PRODUCT MONOGRAPH

Pr STRATTERA®

(atomoxetine capsules)

10, 18, 25, 40, 60, 80 and 100 mg

Selective Norepinephrine Reuptake Inhibitor
for Attention-Deficit/Hyperactivity Disorder (ADHD)

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Date of Revision:
October 1, 2015

Submission Control № 184870

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STRATTERA®
(atomoxetine capsules)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Oral	10, 18, 25, 40, 60, 80 or 100 mg capsules	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, red iron oxide, titanium dioxide.

INDICATIONS AND CLINICAL USE

STRATTERA (atomoxetine hydrochloride) is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children 6 years of age and over, adolescents, and adults.

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, and 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.

Pediatrics (<6 years of age)

The safety and efficacy of STRATTERA in pediatric patients less than 6 years of age have not been established.

CONTRAINDICATIONS

- *Hypersensitivity:* STRATTERA (atomoxetine hydrochloride) is contraindicated in patients known to be hypersensitive to atomoxetine or other constituents of the product (*see* WARNINGS).
- *Monoamine Oxidase Inhibitors:* STRATTERA should not be taken with monoamine oxidase inhibitors (MAOI), or within 2 weeks after discontinuing MAOI. Treatment with 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 MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity.
- *Pheochromocytoma:* STRATTERA should not be used in patients with pheochromocytoma or a history of pheochromocytoma. Serious reactions, including elevated blood pressure and tachyarrhythmia, have been reported in patients with pheochromocytoma or a history of pheochromocytoma who received STRATTERA.
- *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.
- Symptomatic cardiovascular disease.
- *Severe Cardiovascular Disorders:* STRATTERA should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or heart rate that could be clinically important.

- Moderate to severe hypertension.
- Advanced arteriosclerosis.
- Uncontrolled hyperthyroidism.

WARNINGS AND PRECAUTIONS

POTENTIAL ASSOCIATION WITH THE OCCURRENCE OF BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM

- ***Pediatric Placebo-Controlled Clinical Trial Data:*** An increased risk over placebo for suicide-related events in children and adolescents taking STRATTERA, was identified in a pooled analysis of placebo-controlled trials of 6-18 weeks duration. Of 1357 patients who received STRATTERA, 5 (0.37%) had reports of **suicidal ideation** compared to 0% of 851 patients who received placebo. In addition, one **suicide attempt** (overdose) was identified, which occurred in a STRATTERA patient. No completed suicides occurred during these trials. (*See also* WARNINGS AND PRECAUTIONS, Special Populations, *Pediatrics, 6-18 years of age*).

- ***Post-Marketing Data:*** There have been very rare reports of suicidal ideation, suicidal attempts, suicidal depression and completed suicides in children, adolescents and adults (*see* ADVERSE REACTIONS, Post-Market Adverse Drug Reactions, Tables 8 and 9).

  ADHD and its related co-morbidities may be associated with increased risk of suicidal ideation and/or behaviour. Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type of emotional and behavioural changes, and clinical worsening.

  Families and caregivers of pediatric patients being treated with STRATTERA should be alerted about the need to monitor patients for the emergence of agitation, anxiety, panic attacks, hostility, irritability, hypomania or mania, unusual changes in behaviour, and other symptoms, as well as the emergence of suicidality particularly after starting treatment or changing the dose. Such symptoms should be reported immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

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. 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.

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 occur with atomoxetine use 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.

Pre-Existing Psychosis:

Administration of medications for ADHD may also exacerbate symptoms of behaviour disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Severe Liver Injury

Post-marketing reports indicate that STRATTERA (atomoxetine) can cause severe liver injury in rare cases, including acute liver failure. Although no evidence of liver injury was detected in clinical trials of about 6000 patients, there have been rare cases in postmarketing experience of clinically significant liver injury that were considered probably or possibly related to STRATTERA. 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 likely caused the liver injury. This patient recovered from his liver injury, and did not require a liver transplant. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. One case of hepatic failure leading to a liver transplant has been reported in a child taking atomoxetine. Because of probable under-reporting, it is impossible to provide an accurate estimate of the true incidence of these events. Severe liver injury due to any drug may potentially 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* CONSUMER INFORMATION).

Allergic Events

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

Effects on Growth

Growth and development should be monitored during treatment with atomoxetine. Patients requiring long-term therapy should be monitored and consideration should be given to dose reduction or interrupting therapy in patients who are not growing or gaining weight satisfactorily.

Associated with decreased appetite, some patients experienced growth retardation early in therapy in terms of both weight and height gain. On average, after an initial decrease in weight and height gain, patients treated with atomoxetine recovered to mean weight and height as predicted by group baseline data over the long-term treatment.

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 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 gained 19.4 cm on average, 0.4 cm less than predicted by their baseline data.

Cardiovascular

Pre existing Cardiovascular Conditions

STRATTERA can increase heart rate and blood pressure. It is recommended that heart rate and blood pressure be measured before treatment is started, after the dose is increased or decreased, and periodically during treatment to detect possible clinically important increases, particularly during the first few months of therapy.

STRATTERA should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease (*see* CONTRAINDICATIONS and ADVERSE REACTIONS).

In addition, STRATTERA should be used with caution in patients with congenital long QT syndrome, acquired long QT syndrome (for example, due to concomitant use of a drug that may prolong the QT), or a family history of QT prolongation. Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with STRATTERA and monitored for new conditions of the heart or brain during the course of treatment.

Orthostatic hypotension has been reported in subjects taking STRATTERA. In short-term child- and adolescent-controlled trials, 5.2% (34/657) of STRATTERA-treated subjects experienced symptoms of postural hypotension compared with 2.0% (8/408) of placebo-treated subjects. STRATTERA should be used with caution in any condition that may predispose patients to hypotension, or conditions associated with abrupt heart rate or blood pressure changes.

The increase in blood pressure and heart rate observed during treatment with STRATTERA during placebo-controlled clinical trials for pediatric patients and adults with ADHD are shown in Tables 1 and 2, respectively.

Table 1. Proportion of pediatric ADHD patients treated with STRATTERA (any dose) or placebo, in whom a given increase in diastolic and systolic blood pressure and heart rate was observed during acute placebo-controlled trials.

Parameter (unit)	Change from baseline (limit of interest)	Percent of ADHD pediatric patients (%)			
		Time observed			
		Maximum (change at any post-baseline visit)		Endpoint (change at the last visit)	
		STRATTERA N = 2287	Placebo N = 1334	STRATTERA N = 2287	Placebo N = 1334
Diastolic BP (mm Hg)	5 10 20	63 42 10	54 33 7	39 22 4	30 15 2
Systolic BP (mm Hg)	5 10 20	60 42 12	55 36 9	36 22 5	32 17 3
Heart rate (beats/min)	10 20 40	49 23 2	36 11 1	31 12 1	18 4 0

Table 2. Proportion of adult ADHD patients treated with STRATTERA (any dose) or placebo, in whom a given increase in diastolic and systolic blood pressure and heart rate was observed during long-term placebo-controlled trials.

Parameter (unit)	Change from baseline (limit of interest)	Percent of ADHD adult patients (%)			
		Time observed			
		Maximum (change at any post-baseline visit)		Endpoint (change at the last visit)	
		STRATTERA N = 499	Placebo N = 1334	STRATTERA N = 499	Placebo N = 1334
Diastolic BP (mm Hg)	5 10 20	53 31 4	49 23 2	31 15 2	24 10 1
Systolic BP (mm Hg)	5 10 20	59 37 11	56 38 8	33 20 4	25 12 3
Heart rate (beats/min)	10 20 40	57 23 1	38 11 0	30 8 0	18 3 0

The overall increase in blood pressure and heart rate observed during treatment with STRATTERA during controlled and uncontrolled clinical trials for pediatric patients with ADHD are shown in Table 3.

Table 3. Proportion of overall pediatric ADHD patients treated with STRATTERA (any dose), in whom a given increase in diastolic and systolic blood pressure and heart rate was observed during controlled and uncontrolled clinical trials.

Parameter (unit)	Change from baseline (limit of interest)	STRATTERA N = 8417 Percent of ADHD pediatric patients (%)	
		Time observed	
		Maximum (change at any post-baseline visit)	Endpoint (change at the last visit)
Diastolic BP (mm Hg)	5 10 20	74 56 18	41 24 5
Systolic BP (mm Hg)	5 10 20	73 57 23	42 27 8
Heart rate (beats/min)	10 20 40	64 39 5	31 12 1

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 as well as in some patients *without* structural 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.

General

Children: Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: *a)* are involved in strenuous exercise or activities, *b)* use stimulants,

or *c)* have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation. Patients who are considered to need extended treatment with STRATTERA should undergo periodic evaluation of their cardiovascular status (*see* DOSAGE AND ADMINISTRATION).

Genitourinary

Effects on urine outflow from the bladder: In adult ADHD controlled trials, the rates of urinary retention and urinary hesitation were increased among atomoxetine subjects compared with placebo subjects. A complaint of urinary retention or urinary hesitancy should be considered potentially related to atomoxetine.

Priapism: Rare postmarketing cases of priapism, defined as painful and non-painful 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.

Vascular

Peripheral Vasculopathy, Including Raynaud's Phenomenon

Medications used to treat ADHD, including stimulants and non-stimulant-(STRATTERA), are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD medications. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

Special Populations

Pregnant Women: 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. The effect of STRATTERA on labour and delivery in humans is unknown.

The extent of exposure in pregnancy during clinical trials was very limited.

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.

Pediatrics (< 6 years of age): The safety and efficacy of STRATTERA in pediatric patients less than 6 years of age have not been established.

Pediatrics (6–18 years of age):

Risk of Suicide-Related Behaviours and Ideation in Children (*see also* WARNINGS AND PRECAUTIONS – POTENTIAL ASSOCIATION WITH THE OCCURRENCE OF BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM).

Pediatric Placebo-Controlled Clinical Trial Data: An increased risk over placebo, for suicide-related events in children and adolescents taking STRATTERA was identified in a combined analysis of 12 short-term (6 – 18 weeks) placebo-controlled trials (11 in ADHD and 1 in enuresis). Of 1357 patients who received STRATTERA, 5 (0.37%) had reports of **suicidal ideation** compared to 0% of 851 patients who received placebo. In addition, one **suicide attempt** (overdose) was identified which occurred in a STRATTERA patient. These 6 events occurred in STRATTERA patients 7 to 12 years of age who were male. There were no events in older adolescents, who comprised about 25 percent of the study population. Time to onset ranged from 9 to 32 days, and doses ranged from 0.48 to 1.40 mg/kg/day. A similar analysis in adult patients treated with STRATTERA for either ADHD or major depressive disorder (MDD) found no increased risk over placebo of suicidal ideation or behaviour with the use of STRATTERA.

Not included in these numerators were 6 cases (3 in the STRATTERA arms and 3 in the placebo arms) of non-fatal potentially self-injurious actions where the intent is unknown, including burns and taking more than one dose of medication at a time.

Post Marketing Data: There have been very rare reports of suicidal ideation, suicidal attempts, suicidal depression and completed suicides in children and adolescents (*see* ADVERSE REACTIONS, Post-Market Adverse Drug Reactions, Tables 8 and 9).

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring for agitation-type of emotional and behavioural changes, and clinical worsening.

Irritability and Mood Swings: Clinical Trial Data

Clinical trial data in children and adolescents show higher rates than placebo for irritability, mood swings, aggression, crying and tearfulness (*see* ADVERSE REACTIONS, Tables 4 and 5). The relationship, if any, between these events and suicide-related behaviours in children and adolescents with ADHD is unclear.

Aggressive Behaviour or Hostility

Patients beginning treatment for ADHD should be monitored for the appearance of, or worsening of, aggressive behaviour or hostility.

Caregivers/patients should be instructed to call their doctor as soon as possible should they notice an increase in aggression or hostility.

Aggressive behaviour or hostility has been observed in patients with ADHD, and has been reported with some medications indicated for the treatment of ADHD.

Although there is no conclusive evidence that atomoxetine causes aggressive behaviour or hostility, this was observed more frequently in clinical trials among children, adolescents and adults treated with atomoxetine compared to placebo (risk ratios varying from 1.03 in children and adolescents to 1.38 in adults – not statistically significant).

Geriatrics (> 65 years of age): The safety and efficacy of STRATTERA in geriatric patients have not been established.

Monitoring and 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).

ADVERSE REACTIONS

STRATTERA was administered to 3262 children or adolescent patients with ADHD and 471 adults with ADHD in clinical studies. During the ADHD clinical trials, 1409 patients (1236 pediatric and 173 adults) were treated for longer than 1 year and 1940 patients (1704 pediatric and 236 adults) 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, 4.1% (27/661) of atomoxetine subjects and 1.2% (5/410) placebo subjects discontinued for adverse events. For all studies, (including open-label and long-term studies), 5.8% of extensive metabolizer (EM) patients and 8.9% of poor metabolizer (PM) patients discontinued because of an adverse event. Among STRATTERA-treated patients, somnolence (0.8%, N = 5); aggression (0.5%, N = 3); irritability

(0.5%, N = 3); vomiting (0.5%, N = 3) and abdominal pain (0.3%, N = 2) were the reasons for discontinuation reported by more than 1 patient.

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 4 for all acute placebo-controlled trials. Results were similar in the BID trials and QD trials except as shown in Table 5, 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: appetite decreased, dizziness, dyspepsia, fatigue and/or lethargy, irritability, nausea, somnolence, and vomiting (*see* Table 4). Additional data on blood pressure and heart rate from ADHD clinical trials is shown in Tables 1 - 3.

Table 4: Common Treatment-Emergent Adverse Events Reported in STRATTERA Placebo-Controlled Clinical Trials in Children and Adolescents with ADHD[a]

Adverse Event	Percentage of Patients Reporting Events	
	STRATTERA (N = 657)	**Placebo (N = 408)**
Gastrointestinal Disorders		
Abdominal pain upper	18	13
Dyspepsia	5	1
Nausea	9	6
Vomiting	11	6
General Disorders		
Fatigue and/or Lethargy	8	4
Investigations		
Weight decreased	2	0
Metabolism and Nutritional Disorders		
Anorexia	2	<1
Appetite decreased	16	6
Nervous System Disorders		
Dizziness	5	2
Headache	21	20
Somnolence	10	4
Psychiatric Disorders		
Irritability	7	4
Mood swings	2	<1
Respiratory Disorders		
Rhinorrhea	4	2
Skin and Subcutaneous Tissue Disorders		
Rash	3	1

[a] 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: aggression, blood pressure increased, early morning awakening, flushing, mydriasis, sinus tachycardia, crying, tearfulness, suicidal ideation. The following events were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: cough, diarrhea, insomnia, nasal congestion, nasopharyngitis, pharyngitis, pyrexia, upper respiratory tract infection.

Table 5: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 9 weeks) Child and Adolescent Trials[a]

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 = 317)	Placebo (N = 201)
Gastrointestinal Disorders				
Abdominal pain	1	<1	3	<1
Abdominal pain upper	21	16	15	8
Constipation	3	1	<1	0
Dyspepsia	4	2	6	<1
Nausea	7	8	10	4
Vomiting	12	9	11	2
General Disorders				
Fatigue and/or Lethargy	5	5	11	2
Pyrexia	5	7	6	4
Infections and Infestations				
Ear infection	3	1	1	<1
Influenza	3	1	1	<1
Pharyngitis streptococcal	2	<1	<1	<1
Investigations				
Weight decreased	3	0	2	0
Metabolism and Nutritional Disorders				
Anorexia	2	<1	3	<1
Appetite decreased	13	6	19	5
Nervous System Disorders				
Dizziness	6	3	4	<1
Headache	28	25	14	15
Sedation	1	1	3	1
Somnolence	7	5	14	3
Psychiatric Disorders				
Aggression	1	1	3	<1
Crying	2	1	1	0
Mood swings	2	0	3	1
Irritability	8	5	6	3
Respiratory Disorders				
Cough	11	7	6	9
Rhinorrhoea	4	3	3	1
Skin and Subcutaneous Tissue Disorders				
Rash	4	1	2	1

[a] Events reported by at least 2% of patients treated with atomoxetine, and greater than placebo in either BID or QD trials.

The following adverse events occurred in child and adolescent patients, and were obtained from ongoing clinical trials:

Common: depression (including major depression, depressive symptoms, depressed mood, and dysphoria), insomnia (including initial insomnia, middle insomnia, and terminal insomnia), and pruritus.
Uncommon: asthenia, palpitations, sinus tachycardia, syncope (includes syncope vasovagal), and tremor.

The following adverse events occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 EM patients: appetite decreased (24% of PMs, 17% of EMs); insomnia and middle insomnia (14% of PMs, 7% of EMs); weight decreased (7% of PMs, 4% of EMs); constipation (7% of PMs, 4% of EMs); sedation (4% of PMs, 2% of EMs); depression and/or depressed mood (5% of PMs, 3% of EMs); abrasion (4% of PMs, 2% of EMs); tremor (5% of PMs, 1% of EMs); early morning awakening (2% of PMs, 1% of EMs); enuresis (3% of PMs, 1% of EMs); pruritus (3% of PMs, 1% of EMs); mydriasis (2% of PMs, 1% of EMs); conjunctivitis (3% of PMs, 1% of EMs); syncope (2% of PMs, 1% of EMs); animal bite (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.

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 6.

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, erectile disturbance, urinary hesitation and/or urinary retention and/or difficulty in micturition, and dysmenorrhea (*see* Table 6). Additional data on blood pressure and heart rate from ADHD clinical trials is shown in Tables 1 - 3.

Table 6: Common Treatment-Emergent Adverse Events Associated with the Use of STRATTERA in Acute (up to 10 weeks) Adult Trials

	Percentage of Patients Reporting Event	
Adverse Event[a]	**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		
Fatigue and/or Lethargy	7	4
Pyrexia	3	2
Chills	3	1
Infections		
Sinusitis	6	4
Investigations		
Weight decreased	2	1
Metabolism and Nutritional Disorders		
Appetite decreased	10	3
Musculoskeletal Disorders		
Myalgia	3	2
Nervous System Disorders		
Dizziness	6	2
Headache	17	17
Insomnia and/or middle insomnia	17	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 dysuria	8	0
Reproductive System and Breast Disorders		
Dysmenorrhea[c]	7	3
Ejaculation failure[b] and/or ejaculation disorder[b]	5	2
Erectile dysfunction[b]	7	1
Impotence[b]	3	0
Menses delayed [c]	2	1
Menstrual disorder[c]	3	2

Menstruation irregular[c]	2	0
Orgasm abnormal	2	1
Prostatitis[b]	3	0
Skin and Subcutaneous Tissue Disorders		
Rash	2	1
Sweating increased	4	1
Vascular Disorders		
Hot flushes	3	1

[a] 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.

[b] Based on total number of males (STRATTERA, N = 174; placebo, N = 172).

[c] Based on total number of females (STRATTERA, N = 95; placebo, N = 91).

The following adverse events occurred in adult patients, and were obtained from ongoing clinical trials:

Common: agitation, asthenia, dysgeusia, feeling jittery, flushing, hyperhidrosis, pollakiuria, somnolence (including sedation), testicular pain, thirst, and tremor.

Uncommon: feeling cold, muscle spasms, pruritus, restlessness, urticaria, and vision blurred.

The following adverse events occurred in at least 2% of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 extensive metaboliser (EM) patients: vision blurred (3.9% of PMs, 1.3% of EMs); dry mouth (34.5% of PMs, 17.4% of EMs); constipation (11.3% of PMs, 6.7% EMs); feeling jittery (4.9% PMs, 1.9% of EMs); decreased appetite (23.2% of PMs, 14.7% of EMs); tremor (5.4% of PMs, 1.2% of EMs); insomnia (19.2% of PMs, 11.3% of EMs); sleep disorder (6.9% of PMs, 3.4% of EMs); middle insomnia (5.4% of PMs, 2.7% of EMs); terminal insomnia (3.0% of PMs, 0.9% of EMs); urinary retention (5.9% of PMs, 1.2% of EMs); erectile dysfunction (20.9% of PMs, 8.9% of EMs); ejaculation disorder (6.1% of PMs, 2.2% of EMs); hyperhidrosis (14.8% of PMs, 6.8% of EMs); peripheral coldness (3.0% of PMs, 0.5% or EMs).

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 labelling 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 7

	STRATTERA	**Placebo**
Erectile dysfunction[a]	7%	1%
Libido decreased	6%	2%
Ejaculation failure[a] and/or ejaculation disorder[a]	5%	2%

Impotence[a]	3%	0%
Orgasm abnormal	2%	1%

[a] 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.

Post-Market Adverse Drug Reactions

During the first 5 years of post-market experience, it is estimated that over 5 million patients have been treated with STRATTERA, for 1,715,000 patient-years of therapy.

Tables 8 and 9 are based on post-market spontaneous adverse event reports. The percentages shown are calculated by dividing the number of adverse events reported to the company by the estimated number of patients exposed to the drug during the same time period. The causal relationship between STRATTERA and the emergence of these events has not been established.

Table 8: STRATTERA Post-Market Spontaneous Adverse Event Reports in Children and Adolescents with ADHD.

Adverse Event	Frequency			
	≥1%	<1% and ≥0.1%	<0.1% and ≥0.01%	<0.01%
Cardiac Disorders				
Palpitations				X
Sinus tachycardia			X	
Electrocardiogram QT prolonged[a]				X
Eye Disorders				
Mydriasis			X	
Gastrointestinal Disorders				
Abdominal pain			X	
Dyspepsia				X
Hepatobiliary effects				X
Liver Function Tests abnormal				X
Nausea			X	
Vomiting			X	
General Disorders				
Lethargy				X
Sudden death				X
Injury				
Overdose				X
Investigations				
Weight decreased			X	
Metabolism and Nutritional Disorders				
Anorexia			X	
Appetite decreased			X	

Adverse Event	Frequency			
	≥1%	<1% and ≥0.1%	<0.1% and ≥0.01%	<0.01%
Nervous System Disorders				
Dizziness			X	
Hypoaesthesia				X
Paraesthesia				X
Seizure[b]			X	
Somnolence		X		
Syncope[c]				X
Tics				X
Psychiatric Disorders				
Aggression/Hostility			X	
Anxiety			X	
Depression and depressed mood			X	
Early morning awakening				X
Irritability			X	
Mood swings			X	
Sensory disturbances including hallucinations				X
Suicidality[d]				X
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis				X
Pruritis				X
Rash			X	
Urogenital Disorders				
Male genital pain				X
Painful or prolonged penile erection				X
Urinary hesitation				X
Urinary retention				X
Vascular Disorders				
Peripheral vascular instability, e.g., Raynaud's phenomenon				X
Potential to exacerbate pre-existing Raynaud's phenomenon				X

[a] These spontaneously reported cases are not well documented, and the method of correction is unknown.
[b] Frequency of seizures reported = 0.01%
[c] Includes reports of 'loss of consciousness'.
[d] Includes reports of completed suicide, suicidal ideation, suicide attempt and suicidal depression.

Table 9: STRATTERA Post-Market Spontaneous Adverse Event Reports in Adult Patients with ADHD.

Adverse Event	Frequency			
	≥1%	<1% and ≥0.1%	<0.1% and ≥0.01%	<0.01%
Cardiac Disorders				
Palpitations				X
Tachycardia			X	
Electrocardiogram QT prolonged[a]				X
Gastrointestinal Disorders				
Abdominal pain			X	
Constipation			X	
Dry mouth			X	
Dyspepsia				X
Flatulence				X
Hepatobiliary effects				X
Liver Function Tests abnormal				X
Nausea			X	
General Disorders				
Fatigue			X	
Lethargy				X
Chills			X	
Sudden death				X
Injury				
Overdose				X
Investigations				
Weight decreased			X	
Metabolism and Nutritional Disorders				
Appetite decreased			X	
Nervous System Disorders				
Dizziness			X	
Hypoaesthesia				X
Insomnia			X	
Middle insomnia				X
Seizure[b]				X
Sinus headache				X
Syncope[c]				X
Tics				X
Psychiatric Disorders				
Anxiety			X	
Depression and depressed mood			X	
Early morning awakening				X
Libido decreased				X
Sleep disorder				X
Suicidality[d]				X
Renal and Urinary Disorders				
Difficulty in micturition			X	
Urinary hesitation			X	

Adverse Event	Frequency			
	≥1%	<1% and ≥0.1%	<0.1% and ≥0.01%	<0.01%
Urinary retention			X	
Reproductive System and Breast Disorders				
Dysmenorrhea				X
Ejaculation disorder			X	
Ejaculation failure				X
Erectile dysfunction			X	
Male genital pain				X
Menstruation irregular				X
Orgasm abnormal				X
Prostatitis				X
Skin and Subcutaneous Tissue Disorders				
Dermatitis				X
Hyperhidrosis				X
Urogenital Disorders				
Male genital pain				X
Painful or prolonged penile erection				X
Vascular Disorders				
Hot flushes			X	
Peripheral coldness				X
Peripheral vascular instability, e.g., Raynaud's phenomenon				X
Potential to exacerbate pre-existing Raynaud's phenomenon				X

[a] These spontaneously reported cases are not well documented, and the method of correction is unknown.
[b] Frequency of seizures reported = 0.0035%
[c] Includes reports of 'loss of consciousness'.
[d] Includes reports of completed suicide, suicidal ideation, suicide attempt, and suicidal depression.

In post-market experience, serious skin reactions, hepatic failure and severe hepatic injury were reported at a spontaneous reporting rate less than 0.001%.

DRUG ABUSE AND DEPENDENCE

STRATTERA is not a controlled substance.

STRATTERA is not a stimulant drug. 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 trials data in over 4000 children, adolescents, and adults with ADHD 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.

In preclinical studies, atomoxetine did not show a behavioural profile or stimulant properties associated with drugs that have abuse liability.

~~fder~~DRUG INTERACTIONS

Overview

STRATTERA (atomoxetine hydrochloride) is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. In extensive metabolizers (EMs), inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in poor metabolizers (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.

STRATTERA should be used with caution if used concomitantly with other drugs that increase QT interval or disturb electrolyte balance or inhibit CYP2D6.

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

Atomoxetine did not cause clinically significant inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

Drugs that affect norepinephrine should be used cautiously when co-administered with STRATTERA because of the potential for additive or synergistic pharmacological effects.

Drug-Drug Interactions

Table 10. Established or Potential Drug-Drug Interactions with STRATTERA

Drug	Ref	Effect	Clinical comment
MAO Inhibitors	T	There have been reports of serious, sometimes fatal, reactions when MAO Inhibitors are given concurrently or in close proximity to other drugs that affect brain monoamine concentrations.	See CONTRAINDICATIONS
Desipramine	CT	Coadministration of STRATTERA with desipramine did not alter the pharmacokinetics of desipramine.	Because desipramine has noradrenergic effects, it should not be used in combination with STRATTERA.
Fluoxetine, Paroxetine	CT	Coadministration of selective inhibitors of CYP2D6 may increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metabolizer patients.	Slower titration of STRATTERA may be necessary in those patients who are also taking fluoxetine, paroxetine or other CYP2D6 inhibitor drugs (*see* Dosage and Administration, Special Populations).
Salbutamol or other β-adrenergic receptor agonists	CT	There was no significant interaction between salbutamol and atomoxetine	STRATTERA may be used in combination with inhaled β2 agonists, e.g., salbutamol, but should be used with caution in patients being treated with systemically administered (oral or intravenous) β2 agonists, including salbutamol.

Drug	Ref	Effect	Clinical comment
Anti-hypertensive drugs and Pressor Agents	T	Possible effects on blood pressure.	STRATTERA should be used with caution in patients being treated with anti-hypertensive drugs and pressor agents, or other drugs that increase blood pressure.
Methylphenidate	CT	Co-administration of methylphenidate with STRATTERA did not increase cardiovascular effects beyond those seen with methylphenidate administration alone.	
Midazolam	CT	Co-administration of STRATTERA with midazolam resulted in small increases in midazolam plasma concentrations.	No dosage adjustment required.
Drugs highly bound to plasma protein	In vitro	Atomoxetine did not affect the binding of *warfarin, acetylsalicylic acid, phenytoin, or diazepam* to human albumin in-vitro. Similarly, these compounds did not affect the binding of atomoxetine to human albumin.	No dosage adjustment required.
Drugs affecting gastric pH	CT	Drugs that elevate gastric pH *(magnesium hydroxide/aluminum hydroxide, omeprazole)* had no effect on STRATTERA bioavailability.	No dosage adjustment required.

Legend: CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

STRATTERA may be taken with or without food.

Drug-Lifestyle Interactions

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

DOSAGE AND ADMINISTRATION

Dosing Considerations

STRATTERA should be administered starting at the lowest possible dose. Dosage should then be individually and slowly adjusted to the lowest effective dose, since individual patient response to STRATTERA varies widely.

STRATTERA should not be used in patients with symptomatic cardiovascular disease and should not generally be used in patients with known structural cardiac abnormalities (*see* CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Children: Theoretically there exists a pharmacological potential for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse

cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who: *a)* are involved in strenuous exercise or activities, *b)* use stimulants, or *c)* have a family history of sudden/cardiac death. Prior to the initiation of treatment with sympathomimetic medications, a personal and family history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam should be obtained to assess for the presence of cardiac disease. In patients with relevant risk factors and based on the clinician's judgment, further cardiovascular evaluation may be considered (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during ADHD treatment should undergo a prompt cardiac evaluation. Patients who are considered to need extended treatment with STRATTERA should undergo periodic evaluation of their cardiovascular status. (*See* WARNINGS AND PRECAUTIONS).

Rigorous clinical monitoring for suicidal ideation or other indicators of potential for suicidal behaviour is advised in patients of all ages. This includes monitoring of agitation-type emotional and behavioural changes, and clinical worsening (*see* WARNINGS AND PRECAUTIONS – POTENTIAL ASSOCIATION WITH THE OCCURRENCE OF BEHAVIOURAL AND EMOTIONAL CHANGES, INCLUDING SELF-HARM)**.**

STRATTERA (atomoxetine hydrochloride) is intended for oral administration and may be taken with or without food, either as a single daily dose in the morning or as divided doses in the morning and late afternoon/early evening.

Initial improvement of ADHD symptoms is generally observed within 1 to 4 weeks of initiating therapy.

STRATTERA did not worsen tics in pediatric patients, and may be used in patients with ADHD and comorbid motor tics or diagnosis of Tourette's Disorder. STRATTERA did not worsen anxiety in either pediatric or adult patients, and may be used in patients with ADHD and comorbid anxiety disorders. (*See* ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Patients with Concomitant Illness).

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

STRATTERA may be discontinued without tapering the dose.

Recommended Dose and Dosage Adjustment

Children (6 years and over) and Adolescents up to 70 kg Body Weight:

Do not exceed the recommended initial dose and subsequent dose escalations of STRATTERA. More rapid dose escalation may be associated with increased rates of somnolence and digestive system complaints. Do not exceed the recommended maximum total daily dose of 1.4 mg/kg or 100 mg, whichever is less. No additional benefit has been

demonstrated at doses greater than 1.2 mg/kg/day (*see* Clinical Trials). The safety of single doses over 1.8 mg/kg/day and total daily doses above 1.8 mg/kg have not been systematically evaluated, and therefore should not be administered because of potential side-effects (*see* ACTION AND CLINICAL PHARMACOLOGY – Cardiovascular Safety, OVERDOSAGE and DETAILED PHARMACOLOGY [Safety Pharmacology, Cardiac Function and Pharmacokinetics]).

STRATTERA should be initiated at a total daily dose of approximately 0.5 mg/kg (Step 1) for 7 to 14 days. Based on tolerability, the dose should be successively increased to approximately 0.8 mg/kg/day (Step 2) for 7 to 14 days, and then to approximately 1.2 mg/kg/day (Step 3). Table 11 below provides for each titration step the corresponding daily STRATTERA dose according to body weight. After a minimum of 30 days, the maintenance dose should be reassessed and adjusted according to clinical response.

The total daily dose in children and adolescents up to 70 kg should not exceed 1.4 mg/kg or 100 mg, whichever is less.

As the lowest available capsule strength is 10 mg, the child should weigh at least 20 kg at the time of initiation of therapy. Only whole capsules should be administered.

Table 11. Daily STRATTERA Dose for Each Titration Step as per Body Weight, in Children and Adolescents up to 70 kg Body Weight

Body Weight	Step 1 (approx. 0.5 mg/kg/day)	Step 2 (approx. 0.8 mg/kg/day)	Step 3 (approx. 1.2 mg/kg/day)	Maximum Dose
20-29 kg	10 mg/day	18 mg/day	25 mg/day	1.4 mg/kg/day or 100 mg/day (whichever is less)
30-44 kg	18 mg/day	25 mg/day	40 mg/day	
45-64 kg	25 mg/day	40 mg/day	60 mg/day	
65-70 kg	40 mg/day	60 mg/day	80 mg/day	

Children and Adolescents over 70 kg Body Weight, and Adults

Do not exceed the recommended initial dose and subsequent dose escalations of STRATTERA. Do not exceed the recommended maximum total daily dose of 100 mg. The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated and therefore should not be administered because of potential side effects (see ACTION AND CLINICAL PHARMACOLOGY – Cardiovascular Safety, OVERDOSAGE and DETAILED PHARMACOLOGY [Safety Pharmacology, Cardiac Function and Pharmacokinetics]).

STRATTERA should be initiated at a total daily dose of 40 mg/day (Step 1) for 7 to 14 days. Based on tolerability, the dose should be successively increased to 60 mg/day (Step 2) for 7 to 14 days, and then to 80 mg/day (Step 3). After 2 to 4 additional weeks, the total daily dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response.

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

Dosage Adjustment for Special Populations

Hepatic Impaired

Atomoxetine clearance may be reduced in ADHD patients with hepatic impairment. For patients with moderate hepatic impairment (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose. For patients with severe hepatic impairment (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of the normal dose.

Renal Impaired

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 usual dosing regimen. Atomoxetine may exacerbate hypertension in patients with end stage renal disease.

Dosing adjustment for use with a strong CYP2D6 inhibitor

In children (≥ 6 years old) 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 next dose level if symptoms fail to improve after 14 days and the previous dose is well tolerated.

In children (≥ 6 years old) 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 next dose level if symptoms fail to improve after 14 days and the previous dose is well tolerated.

Maintenance/Extended Treatment

Pharmacological treatment of ADHD may be needed for extended periods. The efficacy of STRATTERA in maintaining symptom response during long-term treatment in children and adolescents was studied in an 18-month trial (3 months of acute open-label treatment followed by up to 15 months of placebo-controlled maintenance treatment). The results from this study suggest that atomoxetine may be beneficial in the long-term treatment of ADHD. Too few patients completed the study to permit an adequate assessment of the long-term safety profile of STRATTERA in this study. The long-term safety of STRATTERA has been demonstrated in double-blind and open-label clinical trials of at least 24 months. 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* INDICATIONS AND CLINICAL USE).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

During post-marketing, there have been reports of non-fatal, acute and chronic overdoses of

STRATTERA alone. The most commonly reported symptoms accompanying acute and chronic overdoses were somnolence, dizziness, tremor, abnormal behaviour, and gastrointestinal symptoms. Hyperactivity and agitation have also been reported. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g., mydriasis, tachycardia, dry mouth, blood pressure increased) have also been observed. Most events were mild to moderate. In some cases of overdose with STRATTERA, seizures have also been reported, including myoclonus of the extremities. Less commonly, there have been reports of QT prolongation and mental changes, including disorientation and hallucinations.

There were no deaths involving overdose of STRATTERA alone. There have also been reports of fatal, acute overdoses involving a mixed ingestion of STRATTERA and at least one other drug.

In the first 18 months of market availability in the US, among the mixed overdose reports involving STRATTERA where at least one other drug was taken in overdose amounts, there were 3 deaths reported, all in adults. The largest quantity of STRATTERA alone in a single overdose was 1400 mg, taken by a 17 year old patient. He experienced chest pain and drowsiness and was treated with activated charcoal about 2 hours after the ingestion and recovered fully after an overnight hospital stay for observation.

Management of Overdose: There is no established antidote for STRATTERA overdose. Treatment has been supportive, including establishing an airway when necessary, monitoring of cardiac and vital signs, 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

STRATTERA (atomoxetine hydrochloride) is a selective norepinephrine reuptake inhibitor. Its therapeutic effect in ADHD is thought to be related to its potent inhibition of the pre-synaptic norepinephrine transporter, with minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors.

Pharmacodynamics

In ex vivo uptake and neurotransmitter depletion studies, atomoxetine was found to selectively inhibit the pre-synaptic norepinephrine transporter without directly affecting the serotonin or dopamine transporters. Atomoxetine has minimal affinity for other receptor systems. Atomoxetine is primarily oxidized to 4-hydroxyatomoxetine, which is also a potent inhibitor of the pre-synaptic norepinephrine transporter.

Cardiovascular Safety

The safety and tolerability of gradually increasing multiple-dose regimes of atomoxetine 60 to 150 mg/day was studied in 16 healthy adults (10 EM subjects and 6 PM subjects). None of the

mean or individual $QTc_{(F)}$ intervals exceeded the upper limits of normal for each gender. The EM group had no statistically significant changes in mean $QTc_{(F)}$ interval compared to the placebo treatment. No statistically significant changes in $QTc_{(F)}$ were noted 1 hour post dose (during peak plasma concentrations) in the PM group. The PM group had a statistically significant increase in the mean $QTc_{(F)}$ interval measured at time 0 (during trough plasma concentrations) on the last day of the 60- and 75-mg atomoxetine twice-daily dosing regimens compared to the placebo. The greatest mean prolongation was about 17 msec at the 60-mg BID dose level, with the mean interval length of 417.2 msec. At the 75-mg BID atomoxetine dose level, the greatest mean prolongation was 15 msec, and the mean interval length was 414.9 msec. The 60 mg BID and 75 mg BID doses correspond to 1.4 - 2.24 mg/kg/day and 1.75 - 2.8 mg/kg/day, respectively. Baseline ECGs obtained during screening of pediatric patients for atomoxetine clinical trials were reviewed for cases of QTc prolongation. Using a correction method based on data from baseline ECGs, there were 32/3902 cases (0.8%) with $QTc_{(D)} > 450$ msec and 5/3902 cases (0.1%) with $QTc_{(D)} > 500$ msec. In a meta-analysis of ECG data from patients who received atomoxetine in pediatric clinical trials, no relationship was observed between changes from baseline to final $QTc_{(D)}$ and prescribed atomoxetine dose, or between changes from baseline to $QTc_{(D)}$ at time of expected peak exposure and prescribed atomoxetine dose.

Overall, the data do not suggest a meaningful relationship between atomoxetine plasma concentrations and the length of the QT interval corrected for heart rate in the recommended dosage range. However, since there is no requirement for a priori screening of ADHD patients for CYP2D6 metabolizer status before initiating treatment with atomoxetine, it is important that the lowest effective dose be used, so as to minimize potential cardiac side effects.

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 21.6 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 using a population approach. 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.

Atomoxetine pharmacokinetics are dose proportional within the therapeutic range; hence, administration of STRATTERA once- or twice-daily is expected to result in the same systemic exposure (AUC) over a 24-hour period. Results of efficacy analysis show that once-daily (QD) dosing with STRATTERA is efficacious in the treatment of ADHD.

STRATTERA 80 mg capsules are bioequivalent to 2 x 40 mg capsules. STRATTERA 100 mg capsules are bioequivalent to a combination of one 40 mg and one 60 mg capsule.

***Absorption*:** Atomoxetine is rapidly absorbed after oral administration, with absolute bioavailability of about 63% in extensive metabolizers (EMs) and 94% in poor metabolizers (PMs). Mean maximal plasma concentrations (C_{max}) are reached approximately 1 to 2 hours after dosing.

STRATTERA can be administered with or without food. In clinical trials with children and adolescents, administration of STRATTERA with food resulted in a 9% lower C_{max}. 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.

***Distribution*:** The steady-state volume of distribution after intravenous administration was approximately 0.85 L/kg indicating that atomoxetine distributes primarily into total body water. In children and adolescents, volume of distribution increased nearly proportionally to increases in body weight. 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*:** Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway. People with reduced activity in the CYP2D6 pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine at steady-state is approximately 10-fold higher and $C_{ss,max}$ is about 5-fold greater than for EMs.

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). In EM patients treated with potent CYP2D6 inhibitors such as fluoxetine, and paroxetine, the AUC of atomoxetine is approximately 6- to 8-fold and $C_{ss,max}$ is about 3- to 4-fold greater than with atomoxetine alone.

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

Atomoxetine did not inhibit or induce the CYP2D6 pathway.

The major oxidative metabolite formed regardless of CYP2D6 status is 4-hydroxy-atomoxetine, which is rapidly 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. In individuals that lack CYP2D6 activity (poor metabolizers), 4-hydroxyatomoxetine is formed by several other cytochrome P450 enzymes, but at a slower rate. N-Desmethyl-atomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has much less pharmacological activity than atomoxetine, and

plasma concentrations are lower (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).

Elimination: The mean elimination half-life of atomoxetine after oral administration is 5.2 hours and 21.6 hours in EM and PM subjects, respectively. 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 (less than 3%) of the STRATTERA dose is excreted as unchanged atomoxetine, indicating extensive biotransformation.

Special Populations and Conditions

Pediatrics: 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.

Geriatrics: The pharmacokinetics of atomoxetine have not been systematically evaluated in the geriatric population.

Gender: Gender did not influence atomoxetine disposition.

Race: Ethnic origin did not influence atomoxetine disposition.

Hepatic Insufficiency: Single doses of STRATTERA administered to EM subjects with moderate to severe hepatic insufficiency (Child-Pugh Class B and C) resulted in increased atomoxetine exposure, reduced atomoxetine clearance, and prolonged half-life of parent drug compared with healthy subjects. Dosage adjustment is recommended for patients with moderate or severe hepatic impairment (*see* DOSAGE AND ADMINISTRATION).

Renal Insufficiency: Single doses of STRATTERA administered to EM subjects with end stage renal disease resulted in higher atomoxetine exposure (AUC) than in 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.

Genetic Polymorphism: There are two major phenotypes associated with CYP2D6: extensive metabolizers that comprise > 90% of the population, and poor metabolizers. Approximately 7% of the Caucasian population and 2% of Black population are poor metabolizers of CYP2D6.

Patients with Concomitant Illness

Pediatric Patients with ADHD and Comorbid Tics:

Study LYAS enrolled patients meeting DSM-IV criteria for ADHD and comorbid Tourette's Disorder or chronic motor tics. STRATTERA met the primary study objective of non-inferiority to placebo with respect to worsening of tics and had a beneficial effect in reducing tic severity. STRATTERA was also markedly superior to placebo in reducing symptoms of ADHD as assessed by the ADHDRS-IV-Parent:Inv Total score ($p = 0.002$).

Patients with ADHD and Comorbid Anxiety Disorder

Study LYBP: Pediatric patients (n = 176, age 8 - 17), who met DSM-IV criteria for ADHD and at least one of the anxiety disorders of separation anxiety disorder, generalized anxiety disorder or social phobia were randomized 1:1 into a 12-week double-blind, placebo-controlled trial. The statistical analysis plan specified that patients responding (i.e., > 25% reduction in Pediatric Anxiety Rating Scale (PARS) total scores) during a blinded placebo lead-in period be excluded from the primary efficacy analyses. However, all of the enrolled patients with a baseline and at least one post-baseline score were included in the remaining efficacy analyses. Initial STRATTERA dose was 0.8 mg/kg/day, with increase to a target dose of 1.2 mg/kg/day (median dose 1.3 mg/kg/day ± 0.3 mg/kg/day). STRATTERA was markedly superior to placebo in reducing symptoms of ADHD as assessed by the ADHDRS-IV-Parent: Inv Total score ($p < 0.001$) and mean PARS total score improved significantly for STRATTERA relative to placebo ($p = 0.011$). Worsening of anxiety was defined post-hoc as a 25% increase in PARS, or patient-reported anxiety as an adverse event. Based on these criteria, patients on STRATTERA did not have worsening of anxiety relative to the placebo group. Of the 158 patients who completed the double-blind placebo lead-in, 26 (16%) discontinued the study.

Study LYDQ: Adult patients (n = 442, age 18 - 65) , who met DSM-IV criteria for adult ADHD and social anxiety disorder (23% of whom also had Generalized Anxiety Disorder) were randomized into a 16-week double-blind, placebo-controlled trial. The statistical analysis plan specified that patients responding (i.e., > 25% decrease in social anxiety symptoms as measured by the Liebowitz Social Anxiety Scale) during a blinded placebo lead-in period be excluded from the primary efficacy analyses. However, all of the enrolled patients with a baseline and at least one post-baseline score were included in the remaining efficacy analyses. STRATTERA was initiated at 40 mg/day to a maximum dose of 100 mg/day (mean daily dose 83 mg/day ±19.5 mg/day). STRATTERA was markedly superior to placebo in reducing symptoms of ADHD as assessed by the Conners' Adult ADHD Rating Scale ($p < 0.001$) and mean LSAS total score improved significantly for STRATTERA relative to placebo ($p \leq 0.01$). Worsening of anxiety was defined post-hoc as a 25% increase in LSAS, or patient-reported anxiety as an adverse event. Based on these criteria, patients on STRATTERA did not have worsening of anxiety relative to the placebo group. Of the 436 patients who completed the double-blind placebo lead-in, 172 (39%) discontinued the study.

STORAGE AND STABILITY

Store at controlled room temperature, 15 to 30°C.

Strattera capsules are not intended to be opened, they should be taken whole.

DOSAGE FORMS, COMPOSITION AND PACKAGING

STRATTERA (atomoxetine hydrochloride) capsules are supplied in 10, 18, 25, 40 60, 80 and 100 mg strengths, as atomoxetine base equivalent.

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

STRATTERA 80 mg capsules are bioequivalent to 2 x 40 mg capsules. STRATTERA 100 mg capsules are bioequivalent to a combination of one 40 mg and one 60 mg capsule.

Supplied as: Blisters packages of 28 capsules.

Composition

Each capsule contains atomoxetine hydrochloride equivalent to 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg 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, red iron oxide, titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

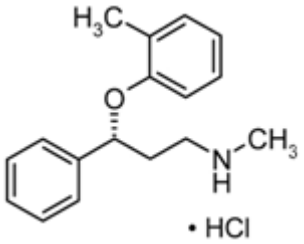
Proper Name: Atomoxetine Hydrochloride

Chemical Name: Benzenepropanamine N-methyl-gamma(2-methylphenoxy) hydrochloride,(-)

Molecular Formula: $C_{17}H_{21}NO \cdot HCl$

Molecular Weight: 291.82

Structural Formula:



Physicochemical Properties: Atomoxetine hydrochloride is a white to practically white solid, which has a solubility of 27.8 mg/mL in water. Atomoxetine hydrochloride is the *R*(-) isomer, as determined by x-ray diffraction.

pH: 4.80 (1% aqueous solution)

pKa: 10.13

Melting Point: Onset temperature 168-169 °C.

CLINICAL TRIALS

The efficacy and safety of STRATTERA for the treatment of ADHD in children, adolescents and adults (Table 12) who met the *Diagnostic and Statistical Manual 4th edition* (DSM-IV) criteria were established in 6 acute, randomized, double-blind, placebo-controlled studies. Examination of population subsets (gender, age) did not reveal any differential responsiveness on the basis of these subgroupings.

Four additional double-blind, placebo-controlled studies were also conducted with children and adolescents in the school setting, and in adults (Table 12). Efficacy and safety were assessed in patients with comorbid tic disorder (pediatrics), and comorbid anxiety disorders (pediatrics and adults). As well, evening efficacy was assessed with once daily dosing (pediatrics and adults).

Long-term efficacy of STRATTERA was established in an 18 month, randomized, double-blind, placebo-controlled relapse-prevention study. Too few patients completed to allow an adequate assessment of long-term safety from this study.

The long-term safety of STRATTERA has been demonstrated in double-blind and open-label clinical trials involving 5382 children or adolescent patients and 525 adult patients with ADHD. During the ADHD clinical trials, 1625 children and adolescent patients were treated for longer than 1 year and 2529 children and adolescent patients were treated for over 6 months.

In both pediatric and adult studies, STRATTERA showed efficacy in patients who had been previously treated with stimulants, as well as in stimulant-naïve patients. STRATTERA has a different mechanism of action from stimulant therapies. Data on evening efficacy suggest that STRATTERA is not associated with the 'on/off' phenomena characteristic of stimulants.

Study Demographics and Trial Design

Table 12. Summary of Patient Demographics for Controlled Clinical Trials in ADHD Patients

Study No.	Trial design	Atomoxetine Dose/Duration	No. of Subjects	Mean Age (range)	Gender
Randomized, Double-Blind Studies in Children and Adolescents					
HFBD	Acute, placebo-controlled, parallel groups.	BID dosing, max 2.0 mg/kg/day; 9 weeks.	n = 147	9.7 years (7 – 13)	M = 119 F = 28
HFBK	Acute, placebo-controlled, parallel groups.	BID dosing, max 2.0 mg/kg/day; 9 weeks.	n = 144	9.9 years (7 – 13)	M = 117 F = 27
LYAC	Acute, dose-ranging, placebo-controlled, parallel groups.	Fixed BID doses 0.5, 1.2, and 1.8 mg/kg/day; 8 weeks.	n = 297	11.2 years (8 – 18)	M = 212 F = 85
LYAT	Once-daily dosing, acute, placebo-controlled, parallel groups.	QD dosing, max 1.5 mg/kg/day; 6 weeks.	n = 171	10.3 years (6 - 16)	M = 120 F = 51
LYBG	Once-daily dosing, acute, placebo-controlled, parallel groups, and assessment of evening efficacy.	QD dosing, max 1.8 mg/kg/day; 8 weeks.	n = 197	9.5 years (6 – 13)	M = 139 F = 58
LYAW	Once- daily dosing, acute, placebo-controlled, parallel groups, and assessment of efficacy in the school setting.	QD dosing, max 1.8 mg/kg/day; 7 weeks.	n = 153	9.9 years (7 - 13)	M = 123 F = 30
LYAS [1]	Acute, placebo-controlled, parallel groups, patients with ADHD and comorbid tic disorder.	BID dosing, max 1.5 mg/kg/day; up to 18 weeks	n = 148	11.2 years (7 – 17)	M = 131 F = 17
LYBI	Parallel-group comparison of atomoxetine, extended-release methylphenidate and placebo.	BID dosing max 1.8 mg/kg/day; approx. 6 weeks.	n = 516	10.2 years (6 – 17)	M = 383 F = 133

Study No.	Trial design	Atomoxetine Dose/Duration	No. of Subjects	Mean Age (range)	Gender
LYAF	Long-term relapse prevention, placebo-controlled, parallel groups.	BID dosing, max 1.8 mg/kg/day; 52 weeks double-blind.	n = 416	10.4 years (6 – 16)	M = 373 F = 43
LYBP [2]	Placebo-controlled, parallel group study in patients with ADHD and comorbid anxiety.	BID dosing max 1.8 mg/kg/day; approx. 12 weeks.	n = 176	12.0 years (8 – 18)	M = 114 F = 62
Randomized, Double-Blind Studies in Adults					
LYAA	Acute, placebo-controlled, parallel groups.	BID dosing, max 120 mg/day 10 weeks	n = 280	40.3 years (18 – 67)	M = 178 F = 102
LYAO	Acute, placebo-controlled, parallel groups.	BID dosing max 120 mg/day 10 weeks	n = 256	42.1 years (19 – 77)	M = 170 F = 86
LYDQ [3]	Placebo-controlled, parallel group study in adult patients with ADHD and comorbid social anxiety.	BID dosing max 100 mg/day; approx. 16 weeks.	n = 442	38.0 years (18 – 65)	M = 237 F = 205

[1, 2, and 3]: See *Action and Clinical Pharmacology, Special Populations, Patients with concomitant illness.*

Children and Adolescents: Improvement on signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for STRATTERA- and placebo-treated patients. The primary efficacy measure in all studies was the *ADHD Rating Scale-IV-Parent Version* (ADHDRS), with the exception of Study LYAW which used the *ADHD Rating Scale-IV-Teacher Version*. Both scales have been well-validated and contain 18 items corresponding exactly to the DSM-IV symptom criteria, thus providing strong content validity. Both scales were administered and scored by an investigator following interviews with a parent or teacher.

Doses ranged from 0.5 to 2.0 mg/kg/day. In clinical trials, the mean weight of children 6 to 12 years of age was 35 kg, and their mean final dose was 45 mg/day. STRATTERA was dosed twice daily, morning and late afternoon/early evening in Studies HFBD, HFBK, and LYAC, or once daily in the morning in Studies LYAT, LYAW, and LYBG.

Adults: The primary outcome measure in the adult studies was the validated Conners' Adult ADHD Rating scale (CAARS), which contains 18 items that correspond exactly to the DSM-IV symptom criteria. This instrument is investigator-administered and scored, with ratings based on patient self-report. Adult patients with current diagnoses of depression and anxiety were excluded, which ensured that improvements related to STRATTERA were attributable to improvements in ADHD. Doses ranged from 30 to 60 mg twice daily, which correspond, on a weight-adjusted basis for a 70 kg adult, to the dosing used in children.

Study Results

Children and Adolescents

Acute, Double-Blind, Placebo-Controlled Studies: The effectiveness of STRATTERA in the treatment of ADHD was established in 6 randomized, double-blind, placebo-controlled studies of pediatric patients, ages 6 to 18 (Studies HFBD, HFBK, LYAC, LYAT, LYAW, LYBG). 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. In all studies, STRATTERA demonstrated a statistically significantly ($p < 0.001$) greater mean reduction in core ADHD symptoms compared with placebo on the primary efficacy measure (Figure 1).

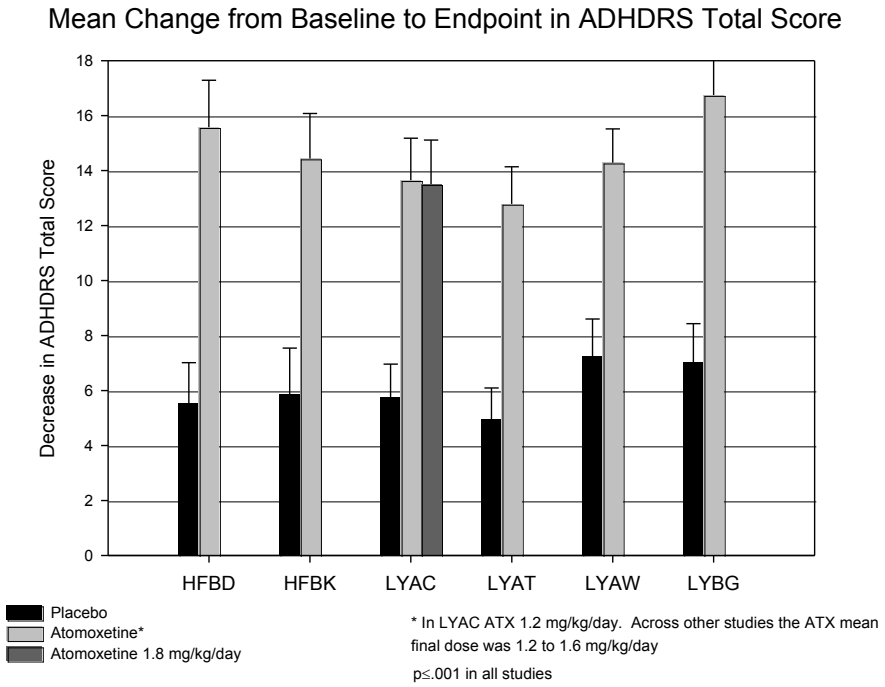


Figure 1. Mean change from baseline to endpoint on the ADHDRS-IV-Parent:Inv Total score in the acute, double-blind, placebo-controlled pediatric studies.

The effect size in the STRATTERA treatment group was similar across studies, providing evidence of a consistent treatment effect regardless of dosing regimen (once or twice daily) or which observer (teacher or parent) was providing information for the primary outcome measure. The efficacy of STRATTERA in children and adolescents was demonstrated in both Hyperactive-Impulsive and Inattentive symptom domains, in ADHD patients with or without comorbidity (e.g., Oppositional Defiant Disorder, depression), and in patients with or without prior stimulant use.

Improvements in the primary outcome measure were consistently accompanied by improvements in broader measures of quality of life and functioning, including behaviour at school, self-esteem and family functioning.

The results of the fixed dose study (LYAC) provided evidence of dose response (onset of effect at 0.5 mg/kg/day, with maximal effect at 1.2 mg/kg/day). For the overall group, no further benefit was demonstrated at 1.8 mg/kg/day.

Study LYAT demonstrated the effectiveness of STRATTERA when administered once daily in the morning (Figure 2). Clinical improvement was typically seen within 1 week of starting treatment, and at 2 to 4 weeks, mean reductions in symptom severity scores were approaching maximal reductions. Study LYBG further demonstrated that the efficacy of STRATTERA persisted from morning until late evening following a once-daily morning dose.

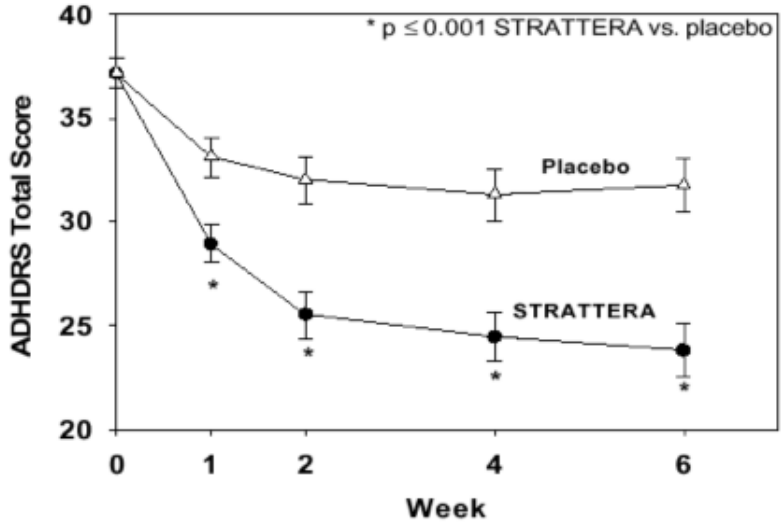


Figure 2. Once-Daily Administration of STRATTERA.

Long-Term Placebo-Controlled Study: The effectiveness of STRATTERA in maintaining symptom response was investigated in Study LYAF, an 18-month study of children and adolescents aged 6 to 15 who met DSM-IV criteria for ADHD. A total of 604 patients were enrolled in this study. Patients who responded to STRATTERA during approximately 3-months open-label treatment (n = 416) were randomized to double-blind, placebo-controlled continuation at their current doses of atomoxetine (n = 292) or on placebo (n = 124) for approximately 9 months to observe for relapse. Patients who were still on STRATTERA (n = 163) at the end of 12 months of treatment were further randomized to an additional 6 months double-blind, placebo-controlled continuation at their current doses of atomoxetine (n = 81) or on placebo (n = 82). The results from this study suggest that atomoxetine may be beneficial in the long-term treatment of ADHD. Too few patients completed to allow an adequate assessment of long-term safety from this study.

Children and adolescents enrolled in acute double-blind, placebo-controlled clinical trials, as well as those enrolled in open-label trials, were followed prospectively to assess safety, tolerability, and effects on growth. The long-term safety of STRATTERA has been demonstrated in double-blind and open-label clinical trials involving 5382 children or adolescent patients. During the ADHD clinical trials, 1625 children and adolescent patients were treated for longer than 1 year and 2529 children and adolescent patients were treated

for over 6 months. In these trials, STRATTERA was safe and well tolerated, and there were minimal, if any, long-term effects on weight and height compared to normal growth curves.

Active Comparator Study: Study LYBI was a randomized, double-blind, parallel group, 6 week pediatric study to test the non-inferiority of atomoxetine to a standard extended-release stimulant comparator. The comparator was shown to be associated with superior response rates compared to atomoxetine (p = 0.016). However, this study excluded patients who were stimulant nonresponders, so it is possible that the results were biased favouring the stimulant comparator. For patients not previously treated with a stimulant, there was no significant difference in response rates between stimulant comparator and atomoxetine (p = 0.423). Both atomoxetine and the comparator were statistically superior to placebo. Both atomoxetine and comparator were safe and well-tolerated. Neither medication produced statistically significant QT prolongation compared to placebo.

Studies in Adult ADHD Patients

The results of 2 large placebo-controlled studies in adult patients with ADHD (N = 536) have demonstrated the efficacy and safety of STRATTERA in this population. STRATTERA was statistically significantly superior to placebo at reducing ADHD symptoms as measured on the CAARS Total ADHD symptom score (Figure 3, LYAA p = 0.004, LYAO p = 0.002). Efficacy was observed for overall ADHD symptoms as well as in the individual domains of Predominately Inattentive and Predominately Hyperactive-Impulsive symptoms.

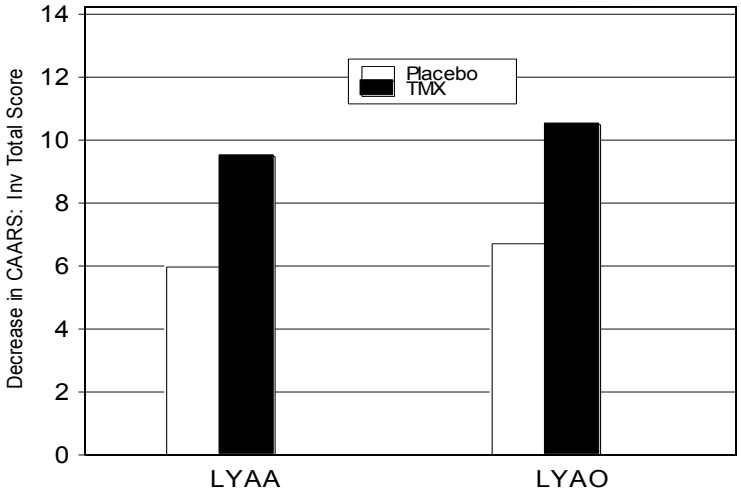


Figure 3. CAARS Total Scores – Mean change from baseline to endpoint in randomized, double-blind, placebo-controlled adult studies

DETAILED PHARMACOLOGY

Efficacy Pharmacology

Atomoxetine hydrochloride was designed to be a potent and selective inhibitor of the norepinephrine transporter. In vitro, atomoxetine was found to have highly selective potency for the norepinephrine transporter over the dopamine and serotonin transporters, and was highly selective for inhibiting the uptake of radiolabelled norepinephrine into hypothalamic synaptosomes. Of the two primary phase I metabolites, 4-hydroxyatomoxetine was found to have similar in vitro potency for the norepinephrine transporter and inhibition of norepinephrine uptake compared to atomoxetine, while *N*-desmethylatomoxetine had lower affinity than atomoxetine for all three monoamine transporters. Further, atomoxetine and these metabolites were found to have relatively low affinities for neurotransmitter receptors and ion channels. In vivo evaluation of atomoxetine also demonstrated high potency and selectivity of atomoxetine for the norepinephrine transporter. In the prefrontal cortex, a site believed to be important for attention in humans, dose-dependent increases in the extracellular concentrations of norepinephrine and dopamine occurred when atomoxetine was given intraperitoneally or when atomoxetine was delivered directly through a microdialysis probe, suggesting that the increases in prefrontal cortex norepinephrine and dopamine were produced by local inhibition of the norepinephrine transporter. Atomoxetine did not produce a significant increase in the extracellular concentrations of dopamine in the nucleus accumbens, an area believed to mediate the rewarding effects of dopamine transporter inhibitors, and the striatum, an area believed to mediate the effects of dopamine transporter inhibitors on locomotor activity.

Safety Pharmacology

Atomoxetine was evaluated in animals or in vitro for potential effects on the central nervous system and behaviour, including abuse potential, and for effects on cardiovascular, respiratory, renal, gastrointestinal, and immune function.

In contrast to the high affinity of atomoxetine for the norepinephrine transporter site, atomoxetine, 4-hydroxyatomoxetine, and *N*-desmethylatomoxetine, have relatively low binding affinities for adrenergic, muscarinic, histaminergic, GABAergic, serotonergic, and dopaminergic receptors, as well as many other receptor sites and ion channels. Atomoxetine exhibited no agonist effects on isolated smooth and cardiac tissues and did not inhibit acetylcholine- or isoproterenol-induced contractions of these respective tissues. Therefore, atomoxetine would not be expected to interfere with the physiologic function mediated by these receptor systems or produce toxicity associated with muscarinic or adrenergic receptors. Importantly, clinical signs observed in rodents and dogs were consistent only with effects on the central nervous system (for example, reduced motor activity, leg weakness, jerky gait, tremors, and convulsions).

Atomoxetine is not associated with abuse potential, based upon its receptor binding profile and nonclinical behavioural pharmacology, as well as animal drug discrimination studies conducted with atomoxetine.

Atomoxetine produced no important changes in respiratory or renal function, gastrointestinal motility, or immune function in animals.

Cardiac Function

Atomoxetine was evaluated for effects on cardiac function in vitro and in dogs. In vitro blockade of the cloned human cardiac I_{Kr} (HERG) channel by atomoxetine occurred with an IC_{50} of 0.869 μM. Studies with canine Purkinje tissue and in dogs given atomoxetine orally did not produce effects predictive or consistent with a compound-related QT interval prolongation. Concomitant inhibition of sodium and calcium inward currents in vitro helps explain the lack of in vivo findings. These observations, together with the clinical experience with atomoxetine, indicate that the in vitro HERG blockade observation is not likely predictive of an increased cardiovascular risk for atomoxetine.

Cardiovascular Safety Study:

The safety and tolerability of gradually increasing multiple-dose regimes of atomoxetine was studied during a 20 day period in a clinical pharmacology study involving 16 healthy adults (10 EM subjects and 6 PM subjects). Placebo or atomoxetine 60 to 150 mg/day, was given as twice daily doses of 30 mg, 45 mg, 60 mg, and 75 mg. None of the mean or individual $QTc_{(F)}$ intervals (QT interval corrected by the Fridericia method) exceeded the upper limits of normal for each gender.

The EM group had no statistically significant changes in mean $QTc_{(F)}$ interval following any dose of atomoxetine compared to the placebo treatment. No statistically significant changes in $QTc_{(F)}$ were noted 1 hour post dose (during peak plasma concentrations) in the PM group. The PM group had a statistically significant increase in the mean $QTc_{(F)}$ interval measured at time 0 (during trough plasma concentrations) on the last day of the 60- and 75-mg atomoxetine twice-daily dosing regimens compared to the placebo. The greatest mean prolongation was about 17 msec at the 60-mg BID dose level, with the mean interval length of 417.2 msec. At the 75-mg BID atomoxetine dose level, the greatest mean prolongation was 15 msec, and the mean interval length was 414.9 msec. The 60 mg BID and 75 mg BID doses correspond to 1.4-2.24 mg/kg/day and 1.75-2.8 mg/kg/day, respectively.

Baseline ECGs obtained during screening of pediatric patients for atomoxetine clinical trials were reviewed for cases of QTc prolongation. Using Bazett's method for correcting QT (the usual method for automated QTc intervals), there were 131/3902 cases (3.4%) with QTc(B) > 450 msec and 5/3902 cases (0.1%) with QTc(B) > 500 msec. Using a correction method based on data from baseline ECGs (the method preferred by most regulatory agencies), there were 32/3902 cases (0.8%) with QTc(D) > 450 msec and 5/3902 cases (0.1%) with QTc(D) > 500 msec. In a meta-analysis of ECG data from patients who received atomoxetine in pediatric clinical trials, no relationship was observed between changes from baseline to final $QTc_{(D)}$ and prescribed atomoxetine dose (n = 3127 patients), or between changes from baseline to $QTc_{(D)}$ at time of expected peak exposure and prescribed atomoxetine dose (n = 2084 all patients, n = 151 PM patients). For clinical trial patients where plasma concentrations were available, no relationship was observed between changes from baseline $QTc_{(D)}$ and atomoxetine plasma concentration during peak atomoxetine exposure (n = 728 all patients, n = 83 PM patients).

Overall, the data do not suggest a meaningful relationship between atomoxetine plasma concentrations and the length of the QT interval corrected for heart rate in the recommended dosage range. However, since there is no requirement for a priori screening of ADHD patients for CYP2D6 metabolizer status before initiating treatment with atomoxetine, it is important that the lowest effective dose be used, so as to minimize potential cardiac side effects.

Pharmacokinetics

Atomoxetine was well absorbed following oral administration to adult mice, rats, and dogs.

The primary oxidative (phase I) metabolite of atomoxetine was identified as 4-hydroxyatomoxetine, and its major ultimate metabolite is 4-hydroxyatomoxetine-*O*-glucuronide, in all species evaluated. The major routes of metabolism are aromatic ring-hydroxylation, benzylic/aliphatic hydroxylation, and *N*-demethylation. Subsequent *O*-glucuronidation and *O*-sulfation of the hydroxylated metabolites are the only phase II metabolic pathways to participate in the conjugation of the oxidized atomoxetine metabolites. Plasma concentrations of atomoxetine and its primary phase I metabolites, *N*-desmethylatomoxetine and 4-hydroxyatomoxetine, increased with dose in each species. There was generally minimal accumulation with repeated dosing, which appeared to be due to the relatively rapid clearance of atomoxetine in each of the species evaluated. The half-life of atomoxetine following a single intravenous dose was 1.2 hr, 1.4 hr and 3.4 hr in the mouse, rat and dog, respectively. The most profound difference observed among species was the low bioavailability in rodents (approximately 4%) compared to the high bioavailability in dog (approximately 74%). These differences appear to be almost purely mediated by the efficient first-pass hepatic clearance of atomoxetine in rodents, resulting in poor systemic exposure to atomoxetine but high exposure to its metabolites. In the dog, atomoxetine does not undergo extensive first-pass metabolism.

Increases in hepatic cytochrome P450 activity were observed in mice and rats after large oral doses of atomoxetine. Slight increases in total cytochrome P450 content were observed at the highest dose tested (16 mg/kg/day) in male dogs. However, no evidence of such changes in cytochrome P450 activity have been observed in clinical studies.

Binding of atomoxetine and *N*-desmethylatomoxetine to plasma protein was high in each species evaluated including humans (82% to 99%), while the binding of 4-hydroxyatomoxetine to plasma protein was substantially lower (55% to 67%).

In the rat, atomoxetine and its metabolites were rapidly and widely distributed in tissues, with the highest levels being observed in the gastrointestinal tract and the liver. Milk excretion is not a major route of elimination for atomoxetine and/or its metabolites. Atomoxetine and/or its metabolites crossed the placenta resulting in relatively low fetal exposure compared to exposure in maternal tissues.

The major route of excretion of atomoxetine-derived radioequivalents was via the urine in each of the species evaluated. A low amount of fecal excretion appears to be due to biliary elimination. Very little atomoxetine was excreted intact, indicating that direct renal or biliary elimination of atomoxetine are minor routes of systemic clearance.

TOXICOLOGY

Acute Toxicity

The median lethal oral dose of atomoxetine hydrochloride in animals was estimated to be 25 mg/kg for cats, >37.5 mg/kg for dogs, and ≥ 190 mg/kg in rats and mice. Premonitory signs of toxicity following single oral doses of atomoxetine in animals included mydriasis and reduced pupillary light reflex, mucoid stools, salivation, vomiting, ataxia, tremors, myoclonic jerking, and convulsions.

Long-Term Toxicity

Toxicity studies of up to 1 year were conducted in adult rats and dogs to evaluate the potential chronic toxicity of atomoxetine. There was no major target organ toxicity observed in dogs given oral doses up to 16 mg/kg/day or in rats given atomoxetine in the diet at time-weighted average doses up to 47 mg/kg/day. These doses are approximately 6 - 7 times the maximum recommended daily oral dose in children, and approximately 4 - 5 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis. Mild hepatic effects, characterized by mottling and pallor of the liver, increased relative liver weights, hepatocellular vacuolation, and slightly increased serum ALT values, occurred in male rats given time-weighted average doses ≥ 14 mg/kg/day. No hepatic effects were observed in dogs. Clinical signs of mydriasis, reduced pupillary light reflex, emesis, and tremors were observed in dogs, and these effects were minimal in adult dogs given ≤ 8 mg/kg/day. Similar clinical signs were observed in young dogs (8 weeks of age) given atomoxetine orally for 1 month.

Toxicity studies were conducted to evaluate potential effects of atomoxetine on growth, neurobehavioural, and sexual development as well as reproductive performance in rats dosed from the early postnatal period to early adulthood. No important effects on bone growth, brain morphology, neurobehavioral or reproductive performance were observed in rats administered atomoxetine hydrochloride from 10 days of age through adulthood, at oral doses up to 50 mg/kg, approximately 7 times the maximum recommended daily oral dose in children on a mg/m^2 basis. There were no effects on the anatomy or morphology of either male or female reproductive organs. There was a minor, dose-related increase in time-to-onset of vaginal patency and preputial separation (1 to 3 days compared with controls), but all animals reached sexual maturity and no malformations of the vagina or prepuce/glans penis were observed. In male rats, spermatogenesis was normal. There were slight decreases in the number of sperm held in the epididymis but no effects on fertility. For both male and female rats, there were no effects on mating or fertility indices, no effects on embryo implantation or embryo viability, and no effects on learning and memory tests. The significance of these findings to humans is not known.

Carcinogenicity

Atomoxetine hydrochloride 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.

Mutagenicity

Atomoxetine hydrochloride 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 hydrochloride was negative in the Ames Test, mouse lymphoma assay, and unscheduled DNA synthesis test.

Teratogenicity

No evidence of drug-associated teratogenicity or retarded fetal development was produced in rabbits or rats administered atomoxetine hydrochloride throughout organogenesis at oral doses up to 100 mg/kg/day and 150 mg/kg/day (at least 20 times the maximum recommended daily oral dose in children and 13 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis). In a rat fertility study, decreased pup weight and survival was observed, predominantly during the first week postpartum following maternal dietary atomoxetine time-weighted average doses of 23 mg/kg/day or higher. No adverse effects were observed in surviving pups.

Atomoxetine hydrochloride did not impair fertility when administered to rats from 10 days of age through adulthood at oral doses up to 50 mg/kg/day (up to 7 times the maximum recommended daily oral dose in children and 4 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis). In addition, no evidence of impaired fertility was observed in either of two fertility studies in adult rats provided atomoxetine HCl in the diet at time-weighted average doses up to 57 mg/kg/day (up to 8 times the maximum recommended daily oral dose in children and 5 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis).

Parturition in rats was not affected by atomoxetine.

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.

Growth and Neurobehavioural/Sexual development in rats

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.

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PART III: CONSUMER INFORMATION

Pr STRATTERA®
(atomoxetine capsules)

This leaflet is part III of a three-part "Product Monograph" published when STRATTERA was approved for sale in Canada and is designed specifically for adults and parents of children/adolescents who will be prescribed this medication. This leaflet is a summary and will not tell you everything about STRATTERA. Contact your doctor or pharmacist if you have any questions about this drug.

ABOUT THIS MEDICATION

What STRATTERA is used for:

STRATTERA is a medicine for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children 6 years of age and over, adolescents, and adults. STRATTERA should not be used in children under 6 years of age.

STRATTERA is a part of your overall treatment program for ADHD that may include other measures (psychological, educational, and social). Your doctor may also recommend other therapy.

What it does:

STRATTERA is a selective norepinephrine reuptake inhibitor medicine that increases the amount of noradrenaline, a natural chemical in the brain. STRATTERA may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

STRATTERA works differently from other medicines used for the treatment of ADHD. STRATTERA is not a stimulant and is not addictive.

What is ADHD:

ADHD has 3 main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and interrupting others. Some patients have more symptoms of hyperactivity and impulsiveness while others have more symptoms of inattentiveness. Some patients have all 3 types of symptoms.

Symptoms of ADHD in adults may include a lack of organization, problems starting tasks, impulsive actions, daydreaming, daytime drowsiness, slow processing of information, difficulty learning new things, irritability, lack of motivation, sensitivity to criticism, forgetfulness, low self-esteem, and excessive effort to maintain some organization. The symptoms shown by adults who primarily have attention problems but not hyperactivity have been commonly described as Attention-Deficit Disorder (ADD).

Many people have these symptoms from time to time. However, people with ADHD have these symptoms most of the time. Symptoms must be present for at least 6 months to be certain of the diagnosis. In addition, the symptoms cause problems in more than one area of life (home, school, work, or social situations).

When it should not be used:

Do not take STRATTERA if you:

- are taking, or have recently taken, an antidepressant medicine known as a monoamine oxidase inhibitor (MAOI). Some names of MAOI medicines are phenelzine and tranylcypromine.
- have narrow angle glaucoma, an eye disease.
- are allergic to atomoxetine or any other ingredient of STRATTERA.
- have symptomatic cardiovascular disease.
- have moderate to severe high blood pressure.
- have advanced arteriosclerosis (hardened arteries).
- have uncontrolled hyperthyroidism (an overactive thyroid gland).
- have a tumour of the adrenal gland (phaeochromocytoma).

What the medicinal ingredient is:

Atomoxetine

What the nonmedicinal ingredients are:

The capsules contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and one or more of the following: FD&C Blue No. 2, synthetic yellow iron oxide, titanium dioxide.

What dosage forms it comes in:

Capsules of STRATTERA contain 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, or 100 mg of atomoxetine.

WARNINGS AND PRECAUTIONS

The following have been reported with use of STRATTERA and also with stimulant medications:

1. **Suicidal thoughts and actions in children and teenagers**

Some children and teenagers may have a higher chance of having suicidal thoughts or actions. 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 suicidal thoughts or actions before starting STRATTERA.

The chance for suicidal thoughts and actions are 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, behaviours, 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
- suicidal 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.

Should any of the above signs also happen to you while taking STRATTERA, it is important that you talk to your doctor about how you are feeling.

2. Severe liver damage

Call your doctor right away if you or your child have 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 as well as in patients without pre-existing cardiac disease.**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

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

Your doctor may wish to check you 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, irregular heart rate, palpitations, shortness of breath, dizziness 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, are suspicious) or new manic symptoms.

Call your child or teenager's doctor right away about any new mental symptoms. STRATTERA treatment may be stopped.

BEFORE you use STRATTERA, talk to your doctor or pharmacist if you or your child:

- have or had suicidal thoughts or actions
- have structural heart abnormalities,
- inborn, acquired or family history of long QT interval
- have mental problems, including psychosis, mania, bipolar illness, or depression;
- have had seizures (convulsions, epilepsy) or abnormal EEGs (electroencephalograms);
- have or had any disorder of the blood vessels in the brain (e.g. aneurysm, stroke, vasculitis);
- have a family history of sudden death or death related to heart problems;
- do strenuous exercise;
- take other drugs for ADHD;
- have or had liver problems. You may need a lower dose;
- have mild high blood pressure. STRATTERA can increase blood pressure;
- have problems with your heart or an irregular heartbeat. STRATTERA can increase heart rate (pulse);
- have low blood pressure. STRATTERA can cause dizziness or fainting in people with low blood pressure
- are nursing, pregnant, or thinking of becoming pregnant;
- have circulation problems in fingers and toes, including numbness; feeling cold or pain (Raynaud's Phenomenon).

Do not drive a car or operate hazardous machinery until you know how STRATTERA affects you.

This medicine was prescribed for your use only. Do not let anyone else take your STRATTERA.

INTERACTIONS WITH STRATTERA

Tell your doctor about all the medicines you/your child take or plan to take, including prescription and non-prescription medicines, dietary supplements, and herbal remedies. Your doctor will decide if you can take STRATTERA with your other medicines. Also tell your doctor if there have been any changes in dosing with your other medicines.

Certain medicines may change the way your body reacts to STRATTERA.

Drugs that may interact with STRATTERA include:

- Anti-depression medicines: Your doctor may need to change your dose of STRATTERA if you are taking paroxetine, fluoxetine, or certain other medicines like quinidine.

  You should not take STRATTERA if you are taking desipramine.

- Asthma medicines: STRATTERA may change the way your body reacts to oral, intravenous, or nebulized salbutamol (or drugs with similar actions), but the effectiveness of these drugs will not be changed.

- Blood pressure medicines: STRATTERA should be used with caution if you are being treated with drugs for high blood pressure.

PROPER USE OF STRATTERA

Usual dose:

Take STRATTERA exactly as directed by your doctor. It is very important that you do not take a larger dose of STRATTERA than prescribed by your doctor.

Your doctor may tell you to take STRATTERA once a day or twice a day (morning and late afternoon/early evening). To help you remember to take STRATTERA, you may want to take it at the same time every day.

Improvement of your ADHD symptoms is generally observed within 1 to 4 weeks of starting STRATTERA.

STRATTERA may be taken with or without food.

You should not open STRATTERA capsules, but if they are accidentally opened or broken, avoid contact with the powder and wash away any loose powder as soon as possible with water. If any of the powder gets in your eyes you should rinse them with water immediately and contact your doctor.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as possible, but do not take more than your total daily dose in any 24-hour period.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

All prescription medicines may cause side effects in some patients. If you have some side-effects such as upset stomach, nausea, sleepiness or tiredness, your doctor may ask you to take STRATTERA twice a day with meals, or in the evening. Most side effects will disappear after the first few weeks.

The following common side effects were reported in clinical trials with STRATTERA:

In teenagers and children over 6:

- upset stomach
- decreased appetite
- nausea or vomiting
- dizziness
- tiredness
- constipation
- low blood pressure
- weight loss may occur especially in the first few weeks.

In Adults:

- constipation
- dry mouth
- nausea
- decreased appetite
- dizziness
- problems sleeping
- sexual side effects
- problems urinating
- menstrual cramps
- rapid or irregular heartbeat
- tiredness

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate emergency help**
		Only if severe	**In all cases**	
Very common	**Heart-related problems**: Blood pressure increased, heart rate increased**.** (see **Warnings and Precautions**)		✓	
Common Rare (in children)	**Urinary retention:** problem passing urine and emptying bladder		✓	
Uncommon	**Allergic Reaction:** Swelling, hives, or difficulty breathing			✓
	Suicidal Behavior: Thoughts or actions about hurting or killing yourself. (see **Warnings and Precautions**)			✓
	New psychotic symptoms: Paranoia, delusions-hallucinations (seeing, feeling or hearing things that are not real)		✓	
	Aggressive Behavior or Hostility		✓	
Rare	**Liver Injury:** Dark urine, yellow skin/ eyes, upper right-sided abdominal tenderness, or flu-like symptoms		✓	
	Priapism: Long-lasting (greater than 4 hours in duration) and painful erection of the penis			✓
	Raynaud's Phenomenon: discoloration of the fingers and toes, pain, sensations of cold and/or numbness		✓	
Unknown	**Slowing of growth in children** (height and weight)		✓	
	New manic symptoms: Mania (feeling unusually excited, overactive, or un-inhibited)		✓	

This is not a complete list of side effects. For any unexpected effects while taking STRATTERA, contact your doctor or pharmacist.

HOW TO STORE IT

STRATTERA should be stored at room temperature (15 to 30°C).

Keep all medicines, including STRATTERA, out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Eli Lilly Canada Inc. at: 1-888-545-5972 or visit the website at *www.lilly.ca.*

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

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This leaflet was prepared by Eli Lilly Canada Inc., Toronto, Ontario, M1N 2E8.

Last revised: October 1, 2015