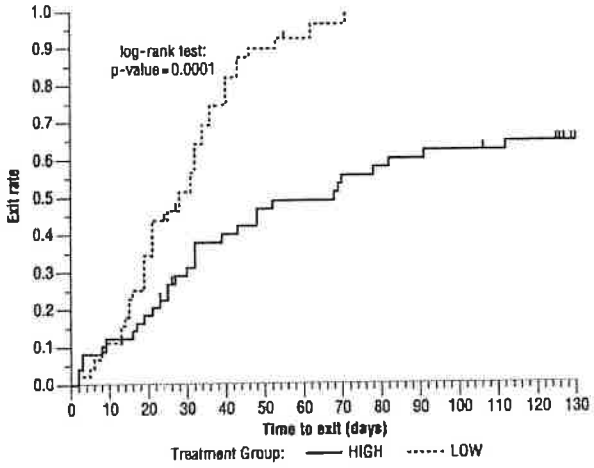
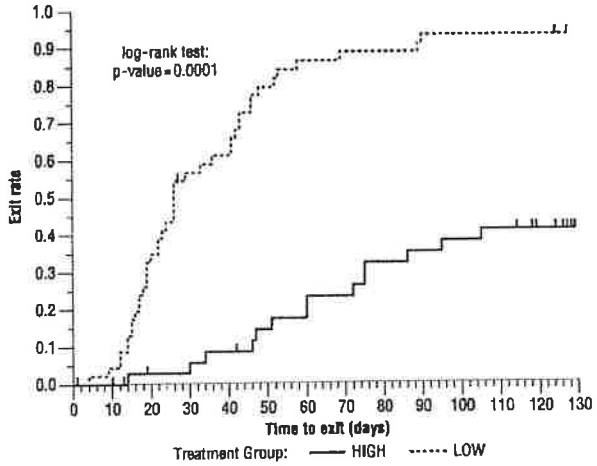
**Figure 3 Kaplan-Meier Estimates of Exit Rate by Treatment Group**




Another monotherapy substitution trial was conducted in 87 patients (11 to 66 years of age) whose seizures were inadequately controlled on 1 or 2 AEDs. Patients were randomized to either TRILEPTAL 2400 mg/day or 300 mg/day and their standard AED regimen(s) were eliminated over the first 6 weeks of double-blind therapy. Double-blind treatment continued for another 84 days (total double-blind treatment of 126 days) or until 1 of the 4 exit criteria described for the previous study occurred. The primary measure of effectiveness was a between-group comparison of the percentage of patients meeting exit criteria. The results were statistically significant in favor of the TRILEPTAL 2400 mg/day group (14/34; 41.2%) compared to the TRILEPTAL 300 mg/day group (42/45; 93.3%) ($p<0.0001$). The time to meeting one of the exit criteria was also statistically significant in favor of the TRILEPTAL 2400 mg/day group (see Figure 4), $p=0.0001$.

**Figure 4 Kaplan-Meier Estimates of Exit Rate by Treatment Group**




A monotherapy trial was conducted in 92 pediatric patients (1 month to 16 years of age) with inadequately-controlled or new-onset partial seizures. Patients were hospitalized and randomized to either TRILEPTAL 10 mg/kg/day or were titrated up to 40 to 60 mg/kg/day within 3 days while withdrawing the previous AED on the second day of TRILEPTAL . Seizures were recorded through continuous video-EEG monitoring from Day 3 to Day 5. Patients either completed the 5-day treatment or met 1 of the 2 exit criteria: 1) three study-specific seizures (i.e., electrographic partial seizures with a behavioral correlate), 2) a prolonged study-specific seizure. The primary measure of effectiveness was a between-group comparison of the time to meet exit criteria in which the difference between the curves was not statistically significant ($p=0.904$). The majority of patients from both dose groups completed the 5-day study without exiting.

Although this study failed to demonstrate an effect of oxcarbazepine as monotherapy in pediatric patients, several design elements, including the short treatment and assessment period, the absence of a true placebo, and the likely persistence of plasma levels of previously administered AEDs during the treatment period, make the results uninterpretable. For this reason, the results do not undermine the conclusion, based on pharmacokinetic/pharmacodynamic considerations, that oxcarbazepine is effective as monotherapy in pediatric patients 4 years old and older.

### 14.2 TRILEPTAL Adjunctive Therapy Trials

The effectiveness of TRILEPTAL as an adjunctive therapy for partial seizures was established in 2 multicenter, randomized, double-blind, placebo-controlled trials, one in 692 patients (15 to 66 years of age) and one in 264 pediatric patients (3 to 17 years of age), and in one multicenter, rater-blind, randomized, age-stratified, parallel-group study comparing 2 doses of oxcarbazepine in 128 pediatric patients (1 month to <4 years of age).

Patients in the 2 placebo-controlled trials were on 1 to 3 concomitant AEDs. In both of the trials, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least 8 (minimum of 1 to 4 per month) partial seizures during the baseline phase were randomly assigned to placebo or to a specific dose of TRILEPTAL in addition to their other AEDs.

In these studies, the dose was increased over a 2-week period until either the assigned dose was reached, or intolerance prevented increases. Patients then entered a 14- (pediatrics) or 24-week (adults) maintenance period.

In the adult trial, patients received fixed doses of 600, 1200 or 2400 mg/day. In the pediatric trial, patients received maintenance doses in the range of 30 to 46 mg/kg/day, depending on baseline weight. The primary measure of effectiveness in both trials was a between-group comparison of the percentage change in partial seizure frequency in the double-blind treatment phase relative to baseline phase. This comparison was statistically significant in favor of TRILEPTAL at all doses tested in both trials (p=0.0001 for all doses for both trials). The number of patients randomized to each dose, the median baseline seizure rate, and the median percentage seizure rate reduction for each trial are shown in Table 8. It is important to note that in the high-dose group in the study in adults, over 65% of patients discontinued treatment because of adverse events; only 46 (27%) of the patients in this group completed the 28-week study [*see Adverse Reactions (6)*], an outcome not seen in the monotherapy studies.

**Table 8 Summary of Percentage Change in Partial Seizure Frequency from Baseline for Placebo-Controlled Adjunctive Therapy Trials**

| Trial | Treatment Group | N | Baseline Median Seizure Rate* | Median % Reduction |
|---|---|---|---|---|
| 1 (pediatrics) | TRILEPTAL | 136 | 12.5 | 34.8[1] |
| | Placebo | 128 | 13.1 | 9.4 |
| 2 (adults) | TRILEPTAL 2400 mg/day | 174 | 10.0 | 49.9[1] |
| | TRILEPTAL 1200 mg/day | 177 | 9.8 | 40.2[1] |
| | TRILEPTAL 600 mg/day | 168 | 9.6 | 26.4[1] |
| | Placebo | 173 | 8.6 | 7.6 |

[1] p=0.0001; * = number of seizures per 28 days

Subset analyses of the antiepileptic efficacy of TRILEPTAL with regard to gender in these trials revealed no important differences in response between men and women. Because there were very few patients over the age of 65 years in controlled trials, the effect of the drug in the elderly has not been adequately assessed.

The third adjunctive therapy trial enrolled 128 pediatric patients (1 month to <4 years of age) with inadequately-controlled partial seizures on 1 to 2 concomitant AEDs. Patients who experienced at least 2 study-specific seizures (i.e., electrographic partial seizures with a behavioral correlate) during the 72-hour baseline period were randomly assigned to either TRILEPTAL 10 mg/kg/day or were titrated up to 60 mg/kg/day within 26 days. Patients were maintained on their randomized target dose for 9 days and seizures were recorded through continuous video-EEG monitoring during the last 72 hours of the maintenance period. The primary measure of effectiveness in this trial was a between-group comparison of the change in seizure frequency per 24 hours compared to the seizure frequency at baseline. For the entire group of patients enrolled, this comparison was statistically significant in favor of TRILEPTAL 60 mg/kg/day. In this study, there was no evidence that TRILEPTAL was effective in patients below the age of 2 years (N=75).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets

*150 mg Film-Coated Tablets:* pale grey-green, ovaloid, slightly biconvex, scored on both sides. Imprinted with T/D on one side and C/G on the other side.

Bottle of 100.....NDC 0078-0456-05

Unit Dose (blister pack)

Box of 100 (strips of 10).....NDC 0078-0456-35

*300 mg Film-Coated Tablets:* yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with TE/TE on one side and CG/CG on the other side.

Bottle of 100.....NDC 0078-0337-05

Unit Dose (blister pack)

Box of 100 (strips of 10).....NDC 0078-0337-06

*600 mg Film-Coated Tablets:* light pink, ovaloid, slightly biconvex, scored on both sides. Imprinted with TF/TF on one side and CG/CG on the other side.

Bottle of 100.....NDC 0078-0457-05

Unit Dose (blister pack)

Box of 100 (strips of 10).....NDC 0078-0457-35

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Dispense in tight container (USP).

Suspension

*300 mg/5 mL (60 mg/mL) Oral Suspension:* off-white to slightly brown or slightly red suspension. Available in amber glass bottles containing 250 mL of oral suspension. Supplied with a 10 mL dosing syringe and press-in bottle adapter.

Bottle containing 250 mL of oral suspension.....NDC 0078-0357-52

Store TRILEPTAL oral suspension in the original container. Shake well before using.

Use within 7 weeks of first opening the bottle.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Administration Information

Counsel patients that TRILEPTAL may be taken with or without food.

For TRILEPTAL oral suspension, advise patients to shake the bottle well and prepare the dose immediately afterwards using the oral dosing syringe supplied. Inform patients that 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. Instruct patients to discard any unused TRILEPTAL oral suspension after 7 weeks of first opening the bottle [*see Dosage and Administration (2.8) and How Supplied/Storage and Handling (16)*].

Hyponatremia

Advise patients that TRILEPTAL may reduce the serum sodium concentrations especially if they are taking other medications that can lower sodium. Instruct patients to report symptoms of low sodium like nausea, tiredness, lack of energy, confusion, and more frequent or more severe seizures [*see Warnings and Precautions (5.1)*].

Anaphylactic Reactions and Angioedema

Anaphylactic reactions and angioedema may occur during treatment with TRILEPTAL. Advise patients to report immediately signs and symptoms suggesting angioedema (swelling of the face, eyes, lips, tongue or difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician [*see Warnings and Precautions (5.2)*].

Cross Hypersensitivity Reaction to Carbamazepine

Inform patients who have exhibited hypersensitivity reactions to carbamazepine that approximately 25% to 30% of these patients may experience hypersensitivity reactions with TRILEPTAL. Patients should be advised that if they experience a

hypersensitivity reaction while taking TRILEPTAL they should consult with their physician immediately [*see Warnings and Precautions (5.3)*].

Serious Dermatological Reactions

Advise patients that serious skin reactions have been reported in association with TRILEPTAL. In the event a skin reaction should occur while taking TRILEPTAL, patients should consult with their physician immediately [*see Warnings and Precautions (5.4)*].

Suicidal Behavior and Ideation

Patients, their caregivers, and families should be counseled that AEDs, including TRILEPTAL, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers *[see Warnings and Precautions (5.5)]*.

Driving and Operating Machinery

Advise patients that TRILEPTAL may cause adverse reactions such as dizziness, somnolence, ataxia, visual disturbances, and depressed level of consciousness. Accordingly, advise patients 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 [*see Warnings and Precautions (5.7) and Adverse Reactions (6)*].

Multi-Organ Hypersensitivity

Instruct patients that a fever associated with other organ system involvement (e.g., rash, lymphadenopathy, hepatic dysfunction) may be drug-related and should be reported to their healthcare provider immediately [*see Warnings and Precautions (5.8)*].

Hematologic Events

Advise patients that there have been rare reports of blood disorders reported in patients treated with TRILEPTAL. Instruct patients to immediately consult with their physician if they experience symptoms suggestive of blood disorders [*see Warnings and Precautions (5.9)*].

Drug Interactions

Caution female patients of reproductive potential that the concurrent use of TRILEPTAL with hormonal contraceptives may render this method of contraception less effective [*see Drug Interactions (7.2)*]. Additional non-hormonal forms of contraception are recommended when using TRILEPTAL.

Caution should be exercised if alcohol is taken in combination with TRILEPTAL, due to a possible additive sedative effect.

Pregnancy Registry

Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy [*see Use in Specific Populations (8.1)*].

T2014-XX
March 2017

**MEDICATION GUIDE**
**TRILEPTAL (try-LĔP-tăl)**
**(oxcarbazepine)**
**film-coated tablets, for oral use**
**and**
**oral suspension**

**What is the most important information I should know about TRILEPTAL?**

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

**TRILEPTAL can cause serious side effects, including:**

1. **TRILEPTAL may cause the level of sodium in your blood to be low.** Symptoms of low blood sodium include:
   - nausea
   - tiredness (lack of energy)
   - headache
   - confusion
   - more frequent or more severe seizures

Similar symptoms that are not related to low sodium may occur from taking TRILEPTAL. You should tell your healthcare provider if you have any of these side effects and if they bother you or they do not go away.

Some other medicines can also cause low sodium in your blood. Be sure to tell your healthcare provider about all the other medicines that you are taking.

Your healthcare provider may do blood tests to check your sodium levels during your treatment with TRILEPTAL.

2. **TRILEPTAL may also cause allergic reactions or serious problems which may affect organs and other parts of your body like the liver or blood cells.** You may or may not have a rash with these types of reactions.

**Call your healthcare provider right away if you have any of the following:**

- swelling of your face, eyes, lips, or tongue
- trouble swallowing or breathing
- a skin rash
- hives
- fever, swollen glands, or sore throat that do not go away or come and go
- painful sores in the mouth or around your eyes
- yellowing of your skin or eyes
- unusual bruising or bleeding
- severe fatigue or weakness
- severe muscle pain
- frequent infections or infections that do not go away

Many people who are allergic to carbamazepine are also allergic to TRILEPTAL. Tell your healthcare provider if you are allergic to carbamazepine.

3. **Like other antiepileptic drugs, TRILEPTAL may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.**

**Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

**How can I watch for early symptoms of suicidal thoughts and actions?**

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

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

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

- Stopping TRILEPTAL suddenly can cause serious problems.
- Stopping a seizure medicine suddenly in a patient who has epilepsy may cause seizures that will not stop (status epilepticus).

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

**What is TRILEPTAL?**

TRILEPTAL is a prescription medicine used:

- alone or with other medicines to treat partial seizures in adults.
- alone to treat partial seizures in children 4 years and older.
- with other medicines to treat partial seizures in children 2 years and older.

It is not known if TRILEPTAL is safe and effective for use alone to treat partial seizures in children less than 4 years of age **or** for use with other medicines to treat partial seizures in children less than 2 years of age.

**Do not take TRILEPTAL if you are** allergic to TRILEPTAL or any of the other ingredients in TRILEPTAL, or to eslicarbazepine acetate. See the end of this Medication Guide for a complete list of ingredients in TRILEPTAL.

Many people who are allergic to carbamazepine are also allergic to TRILEPTAL. Tell your healthcare provider if you are allergic to carbamazepine.

**Before taking TRILEPTAL, tell your healthcare provider about all your medical conditions, including if you:**

- have or have had suicidal thoughts or actions, depression or mood problems.
- have liver problems.
- have kidney problems.
- are allergic to carbamazepine. Many people who are allergic to carbamazepine are also allergic to TRILEPTAL.
- use birth control medicine. TRILEPTAL may cause your birth control medicine to be less effective. Talk to your healthcare provider about the best birth control method to use.
- are pregnant or plan to become pregnant. TRILEPTAL may harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking TRILEPTAL. You and your healthcare provider will decide if you should take TRILEPTAL while you are pregnant.

  If you become pregnant while taking TRILEPTAL, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
- are breastfeeding or plan to breastfeed. TRILEPTAL passes into breast milk. You and your healthcare provider should decide if you will take TRILEPTAL or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking TRILEPTAL with certain other medicines may cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.
Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

**How should I take TRILEPTAL?**

- Do not stop taking TRILEPTAL without talking to your healthcare provider. Stopping TRILEPTAL suddenly can cause serious problems, including seizures that will not stop (status epilepticus).
- Take TRILEPTAL exactly as prescribed. Your healthcare provider may change your dose. Your healthcare provider will tell you how much TRILEPTAL to take.
- Take TRILEPTAL 2 times a day.
- Take TRILEPTAL with or without food.
- Before taking TRILEPTAL oral suspension shake the bottle well and use the oral dosing syringe that comes with your oral suspension to measure the amount of medicine needed. TRILEPTAL oral suspension can be mixed in a small glass of water, or swallowed directly from the syringe. Clean the syringe with warm water and let it dry after each use.
- If you take too much TRILEPTAL, call your healthcare provider right away.

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

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

**What are the possible side effects of TRILEPTAL?**
See "**What is the most important information I should know about TRILEPTAL?**"
**TRILEPTAL may cause other serious side effects including:**

- trouble concentrating
- problems with your speech and language
- feeling confused
- feeling sleepy and tired
- trouble with walking and coordination
- seizures that can happen more often or become worse, especially in children

**Get medical help right away if you have any of the symptoms listed above or listed in "What is the most important information I should know about TRILEPTAL?"**
**The most common side effects of TRILEPTAL include:**

- dizziness
- sleepiness
- double vision
- tiredness
- nausea
- vomiting
- problems with vision
- trembling
- problems with walking and coordination (unsteadiness)
- rash

These are not all the possible side effects of TRILEPTAL. Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

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

**How should I store TRILEPTAL?**

- Store TRILEPTAL film-coated tablets and oral suspension at room temperature between 15°C to 30°C (59°F to 86°F)
- Keep TRILEPTAL film-coated tablets dry.
- Keep TRILEPTAL oral suspension in the original container and use within 7 weeks of first opening the bottle. Shake well before using.

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

**General Information about the safe and effective use of TRILEPTAL.**

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

You can ask your pharmacist or healthcare provider for information about TRILEPTAL that is written for health professionals.

**What are the ingredients in TRILEPTAL?**

**Active ingredient**: oxcarbazepine

**Inactive ingredients**:

- **Film-coated tablets**: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc and titanium dioxide.
- **Oral suspension**: ascorbic acid, dispersible cellulose, ethanol, macrogol stearate, methyl parahydroxybenzoate, propylene glycol, propyl parahydroxybenzoate, purified water, sodium saccharin, sorbic acid, sorbitol, yellow-plum-lemon aroma.

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For more information, go to www.pharma.us.novartis.com or call 1-888-669-6682.
This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 03/2017

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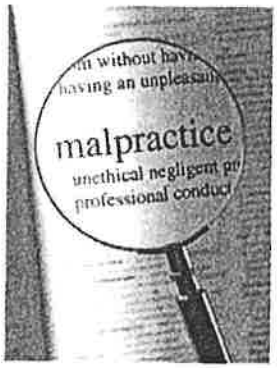
# What is Medical Malpractice?




## ABPLA Board Certified Medical Malpractice Attorneys
## The Top Medical Malpractice Attorneys in America

Medical malpractice occurs when a hospital, doctor or other health care professional, through a negligent act or omission, causes an injury to a patient. The negligence might be the result of errors in diagnosis, treatment, aftercare or health management.

To be considered medical malpractice under the law, the claim must have the following characteristics:

- **A violation of the standard of care** - The law acknowledges that there are certain medical standards that are recognized by the profession as being acceptable medical treatment by reasonably prudent health care professionals under like or similar circumstances. This is known as the standard of care. A patient has the right to expect that health care professionals will deliver care that is consistent with these standards. If it is determined that the standard of care has not been met, then negligence may be established.
- **An injury was caused by the negligence** - For a medical malpractice claim to be valid, it is not sufficient that a health care professional simply violated the standard of care. The patient must also prove he or she sustained an injury that would not have occurred in the absence of negligence. An unfavorable outcome by itself is not malpractice. The patient must prove that the negligence caused the injury. If there is an injury without negligence or negligence that did not cause an injury, there is no case.
- **The injury resulted in significant damages** - Medical malpractice lawsuits are extremely expensive to litigate, frequently requiring testimony of numerous medical experts and countless hours of deposition testimony. For a case to be viable, the patient must show that significant damages resulted from an injury received due to the medical negligence. If the damages are small, the cost of pursuing the case might be greater than the eventual recovery. To pursue a medical malpractice claim, the patient must show that the injury resulted in disability, loss of income, unusual pain, suffering and hardship, or significant past and future medical bills.

**Examples of Medical Malpractice**

## Announcements

**Diplomate Nomination** - Know attorneys who qualify to be a Diplomate of the ABPLA? Nominate them today!

**ABPLA Board of Governors**

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- Thomas G. Rayfield
- John Romano
- Thomas Sartwelle
- Randy Scarlett
- Ben Stewart
- Bennett Wasserman
- Grace Weatherly
- Paul Weathington



Medical malpractice can take many forms. Here are some examples of medical negligence that might lead to a lawsuit:

- Failure to diagnose or misdiagnosis
- Misreading or ignoring laboratory results
- Unnecessary surgery
- Surgical errors or wrong site surgery
- Improper medication or dosage
- Poor follow-up or aftercare
- Premature discharge
- Disregarding or not taking appropriate patient history
- Failure to order proper testing
- Failure to recognize symptoms

#### Choose a Board Certified Medical Malpractice Attorney

If you believe that you or a family member may have been a victim of medical malpractice resulting in serious injury, you should consult a Board Certified medical malpractice attorney.

ABPLA Board Certified medical malpractice attorneys are among the best medical malpractice attorneys in the country. Each Board Certified attorney must meet and exceed rigorous standards through Experience, Ethics, Education, Examination and Excellence in professional liability law.

# What is Legal Malpractice?

## ABPLA Board Certified Legal Malpractice Attorneys

## Experts in Attorney Malpractice

Legal malpractice occurs when a lawyer commits an error, omission or breach of duty to the client or the justice system that results in a negative legal outcome or monetary loss for the client or a third party.

To be considered malpractice under the law, the claim must have the following characteristics:

- **There was a violation of the standard of professional conduct** - The law acknowledges that there are certain legal standards that are recognized by the profession as being acceptable conduct. These standards of professional conduct are largely determined by the ethics rules of the state bar association. Attorneys have an obligation to their clients and the bar to operate within these standards. Clients have the right to expect attorneys will follow the law, behave in an ethical and honest manner, act in the best interests of their clients with integrity, diligence and good faith, and will execute their matters at a level of competency that protects their legal rights. Lawyers must also maintain and supply clients with full and detailed reports of all money and/or property handled for them. Finally, attorneys must not inflict damage on third parties through frivolous litigation or malicious prosecution. If it is determined that the standards of professional conduct have been violated, then negligence may be established.
- **The negligence caused a negative legal outcome** - It is not sufficient that an attorney simply was negligent for a legal malpractice claim to be valid. The plaintiff must also prove that there were legal, monetary or other negative ramifications that were caused by the negligence. An unfavorable outcome by itself is not malpractice. There must be a direct causative link between a violation of the standard of professional conduct and the negative result.
- **The negligence resulted in significant damages** - Legal malpractice lawsuits are expensive to litigate. For a case to be viable, the plaintiff must show significant damages that resulted from the negligence. If the damages are small, the cost of pursuing the case might be greater than the eventual recovery. To be worth pursuing, the plaintiff must show that the outcome resulted in losses far in excess of the amount of legal fees and expenses necessary to bring the action.

#### Examples of Lawyer Negligence

Attorney malpractice can take many forms. Here are some examples of legal negligence that might lead to a

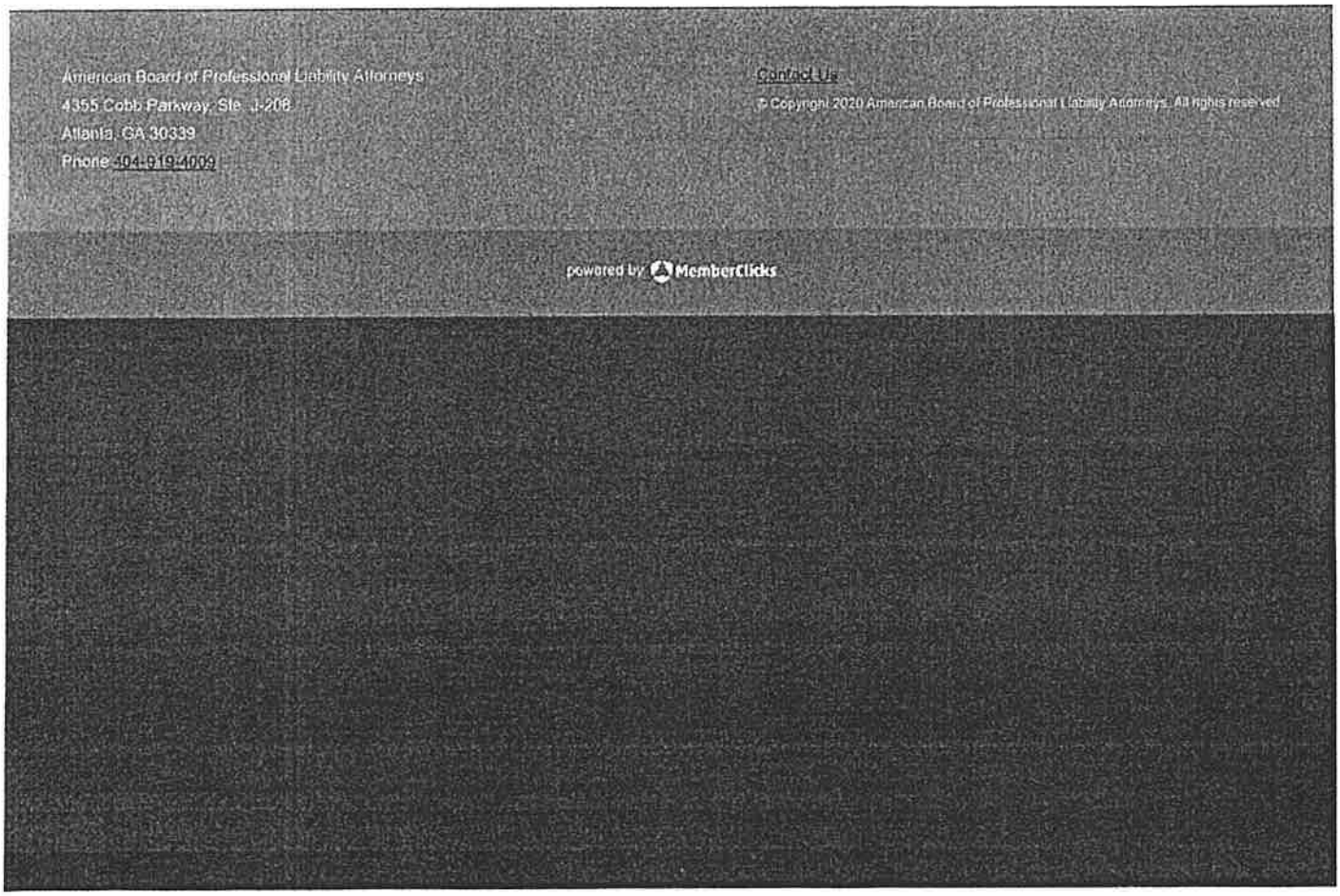
lawsuit:

- Conflicts of interest
- Errors or omissions resulting in dismissal of a client's case
- Missing Statute of Limitations
- Misappropriation of client funds
- Billing fraud
- Poorly written legal documents
- Breach of fiduciary duty
- Breach of attorney-client privilege
- Abandonment of a client's matter or lack of due diligence
- Exerting undue influence adverse to the client's interest
- Improper legal advice
- Malicious or frivolous litigation
- Excessive litigation at the client's expense
- Obstruction of justice
- Presenting false evidence
- Malfeasance or dishonesty

**Choose a Board Certified Legal Malpractice Attorney**

If you believe that you or a family member may have been a victim of attorney malpractice, you should consult a Board Certified legal malpractice attorney.

ABPLA Board Certified legal negligence attorneys are among the best legal malpractice lawyers in the country. Each Board Certified attorney must meet and exceed rigorous standards through Experience, Ethics, Education, Examination and Excellence in professional liability law.



**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use ZYPREXA safely and effectively. See full prescribing information for ZYPREXA.**

**ZYPREXA (olanzapine) Tablet for Oral use**
**ZYPREXA ZYDIS (olanzapine) Tablet, Orally Disintegrating for Oral use**
**ZYPREXA IntraMuscular (olanzapine) Injection, Powder, For Solution for Intramuscular use**
**Initial U.S. Approval: 1996**

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

***See full prescribing information for complete boxed warning.***

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis. (5.1, 8.5, 17)**
- **When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

**---------- RECENT MAJOR CHANGES ----------**

| | | |
|---|---|---|
| Warnings and Precautions, Tardive Dyskinesia (5.6) | | 10/2019 |
| Warnings and Precautions, Use in Patients with Concomitant Illness (5.14) | Removed | 4/2020 |
| Warnings and Precautions, Anticholinergic (antimuscarinic) Effects (5.14) | | 4/2020 |

**---------- INDICATIONS AND USAGE ----------**

ZYPREXA® (olanzapine) is an atypical antipsychotic indicated:

*As oral formulation for the:*

- Treatment of schizophrenia. (1.1)
  - Adults: Efficacy was established in three clinical trials in patients with schizophrenia: two 6-week trials and one maintenance trial. (14.1)
  - Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1). The increased potential (in adolescents compared with adults) for weight gain and dyslipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. (1.2)
  - Adults: Efficacy was established in three clinical trials in patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one maintenance trial. (14.2)
  - Adolescents (ages 13-17): Efficacy was established in one 3-week trial in patients with manic or mixed episodes associated with bipolar I disorder (14.2). The increased potential (in adolescents compared with adults) for weight gain and dyslipidemia may lead clinicians to consider prescribing other drugs first in adolescents. (1.2)
- Medication therapy for pediatric patients with schizophrenia or bipolar I disorder should be undertaken only after a thorough diagnostic evaluation and with careful consideration of the potential risks. (1.3)
- Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with bipolar I disorder. (1.2)
  - Efficacy was established in two 6-week clinical trials in adults (14.2). Maintenance efficacy has not been systematically evaluated.

*As ZYPREXA IntraMuscular for the:*

- Treatment of acute agitation associated with schizophrenia and bipolar I mania. (1.4)
  - Efficacy was established in three 1-day trials in adults. (14.3)

*As ZYPREXA and Fluoxetine in Combination for the:*

- Treatment of depressive episodes associated with bipolar I disorder. (1.5)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination); refer to the product label for Symbyax.
- Treatment of treatment resistant depression. (1.6)
  - Efficacy was established with Symbyax (olanzapine and fluoxetine in combination) in adults; refer to the product label for Symbyax.

**----------DOSAGE AND ADMINISTRATION----------**

| | |
|---|---|
| Schizophrenia in adults (2.1) | Oral: Start at 5-10 mg once daily; Target: 10 mg/day within several days |
| Schizophrenia in adolescents (2.1) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) in adults (2.2) | Oral: Start at 10 or 15 mg once daily |
| Bipolar I Disorder (manic or mixed episodes) in adolescents (2.2) | Oral: Start at 2.5-5 mg once daily; Target: 10 mg/day |
| Bipolar I Disorder (manic or mixed episodes) with lithium or valproate in adults (2.2) | Oral: Start at 10 mg once daily |
| Agitation associated with Schizophrenia and Bipolar I Mania in adults (2.4) | IM: 10 mg (5 mg or 7.5 mg when clinically warranted) Assess for orthostatic hypotension prior to subsequent dosing (max. 3 doses 2-4 hrs apart) |
| Depressive Episodes associated with Bipolar I Disorder in adults (2.5) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |
| Depressive Episodes associated with Bipolar I Disorder in children and adolescents (2.5) | Oral in combination with fluoxetine: Start at 2.5 mg of oral olanzapine and 20 mg of fluoxetine once daily |
| Treatment Resistant Depression in adults (2.6) | Oral in combination with fluoxetine: Start at 5 mg of oral olanzapine and 20 mg of fluoxetine once daily |

- Lower starting dose recommended in debilitated or pharmacodynamically sensitive patients or patients with predisposition to hypotensive reactions, or with potential for slowed metabolism. (2.1)
- Olanzapine may be given without regard to meals. (2.1)

*ZYPREXA and Fluoxetine in Combination:*

- Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability. (2.5, 2.6)
- Olanzapine monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder or treatment resistant depression. (2.5, 2.6)
- Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in adults. (2.5, 2.6)
- Safety of co-administration of doses above 12 mg olanzapine with 50 mg fluoxetine has not been evaluated in children and adolescents ages 10 to 17. (2.5)

**----------DOSAGE FORMS AND STRENGTHS----------**

- Tablets (not scored): 2.5, 5, 7.5, 10, 15, 20 mg. (3)
- Orally Disintegrating Tablets (not scored): 5, 10, 15, 20 mg. (3)
- Intramuscular Injection: 10 mg vial. (3)

**---------- CONTRAINDICATIONS ----------**

- None with ZYPREXA monotherapy. (4)
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax®. (4)
- When using ZYPREXA in combination with lithium or valproate, refer to the Contraindications section of the package inserts for those products. (4)

**----------WARNINGS AND PRECAUTIONS----------**

- *Elderly Patients with Dementia-Related Psychosis:* Increased risk of death and increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack). (5.1)
- *Suicide:* The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy; when using in combination with fluoxetine, also refer to the Boxed Warning and Warnings and Precautions sections of the package insert for Symbyax. (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.3)
- *Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):* Discontinue if DRESS is suspected. (5.4)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. (5.5)
  - *Hyperglycemia and Diabetes Mellitus:* In some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking olanzapine. Patients taking olanzapine should be monitored for symptoms of hyperglycemia and undergo fasting blood glucose testing at the beginning of, and periodically during, treatment. (5.5)
  - *Dyslipidemia:* Undesirable alterations in lipids have been observed. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically during, treatment. (5.5)
  - *Weight Gain:* Potential consequences of weight gain should be considered. Patients should receive regular monitoring of weight. (5.5)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate. (5.6)
- *Orthostatic Hypotension:* Orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, may occur especially during initial dose titration. Use caution in patients with cardiovascular disease, cerebrovascular disease, and those conditions that could affect hemodynamic responses. (5.7)
- *Leukopenia, Neutropenia, and Agranulocytosis:* Has been reported with antipsychotics, including ZYPREXA. Patients with a history of a clinically significant low white blood cell count (WBC) or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. (5.9)
- *Seizures:* Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold. (5.11)
- *Potential for Cognitive and Motor Impairment:* Has potential to impair judgment, thinking, and motor skills. Use caution when operating machinery. (5.12)
- *Anticholinergic (antimuscarinic) Effects:* Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, constipation, paralytic ileus or related conditions. (5.14)
- *Hyperprolactinemia:* May elevate prolactin levels. (5.15)
- *Use in Combination with Fluoxetine, Lithium or Valproate:* Also refer to the package inserts for Symbyax, lithium, or valproate. (5.16)
- *Laboratory Tests:* Monitor fasting blood glucose and lipid profiles at the beginning of, and periodically during, treatment. (5.17)

**----------ADVERSE REACTIONS----------**

Most common adverse reactions (≥5% and at least twice that for placebo) associated with:

*Oral Olanzapine Monotherapy:*

- Schizophrenia (Adults) – postural hypotension, constipation, weight gain, dizziness, personality disorder, akathisia. (6.1)
- Schizophrenia (Adolescents) – sedation, weight increased, headache, increased appetite, dizziness, abdominal pain, pain in extremity, fatigue, dry mouth. (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor. (6.1)
- Manic or Mixed Episodes, Bipolar I Disorder (Adolescents) – sedation, weight increased, increased appetite, headache, fatigue, dizziness, dry mouth, abdominal pain, pain in extremity. (6.1)

*Combination of ZYPREXA and Lithium or Valproate:*

- Manic or Mixed Episodes, Bipolar I Disorder (Adults) – dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia. (6.1)

*ZYPREXA and Fluoxetine in Combination:* Also refer to the Adverse Reactions section of the package insert for Symbyax. (6)

*ZYPREXA IntraMuscular for Injection:*

- Agitation with Schizophrenia and Bipolar I Mania (Adults) – somnolence. (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

**---------- DRUG INTERACTIONS ----------**

- *Diazepam:* May potentiate orthostatic hypotension. (7.1, 7.2)
- *Alcohol:* May potentiate orthostatic hypotension. (7.1)
- *Carbamazepine:* Increased clearance of olanzapine. (7.1)
- *Fluvoxamine:* May increase olanzapine levels. (7.1)
- *ZYPREXA and Fluoxetine in Combination:* Also refer to the Drug Interactions section of the package insert for Symbyax. (7.1)
- *CNS Acting Drugs:* Caution should be used when taken in combination with other centrally acting drugs and alcohol. (7.2)
- *Antihypertensive Agents:* Enhanced antihypertensive effect. (7.2)
- *Levodopa and Dopamine Agonists:* May antagonize levodopa/dopamine agonists. (7.2)
- *Lorazepam (IM):* Increased somnolence with IM olanzapine. (7.2)
- *Other Concomitant Drug Therapy:* When using olanzapine in combination with lithium or valproate, refer to the Drug Interactions sections of the package insert for those products. (7.2)

**----------USE IN SPECIFIC POPULATIONS----------**

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- *Pediatric Use:* Safety and effectiveness of ZYPREXA in children <13 years of age have not been established. Safety and effectiveness of ZYPREXA and fluoxetine in combination in children <10 years of age have not been established. (8.4)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**

**Revised: 4/2020**

**FULL PRESCRIBING INFORMATION: CONTENTS***

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS**

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ZYPREXA (olanzapine) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1), Use in Specific Populations (8.5), and Patient Counseling Information (17)]*.**

**When using ZYPREXA and fluoxetine in combination, also refer to the Boxed Warning section of the package insert for Symbyax.**

## 1 INDICATIONS AND USAGE

### 1.1 Schizophrenia

Oral ZYPREXA is indicated for the treatment of schizophrenia. Efficacy was established in three clinical trials in adult patients with schizophrenia: two 6-week trials and one maintenance trial. In adolescent patients with schizophrenia (ages 13-17), efficacy was established in one 6-week trial *[see Clinical Studies (14.1)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and dyslipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5)]*.

### 1.2 Bipolar I Disorder (Manic or Mixed Episodes)

Monotherapy — Oral ZYPREXA is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder. Efficacy was established in three clinical trials in adult patients with manic or mixed episodes of bipolar I disorder: two 3- to 4-week trials and one monotherapy maintenance trial. In adolescent patients with manic or mixed episodes associated with bipolar I disorder (ages 13-17), efficacy was established in one 3-week trial *[see Clinical Studies (14.2)]*.

When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and dyslipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Warnings and Precautions (5.5)]*.

Adjunctive Therapy to Lithium or Valproate — Oral ZYPREXA is indicated for the treatment of manic or mixed episodes associated with bipolar I disorder as an adjunct to lithium or valproate. Efficacy was established in two 6-week clinical trials in adults. The effectiveness of adjunctive therapy for longer-term use has not been systematically evaluated in controlled trials *[see Clinical Studies (14.2)]*.

### 1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

Pediatric schizophrenia and bipolar I disorder are serious mental disorders; however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, pediatric patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder should be part of a total treatment program that often includes psychological, educational and social interventions.

### 1.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

ZYPREXA IntraMuscular is indicated for the treatment of acute agitation associated with schizophrenia and bipolar I mania.

Efficacy was demonstrated in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients with: schizophrenia or bipolar I disorder (manic or mixed episodes) *[see Clinical Studies (14.3)]*.

"Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care, e.g., threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior, leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation.

### 1.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of depressive episodes associated with bipolar I disorder, based on clinical studies. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

### 1.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression

Oral ZYPREXA and fluoxetine in combination is indicated for the treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode), based on clinical studies in adult patients. When using ZYPREXA and fluoxetine in combination, refer to the Clinical Studies section of the package insert for Symbyax.

ZYPREXA monotherapy is not indicated for the treatment of treatment resistant depression.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Schizophrenia

**Adults**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for olanzapine would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Efficacy in schizophrenia was demonstrated in a dose range of 10 to 15 mg/day in clinical trials. However, doses above 10 mg/day were not demonstrated to be more efficacious than the 10 mg/day dose. An increase to a dose greater than the target dose of 10 mg/day (i.e., to a dose of 15 mg/day or greater) is recommended only after clinical assessment. Olanzapine is not indicated for use in doses above 20 mg/day.

Dosing in Special Populations — The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine (e.g., nonsmoking female patients ≥65 years of age), or who may be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*. When indicated, dose escalation should be performed with caution in these patients.

Maintenance Treatment — The effectiveness of oral olanzapine, 10 mg/day to 20 mg/day, in maintaining treatment response in schizophrenic patients who had been stable on ZYPREXA for approximately 8 weeks and were then followed for relapse has been demonstrated in a placebo-controlled trial *[see Clinical Studies (14.1)]*. The healthcare provider who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with schizophrenia was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 12.5 mg/day (mean dose of 11.1 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.1)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of schizophrenia in the adolescent population has not been systematically evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 2.2 Bipolar I Disorder (Manic or Mixed Episodes)

**Adults**

Dose Selection for Monotherapy — Oral olanzapine should be administered on a once-a-day schedule without regard to meals, generally beginning with 10 or 15 mg. Dosage adjustments, if indicated, should generally occur at intervals of not less than 24 hours, reflecting the procedures in the placebo-controlled trials. When dosage adjustments are necessary, dose increments/decrements of 5 mg QD are recommended.

Short-term (3-4 weeks) antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials. The safety of doses above 20 mg/day has not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Monotherapy — The benefit of maintaining bipolar I patients on monotherapy with oral ZYPREXA at a dose of 5 to 20 mg/day, after achieving a responder status for an average duration of 2 weeks, was demonstrated in a controlled trial *[see Clinical Studies (14.2)]*. The healthcare provider who elects to use ZYPREXA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Dose Selection for Adjunctive Treatment — When administered as adjunctive treatment to lithium or valproate, oral olanzapine dosing should generally begin with 10 mg once-a-day without regard to meals.

Antimanic efficacy was demonstrated in a dose range of 5 mg to 20 mg/day in clinical trials *[see Clinical Studies (14.2)]*. The safety of doses above 20 mg/day has not been evaluated in clinical trials.

**Adolescents**

Dose Selection — Oral olanzapine should be administered on a once-a-day schedule without regard to meals with a recommended starting dose of 2.5 or 5 mg, with a target dose of 10 mg/day. Efficacy in adolescents with bipolar I disorder (manic or mixed episodes) was demonstrated based on a flexible dose range of 2.5 to 20 mg/day in clinical trials, with a mean modal dose of 10.7 mg/day (mean dose of 8.9 mg/day). When dosage adjustments are necessary, dose increments/decrements of 2.5 or 5 mg are recommended.

The safety and effectiveness of doses above 20 mg/day have not been evaluated in clinical trials *[see Clinical Studies (14.2)]*.

Maintenance Treatment — The efficacy of ZYPREXA for the maintenance treatment of bipolar I disorder in the adolescent population has not been evaluated; however, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 2.3 Administration of ZYPREXA ZYDIS (olanzapine orally disintegrating tablets)

After opening sachet, peel back foil on blister. Do not push tablet through foil. Immediately upon opening the blister, using dry hands, remove tablet and place entire ZYPREXA ZYDIS in the mouth. Tablet disintegration occurs rapidly in saliva so it can be easily swallowed with or without liquid.

### 2.4 ZYPREXA IntraMuscular: Agitation Associated with Schizophrenia and Bipolar I Mania

Dose Selection for Agitated Adult Patients with Schizophrenia and Bipolar I Mania — The efficacy of intramuscular olanzapine for injection in controlling agitation in these disorders was demonstrated in a dose range of 2.5 mg to 10 mg. The recommended dose in these patients is 10 mg. A lower dose of 5 or 7.5 mg may be considered when clinical factors warrant *[see Clinical Studies (14.3)]*. If agitation warranting additional intramuscular doses persists following the initial dose, subsequent doses up to 10 mg may be given. However, the efficacy of repeated doses of intramuscular olanzapine for injection in agitated patients has not been systematically evaluated in controlled clinical trials. Also, the safety of total daily doses greater than 30 mg, or 10 mg injections given more frequently than 2 hours after the initial dose, and 4 hours after the second dose have not been evaluated in clinical trials. Maximal dosing of intramuscular olanzapine (e.g., 3 doses of 10 mg administered 2-4 hours apart) may be associated with a substantial occurrence of significant orthostatic hypotension *[see Warnings and Precautions (5.7)]*. Thus, it is recommended that patients requiring subsequent intramuscular injections be assessed for orthostatic hypotension prior to the administration of any subsequent doses of intramuscular olanzapine for injection. The administration of an additional dose to a patient with a clinically significant postural change in systolic blood pressure is not recommended.

If ongoing olanzapine therapy is clinically indicated, oral olanzapine may be initiated in a range of 5-20 mg/day as soon as clinically appropriate *[see Dosage and Administration (2.1, 2.2)]*.

Intramuscular Dosing in Special Populations — A dose of 5 mg/injection should be considered for geriatric patients or when other clinical factors warrant. A lower dose of 2.5 mg/injection should be considered for patients who otherwise might be debilitated, be predisposed to hypotensive reactions, or be more pharmacodynamically sensitive to olanzapine *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

Administration of ZYPREXA IntraMuscular — ZYPREXA IntraMuscular is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Directions for Preparation of ZYPREXA IntraMuscular with Sterile Water for Injection — Dissolve the contents of the vial using 2.1 mL of Sterile Water for Injection to provide a solution containing approximately 5 mg/mL of olanzapine. The resulting solution should appear clear and yellow. ZYPREXA IntraMuscular reconstituted with Sterile Water for Injection should be used immediately (within 1 hour) after reconstitution. *Discard any unused portion.*

The following table provides injection volumes for delivering various doses of intramuscular olanzapine for injection reconstituted with Sterile Water for Injection.

| Dose, mg Olanzapine | Volume of Injection, mL |
|---|---|
| 10 | Withdraw total contents of vial |
| 7.5 | 1.5 |
| 5 | 1 |
| 2.5 | 0.5 |

Physical Incompatibility Information — ZYPREXA IntraMuscular should be reconstituted only with Sterile Water for Injection. ZYPREXA IntraMuscular should not be combined in a syringe with diazepam injection because precipitation

occurs when these products are mixed. Lorazepam injection should not be used to reconstitute ZYPREXA IntraMuscular as this combination results in a delayed reconstitution time. ZYPREXA IntraMuscular should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

**2.5 ZYPREXA and Fluoxetine in Combination: Depressive Episodes Associated with Bipolar I Disorder**

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

**Adults**

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 12.5 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with ZYPREXA and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 12 mg and fluoxetine 25 to 50 mg. Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

**Children and Adolescents (10-17 years of age)**

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 2.5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability. Safety of co-administration of doses above 12 mg olanzapine with 50 mg fluoxetine has not been evaluated in pediatric clinical studies.

Safety and efficacy of ZYPREXA and fluoxetine in combination was determined in clinical trials supporting approval of Symbyax (fixed dose combination of ZYPREXA and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. The following table demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

**Table 1: Approximate Dose Correspondence Between Symbyax[a] and the Combination of ZYPREXA and Fluoxetine**

| For Symbyax (mg/day) | Use in Combination | |
|---|---|---|
| | ZYPREXA (mg/day) | Fluoxetine (mg/day) |
| 3 mg olanzapine/25 mg fluoxetine | 2.5 | 20 |
| 6 mg olanzapine/25 mg fluoxetine | 5 | 20 |
| 12 mg olanzapine/25 mg fluoxetine | 10+2.5 | 20 |
| 6 mg olanzapine/50 mg fluoxetine | 5 | 40+10 |
| 12 mg olanzapine/50 mg fluoxetine | 10+2.5 | 40+10 |

[a] Symbyax (olanzapine/fluoxetine HCl) is a fixed-dose combination of ZYPREXA and fluoxetine.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination should remain on it, it is generally accepted that bipolar I disorder, including the depressive episodes associated with bipolar I disorder, is a chronic illness requiring chronic treatment. The healthcare provider should periodically reexamine the need for continued pharmacotherapy.

ZYPREXA monotherapy is not indicated for the treatment of depressive episodes associated with bipolar I disorder.

**2.6 ZYPREXA and Fluoxetine in Combination: Treatment Resistant Depression**

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

Oral olanzapine should be administered in combination with fluoxetine once daily in the evening, without regard to meals, generally beginning with 5 mg of oral olanzapine and 20 mg of fluoxetine. Dosage adjustments, if indicated, can be made according to efficacy and tolerability within dose ranges of oral olanzapine 5 to 20 mg and fluoxetine 20 to 50 mg. Antidepressant efficacy was demonstrated with olanzapine and fluoxetine in combination in adult patients with a dose range of olanzapine 6 to 18 mg and fluoxetine 25 to 50 mg.

Safety and efficacy of olanzapine in combination with fluoxetine was determined in clinical trials supporting approval of Symbyax (fixed dose combination of olanzapine and fluoxetine). Symbyax is dosed between 3 mg/25 mg (olanzapine/fluoxetine) per day and 12 mg/50 mg (olanzapine/fluoxetine) per day. Table 1 above demonstrates the appropriate individual component doses of ZYPREXA and fluoxetine versus Symbyax. Dosage adjustments, if indicated, should be made with the individual components according to efficacy and tolerability.

While there is no body of evidence to answer the question of how long a patient treated with ZYPREXA and fluoxetine in combination should remain on it, it is generally accepted that treatment resistant depression (major depressive disorder in adult patients who do not respond to 2 separate trials of different antidepressants of adequate dose

and duration in the current episode) is a chronic illness requiring chronic treatment. The healthcare provider should periodically reexamine the need for continued pharmacotherapy.

Safety of co-administration of doses above 18 mg olanzapine with 75 mg fluoxetine has not been evaluated in clinical studies.

ZYPREXA monotherapy is not indicated for treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 antidepressants of adequate dose and duration in the current episode).

### 2.7 ZYPREXA and Fluoxetine in Combination: Dosing in Special Populations

The starting dose of oral olanzapine 2.5-5 mg with fluoxetine 20 mg should be used for patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine or fluoxetine in combination (female gender, geriatric age, nonsmoking status), or those patients who may be pharmacodynamically sensitive to olanzapine. Dosing modification may be necessary in patients who exhibit a combination of factors that may slow metabolism. When indicated, dose escalation should be performed with caution in these patients. ZYPREXA and fluoxetine in combination have not been systematically studied in patients over 65 years of age or in patients under 10 years of age *[see Warnings and Precautions (5.14), Drug Interactions (7), and Clinical Pharmacology (12.3)]*.

## 3 DOSAGE FORMS AND STRENGTHS

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY | LILLY | LILLY | LILLY | LILLY | LILLY |
| | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. Tablets are not scored. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |

ZYPREXA IntraMuscular is available in 10 mg vial (1s).

## 4 CONTRAINDICATIONS

- None with ZYPREXA monotherapy.
- When using ZYPREXA and fluoxetine in combination, also refer to the Contraindications section of the package insert for Symbyax.
- For specific information about the contraindications of lithium or valproate, refer to the Contraindications section of the package inserts for these other products.

## 5 WARNINGS AND PRECAUTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Warnings and Precautions section of the package insert for Symbyax.

### 5.1 Elderly Patients with Dementia-Related Psychosis

Increased Mortality — **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Use in Specific Populations (8.5), and Patient Counseling Information (17)]*.**

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients was significantly greater than placebo-treated patients (3.5% vs 1.5%, respectively).

Cerebrovascular Adverse Events (CVAE), Including Stroke — Cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Patient Counseling Information (17)]*.

### 5.2 Suicide

The possibility of a suicide attempt is inherent in schizophrenia and in bipolar I disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

### 5.3 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported *[see Patient Counseling Information (17)]*.

### 5.4 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported with olanzapine exposure. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. DRESS is sometimes fatal. Discontinue olanzapine if DRESS is suspected *[see Patient Counseling Information (17)]*.

### 5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes including hyperglycemia, dyslipidemia, and weight gain. Metabolic changes may be associated with increased cardiovascular/cerebrovascular risk. Olanzapine's specific metabolic profile is presented below.

**Hyperglycemia and Diabetes Mellitus**

Healthcare providers should consider the risks and benefits when prescribing olanzapine to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level (fasting 100-126 mg/dL, nonfasting 140-200 mg/dL). Patients taking olanzapine should be monitored regularly for worsening of glucose control. Patients starting treatment with olanzapine should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug *[see Patient Counseling Information (17)]*.

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics.

Mean increases in blood glucose have been observed in patients treated (median exposure of 9.2 months) with olanzapine in phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE). The mean increase of serum glucose (fasting and nonfasting samples) from baseline to the average of the 2 highest serum concentrations was 15.0 mg/dL.

In a study of healthy volunteers, subjects who received olanzapine (N=22) for 3 weeks had a mean increase compared to baseline in fasting blood glucose of 2.3 mg/dL. Placebo-treated subjects (N=19) had a mean increase in fasting blood glucose compared to baseline of 0.34 mg/dL.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled adult olanzapine monotherapy studies with a median treatment duration of approximately 3 weeks, olanzapine was associated with a greater mean change in

fasting glucose levels compared to placebo (2.76 mg/dL versus 0.17 mg/dL). The difference in mean changes between olanzapine and placebo was greater in patients with evidence of glucose dysregulation at baseline (patients diagnosed with diabetes mellitus or related adverse reactions, patients treated with anti-diabetic agents, patients with a baseline random glucose level ≥200 mg/dL, and/or a baseline fasting glucose level ≥126 mg/dL). Olanzapine-treated patients had a greater mean $HbA_{1c}$ increase from baseline of 0.04% (median exposure 21 days), compared to a mean $HbA_{1c}$ decrease of 0.06% in placebo-treated subjects (median exposure 17 days).

In an analysis of 8 placebo-controlled studies (median treatment exposure 4-5 weeks), 6.1% of olanzapine-treated subjects (N=855) had treatment-emergent glycosuria compared to 2.8% of placebo-treated subjects (N=599). Table 2 shows short-term and long-term changes in fasting glucose levels from adult olanzapine monotherapy studies.

**Table 2: Changes in Fasting Glucose Levels from Adult Olanzapine Monotherapy Studies**

| | | | Up to 12 weeks exposure | | At least 48 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **N** | **Patients** | **N** | **Patients** |
| Fasting Glucose | Normal to High (<100 mg/dL to ≥126 mg/dL) | Olanzapine | 543 | 2.2% | 345 | 12.8% |
| | | Placebo | 293 | 3.4% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | Olanzapine | 178 | 17.4% | 127 | 26.0% |
| | | Placebo | 96 | 11.5% | NA[a] | NA[a] |

[a] Not Applicable.

The mean change in fasting glucose for patients exposed at least 48 weeks was 4.2 mg/dL (N=487). In analyses of patients who completed 9-12 months of olanzapine therapy, mean change in fasting and nonfasting glucose levels continued to increase over time.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescent patients, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine was associated with a greater mean change from baseline in fasting glucose levels compared to placebo (2.68 mg/dL versus -2.59 mg/dL). The mean change in fasting glucose for adolescents exposed at least 24 weeks was 3.1 mg/dL (N=121). Table 3 shows short-term and long-term changes in fasting blood glucose from adolescent olanzapine monotherapy studies.

**Table 3: Changes in Fasting Glucose Levels from Adolescent Olanzapine Monotherapy Studies**

| | | | Up to 12 weeks exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **N** | **Patients** | **N** | **Patients** |
| Fasting Glucose | Normal to High (<100 mg/dL to ≥126 mg/dL) | Olanzapine | 124 | 0% | 108 | 0.9% |
| | | Placebo | 53 | 1.9% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL) | Olanzapine | 14 | 14.3% | 13 | 23.1% |
| | | Placebo | 13 | 0% | NA[a] | NA[a] |

[a] Not Applicable.

**Dyslipidemia**

Undesirable alterations in lipids have been observed with olanzapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using olanzapine, is recommended *[see Patient Counseling Information (17)]*.

Clinically significant, and sometimes very high (>500 mg/dL), elevations in triglyceride levels have been observed with olanzapine use. Modest mean increases in total cholesterol have also been seen with olanzapine use.

Olanzapine Monotherapy in Adults — In an analysis of 5 placebo-controlled olanzapine monotherapy studies with treatment duration up to 12 weeks, olanzapine-treated patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.3 mg/dL, 3.0 mg/dL, and 20.8 mg/dL respectively compared to decreases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 6.1 mg/dL, 4.3 mg/dL, and 10.7 mg/dL for placebo-treated patients. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated patients and placebo-treated patients. Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline, where lipid dysregulation was defined as patients diagnosed with dyslipidemia or related adverse reactions, patients treated with lipid lowering agents, or patients with high baseline lipid levels.

In long-term studies (at least 48 weeks), patients had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.6 mg/dL, 2.5 mg/dL, and 18.7 mg/dL, respectively, and a mean decrease in fasting

HDL cholesterol of 0.16 mg/dL. In an analysis of patients who completed 12 months of therapy, the mean nonfasting total cholesterol did not increase further after approximately 4-6 months.

The proportion of patients who had changes (at least once) in total cholesterol, LDL cholesterol or triglycerides from normal or borderline to high, or changes in HDL cholesterol from normal or borderline to low, was greater in long-term studies (at least 48 weeks) as compared with short-term studies. Table 4 shows categorical changes in fasting lipids values.

**Table 4: Changes in Fasting Lipids Values from Adult Olanzapine Monotherapy Studies**

| | | | Up to 12 weeks exposure | | At least 48 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **N** | **Patients** | **N** | **Patients** |
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 745 | 39.6% | 487 | 61.4% |
| | | Placebo | 402 | 26.1% | NA[a] | NA[a] |
| | Normal to High (<150 mg/dL to ≥200 mg/dL) | Olanzapine | 457 | 9.2% | 293 | 32.4% |
| | | Placebo | 251 | 4.4% | NA[a] | NA[a] |
| | Borderline to High (≥150 mg/dL and <200 mg/dL to ≥200 mg/dL) | Olanzapine | 135 | 39.3% | 75 | 70.7% |
| | | Placebo | 65 | 20.0% | NA[a] | NA[a] |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 745 | 21.6% | 489 | 32.9% |
| | | Placebo | 402 | 9.5% | NA[a] | NA[a] |
| | Normal to High (<200 mg/dL to ≥240 mg/dL) | Olanzapine | 392 | 2.8% | 283 | 14.8% |
| | | Placebo | 207 | 2.4% | NA[a] | NA[a] |
| | Borderline to High (≥200 mg/dL and <240 mg/dL to ≥240 mg/dL) | Olanzapine | 222 | 23.0% | 125 | 55.2% |
| | | Placebo | 112 | 12.5% | NA[a] | NA[a] |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 536 | 23.7% | 483 | 39.8% |
| | | Placebo | 304 | 14.1% | NA[a] | NA[a] |
| | Normal to High (<100 mg/dL to ≥160 mg/dL) | Olanzapine | 154 | 0% | 123 | 7.3% |
| | | Placebo | 82 | 1.2% | NA[a] | NA[a] |
| | Borderline to High (≥100 mg/dL and <160 mg/dL to ≥160 mg/dL) | Olanzapine | 302 | 10.6% | 284 | 31.0% |
| | | Placebo | 173 | 8.1% | NA[a] | NA[a] |

[a] Not Applicable.

In phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), over a median exposure of 9.2 months, the mean increase in triglycerides in patients taking olanzapine was 40.5 mg/dL. In phase 1 of CATIE, the mean increase in total cholesterol was 9.4 mg/dL.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. In an analysis of 3 placebo-controlled olanzapine monotherapy studies of adolescents, including those with schizophrenia (6 weeks) or bipolar I disorder (manic or mixed episodes) (3 weeks), olanzapine-treated adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 12.9 mg/dL, 6.5 mg/dL, and 28.4 mg/dL, respectively, compared to increases from baseline in mean fasting total cholesterol and LDL cholesterol of 1.3 mg/dL and 1.0 mg/dL, and a decrease in triglycerides of 1.1 mg/dL for placebo-treated adolescents. For fasting HDL cholesterol, no clinically meaningful differences were observed between olanzapine-treated adolescents and placebo-treated adolescents.

In long-term studies (at least 24 weeks), adolescents had increases from baseline in mean fasting total cholesterol, LDL cholesterol, and triglycerides of 5.5 mg/dL, 5.4 mg/dL, and 20.5 mg/dL, respectively, and a mean decrease in fasting HDL cholesterol of 4.5 mg/dL. Table 5 shows categorical changes in fasting lipids values in adolescents.

**Table 5: Changes in Fasting Lipids Values from Adolescent Olanzapine Monotherapy Studies**

| | | | Up to 6 weeks exposure | | At least 24 weeks exposure | |
|---|---|---|---|---|---|---|
| **Laboratory Analyte** | **Category Change (at least once) from Baseline** | **Treatment Arm** | **N** | **Patients** | **N** | **Patients** |
| Fasting Triglycerides | Increase by ≥50 mg/dL | Olanzapine | 138 | 37.0% | 122 | 45.9% |
| | | Placebo | 66 | 15.2% | NA[a] | NA[a] |
| | Normal to High (<90 mg/dL to >130 mg/dL) | Olanzapine | 67 | 26.9% | 66 | 36.4% |
| | | Placebo | 28 | 10.7% | NA[a] | NA[a] |
| | Borderline to High (≥90 mg/dL and ≤130 mg/dL to >130 mg/dL) | Olanzapine | 37 | 59.5% | 31 | 64.5% |
| | | Placebo | 17 | 35.3% | NA[a] | NA[a] |
| | | | | | | |
| Fasting Total Cholesterol | Increase by ≥40 mg/dL | Olanzapine | 138 | 14.5% | 122 | 14.8% |
| | | Placebo | 66 | 4.5% | NA[a] | NA[a] |
| | Normal to High (<170 mg/dL to ≥200 mg/dL) | Olanzapine | 87 | 6.9% | 78 | 7.7% |
| | | Placebo | 43 | 2.3% | NA[a] | NA[a] |
| | Borderline to High (≥170 mg/dL and <200 mg/dL to ≥200 mg/dL) | Olanzapine | 36 | 38.9% | 33 | 57.6% |
| | | Placebo | 13 | 7.7% | NA[a] | NA[a] |
| | | | | | | |
| Fasting LDL Cholesterol | Increase by ≥30 mg/dL | Olanzapine | 137 | 17.5% | 121 | 22.3% |
| | | Placebo | 63 | 11.1% | NA[a] | NA[a] |
| | Normal to High (<110 mg/dL to ≥130 mg/dL) | Olanzapine | 98 | 5.1% | 92 | 10.9% |
| | | Placebo | 44 | 4.5% | NA[a] | NA[a] |
| | Borderline to High (≥110 mg/dL and <130 mg/dL to ≥130 mg/dL) | Olanzapine | 29 | 48.3% | 21 | 47.6% |
| | | Placebo | 9 | 0% | NA[a] | NA[a] |

[a] Not Applicable.

**Weight Gain**

Potential consequences of weight gain should be considered prior to starting olanzapine. Patients receiving olanzapine should receive regular monitoring of weight *[see Patient Counseling Information (17)]*.

Olanzapine Monotherapy in Adults — In an analysis of 13 placebo-controlled olanzapine monotherapy studies, olanzapine-treated patients gained an average of 2.6 kg (5.7 lb) compared to an average 0.3 kg (0.6 lb) weight loss in placebo-treated patients with a median exposure of 6 weeks; 22.2% of olanzapine-treated patients gained at least 7% of their baseline weight, compared to 3% of placebo-treated patients, with a median exposure to event of 8 weeks; 4.2% of olanzapine-treated patients gained at least 15% of their baseline weight, compared to 0.3% of placebo-treated patients, with a median exposure to event of 12 weeks. Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Discontinuation due to weight gain occurred in 0.2% of olanzapine-treated patients and in 0% of placebo-treated patients.

In long-term studies (at least 48 weeks), the mean weight gain was 5.6 kg (12.3 lb) (median exposure of 573 days, N=2021). The percentages of patients who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 64%, 32%, and 12%, respectively. Discontinuation due to weight gain occurred in 0.4% of olanzapine-treated patients following at least 48 weeks of exposure.

Table 6 includes data on adult weight gain with olanzapine pooled from 86 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified.

**Table 6: Weight Gain with Olanzapine Use in Adults**

| **Amount Gained kg (lb)** | **6 Weeks (N=7465) (%)** | **6 Months (N=4162) (%)** | **12 Months (N=1345) (%)** | **24 Months (N=474) (%)** | **36 Months (N=147) (%)** |
|---|---|---|---|---|---|
| ≤0 | 26.2 | 24.3 | 20.8 | 23.2 | 17.0 |
| 0 to ≤5 (0-11 lb) | 57.0 | 36.0 | 26.0 | 23.4 | 25.2 |
| >5 to ≤10 (11-22 lb) | 14.9 | 24.6 | 24.2 | 24.1 | 18.4 |
| >10 to ≤15 (22-33 lb) | 1.8 | 10.9 | 14.9 | 11.4 | 17.0 |
| >15 to ≤20 (33-44 lb) | 0.1 | 3.1 | 8.6 | 9.3 | 11.6 |
| >20 to ≤25 (44-55 lb) | 0 | 0.9 | 3.3 | 5.1 | 4.1 |
| >25 to ≤30 (55-66 lb) | 0 | 0.2 | 1.4 | 2.3 | 4.8 |
| >30 (>66 lb) | 0 | 0.1 | 0.8 | 1.2 | 2 |

Dose group differences with respect to weight gain have been observed. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, mean baseline to endpoint increase in weight (10 mg/day: 1.9 kg; 20 mg/day: 2.3 kg; 40 mg/day: 3 kg) was observed with significant differences between 10 vs 40 mg/day.

Olanzapine Monotherapy in Adolescents — The safety and efficacy of olanzapine have not been established in patients under the age of 13 years. Mean increase in weight in adolescents was greater than in adults. In 4 placebo-controlled trials, discontinuation due to weight gain occurred in 1% of olanzapine-treated patients, compared to 0% of placebo-treated patients.

**Table 7: Weight Gain with Olanzapine Use in Adolescents from 4 Placebo-Controlled Trials**

| | Olanzapine-treated patients | Placebo-treated patients |
|---|---|---|
| Mean change in body weight from baseline (median exposure = 3 weeks) | 4.6 kg (10.1 lb) | 0.3 kg (0.7 lb) |
| Percentage of patients who gained at least 7% of baseline body weight | 40.6% (median exposure to 7% = 4 weeks) | 9.8% (median exposure to 7% = 8 weeks) |
| Percentage of patients who gained at least 15% of baseline body weight | 7.1% (median exposure to 15% = 19 weeks) | 2.7% (median exposure to 15% = 8 weeks) |

In long-term studies (at least 24 weeks), the mean weight gain was 11.2 kg (24.6 lb); (median exposure of 201 days, N=179). The percentages of adolescents who gained at least 7%, 15%, or 25% of their baseline body weight with long-term exposure were 89%, 55%, and 29%, respectively. Among adolescent patients, mean weight gain by baseline BMI category was 11.5 kg (25.3 lb), 12.1 kg (26.6 lb), and 12.7 kg (27.9 lb), respectively, for normal (N=106), overweight (N=26) and obese (N=17). Discontinuation due to weight gain occurred in 2.2% of olanzapine-treated patients following at least 24 weeks of exposure.

Table 8 shows data on adolescent weight gain with olanzapine pooled from 6 clinical trials. The data in each column represent data for those patients who completed treatment periods of the durations specified. Little clinical trial data is available on weight gain in adolescents with olanzapine beyond 6 months of treatment.

**Table 8: Weight Gain with Olanzapine Use in Adolescents**

| Amount Gained kg (lb) | 6 Weeks (N=243) (%) | 6 Months (N=191) (%) |
|---|---|---|
| ≤0 | 2.9 | 2.1 |
| 0 to ≤5 (0-11 lb) | 47.3 | 24.6 |
| >5 to ≤10 (11-22 lb) | 42.4 | 26.7 |
| >10 to ≤15 (22-33 lb) | 5.8 | 22.0 |
| >15 to ≤20 (33-44 lb) | 0.8 | 12.6 |
| >20 to ≤25 (44-55 lb) | 0.8 | 9.4 |
| >25 to ≤30 (55-66 lb) | 0 | 2.1 |
| >30 to ≤35 (66-77 lb) | 0 | 0 |
| >35 to ≤40 (77-88 lb) | 0 | 0 |
| >40 (>88 lb) | 0 | 0.5 |

### 5.6 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, olanzapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients (1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on olanzapine, drug discontinuation should be considered. However, some patients may require treatment with olanzapine despite the presence of the syndrome.

For specific information about the warnings of lithium or valproate, refer to the Warnings section of the package inserts for these other products.

### 5.7 Orthostatic Hypotension

Olanzapine may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its $\alpha_1$-adrenergic antagonistic properties *[see Patient Counseling Information (17)]*.

From an analysis of the vital sign data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, orthostatic hypotension was recorded in ≥20% (1277/6030) of patients.

For oral olanzapine therapy, the risk of orthostatic hypotension and syncope may be minimized by initiating therapy with 5 mg QD *[see Dosage and Administration (2)]*. A more gradual titration to the target dose should be considered if hypotension occurs.

Hypotension, bradycardia with or without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. In an open-label clinical pharmacology study in nonagitated patients with schizophrenia in which the safety and tolerability of intramuscular olanzapine were evaluated under a maximal dosing regimen (three 10 mg doses administered 4 hours apart), approximately one-third of these patients experienced a significant orthostatic decrease in systolic blood pressure (i.e., decrease ≥30 mmHg) *[see Dosage and Administration (2.4)]*. Syncope was reported in 0.6% (15/2500) of olanzapine-treated patients in phase 2-3 oral olanzapine studies and in 0.3% (2/722) of olanzapine-treated patients with agitation in the intramuscular olanzapine for injection studies. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the reactions occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of hypotension, bradycardia, and sinus pause may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. For intramuscular olanzapine for injection therapy, patients should remain recumbent if drowsy or dizzy after injection until examination has indicated that they are not experiencing postural hypotension, bradycardia, and/or hypoventilation.

Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put the patient at increased medical risk.

Caution is necessary in patients who receive treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or central nervous system depression *[see Drug Interactions (7)]*. Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation and cardiorespiratory depression.

### 5.8 Falls

ZYPREXA may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

### 5.9 Leukopenia, Neutropenia, and Agranulocytosis

Class Effect — In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ZYPREXA. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ZYPREXA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm$^3$) should discontinue ZYPREXA and have their WBC followed until recovery.

### 5.10 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine is not approved for the treatment of patients with Alzheimer's disease.

### 5.11 Seizures

During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients. There were confounding factors that may have contributed to the occurrence of seizures in many of these cases. Olanzapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Olanzapine is not approved for the treatment of patients with Alzheimer's disease. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

### 5.12 Potential for Cognitive and Motor Impairment

Somnolence was a commonly reported adverse reaction associated with olanzapine treatment, occurring at an incidence of 26% in olanzapine patients compared to 15% in placebo patients. This adverse reaction was also dose related. Somnolence led to discontinuation in 0.4% (9/2500) of patients in the premarketing database.

Since olanzapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that olanzapine therapy does not affect them adversely *[see Patient Counseling Information (17)]*.

### 5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing olanzapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration *[see Patient Counseling Information (17)]*.

### 5.14 Anticholinergic (antimuscarinic) Effects

Olanzapine exhibits in vitro muscarinic receptor affinity *[see Clinical Pharmacology 12.2]*. In premarketing clinical trials, Zyprexa was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Such adverse reactions were not often the basis for discontinuations, but Zyprexa should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, constipation, or a history of paralytic ileus or related conditions. In post marketing experience, the risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications *[see Drug Interactions (7.1)]*.

### 5.15 Hyperprolactinemia

As with other drugs that antagonize dopamine $D_2$ receptors, olanzapine elevates prolactin levels, and the elevation persists during chronic administration. Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in the olanzapine carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1)]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

In placebo-controlled olanzapine clinical studies (up to 12 weeks), changes from normal to high in prolactin concentrations were observed in 30% of adults treated with olanzapine as compared to 10.5% of adults treated with placebo. In a pooled analysis from clinical studies including 8136 adults treated with olanzapine, potentially associated clinical manifestations included menstrual-related events[1] (2% [49/3240] of females), sexual function-related events[2] (2% [150/8136] of females and males), and breast-related events[3] (0.7% [23/3240] of females, 0.2% [9/4896] of males).

In placebo-controlled olanzapine monotherapy studies in adolescent patients (up to 6 weeks) with schizophrenia or bipolar I disorder (manic or mixed episodes), changes from normal to high in prolactin concentrations were observed in 47% of olanzapine-treated patients compared to 7% of placebo-treated patients. In a pooled analysis from clinical trials including 454 adolescents treated with olanzapine, potentially associated clinical manifestations included menstrual-related events[1] (1% [2/168] of females), sexual function-related events[2] (0.7% [3/454] of females and males), and breast-related events[3] (2% [3/168] of females, 2% [7/286] of males) *[see Use in Specific Populations (8.4)]*.

[1] Based on a search of the following terms: amenorrhea, hypomenorrhea, menstruation delayed, and oligomenorrhea.

[2] Based on a search of the following terms: anorgasmia, delayed ejaculation, erectile dysfunction, decreased libido, loss of libido, abnormal orgasm, and sexual dysfunction.

[3] Based on a search of the following terms: breast discharge, enlargement or swelling, galactorrhea, gynecomastia, and lactation disorder.

Dose group differences with respect to prolactin elevation have been observed. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, incidence of prolactin elevation >24.2 ng/mL (female) or >18.77 ng/mL (male) at any time during the trial (10 mg/day: 31.2%; 20 mg/day: 42.7%; 40 mg/day: 61.1%) indicated significant differences between 10 vs 40 mg/day and 20 vs 40 mg/day.

### 5.16 Use in Combination with Fluoxetine, Lithium, or Valproate

When using ZYPREXA and fluoxetine in combination, the prescriber should also refer to the Warnings and Precautions section of the package insert for Symbyax. When using ZYPREXA in combination with lithium or valproate, the prescriber should refer to the Warnings and Precautions sections of the package inserts for lithium or valproate *[see Drug Interactions (7)]*.

### 5.17 Laboratory Tests

Fasting blood glucose testing and lipid profile at the beginning of, and periodically during, treatment is recommended *[see Warnings and Precautions (5.5) and Patient Counseling Information (17)]*.

## 6 ADVERSE REACTIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Adverse Reactions section of the package insert for Symbyax.

### 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 or predict the rates observed in practice.

**Clinical Trials in Adults**

The information below for olanzapine is derived from a clinical trial database for olanzapine consisting of 10,504 adult patients with approximately 4765 patient-years of exposure to olanzapine plus 722 patients with exposure to intramuscular olanzapine for injection. This database includes: (1) 2500 patients who participated in multiple-dose oral olanzapine premarketing trials in schizophrenia and Alzheimer's disease representing approximately 1122 patient-years of exposure as of February 14, 1995; (2) 182 patients who participated in oral olanzapine premarketing bipolar I disorder (manic or mixed episodes) trials representing approximately 66 patient-years of exposure; (3) 191 patients who participated in an oral olanzapine trial of patients having various psychiatric symptoms in association with Alzheimer's disease representing approximately 29 patient-years of exposure; (4) 5788 additional patients from 88 oral olanzapine clinical trials as of December 31, 2001; (5) 1843 additional patients from 41 olanzapine clinical trials as of October 31, 2011; and (6) 722 patients who participated in intramuscular olanzapine for injection premarketing trials in agitated patients with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia. Also included below is information from the premarketing 6-week clinical study database for olanzapine in combination with lithium or valproate, consisting of 224 patients who participated in bipolar I disorder (manic or mixed episodes) trials with approximately 22 patient-years of exposure.

The conditions and duration of treatment with olanzapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, weights, laboratory analytes, ECGs, chest x-rays, and results of ophthalmologic examinations.

Certain portions of the discussion below relating to objective or numeric safety parameters, namely, dose-dependent adverse reactions, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar I disorder (manic or mixed episodes) or agitation. However, this information is also generally applicable to bipolar I disorder (manic or mixed episodes) and agitation.

Adverse reactions during exposure were obtained by spontaneous report and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories. In the tables and tabulations that follow, MedDRA and COSTART Dictionary terminology has been used to classify reported adverse reactions.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. The reported reactions do not include those reaction terms that were so general as to be uninformative. Reactions listed elsewhere in labeling may not be repeated below. It is important to emphasize that, although the reactions occurred during treatment with olanzapine, they were not necessarily caused by it. The entire label should be read to gain a complete understanding of the safety profile of olanzapine.

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

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled and Combination Trials

The following findings are based on premarketing trials of (1) oral olanzapine for schizophrenia, bipolar I disorder (manic or mixed episodes), a subsequent trial of patients having various psychiatric symptoms in association with Alzheimer's disease, and premarketing combination trials, and (2) intramuscular olanzapine for injection in agitated patients with schizophrenia or bipolar I mania.

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials*

Schizophrenia — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (5% for oral olanzapine vs 6% for placebo). However, discontinuations due to increases in ALT were considered to be drug related (2% for oral olanzapine vs 0% for placebo).

Bipolar I Disorder (Manic or Mixed Episodes) Monotherapy — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (2% for oral olanzapine vs 2% for placebo).

Agitation — Overall, there was no difference in the incidence of discontinuation due to adverse reactions (0.4% for intramuscular olanzapine for injection vs 0% for placebo).

*Adverse Reactions Associated with Discontinuation of Treatment in Short-Term Combination Trials*

Bipolar I Disorder (Manic or Mixed Episodes), Olanzapine as Adjunct to Lithium or Valproate — In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 11% for the combination of oral olanzapine with lithium or valproate compared to 2% for patients who remained on lithium or valproate monotherapy. Discontinuations with the combination of oral olanzapine and lithium or valproate that occurred in more than 1 patient were: somnolence (3%), weight gain (1%), and peripheral edema (1%).

*Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials*

The most commonly observed adverse reactions associated with the use of oral olanzapine (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) were:

**Table 9: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Trials — SCHIZOPHRENIA**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=248)** | **Placebo (N=118)** |
| Postural hypotension | 5 | 2 |
| Constipation | 9 | 3 |
| Weight gain | 6 | 1 |
| Dizziness | 11 | 4 |
| Personality disorder[a] | 8 | 4 |
| Akathisia | 5 | 1 |

[a] Personality disorder is the COSTART term for designating nonaggressive objectionable behavior.

**Table 10: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 3-Week and 4-Week Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine (N=125)** | **Placebo (N=129)** |
| Asthenia | 15 | 6 |
| Dry mouth | 22 | 7 |
| Constipation | 11 | 5 |
| Dyspepsia | 11 | 5 |
| Increased appetite | 6 | 3 |
| Somnolence | 35 | 13 |
| Dizziness | 18 | 6 |
| Tremor | 6 | 3 |

Olanzapine Intramuscular — There was 1 adverse reaction (somnolence) observed at an incidence of 5% or greater among intramuscular olanzapine for injection-treated patients and not observed at an equivalent incidence among placebo-treated patients (olanzapine incidence at least twice that for placebo) during the placebo-controlled premarketing studies. The incidence of somnolence during the 24 hour IM treatment period in clinical trials in agitated patients with schizophrenia or bipolar I mania was 6% for intramuscular olanzapine for injection and 3% for placebo.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 11 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with oral olanzapine (doses ≥2.5 mg/day) and with incidence greater than placebo who participated in the acute phase of placebo-controlled trials.

**Table 11: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials with Oral Olanzapine**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Body System/Adverse Reaction** | **Olanzapine (N=532)** | **Placebo (N=294)** |
| **Body as a Whole** | | |
| Accidental injury | 12 | 8 |
| Asthenia | 10 | 9 |
| Fever | 6 | 2 |
| Back pain | 5 | 2 |
| Chest pain | 3 | 1 |
| **Cardiovascular System** | | |
| Postural hypotension | 3 | 1 |
| Tachycardia | 3 | 1 |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 9 | 5 |
| Constipation | 9 | 4 |
| Dyspepsia | 7 | 5 |
| Vomiting | 4 | 3 |
| Increased appetite | 3 | 2 |
| **Hemic and Lymphatic System** | | |
| Ecchymosis | 5 | 3 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 5 | 3 |
| Peripheral edema | 3 | 1 |
| **Musculoskeletal System** | | |
| Extremity pain (other than joint) | 5 | 3 |
| Joint pain | 5 | 3 |
| **Nervous System** | | |
| Somnolence | 29 | 13 |
| Insomnia | 12 | 11 |
| Dizziness | 11 | 4 |
| Abnormal gait | 6 | 1 |
| Tremor | 4 | 3 |
| Akathisia | 3 | 2 |
| Hypertonia | 3 | 2 |
| Articulation impairment | 2 | 1 |
| **Respiratory System** | | |
| Rhinitis | 7 | 6 |
| Cough increased | 6 | 3 |
| Pharyngitis | 4 | 3 |
| **Special Senses** | | |
| Amblyopia | 3 | 2 |
| **Urogenital System** | | |
| Urinary incontinence | 2 | 1 |
| Urinary tract infection | 2 | 1 |

*Dose Dependency of Adverse Reactions*

A dose group difference has been observed for fatigue, dizziness, weight gain and prolactin elevation. In a single 8-week randomized, double-blind, fixed-dose study comparing 10 (N=199), 20 (N=200) and 40 (N=200) mg/day of oral olanzapine in adult patients with schizophrenia or schizoaffective disorder, incidence of fatigue (10 mg/day: 1.5%; 20 mg/day: 2.1%; 40 mg/day: 6.6%) was observed with significant differences between 10 vs 40 and 20 vs 40 mg/day. The incidence of dizziness (10 mg/day: 2.6%; 20 mg/day: 1.6%; 40 mg/day: 6.6%) was observed with significant differences between 20 vs 40 mg. Dose group differences were also noted for weight gain and prolactin elevation *[see Warnings and Precautions (5.5, 5.15)]*.

The following table addresses dose relatedness for other adverse reactions using data from a schizophrenia trial involving fixed dosage ranges of oral olanzapine. It enumerates the percentage of patients with treatment-emergent adverse reactions for the 3 fixed-dose range groups and placebo. The data were analyzed using the Cochran-Armitage test, excluding the placebo group, and the table includes only those adverse reactions for which there was a trend.

**Table 12: Percentage of Patients from a Schizophrenia Trial with Treatment-Emergent Adverse Reactions for the 3 Dose Range Groups and Placebo**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| **Adverse Reaction** | **Placebo (N=68)** | **Olanzapine 5 ± 2.5 mg/day (N=65)** | **Olanzapine 10 ± 2.5 mg/day (N=64)** | **Olanzapine 15 ± 2.5 mg/day (N=69)** |
| Asthenia | 15 | 8 | 9 | 20 |
| Dry mouth | 4 | 3 | 5 | 13 |
| Nausea | 9 | 0 | 2 | 9 |
| Somnolence | 16 | 20 | 30 | 39 |
| Tremor | 3 | 0 | 5 | 7 |

*Commonly Observed Adverse Reactions in Short-Term Trials of Oral Olanzapine as Adjunct to Lithium or Valproate*

In the bipolar I disorder (manic or mixed episodes) adjunct placebo-controlled trials, the most commonly observed adverse reactions associated with the combination of olanzapine and lithium or valproate (incidence of ≥5% and at least twice placebo) were:

**Table 13: Common Treatment-Emergent Adverse Reactions Associated with the Use of Oral Olanzapine in 6-Week Adjunct to Lithium or Valproate Trials — Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| **Adverse Reaction** | **Olanzapine with lithium or valproate (N=229)** | **Placebo with lithium or valproate (N=115)** |
| Dry mouth | 32 | 9 |
| Weight gain | 26 | 7 |
| Increased appetite | 24 | 8 |
| Dizziness | 14 | 7 |
| Back pain | 8 | 4 |
| Constipation | 8 | 4 |
| Speech disorder | 7 | 1 |
| Increased salivation | 6 | 2 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term Trials of Olanzapine as Adjunct to Lithium or Valproate*

Table 14 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 2% or more of patients treated with the combination of olanzapine (doses ≥5 mg/day) and lithium or valproate and with incidence greater than lithium or valproate alone who participated in the acute phase of placebo-controlled combination trials.

**Table 14: Treatment-Emergent Adverse Reactions: Incidence in Short-Term, Placebo-Controlled Clinical Trials of Oral Olanzapine as Adjunct to Lithium or Valproate**

| | Percentage of Patients Reporting Event |
|---|---|

| Body System/Adverse Reaction | Olanzapine with lithium or valproate (N=229) | Placebo with lithium or valproate (N=115) |
|---|---|---|
| **Body as a Whole** | | |
| Asthenia | 18 | 13 |
| Back pain | 8 | 4 |
| Accidental injury | 4 | 2 |
| Chest pain | 3 | 2 |
| **Cardiovascular System** | | |
| Hypertension | 2 | 1 |
| **Digestive System** | | |
| Dry mouth | 32 | 9 |
| Increased appetite | 24 | 8 |
| Thirst | 10 | 6 |
| Constipation | 8 | 4 |
| Increased salivation | 6 | 2 |
| **Metabolic and Nutritional Disorders** | | |
| Weight gain | 26 | 7 |
| Peripheral edema | 6 | 4 |
| Edema | 2 | 1 |
| **Nervous System** | | |
| Somnolence | 52 | 27 |
| Tremor | 23 | 13 |
| Depression | 18 | 17 |
| Dizziness | 14 | 7 |
| Speech disorder | 7 | 1 |
| Amnesia | 5 | 2 |
| Paresthesia | 5 | 2 |
| Apathy | 4 | 3 |
| Confusion | 4 | 1 |
| Euphoria | 3 | 2 |
| Incoordination | 2 | 0 |
| **Respiratory System** | | |
| Pharyngitis | 4 | 1 |
| Dyspnea | 3 | 1 |
| **Skin and Appendages** | | |
| Sweating | 3 | 1 |
| Acne | 2 | 0 |
| Dry skin | 2 | 0 |
| **Special Senses** | | |
| Amblyopia | 9 | 5 |
| Abnormal vision | 2 | 0 |
| **Urogenital System** | | |
| Dysmenorrhea[a] | 2 | 0 |
| Vaginitis[a] | 2 | 0 |

[a] Denominator used was for females only (olanzapine, N=128; placebo, N=51).

For specific information about the adverse reactions observed with lithium or valproate, refer to the Adverse Reactions section of the package inserts for these other products.

*Adverse Reactions Occurring at an Incidence of 1% or More among Intramuscular Olanzapine for Injection-Treated Patients in Short-Term, Placebo-Controlled Trials*

Table 15 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred in 1% or more of patients treated with intramuscular olanzapine for injection (dose range of 2.5-10 mg/injection) and with incidence greater than placebo who participated in the short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar I mania.

**Table 15: Treatment-Emergent Adverse Reactions: Incidence in Short-Term (24 Hour), Placebo-Controlled Clinical Trials with Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia or Bipolar I Mania**

| Body System/Adverse Reaction | Percentage of Patients Reporting Event | |
|---|---|---|
| | Olanzapine (N=415) | Placebo (N=150) |
| **Body as a Whole** | | |
| Asthenia | 2 | 1 |
| **Cardiovascular System** | | |
| Hypotension | 2 | 0 |
| Postural hypotension | 1 | 0 |
| **Nervous System** | | |
| Somnolence | 6 | 3 |
| Dizziness | 4 | 2 |
| Tremor | 1 | 0 |

**Extrapyramidal Symptoms**

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during acute therapy in a controlled clinical trial comparing oral olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 16: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo | Olanzapine 5 ± 2.5 mg/day | Olanzapine 10 ± 2.5 mg/day | Olanzapine 15 ± 2.5 mg/day |
| Parkinsonism[a] | 15 | 14 | 12 | 14 |
| Akathisia[b] | 23 | 16 | 19 | 27 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy in the same controlled clinical trial comparing olanzapine at 3 fixed doses with placebo in the treatment of schizophrenia in a 6-week trial.

**Table 17: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dosage Range, Placebo-Controlled Clinical Trial of Oral Olanzapine in Schizophrenia — Acute Phase**

| | Percentage of Patients Reporting Event | | | |
|---|---|---|---|---|
| | Placebo (N=68) | Olanzapine 5 ± 2.5 mg/day (N=65) | Olanzapine 10 ± 2.5 mg/day (N=64) | Olanzapine 15 ± 2.5 mg/day (N=69) |
| Dystonic events[a] | 1 | 3 | 2 | 3 |
| Parkinsonism events[b] | 10 | 8 | 14 | 20 |
| Akathisia events[c] | 1 | 5 | 11 | 10 |
| Dyskinetic events[d] | 4 | 0 | 2 | 1 |
| Residual events[e] | 1 | 2 | 5 | 1 |
| Any extrapyramidal event | 16 | 15 | 25 | 32 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

The following table enumerates the percentage of adolescent patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions during acute therapy (dose range: 2.5 to 20 mg/day).

**Table 18: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in Placebo-Controlled Clinical Trials of Oral Olanzapine in Schizophrenia and Bipolar I Disorder — Adolescents**

| Categories[a] | Percentage of Patients Reporting Event | |
|---|---|---|
| | Placebo (N=89) | Olanzapine (N=179) |
| Dystonic events | 0 | 1 |
| Parkinsonism events | 2 | 1 |
| Akathisia events | 4 | 6 |
| Dyskinetic events | 0 | 1 |
| Nonspecific events | 0 | 4 |
| Any extrapyramidal event | 6 | 10 |

[a] Categories are based on Standard MedDRA Queries (SMQ) for extrapyramidal symptoms as defined in MedDRA version 12.0.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by categorical analyses of formal rating scales during controlled clinical trials comparing fixed doses of intramuscular olanzapine for injection with placebo in agitation. Patients in each dose group could receive up to 3 injections during the trials *[see Clinical Studies (14.3)]*. Patient assessments were conducted during the 24 hours following the initial dose of intramuscular olanzapine for injection.

**Table 19: Treatment-Emergent Extrapyramidal Symptoms Assessed by Rating Scales Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo | Olanzapine IM 2.5 mg | Olanzapine IM 5 mg | Olanzapine IM 7.5 mg | Olanzapine IM 10 mg |
| Parkinsonism[a] | 0 | 0 | 0 | 0 | 3 |
| Akathisia[b] | 0 | 0 | 5 | 0 | 0 |

[a] Percentage of patients with a Simpson-Angus Scale total score >3.

[b] Percentage of patients with a Barnes Akathisia Scale global score ≥2.

The following table enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms as assessed by spontaneously reported adverse reactions in the same controlled clinical trial comparing fixed doses of intramuscular olanzapine for injection with placebo in agitated patients with schizophrenia.

**Table 20: Treatment-Emergent Extrapyramidal Symptoms Assessed by Adverse Reactions Incidence in a Fixed Dose, Placebo-Controlled Clinical Trial of Intramuscular Olanzapine for Injection in Agitated Patients with Schizophrenia**

| | Percentage of Patients Reporting Event | | | | |
|---|---|---|---|---|---|
| | Placebo (N=45) | Olanzapine IM 2.5 mg (N=48) | Olanzapine IM 5 mg (N=45) | Olanzapine IM 7.5 mg (N=46) | Olanzapine IM 10 mg (N=46) |
| Dystonic events[a] | 0 | 0 | 0 | 0 | 0 |
| Parkinsonism events[b] | 0 | 4 | 2 | 0 | 0 |
| Akathisia events[c] | 0 | 2 | 0 | 0 | 0 |
| Dyskinetic events[d] | 0 | 0 | 0 | 0 | 0 |
| Residual events[e] | 0 | 0 | 0 | 0 | 0 |
| Any extrapyramidal events | 0 | 4 | 2 | 0 | 0 |

[a] Patients with the following COSTART terms were counted in this category: dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis.

[b] Patients with the following COSTART terms were counted in this category: akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor.

[c] Patients with the following COSTART terms were counted in this category: akathisia, hyperkinesia.

[d] Patients with the following COSTART terms were counted in this category: buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia.

[e] Patients with the following COSTART terms were counted in this category: movement disorder, myoclonus, twitching.

*Dystonia, Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, the frequency and severity are greater with high potency and at higher doses of first generation antipsychotic drugs. In general, an elevated risk of acute dystonia may be observed in males and younger age groups receiving antipsychotics; however, events of dystonia have been reported infrequently (<1%) with olanzapine use.

**Other Adverse Reactions**

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Oral Olanzapine

Following is a list of treatment-emergent adverse reactions reported by patients treated with oral olanzapine (at multiple doses ≥1 mg/day) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients.

**Body as a Whole** — *Infrequent:* chills, face edema, photosensitivity reaction, suicide attempt[1]; *Rare:* chills and fever, hangover effect, sudden death[1].

**Cardiovascular System** — *Infrequent:* cerebrovascular accident, vasodilatation.

**Digestive System** — *Infrequent:* abdominal distension, nausea and vomiting, tongue edema; *Rare:* ileus, intestinal obstruction, liver fatty deposit.

**Hemic and Lymphatic System** — *Infrequent:* thrombocytopenia.

**Metabolic and Nutritional Disorders** — *Frequent:* alkaline phosphatase increased; *Infrequent:* bilirubinemia, hypoproteinemia.

**Musculoskeletal System** — *Rare:* osteoporosis.

**Nervous System** — *Infrequent:* ataxia, dysarthria, libido decreased, stupor; *Rare:* coma.

**Respiratory System** — *Infrequent:* epistaxis; *Rare:* lung edema.

**Skin and Appendages** — *Infrequent:* alopecia.

**Special Senses** — *Infrequent:* abnormality of accommodation, dry eyes; *Rare:* mydriasis.

**Urogenital System** — *Infrequent:* amenorrhea[2], breast pain, decreased menstruation, impotence[2], increased menstruation[2], menorrhagia[2], metrorrhagia[2], polyuria[2], urinary frequency, urinary retention, urinary urgency, urination impaired.

[1] These terms represent serious adverse events but do not meet the definition for adverse drug reactions. They are included here because of their seriousness.

[2] Adjusted for gender.

Other Adverse Reactions Observed During the Clinical Trial Evaluation of Intramuscular Olanzapine for Injection

Following is a list of treatment-emergent adverse reactions reported by patients treated with intramuscular olanzapine for injection (at 1 or more doses ≥2.5 mg/injection) in clinical trials. This listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) for which occurred at a rate equal to or less than placebo. Reactions are classified by body system using the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients.

**Body as a Whole** — *Frequent:* injection site pain.

**Cardiovascular System** — *Infrequent:* syncope.

**Digestive System** — *Infrequent:* nausea.

**Metabolic and Nutritional Disorders** — *Infrequent:* creatine phosphokinase increased.

Clinical Trials in Adolescent Patients (age 13 to 17 years)

*Commonly Observed Adverse Reactions in Oral Olanzapine Short-Term, Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 5% or more and reported at least twice as frequently as placebo-treated patients are listed in Table 21.

**Table 21: Treatment-Emergent Adverse Reactions of ≥5% Incidence among Adolescents (13-17 Years Old) with Schizophrenia or Bipolar I Disorder (Manic or Mixed Episodes)**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| | 6 Week Trial<br>% Schizophrenia Patients | 3 Week Trial<br>% Bipolar Patients |

| Adverse Reactions | Olanzapine (N=72) | Placebo (N=35) | Olanzapine (N=107) | Placebo (N=54) |
|---|---|---|---|---|
| Sedation[a] | 39 | 9 | 48 | 9 |
| Weight increased | 31 | 9 | 29 | 4 |
| Headache | 17 | 6 | 17 | 17 |
| Increased appetite | 17 | 9 | 29 | 4 |
| Dizziness | 8 | 3 | 7 | 2 |
| Abdominal pain[b] | 6 | 3 | 6 | 7 |
| Pain in extremity | 6 | 3 | 5 | 0 |
| Fatigue | 3 | 3 | 14 | 6 |
| Dry mouth | 4 | 0 | 7 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.
[b] Patients with the following MedDRA terms were counted in this category: abdominal pain, abdominal pain lower, abdominal pain upper.

*Adverse Reactions Occurring at an Incidence of 2% or More among Oral Olanzapine-Treated Patients in Short-Term (3-6 weeks), Placebo-Controlled Trials*

Adverse reactions in adolescent patients treated with oral olanzapine (doses ≥2.5 mg) reported with an incidence of 2% or more and greater than placebo are listed in Table 22.

**Table 22: Treatment-Emergent Adverse Reactions of ≥2% Incidence among Adolescents (13-17 Years Old) (Combined Incidence from Short-Term, Placebo-Controlled Clinical Trials of Schizophrenia or Bipolar I Disorder [Manic or Mixed Episodes])**

| | Percentage of Patients Reporting Event | |
|---|---|---|
| Adverse Reaction | Olanzapine (N=179) | Placebo (N=89) |
| Sedation[a] | 44 | 9 |
| Weight increased | 30 | 6 |
| Increased appetite | 24 | 6 |
| Headache | 17 | 12 |
| Fatigue | 9 | 4 |
| Dizziness | 7 | 2 |
| Dry mouth | 6 | 0 |
| Pain in extremity | 5 | 1 |
| Constipation | 4 | 0 |
| Nasopharyngitis | 4 | 2 |
| Diarrhea | 3 | 0 |
| Restlessness | 3 | 2 |
| Liver enzymes increased[b] | 8 | 1 |
| Dyspepsia | 3 | 1 |
| Epistaxis | 3 | 0 |
| Respiratory tract infection[c] | 3 | 2 |
| Sinusitis | 3 | 0 |
| Arthralgia | 2 | 0 |
| Musculoskeletal stiffness | 2 | 0 |

[a] Patients with the following MedDRA terms were counted in this category: hypersomnia, lethargy, sedation, somnolence.
[b] The terms alanine aminotransferase (ALT), aspartate aminotransferase (AST), and hepatic enzyme were combined under liver enzymes.
[c] Patients with the following MedDRA terms were counted in this category: lower respiratory tract infection, respiratory tract infection, respiratory tract infection viral, upper respiratory tract infection, viral upper respiratory tract infection.

**Vital Signs and Laboratory Studies**

Vital Sign Changes — Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials *[see Warnings and Precautions (5)]*.

Laboratory Changes

*Olanzapine Monotherapy in Adults:* An assessment of the premarketing experience for olanzapine revealed an association with asymptomatic increases in ALT, AST, and GGT. Within the original premarketing database of about 2400 adult patients with baseline ALT ≤90 IU/L, the incidence of ALT elevations to >200 IU/L was 2% (50/2381). None of these

patients experienced jaundice or other symptoms attributable to liver impairment and most had transient changes that tended to normalize while olanzapine treatment was continued.

In placebo-controlled olanzapine monotherapy studies in adults, clinically significant ALT elevations (change from <3 times the upper limit of normal [ULN] at baseline to ≥3 times ULN) were observed in 5% (77/1426) of patients exposed to olanzapine compared to 1% (10/1187) of patients exposed to placebo. ALT elevations ≥5 times ULN were observed in 2% (29/1438) of olanzapine-treated patients, compared to 0.3% (4/1196) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

From an analysis of the laboratory data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, high GGT levels were recorded in ≥1% (88/5245) of patients.

Caution should be exercised in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic drugs.

Olanzapine administration was also associated with increases in serum prolactin *[see Warnings and Precautions (5.15)]*, with an asymptomatic elevation of the eosinophil count in 0.3% of patients, and with an increase in CPK.

From an analysis of the laboratory data in an integrated database of 41 completed clinical studies in adult patients treated with oral olanzapine, elevated uric acid was recorded in ≥3% (171/4641) of patients.

*Olanzapine Monotherapy in Adolescents:* In placebo-controlled clinical trials of adolescent patients with schizophrenia or bipolar I disorder (manic or mixed episodes), greater frequencies for the following treatment-emergent findings, at anytime, were observed in laboratory analytes compared to placebo: elevated ALT (≥3X ULN in patients with ALT at baseline <3X ULN), (12% vs 2%); elevated AST (28% vs 4%); low total bilirubin (22% vs 7%); elevated GGT (10% vs 1%); and elevated prolactin (47% vs 7%).

In placebo-controlled olanzapine monotherapy studies in adolescents, clinically significant ALT elevations (change from <3 times ULN at baseline to ≥3 times ULN) were observed in 12% (22/192) of patients exposed to olanzapine compared to 2% (2/109) of patients exposed to placebo. ALT elevations ≥5 times ULN were observed in 4% (8/192) of olanzapine-treated patients, compared to 1% (1/109) of placebo-treated patients. ALT values returned to normal, or were decreasing, at last follow-up in the majority of patients who either continued treatment with olanzapine or discontinued olanzapine. No adolescent patient with elevated ALT values experienced jaundice, liver failure, or met the criteria for Hy's Rule.

ECG Changes — In pooled studies of adults as well as pooled studies of adolescents, there were no significant differences between olanzapine and placebo in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc (Fridericia corrected), and PR intervals. Olanzapine use was associated with a mean increase in heart rate compared to placebo (adults: +2.4 beats per minute vs no change with placebo; adolescents: +6.3 beats per minute vs -5.1 beats per minute with placebo). This increase in heart rate may be related to olanzapine's potential for inducing orthostatic changes *[see Warnings and Precautions (5.7)]*.

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ZYPREXA. Because these reactions are reported voluntarily from a population of uncertain size, it is difficult to reliably estimate their frequency or evaluate a causal relationship to drug exposure.

Adverse reactions reported since market introduction that were temporally (but not necessarily causally) related to ZYPREXA therapy include the following: allergic reaction (e.g., anaphylactoid reaction, angioedema, pruritus or urticaria), cholestatic or mixed liver injury, diabetic coma, diabetic ketoacidosis, discontinuation reaction (diaphoresis, nausea or vomiting), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), hepatitis, jaundice, neutropenia, pancreatitis, priapism, rash, restless legs syndrome, rhabdomyolysis, salivary hypersecretion, stuttering[1], and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

[1] Stuttering was only studied in oral and long acting injection (LAI) formulations.

## 7 DRUG INTERACTIONS

The risks of using olanzapine in combination with other drugs have not been extensively evaluated in systematic studies.

### 7.1 Potential for Other Drugs to Affect Olanzapine

Diazepam — The co-administration of diazepam with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Cimetidine and Antacids — Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine.

Inducers of CYP1A2 — Carbamazepine therapy (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. This increase is likely due to the fact that carbamazepine is a potent inducer of CYP1A2 activity. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance.

Alcohol — Ethanol (45 mg/70 kg single dose) did not have an effect on olanzapine pharmacokinetics. The co-administration of alcohol (i.e., ethanol) with olanzapine potentiated the orthostatic hypotension observed with olanzapine *[see Drug Interactions (7.2)]*.

Inhibitors of CYP1A2

*Fluvoxamine:* Fluvoxamine, a CYP1A2 inhibitor, decreases the clearance of olanzapine. This results in a mean increase in olanzapine Cmax following fluvoxamine of 54% in female nonsmokers and 77% in male smokers. The mean increase in olanzapine AUC is 52% and 108%, respectively. Lower doses of olanzapine should be considered in patients receiving concomitant treatment with fluvoxamine.

Inhibitors of CYP2D6

*Fluoxetine:* Fluoxetine (60 mg single dose or 60 mg daily dose for 8 days) causes a small (mean 16%) increase in the maximum concentration of olanzapine and a small (mean 16%) decrease in olanzapine clearance. The magnitude of the impact of this factor is small in comparison to the overall variability between individuals, and therefore dose modification is not routinely recommended. When using ZYPREXA and fluoxetine in combination, also refer to the Drug Interactions section of the package insert for Symbyax.

Warfarin — Warfarin (20 mg single dose) did not affect olanzapine pharmacokinetics *[see Drug Interactions (7.2)]*.

Inducers of CYP1A2 or Glucuronyl Transferase — Omeprazole and rifampin may cause an increase in olanzapine clearance.

Charcoal — The administration of activated charcoal (1 g) reduced the Cmax and AUC of oral olanzapine by about 60%. As peak olanzapine levels are not typically obtained until about 6 hours after dosing, charcoal may be a useful treatment for olanzapine overdose.

Anticholinergic Drugs — Concomitant treatment with olanzapine and other drugs with anticholinergic activity can increase the risk for severe gastrointestinal adverse reactions related to hypomotility. ZYPREXA should be used with caution in patients receiving medications having anticholinergic (antimuscarinic) effects *[see Warnings and Precautions (5.14)]*.

### 7.2 Potential for Olanzapine to Affect Other Drugs

CNS Acting Drugs — Given the primary CNS effects of olanzapine, caution should be used when olanzapine is taken in combination with other centrally acting drugs and alcohol.

Antihypertensive Agents — Olanzapine, because of its potential for inducing hypotension, may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists — Olanzapine may antagonize the effects of levodopa and dopamine agonists.

Lorazepam (IM) — Administration of intramuscular lorazepam (2 mg) 1 hour after intramuscular olanzapine for injection (5 mg) did not significantly affect the pharmacokinetics of olanzapine, unconjugated lorazepam, or total lorazepam. However, this co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone *[see Warnings and Precautions (5.7)]*.

Lithium — Multiple doses of olanzapine (10 mg for 8 days) did not influence the kinetics of lithium. Therefore, concomitant olanzapine administration does not require dosage adjustment of lithium *[see Warnings and Precautions (5.16)]*.

Valproate — Olanzapine (10 mg daily for 2 weeks) did not affect the steady state plasma concentrations of valproate. Therefore, concomitant olanzapine administration does not require dosage adjustment of valproate *[see Warnings and Precautions (5.16)]*.

Effect of Olanzapine on Drug Metabolizing Enzymes — In vitro studies utilizing human liver microsomes suggest that olanzapine has little potential to inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Thus, olanzapine is unlikely to cause clinically important drug interactions mediated by these enzymes.

Imipramine — Single doses of olanzapine did not affect the pharmacokinetics of imipramine or its active metabolite desipramine.

Warfarin — Single doses of olanzapine did not affect the pharmacokinetics of warfarin *[see Drug Interactions (7.1)]*.

Diazepam — Olanzapine did not influence the pharmacokinetics of diazepam or its active metabolite N-desmethyldiazepam. However, diazepam co-administered with olanzapine increased the orthostatic hypotension observed with either drug given alone *[see Drug Interactions (7.1)]*.

Alcohol — Multiple doses of olanzapine did not influence the kinetics of ethanol *[see Drug Interactions (7.1)]*.

Biperiden — Multiple doses of olanzapine did not influence the kinetics of biperiden.

Theophylline — Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

## 8 USE IN SPECIFIC POPULATIONS

When using ZYPREXA and fluoxetine in combination, also refer to the Use in Specific Populations section of the package insert for Symbyax.

### 8.1 Pregnancy

*Pregnancy Exposure Registry*

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including ZYPREXA, during pregnancy. Healthcare providers are encouraged to register patients by

contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

*Risk Summary*

Neonates exposed to antipsychotic drugs, including ZYPREXA, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations).* Overall available data from published epidemiologic studies of pregnant women exposed to olanzapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data).* There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including ZYPREXA, during pregnancy *(see Clinical Considerations).*

Olanzapine was not teratogenic when administered orally to pregnant rats and rabbits at doses that are 9- and 30-times the daily oral maximum recommended human dose (MRHD), based on mg/m$^2$ body surface area; some fetal toxicities were observed at these doses (*see Data*).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defects, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

*Clinical Considerations*

*Disease-associated maternal and embryo/fetal risk*

There is a risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

*Fetal/Neonatal adverse reactions*

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including ZYPREXA, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

*Data*

*Human Data*

Placental passage has been reported in published study reports; however, the placental passage ratio was highly variable ranging between 7% to 167% at birth following exposure during pregnancy. The clinical relevance of this finding is unknown.

Published data from observational studies, birth registries, and case reports that have evaluated the use of atypical antipsychotics during pregnancy do not establish an increased risk of major birth defects. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects.

*Animal Data*

In oral reproduction studies in rats at doses up to 18 mg/kg/day and in rabbits at doses up to 30 mg/kg/day (9 and 30 times the daily oral MRHD based on mg/m$^2$ body surface area, respectively), no evidence of teratogenicity was observed. In an oral rat teratology study, early resorptions and increased numbers of nonviable fetuses were observed at a dose of 18 mg/kg/day (9 times the daily oral MRHD based on mg/m$^2$ body surface area), and gestation was prolonged at 10 mg/kg/day (5 times the daily oral MRHD based on mg/m$^2$ body surface area). In an oral rabbit teratology study, fetal toxicity manifested as increased resorptions and decreased fetal weight, occurred at a maternally toxic dose of 30 mg/kg/day (30 times the daily oral MRHD based on mg/m$^2$ body surface area).

### 8.2 Lactation

*Risk Summary*

Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk *(see Clinical Considerations).* There is no information on the effects of olanzapine on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZYPREXA and any potential adverse effects on the breastfed child from ZYPREXA or from the mother's underlying condition.

*Clinical Considerations*

Infants exposed to ZYPREXA should be monitored for excess sedation, irritability, poor feeding, and extrapyramidal symptoms (tremors and abnormal muscle movements).

### 8.3 Females and Males of Reproductive Potential

*Infertility*

Females

Based on the pharmacologic action of olanzapine ($D_2$ receptor antagonism), treatment with ZYPREXA may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.15)].*

### 8.4 Pediatric Use

The safety and effectiveness of oral ZYPREXA in the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder were established in short-term studies in adolescents (ages 13 to 17 years). Use of ZYPREXA in adolescents is supported by evidence from adequate and well-controlled studies of ZYPREXA in which 268 adolescents received ZYPREXA in a range of 2.5 to 20 mg/day *[see Clinical Studies (14.1, 14.2)]*. Recommended starting dose for adolescents is lower than that for adults *[see Dosage and Administration (2.1, 2.2)]*. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin and hepatic aminotransferase levels *[see Warnings and Precautions (5.5, 5.15, 5.17) and Adverse Reactions (6.1)]*. When deciding among the alternative treatments available for adolescents, clinicians should consider the increased potential (in adolescents as compared with adults) for weight gain and dyslipidemia. Clinicians should consider the potential long-term risks when prescribing to adolescents, and in many cases this may lead them to consider prescribing other drugs first in adolescents *[see Indications and Usage (1.1, 1.2)]*.

Safety and effectiveness of olanzapine in children <13 years of age have not been established *[see Patient Counseling Information (17)]*.

Safety and efficacy of ZYPREXA and fluoxetine in combination in children and adolescents (10 to 17 years of age) have been established for the acute treatment of depressive episodes associated with bipolar I disorder.

Safety and effectiveness of ZYPREXA and fluoxetine in combination in children <10 years of age have not been established.

### 8.5 Geriatric Use

Of the 2500 patients in premarketing clinical studies with oral olanzapine, 11% (263) were 65 years of age or over. In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. In placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis, there was a higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) in patients treated with olanzapine compared to patients treated with placebo. In 5 placebo-controlled studies of olanzapine in elderly patients with dementia-related psychosis (n=1184), the following adverse reactions were reported in olanzapine-treated patients at an incidence of at least 2% and significantly greater than placebo-treated patients: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth and visual hallucinations. The rate of discontinuation due to adverse reactions was greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1), and Patient Counseling Information (17)]*. Olanzapine is not approved for the treatment of patients with dementia-related psychosis. Also, the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine should lead to consideration of a lower starting dose for any geriatric patient *[see Boxed Warning, Dosage and Administration (2.1), and Warnings and Precautions (5.1)]*.

Clinical studies of ZYPREXA and fluoxetine in combination did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients.

## 9 DRUG ABUSE AND DEPENDENCE

### 9.3 Dependence

In studies prospectively designed to assess abuse and dependence potential, olanzapine was shown to have acute depressive CNS effects but little or no potential of abuse or physical dependence in rats administered oral doses up to 15 times the daily oral MRHD (20 mg) and rhesus monkeys administered oral doses up to 8 times the daily oral MRHD based on mg/m$^2$ body surface area.

Olanzapine has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of olanzapine (e.g., development of tolerance, increases in dose, drug-seeking behavior).

## 10 OVERDOSAGE

### 10.1 Human Experience

In premarketing trials involving more than 3100 patients and/or normal subjects, accidental or intentional acute overdosage of olanzapine was identified in 67 patients. In the patient taking the largest identified amount, 300 mg, the only symptoms reported were drowsiness and slurred speech. In the limited number of patients who were evaluated in hospitals, including the patient taking 300 mg, there were no observations indicating an adverse change in laboratory analytes or ECG. Vital signs were usually within normal limits following overdoses.

In postmarketing reports of overdose with olanzapine alone, symptoms have been reported in the majority of cases. In symptomatic patients, symptoms with ≥10% incidence included agitation/aggressiveness, dysarthria, tachycardia, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma. Among less commonly reported symptoms were the following potentially medically serious reactions: aspiration, cardiopulmonary arrest, cardiac arrhythmias (such as supraventricular tachycardia and 1 patient experiencing sinus pause with spontaneous resumption of normal rhythm), delirium, possible neuroleptic malignant syndrome, respiratory depression/arrest, convulsion, hypertension, and hypotension. Eli Lilly and Company has received reports of fatality in association with overdose of olanzapine alone. In 1 case of death, the amount of acutely ingested olanzapine was reported to be possibly as low as 450 mg of oral olanzapine; however, in another case, a patient was reported to survive an acute olanzapine ingestion of approximately 2 g of oral olanzapine.

### 10.2 Management of Overdose

There is no specific antidote to an overdose of ZYPREXA The possibility of multiple drug involvement should be considered. Establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

Contact a Certified Poison Control Center for the most up to date information on the management of overdosage (1-800-222-1222).

For specific information about overdosage with lithium or valproate, refer to the Overdosage section of the prescribing information for those products. For specific information about overdosage with olanzapine and fluoxetine in combination, refer to the Overdosage section of the Symbyax prescribing information.

## 11 DESCRIPTION

ZYPREXA (olanzapine) is an atypical antipsychotic that belongs to the thienobenzodiazepine class. The chemical designation is 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*] [1,5]benzodiazepine. The molecular formula is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. The chemical structure is:



Olanzapine is a yellow crystalline solid, which is practically insoluble in water.

ZYPREXA tablets are intended for oral administration only.

Each tablet contains olanzapine equivalent to 2.5 mg (8 µmol), 5 mg (16 µmol), 7.5 mg (24 µmol), 10 mg (32 µmol), 15 mg (48 µmol), or 20 mg (64 µmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains Titanium Dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or Synthetic Red Iron Oxide (20 mg). The 2.5, 5, 7.5, and 10 mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) is intended for oral administration only.

Each orally disintegrating tablet contains olanzapine equivalent to 5 mg (16 µmol), 10 mg (32 µmol), 15 mg (48 µmol) or 20 mg (64 µmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.

ZYPREXA IntraMuscular (olanzapine for injection) is intended for intramuscular use only.

Each vial provides for the administration of 10 mg (32 µmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of olanzapine, in the listed indications is unclear. However, the efficacy of olanzapine in schizophrenia could be mediated through a combination of dopamine and serotonin type 2 ($5HT_2$) antagonism.

### 12.2 Pharmacodynamics

Olanzapine binds with high affinity to the following receptors: serotonin $5HT_{2A/2C}$, $5HT_6$ ($K_i$=4, 11, and 5 nM, respectively), dopamine $D_{1-4}$ ($K_i$=11-31 nM), histamine $H_1$ ($K_i$=7 nM), and adrenergic $\alpha_1$ receptors ($K_i$=19 nM). Olanzapine

is an antagonist with moderate affinity binding for serotonin $5HT_3$ ($K_i$=57 nM) and muscarinic $M_{1-5}$ ($K_i$=73, 96, 132, 32, and 48 nM, respectively). Olanzapine binds with low affinity to $GABA_A$, BZD, and β-adrenergic receptors ($K_i$>10 μM).

### 12.3 Pharmacokinetics

Oral Administration, Monotherapy — Olanzapine is well absorbed and reaches peak concentrations in approximately 6 hours following an oral dose. It is eliminated extensively by first pass metabolism, with approximately 40% of the dose metabolized before reaching the systemic circulation. Food does not affect the rate or extent of olanzapine absorption. Pharmacokinetic studies showed that ZYPREXA tablets and ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) dosage forms of olanzapine are bioequivalent.

Olanzapine displays linear kinetics over the clinical dosing range. Its half-life ranges from 21 to 54 hours (5th to 95th percentile; mean of 30 hr), and apparent plasma clearance ranges from 12 to 47 L/hr (5th to 95th percentile; mean of 25 L/hr).

Administration of olanzapine once daily leads to steady-state concentrations in about 1 week that are approximately twice the concentrations after single doses. Plasma concentrations, half-life, and clearance of olanzapine may vary between individuals on the basis of smoking status, gender, and age.

Olanzapine is extensively distributed throughout the body, with a volume of distribution of approximately 1000 L. It is 93% bound to plasma proteins over the concentration range of 7 to 1100 ng/mL, binding primarily to albumin and $\alpha_1$-acid glycoprotein.

Metabolism and Elimination — Following a single oral dose of $^{14}C$ labeled olanzapine, 7% of the dose of olanzapine was recovered in the urine as unchanged drug, indicating that olanzapine is highly metabolized. Approximately 57% and 30% of the dose was recovered in the urine and feces, respectively. In the plasma, olanzapine accounted for only 12% of the AUC for total radioactivity, indicating significant exposure to metabolites. After multiple dosing, the major circulating metabolites were the 10-N-glucuronide, present at steady state at 44% of the concentration of olanzapine, and 4′-N-desmethyl olanzapine, present at steady state at 31% of the concentration of olanzapine. Both metabolites lack pharmacological activity at the concentrations observed.

Direct glucuronidation and cytochrome P450 (CYP) mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studies suggest that CYPs 1A2 and 2D6, and the flavin-containing monooxygenase system are involved in olanzapine oxidation. CYP2D6 mediated oxidation appears to be a minor metabolic pathway in vivo, because the clearance of olanzapine is not reduced in subjects who are deficient in this enzyme.

Intramuscular Administration — ZYPREXA IntraMuscular results in rapid absorption with peak plasma concentrations occurring within 15 to 45 minutes. Based upon a pharmacokinetic study in healthy volunteers, a 5 mg dose of intramuscular olanzapine for injection produces, on average, a maximum plasma concentration approximately 5 times higher than the maximum plasma concentration produced by a 5 mg dose of oral olanzapine. Area under the curve achieved after an intramuscular dose is similar to that achieved after oral administration of the same dose. The half-life observed after intramuscular administration is similar to that observed after oral dosing. The pharmacokinetics are linear over the clinical dosing range. Metabolic profiles after intramuscular administration are qualitatively similar to metabolic profiles after oral administration.

*Specific Populations*

Renal Impairment — Because olanzapine is highly metabolized before excretion and only 7% of the drug is excreted unchanged, renal dysfunction alone is unlikely to have a major impact on the pharmacokinetics of olanzapine. The pharmacokinetic characteristics of olanzapine were similar in patients with severe renal impairment and normal subjects, indicating that dosage adjustment based upon the degree of renal impairment is not required. In addition, olanzapine is not removed by dialysis. The effect of renal impairment on metabolite elimination has not been studied.

Hepatic Impairment — Although the presence of hepatic impairment may be expected to reduce the clearance of olanzapine, a study of the effect of impaired liver function in subjects (n=6) with clinically significant (Childs Pugh Classification A and B) cirrhosis revealed little effect on the pharmacokinetics of olanzapine.

Geriatric — In a study involving 24 healthy subjects, the mean elimination half-life of olanzapine was about 1.5 times greater in elderly (≥65 years) than in nonelderly subjects (<65 years). Caution should be used in dosing the elderly, especially if there are other factors that might additively influence drug metabolism and/or pharmacodynamic sensitivity *[see Dosage and Administration (2)]*.

Gender — Clearance of olanzapine is approximately 30% lower in women than in men. There were, however, no apparent differences between men and women in effectiveness or adverse effects. Dosage modifications based on gender should not be needed.

Smoking Status — Olanzapine clearance is about 40% higher in smokers than in nonsmokers, although dosage modifications are not routinely recommended.

Race — In vivo studies have shown that exposures are similar among Japanese, Chinese and Caucasians, especially after normalization for body weight differences. Dosage modifications for race are, therefore, not recommended.

Combined Effects — The combined effects of age, smoking, and gender could lead to substantial pharmacokinetic differences in populations. The clearance in young smoking males, for example, may be 3 times higher than that in elderly nonsmoking females. Dosing modification may be necessary in patients who exhibit a combination of factors that may result in slower metabolism of olanzapine *[see Dosage and Administration (2)]*.

Adolescents (ages 13 to 17 years) — In clinical studies, most adolescents were nonsmokers and this population had a lower average body weight, which resulted in higher average olanzapine exposure compared to adults.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Oral carcinogenicity studies were conducted in mice and rats. Olanzapine was administered to mice in two 78-week studies at doses of 3, 10, 30/20 mg/kg/day (equivalent to 0.8-5 times the daily oral MRHD based on mg/m$^2$ body surface area) and 0.25, 2, 8 mg/kg/day (equivalent to 0.06-2 times the daily oral MRHD based on mg/m$^2$ body surface area). Rats were dosed for 2 years at doses of 0.25, 1, 2.5, 4 mg/kg/day (males) and 0.25, 1, 4, 8 mg/kg/day (females) (equivalent to 0.13-2 and 0.13-4 times the daily oral MRHD based on mg/m$^2$ body surface area, respectively). The incidence of liver hemangiomas and hemangiosarcomas was significantly increased in 1 mouse study in female mice at 2 times the daily oral MRHD based on mg/m$^2$ body surface area. These tumors were not increased in another mouse study in females dosed up to 2-5 times the daily oral MRHD based on mg/m$^2$ body surface area; in this study, there was a high incidence of early mortalities in males of the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice dosed at ≥2 mg/kg/day and in female rats dosed at ≥4 mg/kg/day (0.5 and 2 times the daily oral MRHD based on mg/m$^2$ body surface area, respectively). Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum prolactin levels were not measured during the olanzapine carcinogenicity studies; however, measurements during subchronic toxicity studies showed that olanzapine elevated serum prolactin levels up to 4-fold in rats at the same doses used in the carcinogenicity study. An increase in mammary gland neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be prolactin mediated. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown *[see Warnings and Precautions (5.15)]*.

Mutagenesis — No evidence of genotoxic potential for olanzapine was found in the Ames reverse mutation test, in vivo micronucleus test in mice, the chromosomal aberration test in Chinese hamster ovary cells, unscheduled DNA synthesis test in rat hepatocytes, induction of forward mutation test in mouse lymphoma cells, or in vivo sister chromatid exchange test in bone marrow of Chinese hamsters.

Impairment of Fertility — In an oral fertility and reproductive performance study in rats, male mating performance, but not fertility, was impaired at a dose of 22.4 mg/kg/day and female fertility was decreased at a dose of 3 mg/kg/day (11 and 1.5 times the daily oral MRHD based on mg/m$^2$ body surface area, respectively). Discontinuance of olanzapine treatment reversed the effects on male mating performance. In female rats, the precoital period was increased and the mating index reduced at 5 mg/kg/day (2.5 times the daily oral MRHD based on mg/m$^2$ body surface area). Diestrous was prolonged and estrous delayed at 1.1 mg/kg/day (0.6 times the daily oral MRHD based on mg/m$^2$ body surface area); therefore olanzapine may produce a delay in ovulation.

### 13.2 Animal Toxicology and/or Pharmacology

In animal studies with olanzapine, the principal hematologic findings were reversible peripheral cytopenias in individual dogs dosed at 10 mg/kg (17 times the daily oral MRHD based on mg/m$^2$ body surface area), dose-related decreases in lymphocytes and neutrophils in mice, and lymphopenia in rats. A few dogs treated with 10 mg/kg developed reversible neutropenia and/or reversible hemolytic anemia between 1 and 10 months of treatment. Dose-related decreases in lymphocytes and neutrophils were seen in mice given doses of 10 mg/kg (equal to 2 times the daily oral MRHD based on mg/m$^2$ body surface area) in studies of 3 months' duration. Nonspecific lymphopenia, consistent with decreased body weight gain, occurred in rats receiving 22.5 mg/kg (11 times the daily oral MRHD based on mg/m$^2$ body surface area) for 3 months or 16 mg/kg (8 times the daily oral MRHD based on mg/m$^2$ body surface area) for 6 or 12 months. No evidence of bone marrow cytotoxicity was found in any of the species examined. Bone marrows were normocellular or hypercellular, indicating that the reductions in circulating blood cells were probably due to peripheral (non-marrow) factors.

## 14 CLINICAL STUDIES

When using ZYPREXA and fluoxetine in combination, also refer to the Clinical Studies section of the package insert for Symbyax.

### 14.1 Schizophrenia

**Adults**

The efficacy of oral olanzapine in the treatment of schizophrenia was established in 2 short-term (6-week) controlled trials of adult inpatients who met DSM III-R criteria for schizophrenia. A single haloperidol arm was included as a comparative treatment in 1 of the 2 trials, but this trial did not compare these 2 drugs on the full range of clinically relevant doses for both.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of

the patient. In addition, 2 more recently developed scales were employed; these included the 30-item Positive and Negative Symptoms Scale (PANSS), in which are embedded the 18 items of the BPRS, and the Scale for Assessing Negative Symptoms (SANS). The trial summaries below focus on the following outcomes: PANSS total and/or BPRS total; BPRS psychosis cluster; PANSS negative subscale or SANS; and CGI Severity. The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=149) involving 2 fixed olanzapine doses of 1 and 10 mg/day (once daily schedule), olanzapine, at 10 mg/day (but not at 1 mg/day), was superior to placebo on the PANSS total score (also on the extracted BPRS total), on the BPRS psychosis cluster, on the PANSS Negative subscale, and on CGI Severity.

(2) In a 6-week, placebo-controlled trial (n=253) involving 3 fixed dose ranges of olanzapine (5 ± 2.5 mg/day, 10 ± 2.5 mg/day, and 15 ± 2.5 mg/day) on a once daily schedule, the 2 highest olanzapine dose groups (actual mean doses of 12 and 16 mg/day, respectively) were superior to placebo on BPRS total score, BPRS psychosis cluster, and CGI severity score; the highest olanzapine dose group was superior to placebo on the SANS. There was no clear advantage for the high-dose group over the medium-dose group.

(3) In a longer-term trial, adult outpatients (n=326) who predominantly met DSM-IV criteria for schizophrenia and who remained stable on olanzapine during open-label treatment for at least 8 weeks were randomized to continuation on their current olanzapine doses (ranging from 10 to 20 mg/day) or to placebo. The follow-up period to observe patients for relapse, defined in terms of increases in BPRS positive symptoms or hospitalization, was planned for 12 months, however, criteria were met for stopping the trial early due to an excess of placebo relapses compared to olanzapine relapses, and olanzapine was superior to placebo on time to relapse, the primary outcome for this study. Thus, olanzapine was more effective than placebo at maintaining efficacy in patients stabilized for approximately 8 weeks and followed for an observation period of up to 8 months.

Examination of population subsets (race and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

**Adolescents**

The efficacy of oral olanzapine in the acute treatment of schizophrenia in adolescents (ages 13 to 17 years) was established in a 6-week double-blind, placebo-controlled, randomized trial of inpatients and outpatients with schizophrenia (n=107) who met diagnostic criteria according to DSM-IV-TR and confirmed by the Kiddie Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL).

The primary rating instrument used for assessing psychiatric signs and symptoms in this trial was the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 12.5 mg/day, mean dose of 11.1 mg/day) was more effective than placebo in the treatment of adolescents diagnosed with schizophrenia, as supported by the statistically significantly greater mean reduction in BPRS-C total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

### 14.2 Bipolar I Disorder (Manic or Mixed Episodes)

**Adults**

Monotherapy — The efficacy of oral olanzapine in the treatment of manic or mixed episodes was established in 2 short-term (one 3-week and one 4-week) placebo-controlled trials in adult patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). The primary outcome in these trials was change from baseline in the Y-MRS total score. The results of the trials follow:

(1) In one 3-week placebo-controlled trial (n=67) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 10 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score. In an identically designed trial conducted simultaneously with the first trial, olanzapine demonstrated a similar treatment difference, but possibly due to sample size and site variability, was not shown to be superior to placebo on this outcome.

(2) In a 4-week placebo-controlled trial (n=115) which involved a dose range of olanzapine (5-20 mg/day, once daily, starting at 15 mg/day), olanzapine was superior to placebo in the reduction of Y-MRS total score.

(3) In another trial, 361 patients meeting DSM-IV criteria for a manic or mixed episode of bipolar I disorder who had responded during an initial open-label treatment phase for about 2 weeks, on average, to olanzapine 5 to 20 mg/day were randomized to either continuation of olanzapine at their same dose (n=225) or to placebo (n=136), for observation of relapse. Approximately 50% of the patients had discontinued from the olanzapine group by day 59 and 50% of the

placebo group had discontinued by day 23 of double-blind treatment. Response during the open-label phase was defined by having a decrease of the Y-MRS total score to ≤12 and HAM-D 21 to ≤8. Relapse during the double-blind phase was defined as an increase of the Y-MRS or HAM-D 21 total score to ≥15, or being hospitalized for either mania or depression. In the randomized phase, patients receiving continued olanzapine experienced a significantly longer time to relapse.

Adjunct to Lithium or Valproate — The efficacy of oral olanzapine with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in 2 controlled trials in patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These trials included patients with or without psychotic features and with or without a rapid-cycling course. The results of the trials follow:

(1) In one 6-week placebo-controlled combination trial, 175 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

(2) In a second 6-week placebo-controlled combination trial, 169 outpatients on lithium or valproate therapy with inadequately controlled manic or mixed symptoms (Y-MRS ≥16) were randomized to receive either olanzapine or placebo, in combination with their original therapy. Olanzapine (in a dose range of 5-20 mg/day, once daily, starting at 10 mg/day) combined with lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.2 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate alone in the reduction of Y-MRS total score.

**Adolescents**

Acute Monotherapy — The efficacy of oral olanzapine in the treatment of acute manic or mixed episodes in adolescents (ages 13 to 17 years) was established in a 3-week, double-blind, placebo-controlled, randomized trial of adolescent inpatients and outpatients who met the diagnostic criteria for manic or mixed episodes associated with bipolar I disorder (with or without psychotic features) according to the DSM-IV-TR (n=161). Diagnosis was confirmed by the K-SADS-PL.

The primary rating instrument used for assessing manic symptoms in this trial was the Adolescent Structured Young-Mania Rating Scale (Y-MRS) total score.

In this flexible-dose trial, olanzapine 2.5 to 20 mg/day (mean modal dose 10.7 mg/day, mean dose of 8.9 mg/day) was more effective than placebo in the treatment of adolescents with manic or mixed episodes associated with bipolar I disorder, as supported by the statistically significantly greater mean reduction in Y-MRS total score for patients in the olanzapine treatment group than in the placebo group.

While there is no body of evidence available to answer the question of how long the adolescent patient treated with ZYPREXA should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of olanzapine pharmacokinetic parameters in adult and adolescent patients. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

**14.3 Agitation Associated with Schizophrenia and Bipolar I Mania**

The efficacy of intramuscular olanzapine for injection for the treatment of agitation was established in 3 short-term (24 hours of IM treatment) placebo-controlled trials in agitated adult inpatients from 2 diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar I mania study). Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥14 on the 5 items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness and excitement items) with at least 1 individual item score ≥4 using a 1-7 scoring system (1=absent, 4=moderate, 7=extreme). In the studies, the mean baseline PANSS Excited Component score was 18.4, with scores ranging from 13 to 32 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. Patients could receive up to 3 injections during the 24 hour IM treatment periods; however, patients could not receive the second injection until after the initial 2 hour period when the primary efficacy measure was assessed. The results of the trials follow:

(1) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=270), 4 fixed intramuscular olanzapine for injection doses of 2.5 mg, 5 mg, 7.5 mg and 10 mg were evaluated. All doses were statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection. However, the effect was larger and more consistent for the 3 highest doses. There were no significant pairwise differences for the 7.5 and 10 mg doses over the 5 mg dose.

(2) In a second placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for schizophrenia (n=311), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

(3) In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (and currently displaying an acute manic or mixed episode with or without psychotic features) (n=201), 1 fixed intramuscular olanzapine for injection dose of 10 mg was evaluated. Olanzapine for injection was statistically superior to placebo on the PANSS Excited Component at 2 hours post-injection.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

The ZYPREXA 2.5 mg, 5 mg, 7.5 mg, and 10 mg tablets are white, round, and imprinted in blue ink with LILLY and tablet number. The 15 mg tablets are elliptical, blue, and debossed with LILLY and tablet number. The 20 mg tablets are elliptical, pink, and debossed with LILLY and tablet number. The tablets are available as follows:

| | TABLET STRENGTH | | | | | |
|---|---|---|---|---|---|---|
| | 2.5 mg | 5 mg | 7.5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4112 | 4115 | 4116 | 4117 | 4415 | 4420 |
| Identification | LILLY 4112 | LILLY 4115 | LILLY 4116 | LILLY 4117 | LILLY 4415 | LILLY 4420 |
| NDC Codes: | | | | | | |
| Bottles 30 | NDC 0002-4112-30 | NDC 0002-4115-30 | NDC 0002-4116-30 | NDC 0002-4117-30 | NDC 0002-4415-30 | NDC 0002-4420-30 |

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) are yellow, round, and debossed with the tablet strength. The tablets are available as follows:

| | TABLET STRENGTH | | | |
|---|---|---|---|---|
| ZYPREXA ZYDIS Tablets | 5 mg | 10 mg | 15 mg | 20 mg |
| Tablet No. | 4453 | 4454 | 4455 | 4456 |
| Debossed | 5 | 10 | 15 | 20 |
| NDC Codes: | | | | |
| Dose Pack 30 (Child Resistant) | NDC 0002-4453-85 | NDC 0002-4454-85 | NDC 0002-4455-85 | NDC 0002-4456-85 |

ZYPREXA is a registered trademark of Eli Lilly and Company.
ZYDIS is a registered trademark of Catalent Pharma Solutions.

ZYPREXA IntraMuscular is available in:

NDC 0002-7597-01 (No. VL7597) – 10 mg vial (1s)

### 16.2 Storage and Handling

Store ZYPREXA tablets, ZYPREXA ZYDIS, and ZYPREXA IntraMuscular vials (before reconstitution) at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP]. Reconstituted ZYPREXA IntraMuscular may be stored at controlled room temperature, 20° to 25°C (68° to 77°F) [*see* USP] for up to 1 hour if necessary. *Discard any unused portion of reconstituted ZYPREXA IntraMuscular.* The USP defines controlled room temperature as a temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.

Protect ZYPREXA tablets and ZYPREXA ZYDIS from light and moisture. Protect ZYPREXA IntraMuscular from light, do not freeze.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) for the oral formulations.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking ZYPREXA as monotherapy or in combination with fluoxetine. If you do not think you are getting better or have any concerns about your condition while taking ZYPREXA, call your doctor. When using ZYPREXA and fluoxetine in combination, also refer to the Patient Counseling Information section of the package insert for Symbyax.

**Elderly Patients with Dementia-Related Psychosis: Increased Mortality and Cerebrovascular Adverse Events (CVAE), Including Stroke**

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with ZYPREXA had a significantly higher incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) compared with placebo.

ZYPREXA is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*.

**Neuroleptic Malignant Syndrome (NMS)**

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs, including ZYPREXA. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

**Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**

Patients should be advised to report to their health care provider at the earliest onset of any signs and symptoms that may be associated with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.4)]*.

**Hyperglycemia and Diabetes Mellitus**

Patients should be advised of the potential risk of hyperglycemia-related adverse reactions. Patients should be monitored regularly for worsening of glucose control. Patients who have diabetes should follow their doctor's instructions about how often to check their blood sugar while taking ZYPREXA *[see Warnings and Precautions (5.5)]*.

**Dyslipidemia**

Patients should be counseled that dyslipidemia has occurred during treatment with ZYPREXA. Patients should have their lipid profile monitored regularly *[see Warnings and Precautions (5.5)]*.

**Weight Gain**

Patients should be counseled that weight gain has occurred during treatment with ZYPREXA. Patients should have their weight monitored regularly *[see Warnings and Precautions (5.5)]*.

**Orthostatic Hypotension**

Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration and in association with the use of concomitant drugs that may potentiate the orthostatic effect of ZYPREXA, e.g., diazepam or alcohol *[see Warnings and Precautions (5.7) and Drug Interactions (7)]*. Patients should be advised to change positions carefully to help prevent orthostatic hypotension, and to lie down if they feel dizzy or faint, until they feel better. Patients should be advised to call their doctor if they experience any of the following signs and symptoms associated with orthostatic hypotension: dizziness, fast or slow heartbeat, or fainting.

**Potential for Cognitive and Motor Impairment**

Because ZYPREXA has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ZYPREXA therapy does not affect them adversely *[see Warnings and Precautions (5.12)]*.

**Body Temperature Regulation**

Patients should be advised regarding appropriate care in avoiding overheating and dehydration. Patients should be advised to call their doctor right away if they become severely ill and have some or all of these symptoms of dehydration: sweating too much or not at all, dry mouth, feeling very hot, feeling thirsty, not able to produce urine *[see Warnings and Precautions (5.13)]*.

**Concomitant Medication**

Patients should be advised to inform their healthcare providers if they are taking, or plan to take, Symbyax. Patients should also be advised to inform their healthcare providers if they are taking, plan to take, or have stopped taking any prescription or over-the-counter drugs, including herbal supplements, since there is a potential for interactions *[see Drug Interactions (7)]*.

**Alcohol**

Patients should be advised to avoid alcohol while taking ZYPREXA *[see Drug Interactions (7)]*.

**Phenylketonurics**

ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains phenylalanine (0.34, 0.45, 0.67, or 0.90 mg per 5, 10, 15, or 20 mg tablet, respectively) *[see Description (11)]*.

**Use in Specific Populations**

Pregnancy — Advise women to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with ZYPREXA. Advise patients that ZYPREXA may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZYPREXA during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation — Advise breastfeeding women using ZYPREXA to monitor infants for excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) and to seek medical care if they notice these signs *[see Use in Specific Populations (8.3)]*.

Infertility — Advise females of reproductive potential that ZYPREXA may impair fertility due to an increase in serum prolactin levels. The effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

Pediatric Use — ZYPREXA is indicated for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adolescents 13 to 17 years of age. Compared to patients from adult clinical trials, adolescents were likely to gain more weight, experience increased sedation, and have greater increases in total cholesterol, triglycerides, LDL cholesterol, prolactin, and hepatic aminotransferase levels. Patients should be counseled about the potential long-term risks associated with ZYPREXA and advised that these risks may lead them to consider other drugs first *[see Indications and Usage (1.1, 1.2)]*. Safety and effectiveness of ZYPREXA in patients under 13 years of age have not been established. Safety and efficacy of ZYPREXA and fluoxetine in combination in patients 10 to 17 years of age have been established for the acute treatment of depressive episodes associated with bipolar I disorder. Safety and effectiveness of ZYPREXA and fluoxetine in combination in patients <10 years of age have not been established *[see Warnings and Precautions (5.5) and Use in Specific Populations (8.4)]*.

**Need for Comprehensive Treatment Program in Pediatric Patients**

ZYPREXA is indicated as an integral part of a total treatment program for pediatric patients with schizophrenia and bipolar disorder that may include other measures (psychological, educational, social) for patients with the disorder. Effectiveness and safety of ZYPREXA have not been established in pediatric patients less than 13 years of age. Atypical antipsychotics are not intended for use in the pediatric patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is often helpful. The decision to prescribe atypical antipsychotic medication will depend upon the healthcare provider's assessment of the chronicity and severity of the patient's symptoms *[see Indications and Usage (1.3)]*.

**Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA**



ZYP-0009-USPI-20200423

I have recently been in contact with the family of T. and, according to her father, she is much better. After leaving my office Mrs. S. did obtain a medical marijuana card for T. and tried edible marijuana products out on her, which did seem to help a bit but made her drowsy. She also returned with T. to the doctors who she was seeing prior to my evaluation of T. , as I had requested that she do, and eventually left there care due to what Mrs. S. described as the verbal abuse these doctors subjected T. to related to her trial of medical marijuana. Mr. and Mrs. S. have since fired these doctors and have taken T. off of all of the above mentioned medications prescribed by them. This resulted in a marked improvement in T.'s general feelings of well being and mood. She is no longer using medical marijuana and, according to her parents, is doing fine. I asked T.'s parents if they would allow me to bring this report to the attention of the Board and they gave me permission to do so. It seems that no harm was done and that the entire episode resulted in T.'s discontinuation of the potent medications that had been prescribed for her and that many of her symptoms were related to side effects caused by these medications. This is not surprising to me now that I have studied the side effect profiles of these meds and feel that their resulting effect on T. was predictable. Fortunately, none of the more serious side effects related to the use of these meds in pediatric patients seem to have occurred.

# Arkansas patients attest: Medical marijuana helps

BY Griffin Coop ON August 27, 2020 1:12 pm

3 Comments

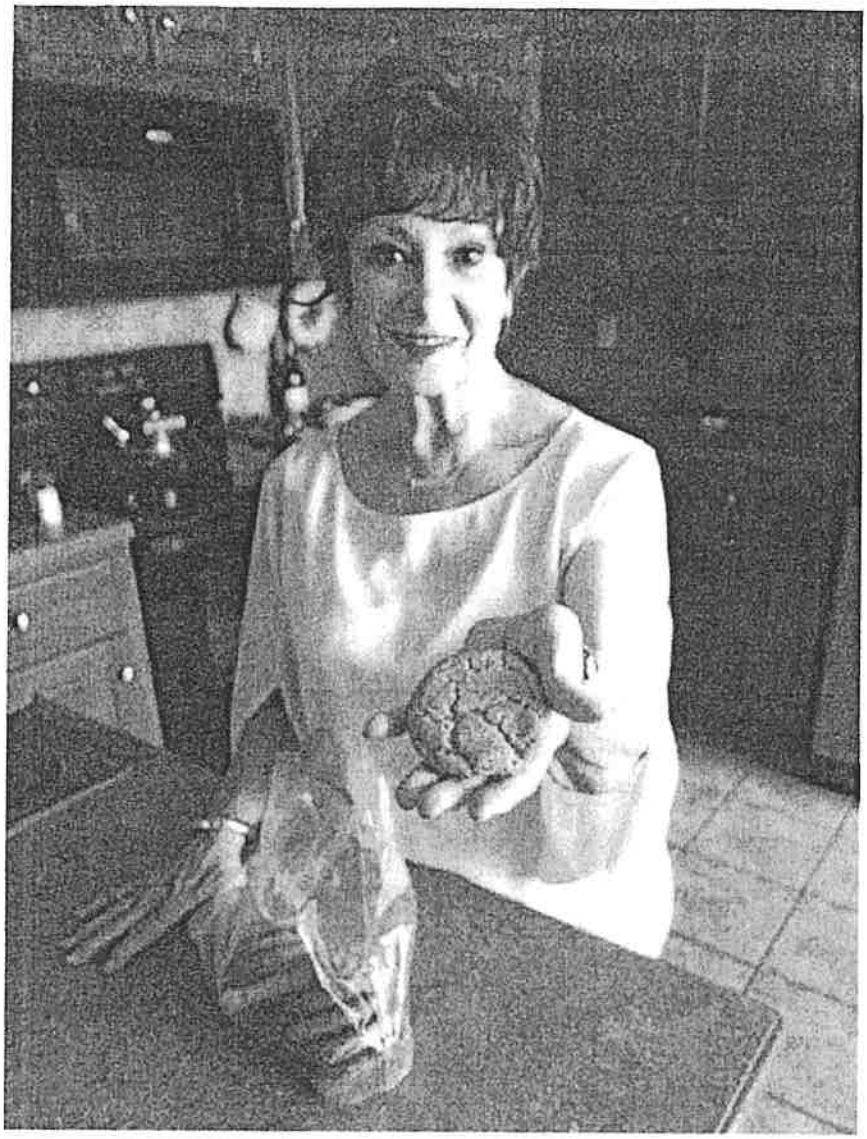
Since Arkansas voters passed the Arkansas Medical Marijuana Amendment in 2016, more than 72,500 Arkansans have obtained Medical Marijuana Prescription Cards in order to obtain products to treat the 18 qualifying conditions.

These Arkansans include a sleepless cancer survivor, a 10-year-old epileptic child with seizures and a combat veteran with post-traumatic stress disorder. Here are the stories of the conditions that led them to pursue medical marijuana as a treatment and their experiences using the drug.



**Senior citizen, cancer survivor**

Like many seniors, Pat Edwards likes to stay in shape by exercising at the local community center. Every Tuesday, she and others would gather at the Bishop Park Senior Activity Center in Benton for line dancing class. One day in 2017, she noticed something a little different about herself.



A REMEDY FOR SLEEPLESSNESS: Cancer survivor Pat Edwards no longer needs her marijuana cookies every night. BRIAN CHILSON

While wiping away some sweat during her workout, Edwards noticed a hard lump in her breast. She'd had a mammogram a few months before and the doctor had noticed a mass that they thought was probably just calcium.

It turned out to be much worse.

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UAMS modeling for Sept. 7: We're already there READ MORE »



Edwards was diagnosed with two types of breast cancer and underwent chemotherapy treatments and the use of an often-painful drug called Neulasta that causes the patient's bones to ache as the drug prevents infection.

"Your bones hurt really bad," Edwards said recently.

As Edwards struggled through the cancer treatments and four surgeries, she battled a common side effect: sleeplessness. Traditional sleeping medications didn't help.

"[Cancer treatment] affects your body in a lot of different ways," Edwards said. "I could not sleep even using my sleeping pills."



While Edwards is cancer-free today, she still struggles with the sleeplessness that began during cancer treatment.

So she thought she'd give a different type of medicine a try: medical marijuana.

"I thought, 'You know, this has got to help,' " Edwards said. "I talked to the doctors, got my medical marijuana card, and I started with the cookies and, I'm telling you, I could sleep. I slept like a baby."

Not only did Edwards finally sleep well, she said she didn't have the same hungover feeling that often accompanies other sleeping meds.

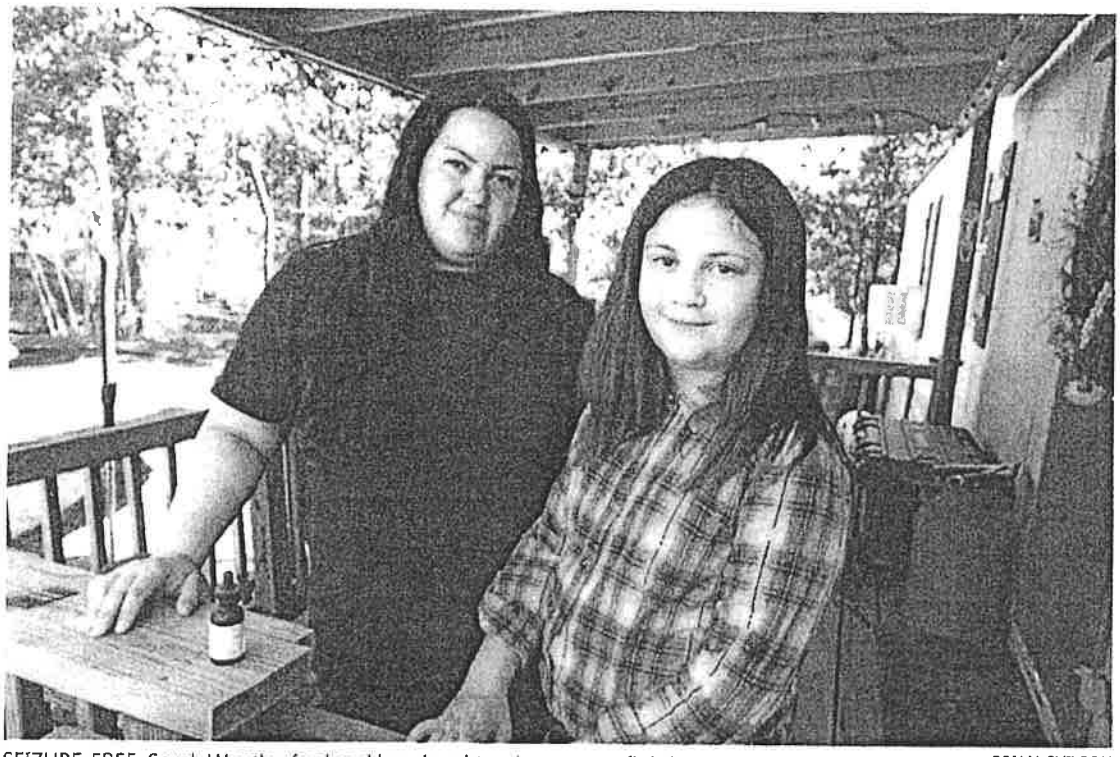
Edwards used the product, in cookie form, every night for a couple of months until she was able to sleep on her own. Now she only needs to use the cookies about once a week.

"It's not an everyday occurrence like it was at first," Edwards said.

In October, Edwards bought about $150 worth of cannabis, which her friend made into cookies and candies as well as a salve for her. Edwards has frozen cookies ready to bake when she needs them and she has not run out of products since her initial purchase last year.

Now that she has seen some benefits of medical marijuana, Edwards wishes she could have taken advantage of it sooner to help with other aches and pains of cancer treatment.

"If I had known I could have gotten the medical marijuana card when I was going through the other stuff with Neulasta, I would have done that in a heartbeat," Edwards said. "I didn't know how to



SEIZURE-FREE: Sarah Weatherford and her daughter, Jaynna, are fighting Jaynna's epilepsy with a tincture of CBD-infused medical marijuana. BRIAN CHILSON

**10-year-old girl suffering from epilepsy**

One morning, when Jaynna Jenson was 5 years old, she woke up and got in bed with her mother, like many children do. But something was different with Jaynna on this particular morning. Her eyes were moving in a strange way that would later be described as "eye deviations." Jaynna even stopped breathing at one point.

Jaynna's mother, Sarah Weatherford, called for an ambulance to come to their home in Romance in western White County. The medics stabilized Jaynna in the ambulance on the way to Arkansas Children's Hospital, where she was diagnosed with epilepsy.

Jaynna had suffered a tonic-clonic seizure, formerly known as a grand mal seizure. She was prescribed a daily anti-epileptic medication as well as an emergency drug to be used in case she suffered any seizures lasting longer than five minutes.

Unfortunately, the medications came with some side effects that were difficult for Jaynna to handle, especially at bedtime.

"She had really bad night terrors," Weatherford said. "She would scream and holler and run around the house while trying to go to sleep."

Because Jaynna is a minor, Weatherford was issued a caregiver card and the two began visiting the dispensary together.

Jaynna uses a tincture, which Weatherford dilutes with a hemp-based CBD oil because she said there aren't many low-THC tinctures available. The bottles of tincture cost about $90 each, but they last for "quite a while," according to Weatherford, since Jaynna uses small amounts.

While using the tincture, Jaynna has kept her seizures at bay.

"We've been pretty lucky here recently," Weatherford said. "She's right at a year and a half seizure-free."

Jaynna, who suffers from some neurological learning disabilities, recently finished the fourth grade in the Mount Vernon-Enola School District, where she earned all A's and B's.

"We have definitely seen a big difference as far as just her normal day-to-day activities and not having neurological issues," Weatherford said. "She's a tough cookie."

**Combat vet fights PTSD**

John Smith has an aversion to society. He's often angry, has a short temper and is described by others as having an intimidating demeanor. Serving eight years in the military, including time in Iraq, can do that.

"[It has] something to do with a look in the eyes, I'm told," said Smith, who requested that we use a pseudonym. "It's the demeanor of a lot of veterans — being quiet."

Smith, of Conway, suffers from post-traumatic stress disorder and struggles with social anxiety. He's had a difficult time finding an effective treatment that will allow him to function in society.

Smith used every treatment offered at the VA Hospital, but without much luck. The drugs he was prescribed were not effective and made him feel overmedicated, so his wife and members of the vet community encouraged him to try medical marijuana.

"Pretty much everybody in the vet community was, 'You should just smoke, man," Smith said.

Smith worried he could lose VA benefits as a result of using marijuana, which is still an illegal drug under federal law.

Smith's wife encouraged him to give it a try as well.

"My wife is the one that introduced me to the idea and kind of gave me the push, because I, and other veterans, were pretty nervous about the way the VA was going to handle things," Smith said.

Fortunately for Smith, the fears about the VA's handling of marijuana use were unfounded. While the VA does not prescribe medical marijuana, the VA cannot withhold treatment or compensatory benefits for its use, according to DAV, a veterans advocacy group.

Smith finally made the decision when a VA psychiatrist suggested it after Smith had exhausted all his other options

Smith tried medical marijuana and has been pleased with the results, spending about $300 per week on edibles and flower at Green Springs Medical Dispensary in Hot Springs. Smith said he prefers hybrids or indicas because the sativas make his heart race and don't soothe his PTSD symptoms as well.

"It calms the storm," Smith said. "[I become] more willing to listen, if you will."

Smith said his wife has been pleased with the results, too.

"My wife says my tone is more aggressive when I don't smoke, almost abrasive," Smith said. "[When I smoke,] I'm much better with my words."

Smith said using medical marijuana to treat his PTSD is better than the alternatives.

"This is just being honest," Smith said. "I'd rather smoke than be [heavily drugged] with meds or drink."

Griffin Coop

Previous article
**Inconsequential News Quiz: Make America WAP Again Edition**

Next article
**How to open a restaurant during a pandemic**

**Tags**

Jaynna Jenson Medical Marijuana Pat Edwards Sarah Weatherford

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# Previously Viewed Documentation

# Health Department
# Medical Marijuana Section
# Response to Board's Subpoena

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**BEFORE THE ARKANSAS STATE MEDICAL BOARD**

**IN THE MATTER OF:**

**Thomas Harold Tvedten, M.D.**

**SUBPOENA DUCES TECUM**

**TO:**

**Alex C. Hooper**
**Section Chief, Medical Marijuana**
**Arkansas Department of Health**
**4815 West Markham, Slot 50**
**Little Rock, AR 72205**

**You are hereby ordered to provide to the Arkansas State Medical Board or any authorized representative thereof a list of all pediatric patients Thomas Harold Tvedten, M.D. has qualified to receive medical marijuana.**

**This Subpoena is issued pursuant to authority granted the Board under Ark. Code Ann. Sec. 25-15-208 (7) (The Administrative Procedure Act), Sec. 17-80-102 and Sec. 17-95-201, et seq. (The Arkansas Medical Practices Act).**

**ARKANSAS STATE MEDICAL BOARD**

Amy E. Embry

**BY: Amy E. Embry**
**Executive Director**

**DATE: 7/1/20**

**PROOF OF SERVICE: I have this _____ day of _____, _____ at _____ duly served the within by showing the original and stating the substance thereof to the within named, _____, as I am therein commanded.**

**SERVER** _____ **SERVEE** _____ **TIME** _____

**Juli Carlson**

**Subject:** RE: Thomas H. Tvedten, M.D.

Good afternoon Juli:

Per our conversation last week prior to the long holiday weekend, I have furthered reviewed the attached subpoenas vis a vis Amendment 98. I did confirm practical challenges in that we don't index our medical marijuana (MMJ) registry info by Doctor name. To do such a search would require some level of assistance from out third party IT Database vendor on the West Coast.

However, as I suspected the bigger roadblock is Amendment 98 itself:

> **(f)**
> **(1)** An application or renewal and **supporting information** submitted by a qualifying patient or designated caregiver under this amendment, **including without limitation information regarding the qualifying patient's physician**, are **considered confidential records** that are exempt from the Freedom of Information Act of 1967, § 25-19-101 et seq.
> **(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.**

Amendment 98 requires ADH hold MMJ information in strict confidence. ADH interprets Amendment 98 to allow for disclosure of MMJ records to the subject of the records; their personal legal representative; or a third party, if directed by the subject via a HIPAA compliant authorization. Accordingly, absent a HIPAA compliant authorization from each individual patient of the Doctors listed in the subpoena, ADH is prohibited from releasing the records. ADH appreciates the Medical Boards need for records in exercise of due diligence in discharge of its duties. Unfortunately, absent a legislative change, ADH is prohibited by law under penalty of criminal sanction from releasing any records regardless of subpoena by a licensing authority.

Please let me know if you have any questions.

Best regards,

Charles "Chuck" Thompson
Managing Attorney
ARKANSAS DEPARTMENT OF HEALTH
4815 W. Markham, Slot 31,
Little Rock, AR 72205-3867
Ph: 501-682-1006
Fax: 501-661-2357



**From:** Alex Hooper <Alex.Hooper@arkansas.gov>
**Sent:** Thursday, July 2, 2020 8:59 AM
**To:** Charles Thompson <Charles.Thompson@arkansas.gov>; Nell Smith <Nell.Smith@arkansas.gov>
**Subject:** FW: Thomas H. Tvedten, M.D.

Chuck,

Please review the attached subpoenas.

Alex C. Hooper
Section Chief, Medical Marijuana

Arkansas Department of Health
4815 West Markham, Slot 50, Little Rock, AR 72205
Email: Alex.Hooper@Arkansas.gov
Office: 501-682-4977

**From:** Juli Carlson <Juli.Carlson@armedicalboard.org>
**Sent:** Thursday, July 2, 2020 8:53 AM
**To:** Alex Hooper <Alex.Hooper@arkansas.gov>
**Subject:** Thomas H. Tvedten, M.D.

Good morning Alex,

Attached is the subpoenas for information involving these physicians that we discussed yesterday. I would appreciate the responsive information no later than July 13, 2020. Let me know if you have any questions.

Juli

Juli Carlson
Regulatory Manager
Arkansas State Medical Board
Arkansas Department of Health

## Juli Carlson

**From:** Alex Hooper <Alex.Hooper@arkansas.gov>
**Sent:** Wednesday, July 1, 2020 11:54 AM
**To:** Juli Carlson
**Subject:** MMJ Law

2.14 Definitions

(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;

5.b Registry Identification Cards

(b) The department shall not issue a registry identification card to a qualifying patient who is under eighteen (18) years of age unless:
(1) The qualifying patient's physician has explained the potential risks and benefits of the medical use of marijuana to the qualifying patient and to a parent, guardian, or person having legal custody of the qualifying patient; and
(2) A parent, guardian, or person having legal custody: (A) Consents in writing to: (i) Allow the qualifying patient's medical use of marijuana; (ii) Assist the qualifying patient in the medical use of marijuana; and (iii) Control the acquisition of the marijuana, the dosage, and the frequency of the medical use of marijuana by the qualifying patient; and

Alex C. Hooper
Section Chief, Medical Marijuana

Arkansas Department of Health
4815 West Markham, Slot 50, Little Rock, AR 72205
Email: Alex.Hooper@Arkansas.gov
Office: 501-682-4977

Arkansas Department of Health

# Medical Marijuana Physician Written Certification

ARKANSAS DEPARTMENT OF HEALTH

## Patient Information

| First Name | MI | Last Name |
|---|---|---|
| | | |

| Street Number and Street Name (or PO Box) |
|---|
| |

| Unit Number | Unit Type (Apt, Unit, Suite, etc.) |
|---|---|
| | |

| City | State | Zip Code |
|---|---|---|
| | | |

| Date of Birth (MM/DD/YYYY) | Under the age of 18? | Physically Disabled? |
|---|---|---|
| | ☐ Yes ☐ No | ☐ Yes ☐ No |

☐ **I hold a valid, unrestricted, existing license to practice as a medical physician or osteopathic physician in Arkansas, and have been issued a registration from U.S. DEA to prescribe controlled substances.**

☐ **It is my professional opinion, after having completed an in-person assessment of the patient's medical history and current medical condition in the course of a physician patient relationship, the patient has a qualifying medical condition identified below.**

**Select the qualifying medical condition(s):**

- ☐ 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
- ☐ 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
- ☐ Severe and persistent muscle spasms, including without limitation those characteristic of multiple sclerosis

**Issue Registry Card for:** ☐ 12 Months ☐ Less than 12 months ___Months ___Weeks

## Physician Information

| First Name | MI | Last Name | Arkansas Medical License Number |
|---|---|---|---|
| | | | |

| Address |
|---|
| |

| Unit Number | Unit Type (Apt, Unit, Suite, etc.) |
|---|---|
| | |

| City | State | Zip Code |
|---|---|---|
| | | |

| Phone | I do hereby attest that this information is true, accurate and complete. Signature | Date |
|---|---|---|
| | | |

**This form must be received with a completed application within 30 days of physician's signature.**

## Parent/legal guardian/legal custodian of minor patient

**As parent/legal guardian or custodian of this minor patient, I am aware of the diagnosis risks, benefits and consent to the minor patient's medical use of marijuana.**

| Signature | Date |
|---|---|
| | |

| Print Name |
|---|
| |

Arkansas Department of Health

# Medical Marijuana Registry Patient Application

Scan the QR code to apply online or go to:
http://www.healthy.arkansas.gov/programs-services/topics/id-card-apply-online

## Patient Information

☐ New Application ☐ Renewal

| First Name | MI | Last Name | Phone |
|---|---|---|---|
| | | | |

## Mailing Address

| Street Number and Street Name (or PO Box) | | | |
|---|---|---|---|
| | | | |
| Unit Number | Unit Type (Apt, Unit, Suite, etc.) | | |
| | | | |
| City | | State | Zip Code |
| | | | |

## Residence Address (if different from mailing address)

☐ Check if homeless

| Street Number and Street Name | | | |
|---|---|---|---|
| | | | |
| Unit Number | Unit Type (Apt, Unit, Suite etc.) | | |
| | | | |
| City | | State | Zip |
| | | | |

| Date of Birth (MM/DD/YYYY) | Sex ☐Male ☐Female | Race | Eye Color | Height ' " | Physically Disabled ☐Yes ☐No |
|---|---|---|---|---|---|
| | | | | | |

| Arkansas DL or ID Number | Expiration Date (MM/DD/YYYY) | Last 4 digits of SSN | Registry ID (for renewals only) |
|---|---|---|---|
| | | | |

☐Yes ☐No Are you a member of the Arkansas National Guard or the United States military?

**By signing, I, the patient pledge not to divert marijuana to anyone who is not allowed to possess marijuana under the Arkansas Medical Marijuana Amendment of 2016**

| Signature | Date |
|---|---|
| | |

Print Name

## Parent / Guardian / Legal Custodian -- Skip if applicant over 18

| First Name | MI | Last Name | Phone |
|---|---|---|---|
| | | | |

| Address | | | |
|---|---|---|---|
| | | | |
| Unit Number | Unit Type (Apt, Unit, Suite, etc.) | | |
| | | | |
| City | | State | Zip Code |
| | | | |

**By signing, I confirm that I, as the parent/guardian/legal custodian allow the qualifying patient's medical use of marijuana, will assist the qualifying patient in the medical use of marijuana and will control the acquisition of the marijuana, dosage and the frequency of the medical use of marijuana by the qualifying patient and will register as a designated caregiver.**

| Signature ☐Parent ☐Custodian ☐Legal Guardian | Date |
|---|---|
| | |

Print Name

# Original Complaint
# and
# Dr. Tvedten's Response

# Psychiatric Services, Inc.

Scott M. Hogan, MD

*Child, Adolescent & Addiction Psychiatry*

P.O. Box 251708 • Little Rock, AR 72225-1708
Office: 501-373-8272 • Fax: 501-312-1011


April 5, 2020

Arkansas State Medical Board
1401 West Capitol Avenue Suite 340
Little Rock, AR 72201
Fax: (501) 296-1805


Scott Hogan, MD
Lynn Thomas, MD
Psychiatric Services, Inc.
PO Box 251708
Little Rock, AR 72225-1708


Members of the Arkansas Medical Board,

Tom Tvedten, MD, (C-5169) has Issued a Medical Marijuana Physician Written Certification for 12-year old patient ..ho both Lynn Thomas, MD, and I have treated and are currently treating on an inpatient basis at Methodist Behavioral Hospital. The attached copy of the certification indicates that Dr. Tvedten prescribed Marijuana for this 12-year old patient for a reported diagnosis of n fact, she has no history of trauma, as documented numerous times in done at Pinnacle Pointe Hospital and Methodist Behavioral Hospital in the last 2 years. This information re absence of trauma was repeatedly provided by her guardians during her intake assessments. current is positive for as was he last month at Pinnacle Pointe Hospital. eports that marijuana makes her feel "very tired" and "confused." It was reported during ast hospitalization at Pinnacle Point Hospital that Dr. Tvedten was, per er "marijuana doctor," and that guardian reported to the hospital that Dr. Tvedten was also her guardian's "marijuana doctor." guardian discharged her last month from Pinnacle Pointe Hospital AMA after apparently being upset when educated about the inappropriateness of a 12-year old girl using marijuana.

I would like to have Dr. Tvedten justify this medical treatment:

(1) How did you arrive at this diagnosis? (I would like to have him provide a copy of the psychiatric evaluation and mental status exam he performed to justify this diagnosis. Also, I'd like to see if her psychiatric medications were listed and address potential interaction of these medications with marijuana.)
(2) Was a UDS performed to evaluate whether was taking any other prescribed or illicit controlled substances?
(3) What was documented in her psychiatric evaluation re previous substance abuse or dependence?
(4) What other diagnoses were considered in the differential?
(5) What training and/or experience do you have in treating child and adolescent psychiatric conditions, especially childhood PTSD?

(6) What other treatment modalities were previously utilized to treat this patient?
(7) What records by previous treating psychiatrists and therapists were obtained and reviewed?
(8) Which previous treating psychiatrists and therapists were consulted?
(9) What modalities of therapy have previously been conducted, and what was her response to such therapy?
(10) What other modalities are being utilized concurrently with medical marijuana? Specifically, what trauma-focused outpatient therapy is being provided, and how often? What psychiatrist is currently treating her? If it is occurring, how is esponding?
(11) What follow-up has occurred to evaluate non-existent PTSD diagnosis? When is her next appointment to evaluate her treatment response to marijuana?

Key points from *Effects of Cannabis on the Adolescent Brain (ncbi.nlm.nih.gov),* a review of neuroimaging, neurocognitive, and preclinical findings on the effects of cannabis on the adolescent brain are listed below.

(1) Marijuana, second to alcohol, is the most widely used intoxicant. Approximately 25% of adolescents (8th, 10th, and 12th grade) report being drunk in the past month and close to the same (23%) report using marijuana in the past. **The literature not only suggests neurocognitive disadvantages to using marijuana in the domains of attention and memory that persist beyond abstinence, but suggest possible macrostructural brain alterations (e.g., morphometry changes in gray matter tissue), changes in white matter tract integrity (e.g., poorer coherence in white matter fibers), and abnormalities of neural functioning (e.g., increased brain activation, changes in neurovascular functioning). Earlier initiation of marijuana use (e.g., before age 17) and more frequent use has also been associated with poorer outcome.**
(2) Differences in brain tissue integrity following marijuana use **does** predict future risky behaviors such as increased marijuana use and aggressive and delinquent behaviors. This suggests imaging biomarkers may provide some clinical utility, despite the underlying pathological processes.
(3) Large longitudinal research would also help clarify the degree to which pre-existing differences and/or chronic marijuana use during adolescence contributes to the development of psychiatric disorders and cognitive impairment in adulthood. Furthermore, we need to better understand the interactive relationships between alcohol and marijuana use as these substances are commonly used together and may result in differing structural, functional, and cognitive brain changes when used alone or in combination.

*Note: These studies address brain alterations and impairments of adolescents who use marijuana, but they do not address the complications associated with CHILDREN. Furthermore, most studies other indicate that marijuana exacerbates anxiety disorders, including PTSD, and that marijuana often merely mask the symptoms of anxiety and does nothing to address the cognitive and emotional impairment the must be addressed to help a patient improve. In fact, some children and adolescents use substances such as marijuana as a means to numb themselves and merely "escape."

I'd be very interested to read literature that contradicts this information, if only Dr. Tvedten could. Even if such literature existed, prescribing marijuana for a 12-year old is clearly malpractice as it is not the community standard and poses unnecessary risks and neurocognitive impairment, macrostructural brain alterations, and abnormalities of neural functioning for adolescents, let alone children. And even more alarming, earlier initiation of marijuana use (e.g., before age 17) has also been associated with poorer outcome. Again, this is a CHILD, only 12-years old.

Who on the Medical Board would allow a physician to prescribe marijuana for their 12-year old child or for their child to take marijuana? I consider this to be an egregious violation of the Medical Practice Act and request the Board consider an Emergency Order of Suspension and report to the DEA.

Sincerely,

Scott Hogan, MD

Scott Hogan, MD

Lynn Thomas, MD

Lynn Thomas, MD

Heber Springs Cannabis Clinic
706 West Quitman
Heber Springs, 72543
Phone (501) 263-8877 Fax (870)201-9780

To: Members of the Arkansas State Medical Board
From: Tom Tvedten, MD
Re: Complaint in your letter dated April 13, 2020

April 16, 2020

Dear Sirs,

I was surprised and disturbed by the complaint made against me by Dr's Hogan and Thomas. As far as I know I have never met either physician. The complaint is well worded and speaks for itself.

I began seeing patients in my Heber Springs Clinic in September, 2019 We temporarily closed our clinic in early March due to Dr. Anthony Faucci's recommendation that only emergency and time sensitive office visits be made in order to "flatten the curve". In the several months that we were open I had occasion to see and certify only two or three minors. One of these was

First, let me assure the board and Drs. Hogan and Thomas that I did not and never have "prescribed" marijuana to any patient. My function is to evaluate patients regarding whether or not they have a "certifying" medical condition that allow them to legally obtain and use THC containing products. Each patient that I see is advised that I am not recommending or "prescribing" marijuana and that I can not advise them as to how much to use or how to use it. The potential negative side effects are reviewed and the lack of evidence based studies proving clinical efficacy is emphasized.

I generally spend about twenty minutes with each patient. In the case of and her mom, the visit was somewhat longer. Mrs. brought with her numerous medical records documenting her daughter's rather extensive medical history and the many interventions that had been tried and failed to adequately control the child's apparently severe symptoms. stated that none of the previously and currently prescribed medications had helped and that most had had undesirable side effects. She had read or been advised that "medical marijuana" might help and wanted to try it but did not want to break the law for fear of losing custody of her child. Some of the medications that was currently taking at the time of her visit have side effect

profiles far in excess of marijuana and the possibility exisited that some of these might be able to be eliminated if the marijuana was effective.

We established a diagnosis of by administering a test used nationally to evaluate for this condition. Mrs. ıelped take this "test".

It was understood that was to continue her care with her current medical providers and that my role was soley to certify that she had a "qualifying condition" and that I would remain available to answer any questions regarding medical marijuana that she or ₹ might have, that I was not her "new doctor" and that no return appointment would be made. I did offer to recertify her in one year if the worked and do so for a discounted price.

mom agreed to be her "care giver" and to obtain, moderate, and control 's use of the medication and that the "edible" form seemed most appropriate in her case. They were advised that when using this modality the effects were slow to begin and could last for up to eight hours.

One of the "benefits" of medical marijuana, if you can call it a benefit, is that it's purchase is not covered by insurance, Medicare, or Medicaid. People must pay for it out of their own pocket. The product is relatively expensive. If it does not work, the patient simply does not buy more.

It is my medical opinion that the side effect profile of marijuana as suggested by Drs Hogan and Thomas is far less severe than the side effect profiles of many medications tried on in the past and less than that of her current medications that she was taking at the time of her visit. These were
The potential for adverse side effects from each of these medications alone is significant and the side effects of them in combination is unstudied and unknown. Trileptal is an anticonvulsive and marijuana has been effectively used in certain pediatric seizure disorders.

Basically, due to the severity of this child's medical problems, I felt at the time and still feel that a therapeutic trial of medical marijuana therapy was in order. After receipt of your letter and order my office reached out to the for follow up. Mrs. said that the "gummies" helped some, but made drowsy. She seemed quite distressed that a complaint had been filed against me.

In my opinion, as time goes by, it will become clear that cannabinoids have a much broader role in the treatment of human disease. Most of the patients I see in my clinic, above 80%, have tried marijuana in the past and found it very helpful in alleviating their particular symptoms. Many have been able to eliminate or markedly decrease their use of opioids for treatment of their chronic pain syndrome, but the PTSD patients I see seem to find the greatest therapeutic benefit. This is why I decided to certify .
Millions of American have taken and currently are using marijuana products on a regular basis. Even with long term use the adverse side effect profile seems low and the risk

benefit ratio seems acceptable. Still, in general, I do not advocate for its use in children or even older adolescents. I feel that in younger people it allows them to justify avoiding unpleasant tasks such as studying and test preparation. In some cases though, such as in case, I feel that the potential benefits of a therapeutic trial outweigh the risks.

I am enclosing a complete copy of clinic record. If you or Drs. Hogan and Thomas have further questions, please do not hesitate to contact me.
My cell number is

Sincerely,

Tom H. Tvedten, MD

P.S. I feel that it is possible that Drs. Hogan and Thomas may be aware of my primary medical practice as an abortion provider in Little Rock and that this may have influenced the intensity of their response to my decision to treat. The long term effects on neurologic development of many of the medicines currently and previously prescribed fo have not been intensely studied and may well be more profound than those of marijuana, which are suggested, and not proven. Had the interventions prescribed by this patients past and current medical providers been effective, she would have never been brought to my attention in the first place.

Heber Springs Cannabis Clinic
706 W. Quitman St.
Heber Springs, AR 72543
501-263-8877

# Welcome to Heber Springs Cannabis Clinic

It is important to understand that we at this clinic are not prescribing Cannabis products, nor are we recommending them as a medical treatment for any pathologic medical condition. Though we feel that these chemicals probably have some therapeutic value, we make no claims or assertions that they will be of benefit to any of the patients we see in this clinic. What the doctor does for the patients that he sees here is simply certify that the patient has a clinical diagnosis that qualifies the patient in the eyes of the state of Arkansas to be issued a "card" that allows them to legally buy and possess cannabis products.

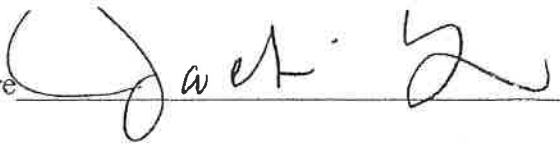
The cannabis plant, marijuana, contains several psychoactive and physiologically active chemicals known as a group as cannabinoids. Like most chemicals we call medicines these biologically active agents have many and varied effects on the body and nervous system. Some of these effects may be beneficial while others may be deleterious (bad for you.) Cannabis products may affect judgment, slow down reaction time, cause drowsiness, increase blood pressure, cause extreme nausea, interact with other medications, and/or have other idiosyncratic unwanted effects. Patients using medical marijuana should inform their primary care provider of this so that his or her doctor takes this into consideration when prescribing for the patient.

We hope that marijuana products help the patient that we see with their medical conditions, but make no assertion that this will be the case. At the present time we are only able to qualify patients for receiving a "card" for up to one year. Should a patient wish to recertify in a year, we will do the "re-certification" for a significantly discounted fee.

Thank you for choosing us as your cannabis clinic. If at any time you have questions that we may be able to answer, feel free to call us. Please sign below showing that you have read and understand the information provided above.

Thanks,
Tom Tvedten MD

Patient Signature _____ 2-25-20
Date

Witness Signature  2-25-2020
Date

Arkansas State Medical Board

In the Matter of: Thomas Harold Tvedten, MD

Order

No. _____ This ~~summons~~ is for Thomas Harold Tvedten (*name of Defendant*).

PROOF OF SERVICE

☑ I personally delivered the ~~summons and complaint~~ to the individual at Emergency Order of Suspension and Noticed Hearing at a parking lot of St. Francis Episcopal Church [place] on 8/13/20 [date]; or Heber Springs, Ark.

☐ I left the summons and complaint in the proximity of the individual by _____ _____ after he/she refused to receive it when I offered it to him/her; or

☐ I left the summons and complaint at the individual's dwelling house or usual place of abode at _____[address] with _____[name], a person at least 14 years of age who resides there, on _____[date]; or

☐ I delivered the summons and complaint to _____[name of individual], an agent authorized by appointment or by law to receive service of summons on behalf of _____[name of defendant] on _____[date]; or

☐ I am the plaintiff or an attorney of record for the plaintiff in this lawsuit, and I served the summons and complaint on the defendant by certified mail, return receipt requested, restricted delivery, as shown by the attached signed return receipt.

☐ I am the plaintiff or an attorney of record for the plaintiff in this lawsuit, and I mailed a copy of the summons and complaint by first-class mail to the defendant together with two copies of a notice and acknowledgment and received the attached notice and acknowledgment form within twenty days after the date of mailing.

☐ Other [specify]: _____

☐ I was unable to execute service because: _____

_____

My fee is $ ____.

**To be completed if service is by a sheriff or deputy sheriff:**

Date: _____ SHERIFF OF _____ COUNTY, ARKANSAS

By: _____
[Signature of server]

_____
[Printed name, title, and badge number]

**To be completed if service is by a person other than a sheriff or deputy sheriff:**

Date: AUG 15 2020

By: _____
[Signature of server]

David G. McCreery
[Printed name]

Address: PROWESS IN PROCESS SERVING
DAVID McCREERY ASSOCIATES
OFFICERS OF THE COURT
POST OFFICE BOX 7600
LITTLE ROCK, AR 72217-7600

Phone: 501-765-2295

Subscribed and sworn to before me this date: AUG 15 2020

_____
Notary Public

EJ OLDNER
NOTARY PUBLIC
PULASKI COUNTY, ARKANSAS
COMM. EXP. 05/20/2029
COMMISSION NO. 12707595

My commission expires: 05/20/2029

Additional information regarding service or attempted service:

While I certainly understand how Dr. & Mrs. Tredten would be reluctant to meet unknowns purporting to represent possible plaintiffs and for the purpose of effecting process & service, it was necessary to spend nearly 3 hours visiting 4 locations, conducting skip trace investigations, meeting neighbors, cajoling relatives for phone numbers, being "waved off" over the phone by Mrs. Tredten, waiting and then being asked to return as I was well into my return home, empty handed.

# Follow Up Discussion #20-154

**Board Meeting: August 6-7, 2020**

*Note:*

## Juli Carlson

**From:** Beck, Michael <Michael.Beck@uhsinc.com>
**Sent:** Tuesday, June 30, 2020 1:33 PM
**To:** Juli Carlson
**Subject:** RE: Subpoena for patient records

Thank you.

**From:** Juli Carlson <Juli.Carlson@armedicalboard.org>
**Sent:** Tuesday, June 30, 2020 1:27 PM
**To:** Beck, Michael <Michael.Beck@uhsinc.com>
**Subject:** [External] Subpoena for patient records



Mr. Beck,

See attached. These records are needed no later than July 6, 2020.

Juli Carlson
Regulatory Manager
Arkansas State Medical Board
Arkansas Department of Health
1401 West Capitol, Suite 340, Little Rock, AR 72201
Office: (501) 296-1807 | Fax: (501) 296-1805
Juli.Carlson@armedicalboard.org
www.armedicalboard.org

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**BEFORE THE ARKANSAS STATE MEDICAL BOARD**

**IN THE MATTER OF:**

**Thomas Harold Tvedten, M.D.**

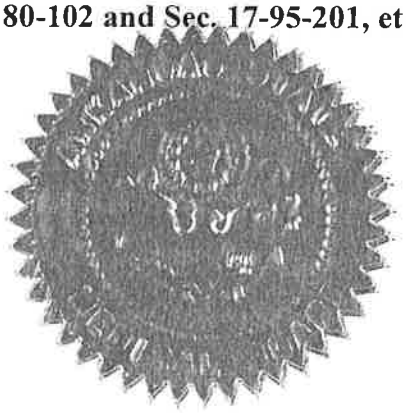
**SUBPOENA DUCES TECUM**

**TO:**

**Pinnacle Pointe Hospital**
**11501 Financial Center Pkwy**
**Little Rock, AR 72211**

**You are hereby ordered to provide to the Arkansas State Medical Board or any authorized representative thereof a copy of any and all medical records including inpatient records to include paper and electronic records for the following patient:**

**This Subpoena is issued pursuant to authority granted the Board under Ark. Code Ann. Sec. 25-15-208 (7) (The Administrative Procedure Act), Sec. 17-80-102 and Sec. 17-95-201, et seq. (The Arkansas Medical Practices Act).**



**ARKANSAS STATE MEDICAL BOARD**

Amy E. Embry

**BY: Amy E. Embry**
**Executive Director**

**DATE: 6/30/20**

**PROOF OF SERVICE: I have this _____ day of _____, _____ at _____ duly served the within by showing the original and stating the substance thereof to the within named, _____, as I am therein commanded.**

**SERVER** _____ **SERVEE** _____ **TIME** _____

## Juli Carlson

**From:** Juli Carlson
**Sent:** Tuesday, June 30, 2020 1:52 PM
**To:** 'Holly Doster'
**Subject:** RE: Subpoena for patient records

Yes, but no need to include Arkansas Department of Health in the address. Mail it to:

Juli Carlson
Regulatory Manager
Arkansas State Medical Board
1401 West Capitol, Suite 340
Little Rock, AR 72201

Juli Carlson
Regulatory Manager
Arkansas State Medical Board
Arkansas Department of Health
1401 West Capitol, Suite 340, Little Rock, AR 72201
Office: (501) 296-1807 | Fax: (501) 296-1805
Juli.Carlson@armedicalboard.org
www.armedicalboard.org

**From:** Holly Doster [mailto:hdoster@methodistfamily.org]
**Sent:** Tuesday, June 30, 2020 1:46 PM
**To:** Juli Carlson
**Subject:** RE: Subpoena for patient records

Thank you. Can I mail the CD to the address below?

Arkansas State Medical Board
Arkansas Department of Health
1401 West Capitol, Suite 340, Little Rock, AR 72201

Thank you,
Holly Doster, RHIA
Manager – Health Information Management
Methodist Behavioral Hospital
1601 Murphy Drive
Maumelle, AR 72113

501-906-4358 direct
501-325-1387 fax

**Our Mission:** to give the best possible care to those who may need our help.

**Follow us:**

- Facebook.com/MethodistFamilyHealth
- Twitter.com/MethodistFamily
- Instagram.com/MethodistFamilyHealth
- YouTube.com/MethodistFamilyHealth
- To learn more about our programs: www.methodistfamily.org
- To make a tax-deductible donation: http://www.methodistfamily.org/ways-to-give

**From:** Juli Carlson <Juli.Carlson@armedicalboard.org>
**Sent:** Tuesday, June 30, 2020 1:29 PM
**To:** Holly Doster <hdoster@methodistfamily.org>
**Subject:** [External Sender] Subpoena for patient records

Good afternoon,

See attached. These records are needed no later than July 6, 2020.

Juli Carlson
Regulatory Manager
Arkansas State Medical Board
Arkansas Department of Health
1401 West Capitol, Suite 340, Little Rock, AR 72201
Office: (501) 296-1807 | Fax: (501) 296-1805
Juli.Carlson@armedicalboard.org
www.armedicalboard.org

# ARKANSAS STATE MEDICAL BOARD

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www.armedicalboard.org




**BEFORE THE ARKANSAS STATE MEDICAL BOARD**

**IN THE MATTER OF:**

**Thomas Harold Tvedten, M.D.**

**SUBPOENA DUCES TECUM**

**TO:**

**Methodist Family Health**
**1601 Murphy Drive**
**Maumelle, AR 72113**

**You are hereby ordered to provide to the Arkansas State Medical Board or any authorized representative thereof a copy of any and all medical records including inpatient records to include paper and electronic records for the following patient:**

**This Subpoena is issued pursuant to authority granted the Board under Ark. Code Ann. Sec. 25-15-208 (7) (The Administrative Procedure Act), Sec. 17-80-102 and Sec. 17-95-201, et seq. (The Arkansas Medical Practices Act).**

**ARKANSAS STATE MEDICAL BOARD**

Amy E. Embry

**BY: Amy E. Embry**
**Executive Director**

**DATE: 6/30/20**

**PROOF OF SERVICE: I have this _____ day of _____, _____ at _____ duly served the within by showing the original and stating the substance thereof to the within named, _____, as I am therein commanded.**

**SERVER** _____ **SERVEE** _____ **TIME** _____

# Discussion #20-154

**Physician:** **TVEDTEN, Thomas Harold, M.D.**

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**BEFORE THE ARKANSAS STATE MEDICAL BOARD**

**IN THE MATTER OF:**

**SUBPOENA DUCES TECUM**

**TO:**

**Tom Tvedten, M.D.**
**4 Office Park Drive**
**Little Rock, AR 72211**

**You are hereby ordered to provide to the Arkansas State Medical Board or any authorized representative thereof a copy of any and all medical records to include paper and electronic records for the following patient:**

**This Subpoena is issued pursuant to authority granted the Board under Ark. Code Ann. Sec. 25-15-208 (7) (The Administrative Procedure Act), Sec. 17-80-102 and Sec. 17-95-201, et seq. (The Arkansas Medical Practices Act).**

**ARKANSAS STATE MEDICAL BOARD**

Amy E. Embry

**BY: Amy E. Embry**
**Executive Director**

**DATE: April 13, 2020**

**PROOF OF SERVICE: I have this _____ day of _____, _____ at _____ duly served the within by showing the original and stating the substance thereof to the within named, _____, as I am therein commanded.**

**SERVER** _____ **SERVEE** _____ **TIME** _____

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**April 13, 2020**

**Tom Tvedten, M.D.**
**4 Office Park Drive**
**Little Rock, AR 72211**

**Dear Dr. Tvedten:**

**Enclosed is a copy of a letter of complaint relative to you which was received in this office. Before this office can proceed, a letter of explanation concerning this matter is needed from you on or before April 27, 2020.**

**Upon receipt of your reply, the complaint and your response will be reviewed at the next meeting of the board. At the completion of that meeting, you will receive notice of the decision of the Board. However, if the Board requires further information in order to provide a ruling, you will be notified.**

**In compliance with the Freedom of Information Act, a copy of our response will be available to the complainant after a final ruling has been rendered.**

**Please understand the purpose of the Medical Board is to ensure public safety, therefore our office must process all complaints regardless of the subject matter.**

**Your prompt reply will allow the Board to resolve this matter as quickly as possible.**

**Sincerely,**

Amy E. Embry

**Amy E. Embry**
**Executive Director**

**AEE/jeb**

**Enclosure**

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**April 13, 2020**

**Scott Hogan M. D. & Lynn Thomas, M.D.**
**Psychiatric Services**
**P.O. Box 251708**
**Little Rock, AR 72225**

**Re: Tom Tvedten, M.D.**

**Dear Dr. Hogan and Dr. Thomas:**

**The Arkansas State Medical Board is in receipt of your letter of complaint concerning the above-mentioned physician. A copy of your letter has been forwarded to the physician for a written response. When the response is received, both your complaint and the physician's responses will be presented to the Board at its next regularly scheduled meeting.**

**The fact that you have registered a complaint indicates you wish for action to be taken against the physician, however; it is important that you know that although you may have a valid complaint, it must fall within the guidelines set out by state law for the Board to take action. A portion of the law, Arkansas Statue 17-95-409 outlining the reasons action can be taken is enclosed for your convenience.**

**Regardless of the ultimate conclusion, your complain and any rebuttal you might want to submit will be maintained in the physician's licensure file and referenced, should further complaints against the physician arise in the future.**

**Just as you have received this letter, you will be notified when we receive the physician's response to your complaint and again when the Board has rendered a decision.**

**We are hopeful that this letter will provide you with the information on how the process works and the guidelines the Board must follow in order to take action.**

**Sincerely,**

Amy E. Embry

**Amy E. Embry**
**Executive Director**

**AEE/jeb**

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**June 24, 2020**

**Thomas Harold Tvedten, M.D.**
**4 Office Park Drive**
**Little Rock, AR 72211**

**Dear Dr. Tvedten:**

**The Arkansas State Medical Board addressed the complaint registered against you regarding above-mentioned physician at their June 4-5, 2020 meeting.**

**Prior to rendering a decision regarding, it was the vote of the Board to further investigate the matter. It is anticipated the matter will be presented again at their August 6-7, 2020 meeting for discussion.**

**Our office will notify you of the Board's decision in writing within approximately two weeks following that meeting. We thank you for your continued patience during this time.**

**Sincerely,**

Amy E. Embry

**Amy E. Embry**
**Executive Director**

**AEE/jeb**

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**June 24, 2020**

**Scott Matthew Hogan, M.D.**
**Lynn C. Thomas, M.D.**
**Psychiatric Services**
**P.O. Box 251708**
**Little Rock, AR 72225**

**Re: Medical Records Subpoena**

**Dear Dr. Hogan and Dr. Thomas:**

**The Board reviewed the complaint you filed against Dr. Thomas Tvedten. At the June 2020 meeting, the Board voted to further investigate the matter.**

**Enclosed you will find a subpoena for medical records related to the patient in the complaint.**

**Please forward any and all requested records to our office no later than July 6, 2020.**

**Sincerely,**

Amy E. Embry

**Amy E. Embry**
**Executive Director**

**AEE/jeb**

**Enclosure**

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**BEFORE THE ARKANSAS STATE MEDICAL BOARD**

**IN THE MATTER OF:**

**Thomas Harold Tredten, M.D.**

**SUBPOENA DUCES TECUM**

**TO:**

**Scott Matthew Hogan, M.D.**
**Lynn C. Thomas, M.D.**
**Psychiatric Services, Inc**
**P.O. Box 251708**
**Little Rock, AR 72225**

**You are hereby ordered to provide to the Arkansas State Medical Board or any authorized representative thereof a copy of any and all medical records including all inpatient records to include paper and electronic records for the following patient:**

**This Subpoena is issued pursuant to authority granted the Board under Ark. Code Ann. Sec. 25-15-208 (7) (The Administrative Procedure Act), Sec. 17-80-102 and Sec. 17-95-201, et seq. (The Arkansas Medical Practices Act).**

**ARKANSAS STATE MEDICAL BOARD**

Amy E. Embry

**BY: Amy E. Embry**
**Executive Director**

**DATE: 6/24/20**

**PROOF OF SERVICE: I have this _____ day of _____, _____ at _____ duly served the within by showing the original and stating the substance thereof to the within named, _____, as I am therein commanded.**

**SERVER** _____ **SERVEE** _____ **TIME** _____

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




**BEFORE THE ARKANSAS STATE MEDICAL BOARD**

**IN THE MATTER OF:**

**TVEDTEN, Thomas Harold, M.D. C-5169**
**Case # 20-11 Tvedten**

**SUBPOENA DUCES TECUM**

**TO:**

**Arkansas Prescription Drug Monitoring Program Administrator**
**Arkansas Department of Health**
**4815 W. Markham**
**Little Rock, AR 72205-3867**

**You are hereby ordered to provide to the Arkansas State Medical Board or any authorized representative thereof a copy of any and all records contained in the Arkansas Prescription Drug Monitoring Program:**

**This Subpoena is issued pursuant to authority granted the Board under Ark. Code Ann. Sec. 25-15-208 (7) (The Administrative Procedure Act), Sec. 17-80-[illegible] 17-95-201, et seq. (The Arkansas Medical Practices Act).**

**ARKANSAS STATE MEDICAL BOARD**

Amy E. Embry

**BY: Amy E. Embry**
**Executive Director**

**DATE: June 24, 2020**

**PROOF OF SERVICE: I have this _____ day of _____, _____ at _____ duly served the within by showing the original and stating the substance thereof to the within named, _____, as I am therein commanded.**

**SERVER _____ SERVEE _____ TIME _____**

# ARKANSAS STATE MEDICAL BOARD

1401 West Capitol, Suite 340, Little Rock, Arkansas 72201 • (501) 296-1802 • FAX (501) 603-3555
www.armedicalboard.org




## BEFORE THE ARKANSAS STATE MEDICAL BOARD

## IN THE MATTER OF:

**TVEDTEN, Thomas Harold, M.D. C-5169**
**Case # 20-11 Tvedten**

## SUBPOENA DUCES TECUM

**TO:**

**Arkansas Prescription Drug Monitoring Program Administrator**
**Arkansas Department of Health**
**4815 W. Markham**
**Little Rock, AR 72205-3867**

**You are hereby ordered to provide to the Arkansas State Medical Board or any authorized representative thereof a copy of any and all records contained in the Arkansas Prescription Drug Monitoring Program:**

**This Subpoena is issued pursuant to authority granted the Board under Ark. Code Ann. Sec. 25-15-208 (7) (The Administrative Procedure Act), Sec. 17-80-[illegible] 17-95-201, et seq. (The Arkansas Medical Practices Act).**

**ARKANSAS STATE MEDICAL BOARD**

Amy E. Embry

**BY: Amy E. Embry**
**Executive Director**

**DATE: June 24, 2020**

**PROOF OF SERVICE: I have this _____ day of _____, _____ at _____ duly served the within by showing the original and stating the substance thereof to the within named, _____, as I am therein commanded.**

**SERVER _____ SERVEE _____ TIME _____**