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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ATOMOXETINE CAPSULES safely and effectively. See full prescribing information for ATOMOXETINE CAPSULES.

ATOMOXETINE capsules, for oral use
Initial U.S. Approval: 2002

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

- See full prescribing information for complete boxed warning.
- Increased risk of suicidal ideation in children or adolescents (5.1)
- No suicides occurred in clinical trials (5.1)
- Patients started on therapy should be monitored closely (5.1)

INDICATIONS AND USAGE

Atomoxetine capsules are a selective norepinephrine reuptake inhibitor indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). (1.1)

DOSE AND ADMINISTRATION

Initial, Target and Maximum Daily Dose (2.1)
(Acute and Maintenance/Extended Treatment)

Body Weight	Initial Daily Dose	Target Total Daily Dose	Maximum Total Daily Dose
Children and adolescents up to 70 kg	0.5 mg/kg	1.2 mg/kg	1.4 mg/kg
Children and adolescents over 70 kg and adults	40 mg	80 mg	100 mg

Dosing adjustment — Hepatic Impairment, Strong CYP2D6 Inhibitor, and in patients known to be CYP2D6 poor metabolizers (PMs). (2.4, 12.3)

DOSE FORMS AND STRENGTHS

Each capsule contains atomoxetine hydrochloride equivalent to 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, or 100 mg of atomoxetine. (3, 11, 16)

CONTRAINDICATIONS

- Hypersensitivity to atomoxetine or other constituents of product. (4.1)
- Atomoxetine capsules use within 2 weeks after discontinuing MAOI or other drugs that affect brain monoamine concentrations. (4.2, 7.1)
- Narrow Angle Glaucoma. (4.3)
- Pheochromocytoma or history of pheochromocytoma. (4.4)
- Severe Cardiovascular Disorders that might deteriorate with clinically important increases in HR and BP. (4.5)

WARNINGS AND PRECAUTIONS

- Suicidal Ideation — Monitor for suicidal ideation, clinical worsening, and unusual changes in behavior. (5.1)
- Severe Liver Injury — Should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury. (5.2)
- Serious Cardiovascular Events — Sudden death, stroke and myocardial infarction have been reported in association with atomoxetine

FULL PRESCRIBING INFORMATION: CHILDREN*

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

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FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

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

Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of atomoxetine in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

1.1 Attention-Deficit/Hyperactivity Disorder (ADHD)

Atomoxetine capsules are indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). The efficacy of atomoxetine was established in seven clinical trials in outpatients with ADHD: four 6 to 9-week trials in pediatric patients (ages 6 to 18), two 10-week trial in adults, and one maintenance trial in pediatrics (ages 6 to 15) [see Clinical Studies (14)].

1.2 Diagnostic Considerations

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.

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.

For the inattentive type, at least 6 of the following symptoms must be present 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.

1.3 Need for Comprehensive Treatment Program

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

2 DOSE AND ADMINISTRATION

2.1 Acute Treatment

Dosing of children and adolescents up to 70 kg body weight — Atomoxetine capsules should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/evening. No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day [see Clinical Studies (14)].

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

Dosing of children and adolescents over 70 kg body weight and adults — Atomoxetine capsules should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/evening. After 2 to 4 additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response. There are no data that support increased effectiveness at higher doses [see Clinical Studies (14)].

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

2.2 Maintenance/Extended Treatment

It is generally agreed that pharmacological treatment of ADHD may be needed for extended periods. The benefit of maintaining pediatric patients (ages 6 to 15 years) with ADHD on atomoxetine capsules after achieving a response in a dose range of 1.2 to 1.8 mg/kg/day was demonstrated in a controlled trial. Patients assigned to atomoxetine capsules in the maintenance phase were generally continued on the same dose used to achieve a response in the open label phase. The physician who elects to use atomoxetine capsules for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient [see Clinical Studies (14.1)].

2.3 General Dosing Information

Atomoxetine capsules may be taken with or without food.

Atomoxetine capsules can be discontinued without being tapered.

Atomoxetine capsules are not intended to be opened, they should be taken whole [see Patient Counseling Information (17.6)].

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

2.4 Dosing in Specific Populations

Dosing adjustment for hepatically impaired patients — For those ADHD patients who have hepatic insufficiency (HI), dosage adjustment is recommended as follows: For patients with moderate HI (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose (for patients without HI). For patients with severe HI (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of normal [see Use in Specific Populations (8.6)].

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

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

3 DOSE FORMS AND STRENGTHS

Each capsule contains atomoxetine hydrochloride USP equivalent to 10 mg (off-white opaque/off-white opaque), 18 mg (golden opaque/off-white opaque), 25 mg (blue opaque/white opaque), 40 mg (blue opaque/blue opaque), 60 mg (blue opaque/golden opaque), 80 mg (brown opaque/off-white opaque), or 100 mg (brown opaque/brown opaque) of atomoxetine.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

Atomoxetine capsules are contraindicated in patients known to be hypersensitive to atomoxetine or other constituents of the product [see Warnings and Precautions (5.8)].

4.2 Monoamine Oxidase Inhibitors (MAOI)

Atomoxetine capsules should not be taken with or within 2 weeks after discontinuing an MAOI. Treatment with an MAOI should not be initiated within 2 weeks after discontinuing atomoxetine capsules. With other drugs that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when taken in combination with an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity [see Drug Interactions (7.1)].

4.3 Narrow Angle Glaucoma

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

4.4 Pheochromocytoma

Serious reactions, including elevated blood pressure and tachyarrhythmia, have been reported in patients with pheochromocytoma or a history of pheochromocytoma who received atomoxetine capsules. Therefore, atomoxetine capsules should not be taken by patients with pheochromocytoma or a history of pheochromocytoma.

4.5 Severe Cardiovascular Disorders

Atomoxetine capsules should not be used in patients with severe cardiac or vascular disorders whose condition would be expected to deteriorate if they experience increases in blood pressure or heart rate that could be clinically important (for example, 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate). [See Warnings and Precautions (5.4)].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Ideation

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

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

The following symptoms have been reported with atomoxetine: anxiety, agitation, panic attacks, insomnia, irritability, hostility,

treatment. Patients should have a careful history and physical exam to assess for presence of cardiovascular disease. 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 its noradrenergic effects. Consideration should be given to not using atomoxetine in adults with clinically significant cardiac abnormalities. (5.3)

- Emergent Cardiovascular Symptoms — Patients should undergo prompt cardiac evaluation. (5.3)
- Effects on Blood Pressure and Heart Rate — Increase in blood pressure and heart rate; orthostasis and syncope may occur. Use with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. (5.4)
- Emergent Psychotic or Manic Symptoms — Consider discontinuing treatment if such new symptoms occur. (5.5)
- Bipolar Disorder — Screen patients to avoid possible induction of a mixed/manic episode. (5.6)
- Aggressive Behavior or Hostility — Aggressive behavior should be monitored. (5.7)
- Possible allergic reactions, including anaphylactic reactions, angioneurotic edema, urticaria, and rash. (5.8)
- Effects on Urine Outflow — Urinary hesitancy and retention may occur. (5.9)
- Priapism — Prompt medical attention is required in the event of suspected priapism. (5.10, 17.5)
- Growth — Height and weight should be monitored in pediatric patients. (5.11)
- Concomitant Use of Potent CYP2D6 Inhibitors or Use in Patients known to be CYP2D6 PMs — Dose adjustment of atomoxetine may be necessary. (5.13)

ADVERSE REACTIONS

- Most common adverse reactions (≥5% and at least twice the incidence of placebo patients)
- Child and Adolescent Clinical Trials — Nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence. (6.1)
- Adult Clinical Trials — Constipation, dry mouth, nausea, decreased appetite, dizziness, erectile dysfunction, and urinary hesitancy.

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Monoamine Oxidase Inhibitors. (4.2, 7.1)
- CYP2D6 Inhibitors — Concomitant use may increase atomoxetine steady-state plasma concentrations in EMs. (7.2)
- Antihypertensive Drugs and Pressor Agents — Possible effects on blood pressure. (7.3)
- Albuterol (or other beta₂ agonists) — Action of albuterol on cardiovascular system can be potentiated. (7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy/Lactation — Pregnant or nursing women should not use unless potential benefit justifies potential risk to fetus or infant. (8.1, 8.2)
- Hepatic Insufficiency — Increased exposure (AUC) to atomoxetine than with normal subjects in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase). (8.6)
- Renal Insufficiency — Higher systemic exposure to atomoxetine than healthy subjects for EM subjects with end stage renal disease (creatinine clearance <30 mL/min) was observed for mg/kg dose. (8.7)
- Patients with Concomitant Illness — Does not worsen tics in patients with ADHD and comorbid Tourette's Disorder. (8.10)
- Patients with Concomitant Illness — Does not worsen anxiety in patients with ADHD and comorbid Anxiety Disorders. (8.10)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

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8 USE IN SPECIFIC POPULATIONS

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- Interference with Psychomotor Performance

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

aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania. Although a causal link between the emergence of such symptoms and the use of atomoxetine has not been established, there is a concern that such symptoms may represent precursors to emerging suicidality. Thus, patients being treated with atomoxetine should be observed for the emergence of such symptoms.

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

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

5.2 Severe Liver Injury

Postmarketing reports indicate that atomoxetine can cause severe liver injury. Although no evidence of liver injury was detected in clinical trials of about 5000 patients, there have been rare cases of clinically significant liver injury that were considered probably or possibly related to atomoxetine use in postmarketing experience. Rare cases of liver failure have also been reported, including a case that resulted in a liver transplant. Because of probable underreporting, it is impossible to provide an accurate estimate of the true incidence of these reactions. Reported cases of liver injury occurred within 120 days of initiation of atomoxetine in the majority of cases and some patients presented with markedly elevated liver enzymes (>20 X upper limit of normal (ULN)), and jaundice with significantly elevated bilirubin levels (>2 X ULN), followed by recovery upon atomoxetine discontinuation. In one patient, liver injury, manifested by elevated hepatic enzymes up to 40 X ULN and jaundice with >20 X ULN, recurred upon rechallenge, and was followed by recovery upon drug discontinuation, providing evidence that atomoxetine likely caused the liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped. The patient described above recovered from his liver injury, and did not require a liver transplant.

Atomoxetine 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 Warnings and Precautions (5.2); Patient Counseling Information (17.3)].

5.3 Serious Cardiovascular Events

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

Children and Adolescents — Sudden death has been reported in association with atomoxetine treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, atomoxetine generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the noradrenergic effects of atomoxetine.

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

Assessing Cardiovascular Status in Patients Being Treated with Atomoxetine

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

5.4 Effects on Blood Pressure and Heart Rate

Atomoxetine should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate such as certain patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. It should not be used in patients with severe cardiac or vascular disorders whose condition would be expected to deteriorate if they experienced clinically important increases in blood pressure or heart rate [see Contraindications (4.5)]. Pulse and blood pressure should be measured at baseline, following atomoxetine dose increases, and periodically while on therapy to detect possible clinically important increases.

The following table provides short-term, placebo-controlled clinical trial data for the proportions of patients having an increase in: diastolic blood pressure ≥15 mm Hg; systolic blood pressure ≥20 mm Hg; heart rate greater than or equal to 20 bpm, in both the pediatric and adult populations (see Table 1).

	Table 1*							
	Pediatric Acute Placebo-Controlled				Adult Acute Placebo-Controlled			
	Maximum ^b	Placebo	Atomoxetine	Placebo	Maximum ^b	Placebo	Atomoxetine	Placebo
DBP (≥15 mm Hg)	21.5	14.1	9.3	4.8	12.6	6.7	4.8	3.5
SBP (≥20 mm Hg)	12.5	8.7	4.9	3.3	12.4	7.8	4.2	3.2
HR (≥20 bpm)	23.4	11.5	12.2	3.8	22.4	8.3	10.2	2.0

* Abbreviations: bpm=beats per minute; DBP=diastolic blood pressure; HR=heart rate; mm Hg=millimeters mercury; SBP=systolic blood pressure.

^b Proportion of patients meeting threshold at any one time during clinical trial.

In placebo-controlled registration studies involving pediatric patients, tachycardia was identified as an adverse event for 0.3% (5/1597) of these atomoxetine patients compared with 0% (0/934) of placebo patients. The mean heart rate increase in extensive metabolizer (EM) patients was 5.0 beats/minute, and in poor metabolizer (PM) patients 9.4 beats/minute.

In adult clinical trials where EM/PM status was available, the mean heart rate increase in PM patients was significantly higher than in EM patients (11 beats/minute versus 7.5 beats/minute). The heart rate effects could be clinically important in some PM patients.

In placebo-controlled registration studies involving adult patients, tachycardia was identified as an adverse event for 1.5% (8/540) of atomoxetine patients compared with 0.5% (2/402) of placebo patients.

In adult clinical trials where EM/PM status was available, the mean change from baseline in diastolic blood pressure in PM patients was higher than in EM patients (4.21 versus 2.13 mm Hg) as was the mean change from baseline in systolic blood pressure in PM patients (2.75 versus EM: 2.40 mm Hg). The blood pressure effects could be clinically important in some PM patients.

Orthostatic hypotension and syncope have been reported in patients taking atomoxetine. In child and adolescent registration studies, 0.2% (12/5596) of atomoxetine-treated patients experienced orthostatic hypotension and 0.8% (46/5596) experienced syncope. In short-term child and adolescent registration studies, 1.8% (6/340) of atomoxetine-treated patients experienced orthostatic hypotension compared with 0.5% (1/207) of placebo-treated patients. Syncope was not reported during short-term child and adolescent placebo-controlled ADHD registration studies. Atomoxetine 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.

5.5 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 psychosis or mania can be caused by atomoxetine at usual doses. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine, and discontinuation of treatment should be considered. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.2% (4 patients with reactions 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.

5.6 Screening Patients for Bipolar Disorder

Adverse Reaction ^a	Percentage of Patients Reporting Reaction	
System Organ Class/Adverse Reaction	Atomoxetine (N=1697)	Placebo (N=1560)
Ejaculation delayed ^d and/or orgasmulation disorder ^d	4	1
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	4	1
Vascular Disorders		
Hot flush	3	0

- ^a Reactions reported by at least 2% of patients treated with atomoxetine, and greater than placebo. The following reactions did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: peripheral coldness, tachycardia, prostatitis, testicular pain, orgasm abnormal, flatulence, asthenia, feeling cold, muscle spasm, dyspnea, agitation, restlessness, micturition urgency, poliakuria, pruritus, urticaria, flushing, tremor, menstruation irregular, rash, and urinary retention. The following reactions were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: anxiety, diarrhea, back pain, headache, and oropharyngeal pain.
- ^b Abdominal pain includes the terms: abdominal pain upper, abdominal pain, stomach discomfort, abdominal discomfort, epigastric discomfort.
- ^c Somnolence includes the terms: sedation, somnolence.
- ^d Insomnia includes the terms: insomnia, initial insomnia, middle insomnia, and terminal insomnia.
- ^e Urinary hesitation includes the terms: urinary hesitation, urine flow decreased.
- ^f Based on total number of males (atomoxetine, N=943; placebo, N=869).
- ^g Based on total number of females (atomoxetine, N=754; placebo, N=691).

The following adverse events occurred in at least 2% of adult CYP2D6 poor metabolizer (PM) patients and were statistically significantly more frequent in PM patients compared to non-PM patients (EM patients): vision blurred (4% of PMs, 1% of EMs); dry mouth (35% of PMs, 17% of EMs); constipation (11% of PMs, 7% of EMs); feeling jittery (5% of PMs, 2% of EMs); decreased appetite (23% of PMs, 15% of EMs); tremor (5% of PMs, 1% of EMs); insomnia (19% of PMs, 11% of EMs); sleep disorder (7% of PMs, 3% of EMs); middle insomnia (5% of PMs, 3% of EMs); terminal insomnia (3% of PMs, 1% of EMs); urinary retention (6% of PMs, 1% of EMs); erectile dysfunction (21% of PMs, 9% of EMs); ejaculation disorder (6% of PMs, 2% of EMs); hyperhidrosis (15% of PMs, 7% of EMs); peripheral coldness (3% of PMs, 1% of 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 labeling are likely to underestimate the actual incidence. Table 4 above displays the incidence of sexual side effects reported by at least 2% of adult patients taking atomoxetine in placebo-controlled trials.

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

6.2 Postmarketing Spontaneous Reports

The following adverse reactions have been identified during post approval use of atomoxetine. Unless otherwise specified, these adverse reactions have occurred in adults and children and adolescents. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cardiovascular system — QT prolongation, syncope.

Periarticular vascular effects — Raynaud's phenomenon.

General disorders and administration site conditions — Lethargy.

Musculoskeletal system — Rhabdomyolysis.

Nervous system disorders — Hypoaesthesia; paraesthesia in children and adolescents; sensory disturbances; tics.

Psychiatric disorders — Depression and depressed mood; anxiety; libido changes.

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

Skin and subcutaneous tissue disorders — Alopecia, hyperhidrosis.

Urogenital system — Male pelvic pain; urinary hesitation in children and adolescents; urinary retention in children and adolescents.

7 DRUG INTERACTIONS

7.1 Monoamine Oxidase Inhibitors

With other drugs that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when taken in combination with an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity [see *Contraindications (4.2)*].

7.2 Effect of CYP2D6 Inhibitors on Atomoxetine

In extensive metabolizers (EMs), inhibitors of CYP2D6 (e.g., paroxetine, fluoxetine, and quinidine) increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in poor metabolizers (PMs). In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and C_{max} is about 3- to 4-fold greater than atomoxetine alone.

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

7.3 Antihypertensive Drugs and Pressor Agents

Because of possible effects on blood pressure, atomoxetine should be used cautiously with antihypertensive drugs and pressor agents (e.g., dopamine, dobutamine) or other drugs that increase blood pressure.

7.4 Albuterol

Atomoxetine should be administered with caution to patients being treated with systemically-administered (oral or intravenous) albuterol (or other beta₂ agonists) because the action of albuterol on the cardiovascular system can be potentiated resulting in increases in heart rate and blood pressure. Albuterol (800 mcg iv over 2 hours) induced increases in heart rate and blood pressure. These effects were potentiated by atomoxetine (60 mg BID for 5 days) and were most marked after the initial coadministration of albuterol and atomoxetine. However, these effects on heart rate and blood pressure were not seen in another study after the coadministration with inhaled dose of albuterol (200 to 800 mcg) and atomoxetine (60 mg QD for 7 days) in 21 healthy Asian subjects who were excluded for poor metabolizer status.

7.5 Effect of Atomoxetine on P450 Enzymes

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

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

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

7.6 Alcohol

Consumption of ethanol with atomoxetine did not change the intoxicating effects of ethanol.

7.7 Methylphenidate

Coadministration of methylphenidate with atomoxetine did not increase cardiovascular effects beyond those seen with methylphenidate alone.

7.8 Drugs Highly Bound to Plasma Protein

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

7.9 Drugs that Affect Gastric pH

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C — Pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, a decrease in live fetuses and an increase in early resorptions was observed. Slight increases in the incidences of atypical clefts of the hard palate and absent subclavian artery were observed. These findings were observed at doses that caused slight maternal toxicity. The no-effect dose for these findings was 30 mg/kg/day. The 100 mg/kg dose is approximately 23 times the maximum human dose on a 4 mg/kg basis; plasma levels (AUC) of atomoxetine at this dose in rabbits are estimated to be 3.3 times (extensive metabolizers) or 0.4 times (poor metabolizers) those in humans receiving the maximum human dose.

Rats were treated with up to approximately 50 mg/kg/day of atomoxetine (approximately 6 times the maximum human dose on a 4 mg/kg basis) in the diet from 2 weeks prior to 10 weeks (males) prior to mating through the periods of organogenesis and lactation. In 1 of 2 studies, decreases in pup weight and pup survival were observed. The decreased pup survival was also seen at 25 mg/kg (but not at 13 mg/kg). In a study in which diet rats were treated with atomoxetine in the diet from 2 weeks (females) or 10 weeks (males) prior to mating throughout the period of organogenesis, a decrease in fetal weight (female only) and an increase in the incidence of incomplete ossification of the vertebral arch in fetuses were observed at 40 mg/kg/day (approximately 5 times the maximum human dose on a 4 mg/kg basis) but not at 20 mg/kg/day.

No adverse fetal effects were seen when pregnant rats were treated with up to 150 mg/kg/day (approximately 17 times the maximum human dose on a mg/m² basis) by gavage throughout the period of organogenesis.

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

8.2 Labor and Delivery

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

8.3 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 atomoxetine is administered to a nursing woman.

8.4 Pediatric Use

Anyone considering the use of atomoxetine in a child or adolescent must balance the potential risks with the clinical need [see *Broad Warning and Warnings and Precautions (5.1)*].

The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The safety, efficacy, and pharmacokinetics of atomoxetine in pediatric patients less than 6 years of age have not been evaluated.

A study was conducted in young rats to evaluate the effects of atomoxetine on growth and neurobehavioral and sexual development. Rats were treated with 1, 10, or 50 mg/kg/day (approximately 0.2, 2, and 8 times, respectively, the maximum human dose on a mg/m² 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 at 15 mg/kg/day in 15 (100%) male and 10 (100%) female rats 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.

8.5 Geriatric Use

The safety, efficacy and pharmacokinetics of atomoxetine in geriatric patients have not been evaluated.

8.6 Hepatic Insufficiency

Atomoxetine exposure (AUC) is increased, compared with normal subjects, in EM subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic insufficiency. Dose adjustment is recommended for patients with moderate or severe hepatic insufficiency [see *Dosage and Administration (2.3)*].

8.7 Renal Insufficiency

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

8.8 Gender

Gender did not influence atomoxetine disposition.

8.9 Ethnic Origin

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

8.10 Patients with Concomitant Illness

Tics in patients with ADHD and comorbid Tourette's Disorder — Atomoxetine administered in a flexible dose range of 0.5 to 1.5 mg/kg/day (mean dose of 1.3 mg/kg/day) and placebo were compared in 148 randomized pediatric (age 7 to 17 years) subjects with a DSM-IV diagnosis of ADHD and comorbid tic disorder in an 18 week, double-blind, placebo-controlled study in which the majority (80%) enrolled in this trial with Tourette's Disorder (Tourette's Disorder: 116 subjects; chronic motor tic disorder: 29 subjects). A non-inferiority analysis revealed that atomoxetine did not worsen tics in these patients as determined by the Yale Global Tic Severity Scale Total Score (YGTS). Out of 148 patients who entered the acute treatment phase, 103 (69.6%) patients discontinued the study. The primary reason for discontinuation in both the atomoxetine (38 of 76 patients, 50.0%) and placebo (45 of 72 patients, 62.5%) treatment groups was identified as lack of efficacy with most of the patients discontinuing at Week 12. This was the first visit where patients with a CGI-S-4 could also meet the criteria for "clinical non-responder" (CGI-S remained the same or increased from study baseline) and be eligible to enter an open-label extension study with atomoxetine. There have been postmarketing reports of tics [see *Adverse Reactions (6.2)*].

Anxiety in patients with ADHD and comorbid Anxiety Disorders — In two post-marketing, double-blind, placebo-controlled trials, it has been demonstrated that treating patients with ADHD and comorbid anxiety disorders with atomoxetine does not worsen their anxiety.

In a 12-week double-blind, placebo-controlled trial, 176 patients, aged 8 to 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. Following a 2-week double-blind placebo lead-in, atomoxetine was initiated at 40 mg/day to a maximum dose of 100 mg/day (mean daily dose 83 mg/day +/- 19.5 mg/day). Atomoxetine did not worsen anxiety in these patients as determined by the Liebowitz Social Anxiety Scale (LSAS). Of the 413 patients who completed the double-blind placebo lead-in, 149 (36.1%) patients discontinued the study. There have been postmarketing reports of anxiety [see *Adverse Reactions (6.2)*].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Atomoxetine is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

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

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

10 OVERDOSAGE

10.1 Human Experience

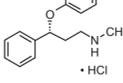
There is limited clinical trial experience with atomoxetine overdose. During postmarketing, there have been fatalities reported involving a mixed ingestion overdose of atomoxetine and at least one other drug. There have been no reports of death involving overdose of atomoxetine alone, including intentional overdoses at amounts up to 1400 mg. In some cases of overdose involving atomoxetine, seizures have been reported. The most commonly reported symptoms accompanying acute and chronic overdoses of atomoxetine were gastrointestinal symptoms, somnolence, dizziness, tremor, and abnormal behavior. Hyperactivity and agitation have also been reported. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g., tachycardia, blood pressure increased, mydriasis, dry mouth) have also been observed. Most events were mild to moderate. Less commonly, there have been reports of QT prolongation and mental changes, including disorientation and hallucinations [see *Clinical Pharmacology (12.2)*].

10.2 Management of Overdose

Consult with a Certified Poison Control Center for up to date guidance and advice. Because atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

11 DESCRIPTION

Atomoxetine is a selective norepinephrine reuptake inhibitor. Atomoxetine hydrochloride is the (R) isomer as determined by x-ray diffraction. The chemical designation is (+)-1-Methyl-3-phenyl-3-(o-tolylpropyl)propanamine hydrochloride. The molecular formula is C₁₇H₂₁NO·HCl, which corresponds to a molecular weight of 291.82. The chemical structure is:



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

Atomoxetine capsules USP are intended for oral administration only.

Each capsule contains atomoxetine hydrochloride USP equivalent to 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg, or 100 mg of atomoxetine. The capsules also contain the following inactive ingredients: pregelatinized starch and simethicone emulsion. The empty hard gelatin capsule shells consist of titanium dioxide and sodium lauryl sulfate. The 18 mg capsules contain iron oxide yellow, 25 mg and 40 mg capsules FD&C Blue No. 2, 60 mg capsules FD&C Blue No. 2 and iron oxide yellow, 80 mg and 100 mg contain iron oxide red and iron oxide yellow. The capsules are printed with edible ink containing black iron oxide and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

An exposure-response analysis encompassing doses of atomoxetine (0.5, 1.2 or 1.8 mg/kg/day) or placebo demonstrated atomoxetine exposure correlates with efficacy as measured by the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Parent Version. Investigator administered and scored. The exposure-efficacy relationship was similar to that observed between dose and efficacy with median exposures at the two highest doses resulting in near maximal changes from baseline [see *Clinical Studies (14.2)*].

Cardiac Electrophysiology — The effect of atomoxetine on QTc prolongation was evaluated in a randomized, double-blind, positive-(moxifloxacin 400 mg) and placebo-controlled, cross-over study in healthy male CYP2D6 poor metabolizers. A total of 120 healthy subjects were administered atomoxetine (20 mg and 60 mg) twice daily for 7 days. No large changes in QTc interval (i.e., increases >60 msec from baseline, absolute QTc >480 msec) were observed in the study. However, small changes in QTc interval cannot be excluded from the current study, because the study failed to demonstrate assay sensitivity. There was a slight increase in QTc interval with increased atomoxetine concentration.

12.3 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. For PMs, AUC of atomoxetine is approximately 10-fold and C_{max} is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of D-desmethylyatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylyatomoxetine is much longer in PM subjects (34 to 40 hours).

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

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

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

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

Metabolism and elimination — Atomoxetine is metabolized primarily through the CYP2D6 enzymatic pathway. People with reduced activity in this pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). For PMs, AUC of atomoxetine is approximately 10-fold and C_{max} is about 5-fold greater than EMs. Laboratory tests are available to identify CYP2D6 PMs. Coadministration of atomoxetine 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 *Warnings and Precautions (5.3)*]. Atomoxetine did not inhibit or induce the CYP2D6 pathway.

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

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis — 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/m² 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/m² basis.

Mutagenesis — 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 Chinese hamster ovary cells, and *in vivo* sister chromatid exchange test in Chinese hamster ovary cells with dichloromethane, suggesting endoreplication (numerical aberration).

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

Impairment of fertility — Atomoxetine hydrochloride 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/m² basis.

14 CLINICAL STUDIES

14.1 ADHD Studies in Children and Adolescents

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

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

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

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

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

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

Maintenance Study — The effectiveness of atomoxetine in the maintenance treatment of ADHD was established in an outpatient study of children and adolescents (ages 6 to 15 years). Patients meeting DSM-IV criteria for ADHD who showed continuous response for about 4 weeks during an initial 10-week open-label treatment phase with atomoxetine (1.2 to 1.8 mg/kg/day) were randomized to continuation of their current dose of atomoxetine (N=292) or to placebo (N=124) under double-blind treatment for observation of relapse. Response during the open-label phase was defined as CGI-ADHD-S score <2 and a reduction of at least 25% from baseline in ADHDRS-IV-Parent-IV total score. Patients who were assigned to atomoxetine and showed continuous response for approximately 8 months during the first double-blind treatment phase were again randomized to continuation of their current dose of atomoxetine (N=81) or to placebo (N=82) under double-blind treatment for observation of relapse. Relapse during the double-blind phase was defined as CGI-ADHD-S score increases of at least 2 from the end of open-label phase and ADHDRS-IV-Parent-IV total score returns to >90% of study entry score for 2 consecutive visits. In both double-blind phases, patients receiving continued atomoxetine treatment experienced significantly longer times to relapse than those receiving placebo.

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