 mg/day group. In these trials, no patients discontinued because of ataxia or gait disturbances in either treatment group.

Pediatric Patients

A study was conducted in pediatric patients (3 to 17 years old) with inadequately controlled partial seizures in which TRILEPTAL was added to existing AED therapy (up to 2 concomitant AEDs). By protocol, the dosage of concomitant AEDs could not be reduced as TRILEPTAL was added. TRILEPTAL was titrated to reach a target dose ranging from 30 mg/kg to 46 mg/kg (based on a patient's body weight with fixed doses for predefined weight ranges).

Cognitive adverse events occurred in 5.8% of oxcarbazepine-treated patients (the single most common event being concentration impairment, 4 of 138 patients) and in 3.1% of patients treated with placebo. In addition, 34.8% of oxcarbazepine-treated patients and 14.0% of placebo-treated patients experienced somnolence. (No patient discontinued due to a cognitive adverse reaction or somnolence.). Finally, 23.2% of oxcarbazepine-treated patients and 7.0% of

placebo-treated patients experienced ataxia or gait disturbances. Two (1.4%) oxcarbazepine-treated patients and 1 (0.8%) placebo-treated patient discontinued due to ataxia or gait disturbances.

5.8 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multi-organ hypersensitivity, has occurred with TRILEPTAL. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy and/or facial swelling, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present eventhough rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. TRILEPTAL should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

5.9 Hematologic Events

Rare reports of pancytopenia, agranulocytosis, and leukopenia have been seen in patients treated with TRILEPTAL during postmarketing experience. Discontinuation of the drug should be considered if any evidence of these hematologic events develops.

5.10 Seizure Control During Pregnancy

Due to physiological changes during pregnancy, plasma levels of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy. It is recommended that patients be monitored carefully during pregnancy. Close monitoring should continue through the postpartum period because MHD levels may return after delivery.

5.11 Risk of Seizure Aggravation

Exacerbation of or new onset primary generalized seizures has been reported with TRILEPTAL. The risk of aggravation of primary generalized seizures is seen especially in children but may also occur in adults. In case of seizure aggravation, TRILEPTAL should be discontinued.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in the labeling:

- Hyponatremia *[see Warnings and Precautions (5.1)]*
- Anaphylactic Reactions and Angioedema *[see Warnings and Precautions (5.2)]*
- Cross Hypersensitivity Reaction to Carbamazepine *[see Warnings and Precautions (5.3)]*
- Serious Dermatological Reactions *[see Warnings and Precautions (5.4)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.5)]*
- Cognitive/Neuropsychiatric Adverse Reactions *[see Warnings and Precautions (5.7)]*
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-Organ Hypersensitivity *[see Warnings and Precautions (5.8)]*
- Hematologic Events *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Most Common Adverse Reactions in All Clinical Studies

Adjunctive Therapy/Monotherapy in Adults Previously Treated with Other AEDs

The most common (≥10% more than placebo for adjunctive or low dose for monotherapy) adverse reactions with TRILEPTAL: dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, headache, nystagmus tremor, and abnormal gait.

Approximately 23% of these 1,537 adult patients discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: dizziness (6.4%), diplopia (5.9%), ataxia (5.2%), vomiting (5.1%), nausea (4.9%), somnolence (3.8%), headache (2.9%), fatigue (2.1%), abnormal vision (2.1%), tremor (1.8%), abnormal gait (1.7%), rash (1.4%), hyponatremia (1.0%).

Monotherapy in Adults Not Previously Treated with Other AEDs

The most common (≥5%) adverse reactions with TRILEPTAL in these patients were similar to those in previously treated patients.

Approximately 9% of these 295 adult patients discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: dizziness (1.7%), nausea (1.7%), rash (1.7%), headache (1.4%).

Adjunctive Therapy/Monotherapy in Pediatric Patients 4 Years Old and Above Previously Treated with Other AEDs

The most common (≥5%) adverse reactions with TRILEPTAL in these patients were similar to those seen in adults.

Approximately 11% of these 456 pediatric patients discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: somnolence (2.4%), vomiting (2.0%), ataxia (1.8%), diplopia (1.3%), dizziness (1.3%), fatigue (1.1%), nystagmus (1.1%).

Monotherapy in Pediatric Patients 4 Years Old and Above Not Previously Treated with Other AEDs

The most common (≥5%) adverse reactions with TRILEPTAL in these patients were similar to those in adults.

Approximately 9.2% of 152 pediatric patients discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated (≥1%) with discontinuation were rash (5.3%) and maculopapular rash (1.3%).

Adjunctive Therapy/Monotherapy in Pediatric Patients 1 Month to <4 Years Old Previously Treated or Not Previously Treated with Other AEDs:

The most common (≥5%) adverse reactions with TRILEPTAL in these patients were similar to those seen in older children and adults except for infections and infestations which were more frequently seen in these younger children.

Approximately 11% of these 241 pediatric patients discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were: convulsions (3.7%), status epilepticus (1.2%), and ataxia (1.2%).

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Adults Previously Treated with Other AEDs

Table 3 lists adverse reactions that occurred in at least 2% of adult patients with epilepsy treated with TRILEPTAL or placebo as adjunctive treatment and were numerically more common in the patients treated with any dose of TRILEPTAL.

Table 4 lists adverse reactions in patients converted from other AEDs to either high-dose TRILEPTAL (2400 mg/day) or low-dose (300 mg/day) TRILEPTAL. Note that in some of these monotherapy studies patients who dropped out during a preliminary tolerability phase are not included in the tables.

Table 3 Adverse Reactions in a Controlled Clinical Study of Adjunctive Therapy with TRILEPTAL in Adults

Body System/ Adverse Reaction	TRILEPTAL Dosage (mg/day)			
	TRILEPTAL 600 N=163 %	TRILEPTAL 1200 N=171 %	TRILEPTAL 2400 N=126 %	Placebo N=166 %
Body as a Whole				
Fatigue	15	12	15	7
Asthenia	6	3	6	5
Leg Edema	2	1	2	1
Increased Weight	1	2	2	1
Feeling Abnormal	0	1	2	0
Cardiovascular System				
Hypotension	0	1	2	0
Digestive System				
Nausea	15	25	29	10
Vomiting	13	25	36	5
Abdominal Pain	10	13	11	5
Diarrhea	5	6	7	6
Dyspepsia	5	5	6	2
Constipation	2	2	6	4
Gastritis	2	1	2	1
Metabolic and Nutritional Disorders				
Hyponatremia	3	1	2	1
Musculoskeletal System				
Muscle Weakness	1	2	2	0
Sprains and Strains	0	2	2	1
Nervous System				
Headache	32	28	26	23
Dizziness	26	32	49	13
Somnolence	20	28	36	12
Ataxia	9	17	31	5
Nystagmus	7	20	26	5
Abnormal Gait	5	10	17	1
Insomnia	4	2	3	1
Tremor	3	8	16	5
Nervousness	2	4	2	1
Agitation	1	1	2	1
Abnormal Coordination	1	3	2	1
Abnormal EEG	0	0	2	0
Speech Disorder	1	1	3	0
Confusion	1	1	2	1
Cranial Injury NOS	1	0	2	1
Dysmetria	1	2	3	0
Abnormal Thinking	0	2	4	0
Respiratory System				
Rhinitis	2	4	5	4
Skin and Appendages				
Acne	1	2	2	0
Special Senses				
Diplopia	14	30	40	5
Vertigo	6	12	15	2

Abnormal Vision	6	14	13	4
Abnormal Accommodation	0	0	2	0

Table 4 Adverse Reactions in Controlled Clinical Studies of Monotherapy with TRILEPTAL in Adults Previously Treated with Other AEDs

Body System/ Adverse Reaction	TRILEPTAL 2400 mg/day N=86 %	TRILEPTAL 300 mg/day N=86 %
Body as a Whole		
Fatigue	21	5
Fever	3	0
Allergy	2	0
Generalized Edema	2	1
Chest Pain	2	0
Digestive System		
Nausea	22	7
Vomiting	15	5
Diarrhea	7	5
Dyspepsia	6	1
Anorexia	5	3
Abdominal Pain	5	3
Dry Mouth	3	0
Hemorrhage Rectum	2	0
Toothache	2	1
Hemic and Lymphatic System		
Lymphadenopathy	2	0
Infections and Infestations		
Viral Infection	7	5
Infection	2	0
Metabolic and Nutritional Disorders		
Hyponatremia	5	0
Thirst	2	0
Nervous System		
Headache	31	15
Dizziness	28	8
Somnolence	19	5
Anxiety	7	5
Ataxia	7	1
Confusion	7	0
Nervousness	7	0
Insomnia	6	3
Tremor	6	3
Amnesia	5	1
Aggravated Convulsions	5	2
Emotional Lability	3	2
Hypoesthesia	3	1
Abnormal Coordination	2	1
Nystagmus	2	0
Speech Disorder	2	0
Respiratory System		
Upper Respiratory Tract Infection	10	5
Coughing	5	0

Bronchitis	3	0
Pharyngitis	3	0
Skin and Appendages		
Hot Flushes	2	1
Purpura	2	0
Special Senses		
Abnormal Vision	14	2
Diplopia	12	1
Taste Perversion	5	0
Vertigo	3	0
Earache	2	1
Ear Infection NOS	2	0
Urogenital and Reproductive System		
Urinary Tract Infection	5	1
Micturition Frequency	2	1
Vaginitis	2	0

Controlled Clinical Study of Monotherapy in Adults Not Previously Treated with Other AEDs

Table 5 lists adverse reactions in a controlled clinical study of monotherapy in adults not previously treated with other AEDs that occurred in at least 2% of adult patients with epilepsy treated with TRILEPTAL or placebo and were numerically more common in the patients treated with TRILEPTAL.

Table 5 Adverse Reactions in a Controlled Clinical Study of Monotherapy with TRILEPTAL in Adults Not Previously Treated with Other AEDs

Body System/ Adverse Reaction	TRILEPTAL N=55 %	Placebo N=49 %
Body as a Whole		
Falling Down NOS	4	0
Digestive System		
Nausea	16	12
Diarrhea	7	2
Vomiting	7	6
Constipation	5	0
Dyspepsia	5	4
Musculoskeletal System		
Back Pain	4	2
Nervous System		
Dizziness	22	6
Headache	13	10
Ataxia	5	0
Nervousness	5	2
Amnesia	4	2
Abnormal Coordination	4	2
Tremor	4	0
Respiratory System		
Upper Respiratory Tract Infection	7	0
Epistaxis	4	0
Infection Chest	4	0
Sinusitis	4	2
Skin and Appendages		
Rash	4	2
Special Senses		
Vision Abnormal	4	0

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated with Other AEDs

Table 6 lists adverse reactions that occurred in at least 2% of pediatric patients with epilepsy treated with TRILEPTAL or placebo as adjunctive treatment and were numerically more common in the patients treated with TRILEPTAL.

Table 6 Adverse Reactions in Controlled Clinical Studies of Adjunctive Therapy/Monotherapy with TRILEPTAL in Pediatric Patients Previously Treated with Other AEDs

Body System/ Adverse Reaction	TRILEPTAL N=171 %	Placebo N=139 %
Body as a Whole		
Fatigue	13	9
Allergy	2	0
Asthenia	2	1
Digestive System		
Vomiting	33	14
Nausea	19	5
Constipation	4	1
Dyspepsia	2	0
Nervous System		
Headache	31	19
Somnolence	31	13
Dizziness	28	8
Ataxia	13	4
Nystagmus	9	1
Emotional Lability	8	4
Abnormal Gait	8	3
Tremor	6	4
Speech Disorder	3	1
Impaired Concentration	2	1
Convulsions	2	1
Involuntary Muscle Contractions	2	1
Respiratory System		
Rhinitis	10	9
Pneumonia	2	1
Skin and Appendages		
Bruising	4	2
Increased Sweating	3	0
Special Senses		
Diplopia	17	1
Abnormal Vision	13	1
Vertigo	2	0

Other Events Observed in Association with the Administration of TRILEPTAL

In the paragraphs that follow, the adverse reactions, other than those in the preceding tables or text, that occurred in a total of 565 children and 1,574 adults exposed to TRILEPTAL and that are reasonably likely to be related to drug use are presented. Events common in the population, events reflecting chronic illness and events likely to reflect concomitant illness are omitted particularly if minor. They are listed in order of decreasing frequency. Because the reports cite events observed in open label and uncontrolled trials, the role of TRILEPTAL in their causation cannot be reliably determined.

Body as a Whole: fever, malaise, pain chest precordial, rigors, weight decrease.

Cardiovascular System: bradycardia, cardiac failure, cerebral hemorrhage, hypertension, hypotension postural, palpitation, syncope, tachycardia.

Digestive System: appetite increased, blood in stool, cholelithiasis, colitis, duodenal ulcer, dysphagia, enteritis, eructation, esophagitis, flatulence, gastric ulcer, gingival bleeding, gum hyperplasia, hematemesis, hemorrhage rectum, hemorrhoids, hiccup, mouth dry, pain biliary, pain right hypochondrium, retching, sialoadenitis, stomatitis, stomatitis ulcerative.

Hematologic and Lymphatic System: thrombocytopenia.

Laboratory Abnormality: gamma-GT increased, hyperglycemia, hypocalcemia, hypoglycemia, hypokalemia, liver enzymes elevated, serum transaminase increased.

Musculoskeletal System: hypertonia muscle.

Nervous System: aggressive reaction, amnesia, anguish, anxiety, apathy, aphasia, aura, convulsions aggravated, delirium, delusion, depressed level of consciousness, dysphonia, dystonia, emotional lability, euphoria, extrapyramidal disorder, feeling drunk, hemiplegia, hyperkinesia, hyperreflexia, hypoesthesia, hypokinesia, hyporeflexia, hypotonia, hysteria, libido decreased, libido increased, manic reaction, migraine, muscle contractions involuntary, nervousness, neuralgia, oculogyric crisis, panic disorder, paralysis, paroniria, personality disorder, psychosis, ptosis, stupor, tetany.

Respiratory System: asthma, dyspnea, epistaxis, laryngismus, pleurisy.

Skin and Appendages: acne, alopecia, angioedema, bruising, dermatitis contact, eczema, facial rash, flushing, folliculitis, heat rash, hot flushes, photosensitivity reaction, pruritus genital, psoriasis, purpura, rash erythematous, rash maculopapular, vitiligo, urticaria.

Special Senses: accommodation abnormal, cataract, conjunctival hemorrhage, edema eye, hemianopia, mydriasis, otitis externa, photophobia, scotoma, taste perversion, tinnitus, xerophthalmia.

Surgical and Medical Procedures: procedure dental oral, procedure female reproductive, procedure musculoskeletal, procedure skin.

Urogenital and Reproductive System: dysuria, hematuria, intermenstrual bleeding, leukorrhea, menorrhagia, micturition frequency, pain renal, pain urinary tract, polyuria, priapism, renal calculus.

Other: Systemic lupus erythematosus.

Laboratory Tests

Serum sodium levels below 125 mmol/L have been observed in patients treated with TRILEPTAL [*see Warnings and Precautions (5.1)*]. Experience from clinical trials indicates that serum sodium levels return toward normal when the TRILEPTAL dosage is reduced or discontinued, or when the patient was treated conservatively (e.g., fluid restriction).

Laboratory data from clinical trials suggest that TRILEPTAL use was associated with decreases in T_4, without changes in T_3 or TSH.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TRILEPTAL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: multi-organ hypersensitivity disorders characterized by features such as rash, fever, lymphadenopathy, abnormal liver function tests, eosinophilia and arthralgia [*see Warnings and Precautions (5.8)*]

Cardiovascular System: atrioventricular block

Immune System Disorders: anaphylaxis [*see Warnings and Precautions (5.2)*]

Digestive System: pancreatitis and/or lipase and/or amylase increase

Hematologic and Lymphatic Systems: aplastic anemia [*see Warnings and Precautions (5.9)*]

Metabolism and Nutrition Disorders: hypothyroidism and syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Skin and Subcutaneous Tissue Disorders: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis [*see Warnings and Precautions (5.4)*], Acute Generalized Exanthematous Pustulosis (AGEP)

Musculoskeletal, connective tissue and bone disorders: There have been reports of decreased bone mineral density, osteoporosis and fractures in patients on long-term therapy with TRILEPTAL.

Injury, Poisoning, and Procedural Complications: fall

Nervous System Disorders: dysarthria

7 DRUG INTERACTIONS

7.1 Antiepileptic Drugs

Potential interactions between TRILEPTAL and other AEDs were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarized in Table 7.

Table 7 Summary of AED Interactions with TRILEPTAL

AED Coadministered	Dose of AED (mg/day)	TRILEPTAL Dose (mg/day)	Influence of TRILEPTAL on AED Concentration (Mean Change, 90% Confidence Interval)	Influence of AED on MHD Concentration (Mean Change, 90% Confidence Interval)
Carbamazepine	400-2000	900	nc[1]	40% decrease [CI: 17% decrease, 57% decrease]
Phenobarbital	100-150	600-1800	14% increase [CI: 2% increase, 24% increase]	25% decrease [CI: 12% decrease, 51% decrease]
Phenytoin	250-500	600-1800 >1200-2400	nc[1,2] up to 40% increase[3] [CI: 12% increase, 60% increase]	30% decrease [CI: 3% decrease, 48% decrease]
Valproic acid	400-2800	600-1800	nc[1]	18% decrease [CI: 13% decrease, 40% decrease]
Lamotrigine	200	1200	nc[1]	nc[1]

[1] nc denotes a mean change of less than 10%
[2] Pediatrics
[3] Mean increase in adults at high TRILEPTAL doses

When using doses of TRILEPTAL greater than 1200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required.

Strong inducers of cytochrome P450 enzymes (i.e., carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of MHD (29% to 40%).

7.2 Hormonal Contraceptives

Concurrent use of TRILEPTAL with hormonal contraceptives may render these contraceptives less effective *[see Clinical Pharmacology (12.3)]*. Studies with other oral or implant contraceptives have not been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

TRILEPTAL levels may decrease during pregnancy [*see Warnings and Precautions (5.10)*].

Pregnancy Category C

Fetal Risk Summary

There are no adequate and well-controlled clinical studies of TRILEPTAL in pregnant women; however, TRILEPTAL is closely related structurally to carbamazepine, which is considered to be teratogenic in humans. Data on a limited number

of pregnancies from pregnancy registries suggest congenital malformations associated with TRILEPTAL monotherapy use (e.g., craniofacial defects such as oral clefts and cardiac malformations such as ventricular septal defects). TRILEPTAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Data

Animal

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity (embryolethality, growth retardation) were observed in the offspring of animals treated with either oxcarbazepine or its active 10-hydroxy metabolite (MHD) during pregnancy at doses similar to the maximum recommended human dose (MRHD).

When pregnant rats were given oxcarbazepine (30, 300, or 1000 mg/kg) orally throughout the period of organogenesis, increased incidences of fetal malformations (craniofacial, cardiovascular, and skeletal) and variations were observed at the intermediate and high doses (approximately 1.2 and 4 times, respectively, the MRHD on a mg/m^2 basis). Increased embryofetal death and decreased fetal body weights were seen at the high dose. Doses ≥300 mg/kg were also maternally toxic (decreased body weight gain, clinical signs), but there is no evidence to suggest that teratogenicity was secondary to the maternal effects.

In a study in which pregnant rabbits were orally administered MHD (20, 100, or 200 mg/kg) during organogenesis, embryofetal mortality was increased at the highest dose (1.5 times the MRHD on a mg/m^2 basis). This dose produced only minimal maternal toxicity.

In a study in which female rats were dosed orally with oxcarbazepine (25, 50, or 150 mg/kg) during the latter part of gestation and throughout the lactation period, a persistent reduction in body weights and altered behavior (decreased activity) were observed in offspring exposed to the highest dose (0.6 times the MRHD on a mg/m^2 basis). Oral administration of MHD (25, 75, or 250 mg/kg) to rats during gestation and lactation resulted in a persistent reduction in offspring weights at the highest dose (equivalent to the MRHD on a mg/m^2 basis).

Pregnancy Registry

To provide information regarding the effects of in utero exposure to TRILEPTAL, physicians are advised to recommend that pregnant patients taking TRILEPTAL 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 the registry can also be found at the website: http://www.aedpregnancyregistry.org/.

8.3 Nursing Mothers

Oxcarbazepine and its active metabolite (MHD) are excreted in human milk. A milk-to-plasma concentration ratio of 0.5 was found for both. Because of the potential for serious adverse reactions to TRILEPTAL in nursing infants, a decision should be made about whether to discontinue nursing or to discontinue the drug in nursing women, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

TRILEPTAL is indicated for use as adjunctive therapy for partial seizures in patients aged 2 to 16 years.

The safety and effectiveness for use as adjunctive therapy for partial seizures in pediatric patients below the age of 2 have not been established.

TRILEPTAL is also indicated as monotherapy for partial seizures in patients aged 4 to 16 years.

The safety and effectiveness for use as monotherapy for partial seizures in pediatric patients below the age of 4 have not been established.

TRILEPTAL has been given to 898 patients between the ages of 1 month to 17 years in controlled clinical trials (332 treated as monotherapy) and about 677 patients between the ages of 1 month to 17 years in other trials [*see Warnings and Precautions (5.11), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)*].

8.5 Geriatric Use

There were 52 patients over age 65 in controlled clinical trials and 565 patients over the age of 65 in other trials. Following administration of single (300 mg) and multiple (600 mg/day) doses of TRILEPTAL in elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the

difference was due to age-related reductions in creatinine clearance. Close monitoring of sodium levels is required in elderly patients at risk for hyponatremia [*see Warnings and Precautions (5.1)*].

8.6 Renal Impairment

Dose adjustment is recommended for renally impaired patients (CLcr<30 mL/min) [*see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

The abuse potential of TRILEPTAL has not been evaluated in human studies.

9.3 Dependence

Intragastric injections of oxcarbazepine to 4 cynomolgus monkeys demonstrated no signs of physical dependence as measured by the desire to self-administer oxcarbazepine by lever pressing activity.

10 OVERDOSAGE

10.1 Human Overdose Experience

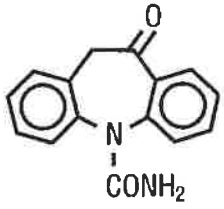
Isolated cases of overdose with TRILEPTAL have been reported. The maximum dose taken was approximately 48,000 mg. All patients recovered with symptomatic treatment. Nausea, vomiting, somnolence, aggression, agitation, hypotension, and tremor each occurred in more than one patient. Coma, confusional state, convulsion, dyscoordination, depressed level of consciousness, diplopia, dizziness, dyskinesia, dyspnea, QT prolongation, headache, miosis, nystagmus, overdose, decreased urine output, blurred vision also occurred.

10.2 Treatment and Management

There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

11 DESCRIPTION

TRILEPTAL is an antiepileptic drug available as 150 mg, 300 mg, and 600 mg film-coated tablets for oral administration. TRILEPTAL is also available as a 300 mg/5 mL (60 mg/mL) oral suspension. Oxcarbazepine is 10,11-Dihydro-10-oxo-5*H*-dibenz[b,*f*]azepine-5-carboxamide, and its structural formula is:



Oxcarbazepine is a white to faintly orange crystalline powder. It is slightly soluble in chloroform, dichloromethane, acetone, and methanol and practically insoluble in ethanol, ether and water. Its molecular weight is 252.27.

TRILEPTAL film-coated tablets contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

TRILEPTAL oral suspension contains the following inactive ingredients: ascorbic acid; dispersible cellulose; ethanol; macrogol stearate; methyl parahydroxybenzoate; propylene glycol; propyl parahydroxybenzoate; purified water; sodium saccharin; sorbic acid; sorbitol; yellow-plum-lemon aroma.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The pharmacological activity of TRILEPTAL is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine [see *Clinical Pharmacology (12.3)*]. The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, in vitro electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-

voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

12.2 Pharmacodynamics

Oxcarbazepine and its active metabolite (MHD) exhibit anticonvulsant properties in animal seizure models. They protected rodents against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures, and abolished or reduced the frequency of chronically recurring focal seizures in Rhesus monkeys with aluminum implants. No development of tolerance (i.e., attenuation of anticonvulsive activity) was observed in the maximal electroshock test when mice and rats were treated daily for 5 days and 4 weeks, respectively, with oxcarbazepine or MHD.

12.3 Pharmacokinetics

Following oral administration of TRILEPTAL tablets, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). In a mass balance study in people, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, with approximately 70% present as MHD, and the remainder attributable to minor metabolites.

The half-life of the parent is about 2 hours, while the half-life of MHD is about 9 hours, so that MHD is responsible for most antiepileptic activity.

Absorption

Based on MHD concentrations, TRILEPTAL tablets and suspension were shown to have similar bioavailability.

After single-dose administration of TRILEPTAL tablets to healthy male volunteers under fasted conditions, the median t_{max} was 4.5 (range 3 to 13) hours. After single-dose administration of TRILEPTAL oral suspension to healthy male volunteers under fasted conditions, the median t_{max} was 6 hours.

Steady-state plasma concentrations of MHD are reached within 2 to 3 days in patients when TRILEPTAL is given twice a day. At steady state the pharmacokinetics of MHD are linear and show dose proportionality over the dose range of 300 to 2400 mg/day.

Food has no effect on the rate and extent of absorption of oxcarbazepine from TRILEPTAL tablets. Although not directly studied, the oral bioavailability of the TRILEPTAL suspension is unlikely to be affected under fed conditions. Therefore, TRILEPTAL tablets and suspension can be taken with or without food.

Distribution

The apparent volume of distribution of MHD is 49 L.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Metabolism and Excretion

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of TRILEPTAL. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD).

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

The half-life of the parent is about 2 hours, while the half-life of MHD is about 9 hours.

Specific Populations

Geriatrics

Following administration of single (300 mg) and multiple (600 mg/day) doses of TRILEPTAL to elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger

volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

Pediatrics

Weight-adjusted MHD clearance decreases as age and weight increases, approaching that of adults. The mean weight-adjusted clearance in children 2 years to <4 years of age is approximately 80% higher on average than that of adults. Therefore, MHD exposure in these children is expected to be about one-half that of adults when treated with a similar weight-adjusted dose. The mean weight-adjusted clearance in children 4 to 12 years of age is approximately 40% higher on average than that of adults. Therefore, MHD exposure in these children is expected to be about three-quarters that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, the weight-adjusted MHD clearance is expected to reach that of adults.

Gender

No gender-related pharmacokinetic differences have been observed in children, adults, or the elderly.

Race

No specific studies have been conducted to assess what effect, if any, race may have on the disposition of oxcarbazepine.

Renal Impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When TRILEPTAL is administered as a single 300 mg dose in renally-impaired patients (creatinine clearance <30 mL/min), the elimination half-life of MHD is prolonged to 19 hours, with a 2-fold increase in AUC [*see Dosage and Administration (2.7) and Use in Specific Populations (8.6)*].

Hepatic Impairment

The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900-mg oral dose. Mild-to-moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD[*see Dosage and Administration (2.8)*].

Pregnancy

Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy [*see Use in Specific Populations (8.1)*]

Drug Interactions:

- In Vitro

Oxcarbazepine can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs. In addition, several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD. No autoinduction has been observed with TRILEPTAL.

Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. Results demonstrate that oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite (MHD) have little or no capacity to function as inhibitors for most of the human cytochrome P450 enzymes evaluated (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11) with the exception of CYP2C19 and CYP3A4/5. Although inhibition of CYP3A4/5 by oxcarbazepine and MHD did occur at high concentrations, it is not likely to be of clinical significance. The inhibition of CYP2C19 by oxcarbazepine and MHD can cause increased plasma concentrations of drugs that are substrates of CYP2C19, which is clinically relevant.

In vitro, the UDP-glucuronyl transferase level was increased, indicating induction of this enzyme. Increases of 22% with MHD and 47% with oxcarbazepine were observed. As MHD, the predominant plasma substrate, is only a weak inducer of UDP-glucuronyl transferase, it is unlikely to have an effect on drugs that are mainly eliminated by conjugation through UDP-glucuronyl transferase (e.g., valproic acid, lamotrigine).

In addition, oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family (CYP3A4 and CYP3A5) responsible for the metabolism of dihydropyridine calcium antagonists, oral contraceptives and cyclosporine resulting in a lower plasma concentration of these drugs.

As binding of MHD to plasma proteins is low (40%), clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

- In Vivo

For *in vivo* drug interactions [*see Drug Interactions (7)*]. *Hormonal Contraceptives*

Coadministration of TRILEPTAL with an oral contraceptive has been shown to influence the plasma concentrations of the two hormonal components, ethinylestradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE were decreased by 48% [90% CI: 22 to 65] in one study and 52% [90% CI: 38 to 52] in another study. The mean AUC values of LNG were decreased by 32% [90% CI: 20 to 45] in one study and 52% [90% CI: 42 to 52] in another study.

Other Drug Interactions

Calcium Antagonists: After repeated coadministration of TRILEPTAL, the AUC of felodipine was lowered by 28% [90% CI: 20 to 33]. Verapamil produced a decrease of 20% [90% CI: 18 to 27] of the plasma levels of MHD.

Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD. Results with warfarin show no evidence of interaction with either single or repeated doses of TRILEPTAL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In 2-year carcinogenicity studies, oxcarbazepine was administered in the diet at doses of up to 100 mg/kg/day to mice and by gavage at doses of up to 250 mg/kg/day to rats, and the pharmacologically active 10-hydroxy metabolite (MHD) was administered orally at doses of up to 600 mg/kg/day to rats. In mice, a dose-related increase in the incidence of hepatocellular adenomas was observed at oxcarbazepine doses ≥70 mg/kg/day or approximately 0.1 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. In rats, the incidence of hepatocellular carcinomas was increased in females treated with oxcarbazepine at doses ≥25 mg/kg/day (0.1 times the MRHD on a mg/m^2 basis), and incidences of hepatocellular adenomas and/or carcinomas were increased in males and females treated with MHD at doses of 600 mg/kg/day (2.4 times the MRHD on a mg/m^2 basis) and ≥250 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis), respectively. There was an increase in the incidence of benign testicular interstitial cell tumors in rats at 250 mg oxcarbazepine/kg/day and at ≥250 mg MHD/kg/day, and an increase in the incidence of granular cell tumors in the cervix and vagina in rats at 600 mg MHD/kg/day.

Mutagenesis

Oxcarbazepine increased mutation frequencies in the in vitro Ames test in the absence of metabolic activation. Both oxcarbazepine and MHD produced increases in chromosomal aberrations and polyploidy in the Chinese hamster ovary assay in vitro in the absence of metabolic activation. MHD was negative in the Ames test, and no mutagenic or clastogenic activity was found with either oxcarbazepine or MHD in V79 Chinese hamster cells in vitro. Oxcarbazepine and MHD were both negative for clastogenic or aneugenic effects (micronucleus formation) in an in vivo rat bone marrow assay.

Impairment of Fertility

In a fertility study in which rats were administered MHD (50, 150, or 450 mg/kg) orally prior to and during mating and early gestation, estrous cyclicity was disrupted and numbers of corpora lutea, implantations, and live embryos were reduced in females receiving the highest dose (approximately 2 times the MRHD on a mg/m^2 basis).

14 CLINICAL STUDIES

The effectiveness of TRILEPTAL as adjunctive and monotherapy for partial seizures in adults, and as adjunctive therapy in children aged 2 to 16 years was established in seven multicenter, randomized, controlled trials.

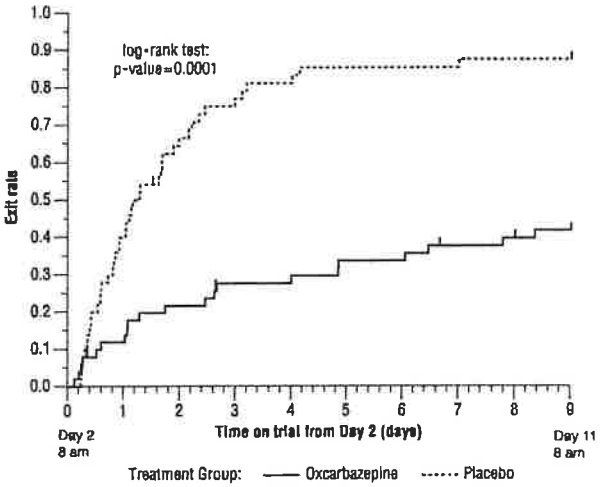
The effectiveness of TRILEPTAL as monotherapy for partial seizures in children aged 4 to 16 years was determined from data obtained in the studies described, as well as by pharmacokinetic/pharmacodynamic considerations.

14.1 TRILEPTAL Monotherapy Trials

Four randomized, controlled, double-blind, multicenter trials, conducted in a predominately adult population, demonstrated the efficacy of TRILEPTAL as monotherapy. Two trials compared TRILEPTAL to placebo and 2 trials used a randomized withdrawal design to compare a high dose (2400 mg) with a low dose (300 mg) of TRILEPTAL, after substituting TRILEPTAL 2400 mg/day for 1 or more antiepileptic drugs (AEDs). All doses were administered on a twice-a-day schedule. A fifth randomized, controlled, rater-blind, multicenter study, conducted in a pediatric population, failed to demonstrate a statistically significant difference between low and high dose TRILEPTAL treatment groups.

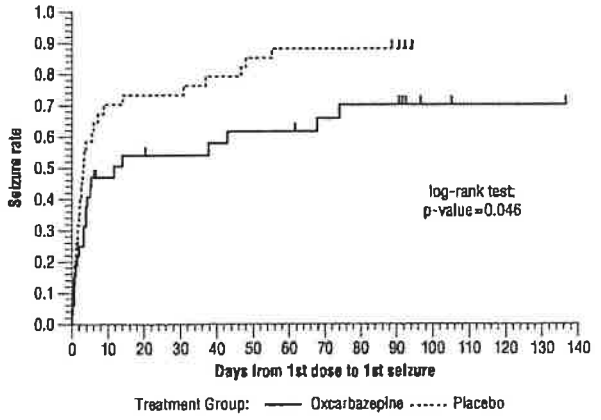
One placebo-controlled trial was conducted in 102 patients (11 to 62 years of age) with refractory partial seizures who had completed an inpatient evaluation for epilepsy surgery. Patients had been withdrawn from all AEDs and were required to have 2 to 10 partial seizures within 48 hours prior to randomization. Patients were randomized to receive either placebo or TRILEPTAL given as 1500 mg/day on Day 1 and 2400 mg/day thereafter for an additional 9 days, or until 1 of the following 3 exit criteria occurred: 1) the occurrence of a fourth partial seizure, excluding Day 1, 2) 2 new-onset secondarily generalized seizures, where such seizures were not seen in the 1-year period prior to randomization, or 3) occurrence of serial seizures or status epilepticus. The primary measure of effectiveness was a between-group comparison of the time to meet exit criteria. There was a statistically significant difference in favor of TRILEPTAL (see Figure 1), p=0.0001.

Figure 1 Kaplan-Meier Estimates of Exit Rate by Treatment Group



The second placebo-controlled trial was conducted in 67 untreated patients (8 to 69 years of age) with newly-diagnosed and recent-onset partial seizures. Patients were randomized to placebo or TRILEPTAL, initiated at 300 mg twice a day and titrated to 1200 mg/day (given as 600 mg twice a day) in 6 days, followed by maintenance treatment for 84 days. The primary measure of effectiveness was a between-group comparison of the time to first seizure. The difference between the 2 treatments was statistically significant in favor of TRILEPTAL (see Figure 2), p=0.046.

Figure 2 Kaplan-Meier Estimates of First Seizure Event Rate by Treatment Group



A third trial substituted TRILEPTAL monotherapy at 2400 mg/day for carbamazepine in 143 patients (12 to 65 years of age) whose partial seizures were inadequately controlled on carbamazepine (CBZ) monotherapy at a stable dose of 800 to 1600 mg/day, and maintained this TRILEPTAL dose for 56 days (baseline phase). Patients who were able to tolerate titration of TRILEPTAL to 2400 mg/day during simultaneous carbamazepine withdrawal were randomly assigned to either 300 mg/day of TRILEPTAL or 2400 mg/day TRILEPTAL. Patients were observed for 126 days or until 1 of the following 4 exit criteria occurred: 1) a doubling of the 28-day seizure frequency compared to baseline, 2) a 2-fold increase in the highest consecutive 2-day seizure frequency during baseline, 3) a single generalized seizure if none had occurred during baseline, or 4) a prolonged generalized seizure. The primary measure of effectiveness was a between-group comparison of the time to meet exit criteria. The difference between the curves was statistically significant in favor of the TRILEPTAL 2400 mg/day group (see Figure 3), p=0.0001.