STRATTERA®
(atomoxetine HCl)

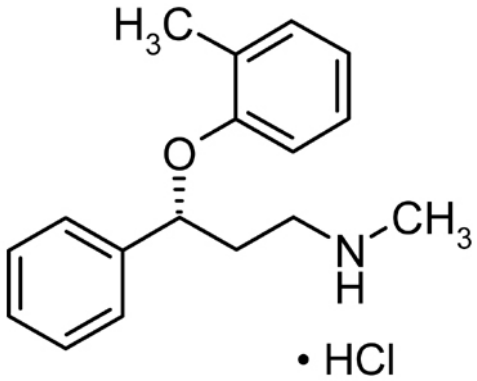
WARNING

Suicidal Ideation in Children and Adolescents — STRATTERA (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of STRATTERA in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. STRATTERA is approved for ADHD in pediatric and adult patients. STRATTERA is not approved for major depressive disorder.

Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of STRATTERA in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA compared to placebo. The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials. (*See* WARNINGS *and* PRECAUTIONS, Pediatric Use).

DESCRIPTION

STRATTERA® (atomoxetine HCl) is a selective norepinephrine reuptake inhibitor. Atomoxetine HCl is the *R*(-) isomer as determined by x-ray diffraction. The chemical designation is (-)-*N*-Methyl-3-phenyl-3-(*o*-tolyloxy)-propylamine hydrochloride. The molecular formula is $C_{17}H_{21}NO$•HCl, which corresponds to a molecular weight of 291.82. The chemical structure is:



Atomoxetine HCl is a white to practically white solid, which has a solubility of 27.8 mg/mL in water.

STRATTERA capsules are intended for oral administration only.

Each capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, 60, 80, or 100 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells

contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain one or more of the following: FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide, red iron oxide. The capsules are imprinted with edible black ink.

CLINICAL PHARMACOLOGY

Pharmacodynamics and Mechanism of Action

The precise mechanism by which atomoxetine produces its therapeutic effects in Attention-Deficit/Hyperactivity Disorder (ADHD) is unknown, but is thought to be related to selective inhibition of the pre-synaptic norepinephrine transporter, as determined in ex vivo uptake and neurotransmitter depletion studies.

Human Pharmacokinetics

Atomoxetine is well-absorbed after oral administration and is minimally affected by food. It is eliminated primarily by oxidative metabolism through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway and subsequent glucuronidation. Atomoxetine has a half-life of about 5 hours. A fraction of the population (about 7% of Caucasians and 2% of African Americans) are poor metabolizers (PMs) of CYP2D6 metabolized drugs. These individuals have reduced activity in this pathway resulting in 10-fold higher AUCs, 5-fold higher peak plasma concentrations, and slower elimination (plasma half-life of about 24 hours) of atomoxetine compared with people with normal activity [extensive metabolizers (EMs)]. Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine, and quinidine, cause similar increases in exposure.

The pharmacokinetics of atomoxetine have been evaluated in more than 400 children and adolescents in selected clinical trials, primarily using population pharmacokinetic studies. Single-dose and steady-state individual pharmacokinetic data were also obtained in children, adolescents, and adults. When doses were normalized to a mg/kg basis, similar half-life, C_{max}, and AUC values were observed in children, adolescents, and adults. Clearance and volume of distribution after adjustment for body weight were also similar.

Absorption and distribution — Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in EMs and 94% in PMs. Maximal plasma concentrations (C_{max}) are reached approximately 1 to 2 hours after dosing.

STRATTERA can be administered with or without food. Administration of STRATTERA with a standard high-fat meal in adults did not affect the extent of oral absorption of atomoxetine (AUC), but did decrease the rate of absorption, resulting in a 37% lower C_{max}, and delayed T_{max} by 3 hours. In clinical trials with children and adolescents, administration of STRATTERA with food resulted in a 9% lower C_{max}.

The steady-state volume of distribution after intravenous administration is 0.85 L/kg indicating that atomoxetine distributes primarily into total body water. Volume of distribution is similar across the patient weight range after normalizing for body weight.

At therapeutic concentrations, 98% of atomoxetine in plasma is bound to protein, primarily albumin.

Metabolism and elimination — Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of STRATTERA with potent inhibitors of CYP2D6, such as fluoxetine, paroxetine, or quinidine, results in a substantial

increase in atomoxetine plasma exposure, and dosing adjustment may be necessary (*see* Drug-Drug Interactions). Atomoxetine did not inhibit or induce the CYP2D6 pathway.

The major oxidative metabolite formed, regardless of CYP2D6 status, is 4-hydroxyatomoxetine, which is glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter but circulates in plasma at much lower concentrations (1% of atomoxetine concentration in EMs and 0.1% of atomoxetine concentration in PMs). 4-Hydroxyatomoxetine is primarily formed by CYP2D6, but in PMs, 4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has substantially less pharmacological activity compared with atomoxetine and circulates in plasma at lower concentrations (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).

Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours).

Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-*O*-glucuronide, mainly in the urine (greater than 80% of the dose) and to a lesser extent in the feces (less than 17% of the dose). Only a small fraction of the STRATTERA dose is excreted as unchanged atomoxetine (less than 3% of the dose), indicating extensive biotransformation.

Special Populations

Hepatic insufficiency — Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency (*see* DOSAGE AND ADMINISTRATION).

Renal insufficiency — EM subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. STRATTERA can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the normal dosing regimen.

Geriatric — The pharmacokinetics of atomoxetine have not been evaluated in the geriatric population.

Pediatric — The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under 6 years of age.

Gender — Gender did not influence atomoxetine disposition.

Ethnic origin — Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians).

Drug-Drug Interactions

CYP2D6 activity and atomoxetine plasma concentration — Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed

in PMs. Dosage adjustment of STRATTERA in EMs may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* Drug-Drug Interactions *under* PRECAUTIONS). In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

Effect of atomoxetine on P450 enzymes — Atomoxetine did not cause clinically important inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

Albuterol — Albuterol (600 mcg iv over 2 hours) induced increases in heart rate and blood pressure. These effects were potentiated by atomoxetine (60 mg BID for 5 days) and were most marked after the initial coadministration of albuterol and atomoxetine (*see* Drug-Drug Interactions *under* PRECAUTIONS).

Alcohol — Consumption of ethanol with STRATTERA did not change the intoxicating effects of ethanol.

Desipramine — Coadministration of STRATTERA (40 or 60 mg BID for 13 days) with desipramine, a model compound for CYP2D6 metabolized drugs (single dose of 50 mg), did not alter the pharmacokinetics of desipramine. No dose adjustment is recommended for drugs metabolized by CYP2D6.

Methylphenidate — Coadministration of methylphenidate with STRATTERA did not increase cardiovascular effects beyond those seen with methylphenidate alone.

Midazolam — Coadministration of STRATTERA (60 mg BID for 12 days) with midazolam, a model compound for CYP3A4 metabolized drugs (single dose of 5 mg), resulted in 15% increase in AUC of midazolam. No dose adjustment is recommended for drugs metabolized by CYP3A.

Drugs highly bound to plasma protein — In vitro drug-displacement studies were conducted with atomoxetine and other highly-bound drugs at therapeutic concentrations. Atomoxetine did not affect the binding of warfarin, acetylsalicylic acid, phenytoin, or diazepam to human albumin. Similarly, these compounds did not affect the binding of atomoxetine to human albumin.

Drugs that affect gastric pH — Drugs that elevate gastric pH (magnesium hydroxide/aluminum hydroxide, omeprazole) had no effect on STRATTERA bioavailability.

CLINICAL STUDIES

The effectiveness of STRATTERA in the treatment of ADHD was established in 6 randomized, double-blind, placebo-controlled studies in children, adolescents, and adults who met Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD (*see* INDICATIONS AND USAGE).

Children and Adolescents

The effectiveness of STRATTERA in the treatment of ADHD was established in 4 randomized, double-blind, placebo-controlled studies of pediatric patients (ages 6 to 18). Approximately one-third of the patients met DSM-IV criteria for inattentive subtype and two-thirds met criteria for both inattentive and hyperactive/impulsive subtypes (*see* INDICATIONS AND USAGE).

Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for STRATTERA- and placebo-treated patients using an intent-to-treat analysis of the primary outcome measure, the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive subscales. Each item on the ADHDRS maps directly to one symptom criterion for ADHD in the DSM-IV.

In Study 1, an 8-week randomized, double-blind, placebo-controlled, dose-response, acute treatment study of children and adolescents aged 8 to 18 (N=297), patients received either a fixed dose of STRATTERA (0.5, 1.2, or 1.8 mg/kg/day) or placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon/early evening. At the 2 higher doses, improvements in ADHD symptoms were statistically significantly superior in STRATTERA-treated patients compared with placebo-treated patients as measured on the ADHDRS scale. The 1.8-mg/kg/day STRATTERA dose did not provide any additional benefit over that observed with the 1.2-mg/kg/day dose. The 0.5-mg/kg/day STRATTERA dose was not superior to placebo.

In Study 2, a 6-week randomized, double-blind, placebo-controlled, acute treatment study of children and adolescents aged 6 to 16 (N=171), patients received either STRATTERA or placebo. STRATTERA was administered as a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response, up to a maximum dose of 1.5 mg/kg/day. The mean final dose of STRATTERA was approximately 1.3 mg/kg/day. ADHD symptoms were statistically significantly improved on STRATTERA compared with placebo, as measured on the ADHDRS scale. This study shows that STRATTERA is effective when administered once daily in the morning.

In 2 identical, 9-week, acute, randomized, double-blind, placebo-controlled studies of children aged 7 to 13 (Study 3, N=147; Study 4, N=144), STRATTERA and methylphenidate were compared with placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon (after school) and titrated on a weight-adjusted basis according to clinical response. The maximum recommended STRATTERA dose was 2.0 mg/kg/day. The mean final dose of STRATTERA for both studies was approximately 1.6 mg/kg/day. In both studies, ADHD symptoms statistically significantly improved more on STRATTERA than on placebo, as measured on the ADHDRS scale.

Examination of population subsets based on gender and age (<12 and 12 to 17) did not reveal any differential responsiveness on the basis of these subgroupings. There was not sufficient exposure of ethnic groups other than Caucasian to allow exploration of differences in these subgroups.

Adults

The effectiveness of STRATTERA in the treatment of ADHD was established in 2 randomized, double-blind, placebo-controlled clinical studies of adult patients, age 18 and older, who met DSM-IV criteria for ADHD.

Signs and symptoms of ADHD were evaluated using the investigator-administered Conners Adult ADHD Rating Scale Screening Version (CAARS), a 30-item scale. The primary effectiveness measure was the 18-item Total ADHD Symptom score (the sum of the inattentive and hyperactivity/impulsivity subscales from the CAARS) evaluated by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis.

In 2 identical, 10-week, randomized, double-blind, placebo-controlled acute treatment studies (Study 5, N=280; Study 6, N=256), patients received either STRATTERA or placebo. STRATTERA was administered as a divided dose in the early morning and late afternoon/early evening and titrated according to clinical response in a range of 60 to 120 mg/day. The mean final dose of STRATTERA for both studies was approximately 95 mg/day. In both studies, ADHD symptoms were statistically significantly improved on STRATTERA, as measured on the ADHD Symptom score from the CAARS scale.

Examination of population subsets based on gender and age (<42 and ≥42) did not reveal any differential responsiveness on the basis of these subgroupings. There was not sufficient exposure of ethnic groups other than Caucasian to allow exploration of differences in these subgroups.

INDICATIONS AND USAGE

STRATTERA is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).

The effectiveness of STRATTERA in the treatment of ADHD was established in 2 placebo-controlled trials in children, 2 placebo-controlled trials in children and adolescents, and 2 placebo-controlled trials in adults who met DSM-IV criteria for ADHD (*see* CLINICAL STUDIES).

A diagnosis of ADHD (DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that cause impairment and that were present before age 7 years. The symptoms must be persistent, must be more severe than is typically observed in individuals at a comparable level of development, must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and must be present in 2 or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least 6 of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes, lack of sustained attention, poor listener, failure to follow through on tasks, poor organization, avoids tasks requiring sustained mental effort, loses things, easily distracted, forgetful. For the Hyperactive-Impulsive Type, at least 6 of the following symptoms must have persisted for at least 6 months: fidgeting/squirming, leaving seat, inappropriate running/climbing, difficulty with quiet activities, “on the go,” excessive talking, blurting answers, can’t wait turn, intrusive. For a Combined Type diagnosis, both inattentive and hyperactive-impulsive criteria must be met.

Special Diagnostic Considerations

The specific etiology of ADHD is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

STRATTERA is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all patients with this syndrome. Drug treatment is not intended for use in the patient who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential in children and adolescents with this diagnosis and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe drug treatment medication will depend upon the physician’s assessment of the chronicity and severity of the patient’s symptoms.

Long-Term Use

The effectiveness of STRATTERA for long-term use, i.e., for more than 9 weeks in child and adolescent patients and 10 weeks in adult patients, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use STRATTERA for extended periods

should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Hypersensitivity

STRATTERA is contraindicated in patients known to be hypersensitive to atomoxetine or other constituents of the product (*see* WARNINGS).

Monoamine Oxidase Inhibitors (MAOI)

STRATTERA should not be taken with an MAOI, or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing STRATTERA. With other drugs that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when taken in combination with an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity.

Narrow Angle Glaucoma

In clinical trials, STRATTERA use was associated with an increased risk of mydriasis and therefore its use is not recommended in patients with narrow angle glaucoma.

WARNINGS

Suicidal Ideation

STRATTERA increased the risk of suicidal ideation in short-term studies in children and adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of STRATTERA in children and adolescents have revealed a greater risk of suicidal ideation early during treatment in those receiving STRATTERA. There were a total of 12 trials (11 in ADHD and 1 in enuresis) involving over 2200 patients (including 1357 patients receiving STRATTERA and 851 receiving placebo). The average risk of suicidal ideation in patients receiving STRATTERA was 0.4% (5/1357 patients), compared to none in placebo-treated patients. There was 1 suicide attempt among these approximately 2200 patients, occurring in a patient treated with STRATTERA. **No suicides occurred in these trials.** All events occurred in children 12 years of age or younger. All events occurred during the first month of treatment. It is unknown whether the risk of suicidal ideation in pediatric patients extends to longer-term use. A similar analysis in adult patients treated with STRATTERA for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behavior in association with the use of STRATTERA.

All pediatric patients being treated with STRATTERA should be monitored closely for suicidality, clinical worsening, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes. Such monitoring would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment, then every other week visits for the next 4 weeks, then at 12 weeks, and as clinically indicated beyond 12 weeks. Additional contact by telephone may be appropriate between face-to-face visits.

The following symptoms have been reported with STRATTERA: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania. Although a causal link between the emergence of such

symptoms and the emergence of suicidal impulses has not been established, there is a concern that such symptoms may represent precursors to emerging suicidality. Thus, patients being treated with STRATTERA should be observed for the emergence of such symptoms.

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

Families and caregivers of pediatric patients being treated with STRATTERA should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder — In general, particular care should be taken in treating ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with STRATTERA, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Severe Liver Injury

Postmarketing reports indicate that STRATTERA can cause severe liver injury in rare cases. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors, out of more than 2 million patients during the first two years of postmarketing experience. In one patient, liver injury, manifested by elevated hepatic enzymes (up to 40 X upper limit of normal (ULN)) and jaundice (bilirubin up to 12 X ULN), recurred upon rechallenge, and was followed by recovery upon drug discontinuation providing evidence that STRATTERA caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. Because of probable underreporting, it is impossible to provide an accurate estimate of the true incidence of these events. The patients described above recovered from their liver injury, and did not require a liver transplant. However, in a small percentage of patients, severe drug-related liver injury may progress to acute liver failure resulting in death or the need for a liver transplant.

STRATTERA should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be done upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). (*See also* **Information for Patients** *under* PRECAUTIONS.)

Serious Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents — Sudden death has been reported in association with atomoxetine treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of

sudden death, atomoxetine generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the noradrenergic effects of atomoxetine.

Adults — Sudden deaths, stroke, and myocardial infarction have been reported in adults taking atomoxetine at usual doses for ADHD. Although the role of atomoxetine in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Consideration should be given to not treating adults with clinically significant cardiac abnormalities.

Assessing Cardiovascular Status in Patients being Treated with Atomoxetine

Children, adolescents, or adults who are being considered for treatment with atomoxetine should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during atomoxetine treatment should undergo a prompt cardiac evaluation.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by atomoxetine at usual doses. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine, and discontinuation of treatment should be considered. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.2% (4 patients with events out of 1939 exposed to atomoxetine for several weeks at usual doses) of atomoxetine-treated patients compared to 0 out of 1056 placebo-treated patients.

Allergic Events

Although uncommon, allergic reactions, including angioneurotic edema, urticaria, and rash, have been reported in patients taking STRATTERA.

PRECAUTIONS

General

Effects on blood pressure and heart rate — STRATTERA should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease because it can increase blood pressure and heart rate. Pulse and blood pressure should be measured at baseline, following STRATTERA dose increases, and periodically while on therapy.

In pediatric placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of about 6 beats/minute compared with placebo subjects. At the final study visit before drug discontinuation, 3.6% (12/335) of STRATTERA-treated subjects had heart rate increases of at least 25 beats/minute and a heart rate of at least 110 beats/minute, compared with 0.5% (1/204) of placebo subjects. No pediatric subject had a heart rate increase of at least 25 beats/minute and a heart rate of at least 110 beats/minute on more than one occasion. Tachycardia was identified as an adverse event for 1.5% (5/340) of these pediatric subjects compared with 0.5% (1/207) of placebo subjects. The mean heart rate increase in extensive metabolizer (EM) patients was 6.7 beats/minute, and in poor metabolizer (PM) patients 10.4 beats/minute.

STRATTERA-treated pediatric subjects experienced mean increases of about 1.5 mm Hg in systolic and diastolic blood pressures compared with placebo. At the final study visit before drug discontinuation, 6.8% (22/324) of STRATTERA-treated pediatric subjects had high systolic blood pressure measurements compared with 3.0% (6/197) of placebo subjects. High systolic blood pressures were measured on 2 or more occasions in 8.6% (28/324) of STRATTERA-treated subjects and 3.6% (7/197) of placebo subjects. At the final study visit before drug discontinuation, 2.8% (9/326) of STRATTERA-treated pediatric subjects had high diastolic blood pressure measurements compared with 0.5% (1/200) of placebo subjects. High diastolic blood pressures were measured on 2 or more occasions in 5.2% (17/326) of STRATTERA-treated subjects and 1.5% (3/200) of placebo subjects. (High systolic and diastolic blood pressure measurements were defined as those exceeding the 95th percentile, stratified by age, gender, and height percentile - National High Blood Pressure Education Working Group on Hypertension Control in Children and Adolescents.)

In adult placebo-controlled trials, STRATTERA-treated subjects experienced a mean increase in heart rate of 5 beats/minute compared with placebo subjects. Tachycardia was identified as an adverse event for 3% (8/269) of these adult atomoxetine subjects compared with 0.8% (2/263) of placebo subjects.

STRATTERA-treated adult subjects experienced mean increases in systolic (about 3 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo. At the final study visit before drug discontinuation, 1.9% (5/258) of STRATTERA-treated adult subjects had systolic blood pressure measurements ≥150 mm Hg compared with 1.2% (3/256) of placebo subjects. At the final study visit before drug discontinuation, 0.8% (2/257) of STRATTERA-treated adult subjects had diastolic blood pressure measurements ≥100 mm Hg compared with 0.4% (1/257) of placebo subjects. No adult subject had a high systolic or diastolic blood pressure detected on more than one occasion.

Orthostatic hypotension and syncope have been reported in patients taking STRATTERA. In child and adolescent trials, 0.2% (12/5596) of STRATTERA-treated patients experienced orthostatic hypotension and 0.8% (46/5596) experienced syncope. In short-term child and adolescent controlled trials, 1.8% (6/340) of STRATTERA-treated patients experienced orthostatic hypotension compared with 0.5% (1/207) of placebo-treated patients. Syncope was not reported during short-term child and adolescent placebo-controlled ADHD trials. STRATTERA should be used with caution in any condition that may predispose patients to hypotension.

Peripheral vascular effects — There have been spontaneous postmarketing reports of Raynaud's phenomenon (new onset and exacerbation of preexisting condition).

Effects on urine outflow from the bladder — In adult ADHD controlled trials, the rates of urinary retention (3%, 7/269) and urinary hesitation (3%, 7/269) were increased among atomoxetine subjects compared with placebo subjects (0%, 0/263). Two adult atomoxetine subjects and no placebo subjects discontinued from controlled clinical trials because of urinary retention. A complaint of urinary retention or urinary hesitancy should be considered potentially related to atomoxetine.

Effects on Growth — Data on the long-term effects of STRATTERA on growth come from open-label studies, and weight and height changes are compared to normative population data. In general, the weight and height gain of pediatric patients treated with STRATTERA lags behind that predicted by normative population data for about the first 9-12 months of treatment. Subsequently, weight gain rebounds and at about 3 years of treatment, patients treated with

STRATTERA have gained 17.9 kg on average, 0.5 kg more than predicted by their baseline data. After about 12 months, gain in height stabilizes, and at 3 years, patients treated with STRATTERA have gained 19.4 cm on average, 0.4 cm less than predicted by their baseline data (*see* Figure 1 below).

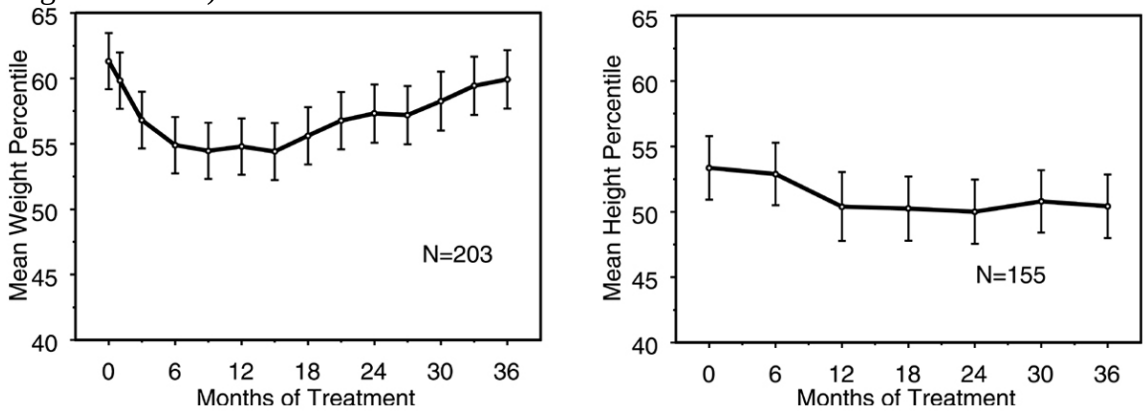


Figure 1: Mean Weight and Height Percentiles Over Time for Patients With Three Years of STRATTERA Treatment

This growth pattern was generally similar regardless of pubertal status at the time of treatment initiation. Patients who were pre-pubertal at the start of treatment (girls ≤8 years old, boys ≤9 years old) gained an average of 2.1 kg and 1.2 cm less than predicted after three years. Patients who were pubertal (girls >8 to ≤13 years old, boys >9 to ≤14 years old) or late pubertal (girls >13 years old, boys >14 years old) had average weight and height gains that were close to or exceeded those predicted after three years of treatment.

Growth followed a similar pattern in both extensive and poor metabolizers (EMs, PMs). PMs treated for at least two years gained an average of 2.4 kg and 1.1 cm less than predicted, while EMs gained an average of 0.2 kg and 0.4 cm less than predicted.

In short-term controlled studies (up to 9 weeks), STRATTERA-treated patients lost an average of 0.4 kg and gained an average of 0.9 cm, compared to a gain of 1.5 kg and 1.1 cm in the placebo-treated patients. In a fixed-dose controlled trial, 1.3%, 7.1%, 19.3%, and 29.1% of patients lost at least 3.5% of their body weight in the placebo, 0.5, 1.2, and 1.8 mg/kg/day dose groups.

Growth should be monitored during treatment with STRATTERA.

Aggressive Behavior or Hostility — Patients beginning treatment for ADHD should be monitored for the appearance or worsening of aggressive behavior or hostility. Aggressive behavior or hostility is often observed in children and adolescents with ADHD. In short-term controlled clinical trials, 21/1308 (1.6%) of atomoxetine patients versus 9/806 (1.1%) of placebo-treated patients spontaneously reported treatment emergent hostility-related adverse events. Although this is not conclusive evidence that STRATTERA causes aggressive behavior or hostility, these behaviors were more frequently observed in clinical trials among children and adolescents treated with STRATTERA compared to placebo (overall risk ratio of 1.33 [95% C.I. 0.67-2.64 - not statistically significant]).

Priapism — Rare postmarketing cases of priapism, defined as painful and nonpainful penile erection lasting more than 4 hours, have been reported for pediatric and adult patients treated with STRATTERA. The erections resolved in cases in which follow-up information was available, some following discontinuation of STRATTERA. Prompt medical attention is required in the event of suspected priapism.

Information for Patients

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

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

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

Hepatic Risk - Patients initiating STRATTERA should be cautioned that liver dysfunction may develop rarely. Patients should be instructed to contact their physician immediately should they develop pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms.

Aggressive Behavior or Hostility - Patients should be instructed to call their doctor as soon as possible should they notice an increase in aggression or hostility.

Ocular Irritant - STRATTERA is an ocular irritant. STRATTERA capsules are not intended to be opened. In the event of capsule content coming in contact with the eye, the affected eye should be flushed immediately with water, and medical advice obtained. Hands and any potentially contaminated surfaces should be washed as soon as possible.

Patients should consult a physician if they are taking or plan to take any prescription or over-the-counter medicines, dietary supplements, or herbal remedies.

Patients should consult a physician if they are nursing, pregnant, or thinking of becoming pregnant while taking STRATTERA.

Patients may take STRATTERA with or without food.

If patients miss a dose, they should take it as soon as possible, but should not take more than the prescribed total daily amount of STRATTERA in any 24-hour period.

Patients should use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

Rare postmarketing cases of priapism, defined as painful and nonpainful penile erection lasting more than 4 hours, have been reported for pediatric and adult patients treated with STRATTERA. The parents or guardians of pediatric patients taking STRATTERA and adult patients taking STRATTERA should be instructed that priapism requires prompt medical attention.

Laboratory Tests

Routine laboratory tests are not required.

CYP2D6 metabolism — Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA (*see* ADVERSE REACTIONS).

Drug-Drug Interactions

Albuterol — STRATTERA should be administered with caution to patients being treated with systemically-administered (oral or intravenous) albuterol (or other $beta_2$ agonists) because the action of albuterol on the cardiovascular system can be potentiated resulting in increases in heart rate and blood pressure.

CYP2D6 inhibitors — Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In EMs, selective inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in PMs. Dosage adjustment of STRATTERA may be necessary when coadministered with CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine (*see* DOSAGE AND ADMINISTRATION). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and $C_{ss,max}$ is about 3- to 4-fold greater than atomoxetine alone.

In vitro studies suggest that coadministration of cytochrome P450 inhibitors to PMs will not increase the plasma concentrations of atomoxetine.

Monoamine oxidase inhibitors — See CONTRAINDICATIONS.

Pressor agents — Because of possible effects on blood pressure, STRATTERA should be used cautiously with pressor agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — Atomoxetine HCl was not carcinogenic in rats and mice when given in the diet for 2 years at time-weighted average doses up to 47 and 458 mg/kg/day, respectively. The highest dose used in rats is approximately 8 and 5 times the maximum human dose in children and adults, respectively, on a mg/m^2 basis. Plasma levels (AUC) of atomoxetine at this dose in rats are estimated to be 1.8 times (extensive metabolizers) or 0.2 times (poor metabolizers) those in humans receiving the maximum human dose. The highest dose used in mice is approximately 39 and 26 times the maximum human dose in children and adults, respectively, on a mg/m^2 basis.

Mutagenesis — Atomoxetine HCl was negative in a battery of genotoxicity studies that included a reverse point mutation assay (Ames Test), an in vitro mouse lymphoma assay, a chromosomal aberration test in Chinese hamster ovary cells, an unscheduled DNA synthesis test in rat hepatocytes, and an in vivo micronucleus test in mice. However, there was a slight increase in the percentage of Chinese hamster ovary cells with diplochromosomes, suggesting endoreduplication (numerical aberration).

The metabolite N-desmethylatomoxetine HCl was negative in the Ames Test, mouse lymphoma assay, and unscheduled DNA synthesis test.

Impairment of fertility — Atomoxetine HCl did not impair fertility in rats when given in the diet at doses of up to 57 mg/kg/day, which is approximately 6 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C — Pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, a decrease in live fetuses and an increase in early resorptions was observed. Slight increases in the incidences of atypical origin of carotid artery and absent subclavian artery were observed. These findings were observed at doses that caused slight maternal toxicity. The no-effect dose for these findings was 30 mg/kg/day. The 100-mg/kg dose is approximately 23 times the maximum human dose on a mg/m^2 basis; plasma levels (AUC) of atomoxetine at this dose in rabbits are estimated to be 3.3 times (extensive metabolizers) or 0.4 times (poor metabolizers) those in humans receiving the maximum human dose.

Rats were treated with up to approximately 50 mg/kg/day of atomoxetine (approximately 6 times the maximum human dose on a mg/m^2 basis) in the diet from 2 weeks (females) or 10 weeks (males) prior to mating through the periods of organogenesis and lactation. In 1 of 2 studies, decreases in pup weight and pup survival were observed. The decreased pup survival was also seen at 25 mg/kg (but not at 13 mg/kg). In a study in which rats were treated with atomoxetine in the diet from 2 weeks (females) or 10 weeks (males) prior to mating throughout the period of organogenesis, a decrease in fetal weight (female only) and an increase in the incidence of incomplete ossification of the vertebral arch in fetuses were observed at 40 mg/kg/day (approximately 5 times the maximum human dose on a mg/m^2 basis) but not at 20 mg/kg/day.

No adverse fetal effects were seen when pregnant rats were treated with up to 150 mg/kg/day (approximately 17 times the maximum human dose on a mg/m^2 basis) by gavage throughout the period of organogenesis.

No adequate and well-controlled studies have been conducted in pregnant women. STRATTERA should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

Parturition in rats was not affected by atomoxetine. The effect of STRATTERA on labor and delivery in humans is unknown.

Nursing Mothers

Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Caution should be exercised if STRATTERA is administered to a nursing woman.

Pediatric Use

Anyone considering the use of STRATTERA in a child or adolescent must balance the potential risks with the clinical need (*see* BOX WARNING *and* WARNINGS, Suicidal Ideation).

The safety and efficacy of STRATTERA in pediatric patients less than 6 years of age have not been established. The efficacy of STRATTERA beyond 9 weeks and safety of STRATTERA beyond 1 year of treatment have not been systematically evaluated.

A study was conducted in young rats to evaluate the effects of atomoxetine on growth and neurobehavioral and sexual development. Rats were treated with 1, 10, or 50 mg/kg/day (approximately 0.2, 2, and 8 times, respectively, the maximum human dose on a mg/m^2 basis) of atomoxetine given by gavage from the early postnatal period (Day 10 of age) through adulthood. Slight delays in onset of vaginal patency (all doses) and preputial separation (10 and 50 mg/kg),

slight decreases in epididymal weight and sperm number (10 and 50 mg/kg), and a slight decrease in corpora lutea (50 mg/kg) were seen, but there were no effects on fertility or reproductive performance. A slight delay in onset of incisor eruption was seen at 50 mg/kg. A slight increase in motor activity was seen on Day 15 (males at 10 and 50 mg/kg and females at 50 mg/kg) and on Day 30 (females at 50 mg/kg) but not on Day 60 of age. There were no effects on learning and memory tests. The significance of these findings to humans is unknown.

Geriatric Use

The safety and efficacy of STRATTERA in geriatric patients have not been established.

ADVERSE REACTIONS

STRATTERA was administered to 2067 children or adolescent patients with ADHD and 270 adults with ADHD in clinical studies. During the ADHD clinical trials, 169 patients were treated for longer than 1 year and 526 patients were treated for over 6 months.

The data in the following tables and text 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 data obtained from other clinical investigations involving different treatments, uses, or investigators. The cited data provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence in the population studied.

Child and Adolescent Clinical Trials

Reasons for discontinuation of treatment due to adverse events in child and adolescent clinical trials — In acute child and adolescent placebo-controlled trials, 3.5% (15/427) of atomoxetine subjects and 1.4% (4/294) placebo subjects discontinued for adverse events. For all studies, (including open-label and long-term studies), 5% of extensive metabolizer (EM) patients and 7% of poor metabolizer (PM) patients discontinued because of an adverse event. Among STRATTERA-treated patients, aggression (0.5%, N=2); irritability (0.5%, N=2); somnolence (0.5%, N=2); and vomiting (0.5%, N=2) were the reasons for discontinuation reported by more than 1 patient.

Seizures — STRATTERA has not been systematically evaluated in pediatric patients with seizure disorder as these patients were excluded from clinical studies during the product's premarket testing. In the clinical development program, seizures were reported in 0.2% (12/5073) of children whose average age was 10 years (range 6 to 16 years). In these clinical trials, the seizure risk among poor metabolizers was 0.3% (1/293) compared to 0.2% (11/4741) for extensive metabolizers.

Commonly observed adverse events in acute child and adolescent, placebo-controlled trials — Commonly observed adverse events associated with the use of STRATTERA (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (STRATTERA incidence greater than placebo) are listed in Table 1 for the BID trials. Results were similar in the QD trial except as shown in Table 2, which shows both BID and QD results for selected adverse events. The most commonly observed adverse events in patients treated with STRATTERA (incidence of 5% or greater and at least twice the incidence in placebo patients, for either BID or QD dosing) were: dyspepsia, nausea, vomiting, fatigue, appetite decreased, dizziness, and mood swings (*see* Tables 1 *and* 2).

Table 1: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials

Adverse Event[1]	Percentage of Patients Reporting Events from BID Trials	
	STRATTERA (N=340)	Placebo (N=207)
Gastrointestinal Disorders		
Abdominal pain upper	20	16
Constipation	3	1
Dyspepsia	4	2
Vomiting	11	9
Infections		
Ear infection	3	1
Influenza	3	1
Investigations		
Weight decreased	2	0
Metabolism and Nutritional Disorders		
Appetite decreased	14	6
Nervous System Disorders		
Dizziness (exc vertigo)	6	3
Headache	27	25
Somnolence	7	5
Psychiatric Disorders		
Crying	2	1
Irritability	8	5
Mood swings	2	0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	11	7
Rhinorrhea	4	3
Skin and Subcutaneous Tissue Disorders		
Dermatitis	4	1

[1] Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: anorexia, blood pressure increased, early morning awakening, flushing, mydriasis, sinus tachycardia, tearfulness. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: arthralgia, gastroenteritis viral, insomnia, sore throat, nasal congestion, nasopharyngitis, pruritus, sinus congestion, upper respiratory tract infection.

Table 2: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials

Adverse Event	Percentage of Patients Reporting Events from BID Trials	Percentage of Patients Reporting Events from QD Trials

	STRATTERA (N=340)	Placebo (N=207)	STRATTERA (N=85)	Placebo (N=85)
Gastrointestinal Disorders				
Abdominal pain upper	20	16	16	9
Constipation	3	1	0	0
Diarrhea	3	6	4	1
Dry mouth	1	2	4	1
Dyspepsia	4	2	8	0
Nausea	7	8	12	2
Vomiting	11	9	15	1
General Disorders				
Fatigue	4	5	9	1
Psychiatric Disorders				
Mood swings	2	0	5	2

The following adverse events occurred in at least 2% of PM patients and were either twice as frequent or statistically significantly more frequent in PM patients compared with EM patients: decreased appetite (23% of PMs, 16% of EMs); insomnia (13% of PMs, 7% of EMs); sedation (4% of PMs, 2% of EMs); depression (6% of PMs, 2% of EMs); tremor (4% of PMs, 1% of EMs); early morning awakening (3% of PMs, 1% of EMs); pruritus (2% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs).

Adult Clinical Trials

Reasons for discontinuation of treatment due to adverse events in acute adult placebo-controlled trials — In the acute adult placebo-controlled trials, 8.5% (23/270) atomoxetine subjects and 3.4% (9/266) placebo subjects discontinued for adverse events. Among STRATTERA-treated patients, insomnia (1.1%, N=3); chest pain (0.7%, N=2); palpitations (0.7%, N=2); and urinary retention (0.7%, N=2) were the reasons for discontinuation reported by more than 1 patient.

Seizures — STRATTERA has not been systematically evaluated in adult patients with a seizure disorder as these patients were excluded from clinical studies during the product's premarket testing. In the clinical development program, seizures were reported on 0.1% (1/748) of adult patients. In these clinical trials, no poor metabolizers (0/43) reported seizures compared to 0.1% (1/705) for extensive metabolizers.

Commonly observed adverse events in acute adult placebo-controlled trials — Commonly observed adverse events associated with the use of STRATTERA (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (STRATTERA incidence greater than placebo) are listed in Table 3. The most commonly observed adverse events in patients treated with STRATTERA (incidence of 5% or greater and at least twice the incidence in placebo patients) were: constipation, dry mouth, nausea, appetite decreased, dizziness, insomnia, decreased libido, ejaculatory problems, impotence, urinary hesitation and/or urinary retention and/or difficulty in micturition, and dysmenorrhea (*see* Table 3).

Table 3: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 10 weeks) Adult Trials

Adverse Event[1]	Percentage of Patients Reporting Event

System Organ Class/Adverse Event	STRATTERA (N=269)	Placebo (N=263)
Cardiac Disorders		
Palpitations	4	1
Gastrointestinal Disorders		
Constipation	10	4
Dry mouth	21	6
Dyspepsia	6	4
Flatulence	2	1
Nausea	12	5
General Disorders and Administration Site Conditions		
Fatigue and/or lethargy	7	4
Pyrexia	3	2
Rigors	3	1
Infections		
Sinusitis	6	4
Investigations		
Weight decreased	2	1
Metabolism and Nutritional Disorders		
Appetite decreased	10	3
Musculoskeletal, Connective Tissue, and Bone Disorders		
Myalgia	3	2
Nervous System Disorders		
Dizziness	6	2
Headache	17	17
Insomnia and/or middle insomnia	16	8
Paraesthesia	4	2
Sinus headache	3	1
Psychiatric Disorders		
Abnormal dreams	4	3
Libido decreased	6	2
Sleep disorder	4	2
Renal and Urinary Disorders		
Urinary hesitation and/or urinary retention and/or difficulty in micturition	8	0
Reproductive System and Breast Disorders		
Dysmenorrhea[3]	7	3
Ejaculation failure[2] and/or ejaculation disorder[2]	5	2
Erectile disturbance[2]	7	1
Impotence[2]	3	0
Menses delayed[3]	2	1
Menstrual disorder[3]	3	2
Menstruation irregular[3]	2	0

Orgasm abnormal	2	1
Prostatitis[2]	3	0
Skin and Subcutaneous Tissue Disorders		
Dermatitis	2	1
Sweating increased	4	1
Vascular Disorders		
Hot flushes	3	1

[1] Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: early morning awakening, peripheral coldness, tachycardia. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: abdominal pain upper, arthralgia, back pain, cough, diarrhea, influenza, irritability, nasopharyngitis, sore throat, upper respiratory tract infection, vomiting.
[2] Based on total number of males (STRATTERA, N=174; placebo, N=172).
[3] Based on total number of females (STRATTERA, N=95; placebo, N=91).

Male and female sexual dysfunction — Atomoxetine appears to impair sexual function in some patients. Changes in sexual desire, sexual performance, and sexual satisfaction are not well assessed in most clinical trials because they need special attention and because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate the actual incidence. The table below displays the incidence of sexual side effects reported by at least 2% of adult patients taking STRATTERA in placebo-controlled trials.

Table 4

	STRATTERA	Placebo
Erectile disturbance[1]	7%	1%
Impotence[1]	3%	0%
Orgasm abnormal	2%	1%

[1] Males only.

There are no adequate and well-controlled studies examining sexual dysfunction with STRATTERA treatment. While it is difficult to know the precise risk of sexual dysfunction associated with the use of STRATTERA, physicians should routinely inquire about such possible side effects.

Postmarketing Spontaneous Reports

The following postmarketing adverse events have been reported in temporal association with STRATTERA treatment and were not associated with STRATTERA use during the premarketing evaluation of STRATTERA. Given the limitations associated with spontaneous reporting, it is difficult to accurately estimate the incidence rates for or causality of these events.

Cardiovascular system — QT prolongation, syncope.

Seizures — Seizures have been reported in the postmarketing period. The postmarketing seizure cases include patients with pre-existing seizure disorders and those with identified risk factors for seizures, as well as patients with neither a history of nor identified risk factors for seizures. The exact relationship between STRATTERA and seizures is difficult to evaluate due to uncertainty about the background risk of seizures in ADHD patients.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

STRATTERA is not a controlled substance.

Physical and Psychological Dependence

In a randomized, double-blind, placebo-controlled, abuse-potential study in adults comparing effects of STRATTERA and placebo, STRATTERA was not associated with a pattern of response that suggested stimulant or euphoriant properties.

Clinical study data in over 2000 children, adolescents, and adults with ADHD and over 1200 adults with depression showed only isolated incidents of drug diversion or inappropriate self-administration associated with STRATTERA. There was no evidence of symptom rebound or adverse events suggesting a drug-discontinuation or withdrawal syndrome.

Animal Experience

Drug discrimination studies in rats and monkeys showed inconsistent stimulus generalization between atomoxetine and cocaine.

OVERDOSAGE

Human Experience

No fatal overdoses occurred in clinical trials. There is limited clinical trial experience with STRATTERA overdose. During postmarketing, there have been fatalities reported involving a mixed ingestion overdose of STRATTERA and at least one other drug. There have been no reports of death involving overdose of STRATTERA alone, including intentional overdoses at amounts up to 1400 mg. In some cases of overdose involving STRATTERA, seizures have been reported. The most commonly reported symptoms accompanying acute and chronic overdoses of STRATTERA were somnolence, agitation, hyperactivity, abnormal behavior, and gastrointestinal symptoms. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g., mydriasis, tachycardia, dry mouth) have also been observed. Less commonly, there have been reports of QT prolongation and mental changes, including disorientation and hallucinations.

Management of Overdose

An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion. Activated charcoal may be useful in limiting absorption. Because atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosing of children and adolescents up to 70 kg body weight — STRATTERA should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day (*see* CLINICAL STUDIES).

The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg, whichever is less.

Dosing of children and adolescents over 70 kg body weight and adults — STRATTERA should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After 2 to 4 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response. There are no data that support increased effectiveness at higher doses (*see* CLINICAL STUDIES).

The maximum recommended total daily dose in children and adolescents over 70 kg and adults is 100 mg.

Maintenance/Extended Treatment

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with STRATTERA. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use STRATTERA for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

General Dosing Information

STRATTERA may be taken with or without food.

The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

Dosing adjustment for hepatically impaired patients — For those ADHD patients who have hepatic insufficiency (HI), dosage adjustment is recommended as follows: For patients with moderate HI (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose (for patients without HI). For patients with severe HI (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of normal (*see* Special Populations *under* CLINICAL PHARMACOLOGY).

Dosing adjustment for use with a strong CYP2D6 inhibitor — In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Atomoxetine can be discontinued without being tapered.

Instructions for Use/Handling

STRATTERA capsules are not intended to be opened, they should be taken whole. (*See also* Information for Patients *under* PRECAUTIONS.)

HOW SUPPLIED

STRATTERA® (atomoxetine HCl) capsules are supplied in 10-, 18-, 25-, 40-, 60-, 80-, and 100-mg strengths.

STRATTERA® Capsules	10 mg*	18 mg*	25 mg*	40 mg*	60 mg*	80 mg*	100 mg*

Color	Opaque White, Opaque White	Gold, Opaque White	Opaque Blue, Opaque White	Opaque Blue, Opaque Blue	Opaque Blue, Gold	Opaque Brown, Opaque White	Opaque Brown, Opaque Brown
Identification	LILLY 3227 10 mg	LILLY 3238 18 mg	LILLY 3228 25 mg	LILLY 3229 40 mg	LILLY 3239 60 mg	LILLY 3250 80 mg	LILLY 3251 100 mg
NDC Codes:							
Bottles of 30	0002-3227-30	0002-3238-30	0002-3228-30	0002-3229-30	0002-3239-30	0002-3250-30	0002-3251-30

* Atomoxetine base equivalent.

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

Literature revised November 21, 2006

PV 5851 AMP

MEDICATION GUIDE

STRATTERA® (Stra-TAIR-a)
(atomoxetine hydrochloride)

Read the Medication Guide that comes with STRATTERA® before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your treatment or your child's treatment with STRATTERA.

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

The following have been reported with use of STRATTERA:

1. Suicidal thoughts and actions in children and teenagers:

Children and teenagers sometimes think about suicide, and many report trying to kill themselves. Results from STRATTERA clinical studies with over 2200 child or teenage ADHD patients suggest that some children and teenagers may have a higher chance of having suicidal thoughts or actions. Although no suicides occurred in these studies, 4 out of every 1000 patients developed suicidal thoughts. Tell your child or teenager's doctor if your child or teenager (or there is a family history of):

- has bipolar illness (manic-depressive illness)
- had suicide thoughts or actions before starting STRATTERA

The chance for suicidal thoughts and actions may be higher:

- early during STRATTERA treatment
- during dose adjustments

Prevent suicidal thoughts and action in your child or teenager by:

- paying close attention to your child or teenager's moods, behaviors, thoughts, and feelings during STRATTERA treatment
- keeping all follow-up visits with your child or teenager's doctor as scheduled

Watch for the following signs in your child or teenager during STRATTERA treatment:

- anxiety
- agitation
- panic attacks
- trouble sleeping
- irritability
- hostility
- aggressiveness
- impulsivity
- restlessness
- mania
- depression
- suicide thoughts

Call your child or teenager's doctor right away if they have any of the above signs, especially if they are new, sudden, or severe. Your child or teenager may need to be closely watched for suicidal thoughts and actions or need a change in medicine.

2. Severe liver damage:

STRATTERA can cause liver injury in some patients. Call your doctor right away if you or your child has the following signs of liver problems:

- itching
- right upper belly pain
- dark urine
- yellow skin or eyes
- unexplained flu-like symptoms

3. Heart-related problems:

- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Tell your doctor if you or your child has any heart problems, heart defects, high blood pressure, or a family history of these problems. Your doctor should check you or your child carefully for heart problems before starting STRATTERA.

Your doctor should check your blood pressure or your child's blood pressure and heart rate regularly during treatment with STRATTERA.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking STRATTERA.

4. New mental (psychiatric) problems in children and teenagers:

- new psychotic symptoms (such as hearing voices, believing things that are not true, being suspicious) or new manic symptoms

Call your child or teenager's doctor right away about any new mental symptoms because adjusting or stopping STRATTERA treatment may need to be considered.

What Is STRATTERA?

STRATTERA is a selective norepinephrine reuptake inhibitor medicine. It is used for the treatment of attention deficit and hyperactivity disorder (ADHD). STRATTERA may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

STRATTERA should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

STRATTERA has not been studied in children less than 6 years old.

Who should not take STRATTERA?

STRATTERA should not be taken if you or your child:

- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI. Some names of MAOI medicines are Nardil® (phenelzine sulfate), Parnate® (tranylcypromine sulfate) and Emsam® (selegiline transdermal system).
- have an eye problem called narrow angle glaucoma
- are allergic to anything in STRATTERA. See the end of this Medication Guide for a complete list of ingredients.

STRATTERA may not be right for you or your child. Before starting STRATTERA tell your doctor or your child's doctor about all health conditions (or a family history of) including:

- have or had suicide thoughts or actions
- heart problems, heart defects, irregular heart beat, high blood pressure, or low blood pressure
- mental problems, psychosis, mania, bipolar illness, or depression

- liver problems

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breastfeeding.

Can STRATTERA be taken with other medicines?

Tell your doctor about all the medicines that you or your child takes including prescription and nonprescription medicines, vitamins, and herbal supplements. STRATTERA and some medicines may interact with each other and cause serious side effects.

Your doctor will decide whether STRATTERA can be taken with other medicines.

Especially tell your doctor if you or your child takes:

- asthma medicines
- anti-depression medicines including MAOIs
- blood pressure medicines
- cold or allergy medicines that contain decongestants

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.

Do not start any new medicine while taking STRATTERA without talking to your doctor first.

How should STRATTERA be taken?

- **Take STRATTERA exactly as prescribed. STRATTERA comes in different dose strength capsules.** Your doctor may adjust the dose until it is right for you or your child.
- **Do not chew, crush, or open the capsules.** Swallow STRATTERA capsules whole with water or other liquids. Tell your doctor if you or your child cannot swallow STRATTERA whole. A different medicine may need to be prescribed.
- Avoid touching a broken STRATTERA capsule. Wash hands and surfaces that touched an open STRATTERA capsule. If any of the powder gets in your eyes or your child's eyes, rinse them with water right away and call your doctor.
- STRATTERA can be taken with or without food.
- STRATTERA is usually taken once or twice a day. Take STRATTERA at the same time each day to help you remember. If you miss a dose of STRATTERA, take it as soon as you remember that day. If you miss a day of STRATTERA, do not double your dose the next day. Just skip the day you missed.
- From time to time, your doctor may stop STRATTERA treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking STRATTERA. Children should have their height and weight checked often while taking STRATTERA. STRATTERA treatment may be stopped if a problem is found during these check-ups.
- **If you or your child takes too much STRATTERA or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of STRATTERA?

See **"What is the most important information I should know about STRATTERA?"** for information on reported suicidal thoughts and actions, other mental problems, severe liver damage, and heart problems.

Other serious side effects include:

- serious allergic reactions (call your doctor if you see swelling, hives, or experience other allergic reactions)
- slowing of growth (height and weight) in children
- problems passing urine including:

- trouble starting or keeping a urine stream
- cannot fully empty the bladder

Common side effects in children and teenagers include:

- upset stomach
- decreased appetite
- nausea or vomiting
- dizziness
- tiredness
- mood swings

Common side effects in adults include:

- constipation
- dry mouth
- nausea
- decreased appetite
- dizziness
- trouble sleeping
- sexual side effects
- menstrual cramps
- problems passing urine

Other information for children, teenagers, and adults:

- Erections that won't go away (priapism) have occurred rarely during treatment with STRATTERA. If you have an erection that lasts more than 4 hours, seek medical help right away. Because of the potential for lasting damage, including the potential inability to have erections, priapism should be evaluated by a doctor immediately.
- STRATTERA may affect your ability or your child's ability to drive or operate heavy machinery. Be careful until you know how STRATTERA affects you or your child.
- Talk to your doctor if you or your child has side effects that are bothersome or do not go away.

This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information.

How should I store STRATTERA?

- Store STRATTERA in a safe place at room temperature, 59 to 86°F (15 to 30°C).
- **Keep STRATTERA and all medicines out of the reach of children.**

General information about STRATTERA

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

This Medication Guide summarizes the most important information about STRATTERA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about STRATTERA that was written for healthcare professionals. For more information about STRATTERA call 1-800-Lilly-Rx (1-800-545-5979) or visit www.strattera.com.

What are the ingredients in STRATTERA?

Active ingredient: atomoxetine hydrochloride.

Inactive ingredients: pregelatinized starch, dimethicone, gelatin, sodium lauryl sulfate, FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide, red iron oxide, and edible black ink.

Nardil® is the register trademark of Pfizer, Inc.
Parnate® is a registered trademark of GlaxoSmithKline.
Emsam® is a trademark of Somerset Pharmaceuticals, Inc.

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