ATOMOXETINE HYDROCHLORIDE- atomoxetine hydrochloride capsule
REMEDYREPACK INC.

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

ATOMOXETINEcapsules, for oral use
Initial U.S. Approval: 2002

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS IN PEDIATRIC PATIENTS 6 YEARS OF AGE AND OLDER

See full prescribing information for complete boxed warning.

- **All atomoxetine-treated pediatric patients 6 years of age or older should be monitored and observed closely for suicidal thoughts and behavior, clinical worsening, or unusual changes in behavior, especially during the initial months of therapy or at times of dosage changes (5.1)**
- **Consider stopping atomoxetine capsules in patients who experience emergent suicidal thoughts and behavior (5.1)**
- **Atomoxetine capsules increased the risk of suicidal ideation in pediatric patients aged 6 years of age and older with attention-deficit/hyperactivity disorder (ADHD) in short-term studies(5.1)**

INDICATIONS AND USAGE

Atomoxetine capsules are a selective norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of ADHD in adults and pediatric patients 6 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Prior to initiating treatment with atomoxetine capsules, screen patients for a personal or family history of bipolar disorder, mania, or hypomania. (2.1, 5.6)
- See table below for the recommended atomoxetine capsule dosage. (2.3)

Age and Body Weight	Starting Dosage	Target Dosage [1]	Maximum Total Daily Dose [1]
Pediatrics who weigh less than 70 kg	0.5 mg/kg/day	1.2 mg/kg/day	1.4 mg/kg/day or 100 mg/day (whichever is less)
Pediatrics who weigh 70 kg or more and adults	40 mg/day	80 mg/day	100 mg/day

[1] Administer either as once daily dosage in the morning or as evenly divided twice daily dosage in the morning and late afternoon/early evening.

- For the recommended dosage in patients with hepatic impairment, see Full Prescribing Information. (2.4)
- For the recommended dosage with concomitant use of a strong CYP2D6 inhibitor or in CYP2D6 poor metabolizers, see Full Prescribing Information. (2.5)

DOSAGE FORMS AND STRENGTHS

Capsules: contain 10 mg of atomoxetine. (3, 11, 16)

CONTRAINDICATIONS

Contraindicated in patients (4):

- With known hypersensitivity to atomoxetine or other constituents of atomoxetine capsules.
- Taking or within 14 days of stopping, a monoamine oxidase inhibitor (MAOI)
- With narrow angle glaucoma
- With pheochromocytoma or history of pheochromocytoma
- With severe cardiac or vascular disorders whose condition would be expected to deteriorate with clinically important increases in blood pressure or heart rate

WARNINGS AND PRECAUTIONS

- *Severe Liver Injury:*Atomoxetine capsules should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury. (5.2)
- *Serious Cardiovascular Reactions:*Prior to atomoxetine capsules treatment, patients should have a careful history and physical exam to assess for presence of cardiovascular (CV) disease. Atomoxetine capsules generally should not be used in pediatric patients with known serious cardiac abnormalities,

cardiomyopathy, serious arrhythmias. Consideration should be given to not using atomoxetine capsules in adults with clinically significant cardiac abnormalities. Patients who develop symptoms suggestive of cardiac disease during atomoxetine capsules treatment should stop atomoxetine capsules and undergo a prompt cardiac evaluation. (5.3)
- *Increase in Blood Pressure and Heart Rate:*Heart rate and blood pressure should be measured at baseline, following atomoxetine dosage increase, and periodically while on therapy. (5.4)
- *New Psychotic or Manic Symptoms and Activation of Mania:*If psychotic or manic symptoms occur, consider discontinuing atomoxetine capsules. (5.5)
- *Aggressive Behavior or Hostility:*Monitor for the appearance or worsening of aggressive behavior or hostility. (5.7)
- *Effects on Urine Outflow:*Urinary retention or hesitancy may occur. (5.9)
- *Priapism:*Prompt medical attention is required in the event of suspected priapism. (5.10)
- *Effect on Growth in Pediatric Patients:*Closely monitor growth (e.g., weight, height) in pediatric patients. (5.11)

ADVERSE REACTIONS

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

Patients should be instructed to use caution when driving a car or operating hazardous machinery (because of somnolence) until they are reasonably certain that their performance is not affected by atomoxetine capsules. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Apotex Corp. at 1-800-706-5575 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Monoamine Oxidase Inhibitors:*Concomitant use contraindicated. (4, 7)
- *Strong CYP2D6 Inhibitors:*With concomitant use of atomoxetine capsules and strong CYP2D6 inhibitors, increase the titration intervals. (7)
- *Antihypertensives:*Increase the frequency of monitoring blood pressure and adjust atomoxetine capsules dosage as clinically appropriate. (7)
- *Albuterol (or other beta2 agonists):*Increase the frequency of monitoring blood pressure and heart rate. (7)

USE IN SPECIFIC POPULATIONS

- *Hepatic Impairment:*Increased exposure (AUC) to atomoxetine in subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) compared to subjects with normal liver function. (8.6and 12.3)
- *Use in Genomic Subgroups:*CYP2D6 poor metabolizers have higher systemic exposures which may increase the risks of atomoxetine capsules-related adverse reactions compared to other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 9/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS IN PEDIATRIC PATIENTS 6 YEARS OF AGE AND OLDER

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations Prior to Initiating Atomoxetine Capsules Treatment

2.2 Administration Instructions

2.3 Recommended Dosage

2.4 Recommended Dosage in Patients with Hepatic Impairment

2.5 Recommended Dosage with Concomitant Use of Strong CYP2D6 Inhibitors or in CYP2D6 Poor Metabolizers

2.6 Switching to or from a Monoamine Oxidase Inhibitor Antidepressant

2.7 Recommendations for a Missed Dose

2.8 Recommendations for Discontinuation
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Suicidal Thoughts and Behaviors in Pediatric Patients 6 Years of Age and Older
5.2 Severe Liver Injury
5.3 Serious Cardiovascular Reactions
5.4 Increase in Blood Pressure and Heart Rate
5.5 New Psychotic or Manic Symptoms and Activation of Mania
5.6 Screening Patients for Bipolar Disorder
5.7 Aggressive Behavior or Hostility
5.8 Hypersensitivity Reactions
5.9 Effects on Urine Outflow
5.10 Priapism
5.11 Effect on Growth in Pediatric Patients
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Patients with Hepatic Impairment
8.7 Use in Genomic Subgroups
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
14.1 ADHD Studies in Pediatric Patients 6 Years of Age and Older
14.2 ADHD Studies in Adults
14.3 Safety Studies in ADHD Patients with Tourette's Disorder or Chronic Motor Tic Disorder OR Anxiety Disorder
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

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

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS IN PEDIATRIC PATIENTS 6 YEARS OF AGE AND OLDER

All atomoxetine-treated pediatric patients 6 years of age or older should be monitored and observed closely for suicidal thoughts and behavior, clinical worsening, or unusual changes in behavior, especially during the initial months of therapy or at times of dosage changes. Families and caregivers should be advised of the need for close observation and communication with the health care provider. Consider stopping atomoxetine capsules in patients who experience emergent suicidal thoughts and behavior*[see Warnings and Precautions (5.1)].*

Atomoxetine capsules increased the risk of suicidal ideation in pediatric patients aged 6 years of age and older with attention-deficit/hyperactivity disorder (ADHD) in short-term studies.

1 INDICATIONS AND USAGE

Atomoxetine capsules are indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adults and pediatric patients 6 years of age and older.

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 ADHD.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations Prior to Initiating Atomoxetine Capsules Treatment

Prior to initiating treatment with atomoxetine capsules, screen patients for a personal or family history of bipolar disorder, mania, or hypomania *[see Warnings and Precautions (5.6)].*

2.2 Administration Instructions

Atomoxetine capsules may be taken with or without food. Take atomoxetine capsules whole; do not open the capsules.

2.3 Recommended Dosage

Table 1 includes the recommended atomoxetine capsules dosage in adult patients and pediatric patients 6 years of age and older for acute treatment of ADHD.

Table 1: Recommended Dosage of Atomoxetine Capsules for Acute Treatment of ADHD

Age and BodyWeight	Starting Dosage	Titration Interval	Target Dosage	Maximum Dosage
Pediatric patients who weigh less than 70 kg	0.5 mg/kg/day	Minimum of 3 days	1.2 mg/kg/day [a,b]	1.4 mg/kg/day or 100 mg/day, whichever is less [a]

Pediatric patients who weigh 70 kg or more and adult patients	40 mg/day	Minimum of 3 days	80 mg/day [a]	100 mg/day [a,c]

[a]Administer either as once daily dosage in the morning or as evenly divided twice daily dosage in the morning and late afternoon/early evening.

[b]No additional benefit has been demonstrated with atomoxetine capsules dosages higher than 1.2 mg/kg/day *[see Clinical Studies (14)].*

[c] If a patient has not achieved an optimal response at 80 mg/day after 2 to 4 additional weeks, may increase the dosage to a maximum of 100 mg/day. There is no data that supports increased effectiveness at a dosage higher than 100 mg/day *[see Clinical Studies (14)].*

The health care provider who elects to use atomoxetine capsules for extended periods should periodically reevaluate the long-term usefulness of atomoxetine capsules for the individual patient.

2.4 Recommended Dosage in Patients with Hepatic Impairment

For patients aged 6 years of age or older with:

- Severe hepatic impairment (HI) (Child-Pugh Class C), the recommended initial and target atomoxetine capsules dosage is 25% of recommended dosage in patients with normal hepatic function *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*
- Moderate HI (Child-Pugh Class B), the recommended initial and target atomoxetine capsules dosage is 50% of the recommended dosage in patients with normal hepatic function *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)].*
- Mild HI (Child-Pugh Class A), the recommended initial and target atomoxetine capsules dosage is the same as those with normal hepatic function.

2.5 Recommended Dosage with Concomitant Use of Strong CYP2D6 Inhibitors or in CYP2D6 Poor Metabolizers

Consider genetic testing to determine the patient's CYP2D6 metabolizer status.

In patients taking a concomitant strong CYP2D6 inhibitor or who are CYP2D6 poor metabolizers, a longer titration interval of 4 weeks is recommended, if ADHD symptoms fail to improve and the initial atomoxetine capsules dosage is well tolerated. The recommended starting, target, and maximum atomoxetine capsules dosages are the same as outlined in Table 1 *[see Dosage and Administration (2.3)].*

For other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate), follow the recommended dosage, including the recommended titration interval (minimum of 3 days), as outlined in Table 1 *[see Dosage and Administration (2.3)].*

2.6 Switching to or from a Monoamine Oxidase Inhibitor Antidepressant

At least 14 days must elapse between discontinuation of a monoamine oxidase inhibitor (MAOI) antidepressant and initiation of atomoxetine capsules. In addition, at least 14 days must elapse after stopping atomoxetine capsules before starting an MAOI antidepressant.

2.7 Recommendations for a Missed Dose

If an atomoxetine capsule dose is missed, take the dose as soon as possible, but do not take more than the prescribed total daily amount of atomoxetine capsules in any 24-hour period.

2.8 Recommendations for Discontinuation

When discontinuing atomoxetine capsules, no taper is needed *[see Drug Abuse and Dependence (9.2, 9.3)]* .

3 DOSAGE FORMS AND STRENGTHS

Each capsule contains atomoxetine hydrochloride, USP equivalent to:

- 10 mg of atomoxetine (Opaque White, Opaque White)

4 CONTRAINDICATIONS

Atomoxetine capsules are contraindicated in patients:

- With known hypersensitivity reaction to atomoxetine or other constituents of atomoxetine capsules. Hypersensitivity reactions included anaphylaxis, angioneurotic edema, urticaria, and rash *[see Warnings and Precautions (5.8)].*
- Taking, or within 14 days of stopping, a monoamine oxidase inhibitor (MAOI) *[see Drug Interactions (7)].*
- With narrow angle glaucoma. In clinical trials, atomoxetine capsules use was associated with an increased risk of mydriasis.
- 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 atomoxetine capsules.
- With severe cardiac or vascular disorders whose condition would be expected to deteriorate if they had a clinically important increase in blood pressure or heart rate (e.g., 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 Thoughts and Behaviors in Pediatric Patients 6 Years of Age and Older

- All atomoxetine-treated pediatric patients should be monitored and observed closely for clinical worsening, suicidal thoughts and behavior, and unusual changes in behavior, especially during the initial few months of atomoxetine therapy, or at times of dosage changes, either increases or decreases.
- Families and caregivers of atomoxetine-treated pediatric patients should be alerted about the need to monitor patients daily for the emergence of agitation, irritability, unusual changes in behavior, and mental health-related symptoms, as well as the emergence of suicidal thoughts and behavior, and to report such symptoms immediately to a health care provider.
- Consider changing the therapeutic regimen, including stopping atomoxetine capsules, in patients who experience emergent suicidality or symptoms that might be precursors to emerging suicidal thoughts and behavior, especially if these symptoms are severe or abrupt in onset, or were not part of the patient’s presenting symptoms.

Atomoxetine capsules increased the risk of suicidal ideation in pediatric patients 6 years and older with ADHD in pooled placebo-controlled short-term studies (6 to 18 weeks). In 12 studies (11 studies in patients with ADHD and 1 study in another population) with over 2,200 pediatric patients, the mean incidence of suicidal ideation in atomoxetine-treated pediatric patients was 0.4% (5/1,357) (including one patient with a suicide attempt) compared to 0% (0/851) in placebo-treated pediatric patients. No suicides occurred in these studies. All the suicidal ideations occurred in pediatric patients 6 to 12 years of age, and all occurred during the first month of atomoxetine capsules

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 capsules for ADHD did not reveal an increased risk of suicidal ideation or behavior.

The following psychiatric symptoms have been reported with atomoxetine capsules: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania. Although a causal link between the emergence of such symptoms and the emergence of suicidal impulses has not been established, there is a concern that such symptoms may represent precursors to emerging suicidality.

5.2 Severe Liver Injury

Atomoxetine capsules should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury. Liver enzyme and function tests should be obtained upon the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained “flu like” symptoms).

Postmarketing reports indicate that atomoxetine can cause severe liver injury.

Although no evidence of liver injury was detected in clinical trials of about 6,000 patients, there have been rare cases of clinically significant liver injury that were considered probably or possibly related to atomoxetine use during postmarketing use:

- Rare cases of liver failure have been reported during postmarketing use, including a case that resulted in a liver transplant.
- Reported cases of liver injury occurred within 120 days of initiation of atomoxetine in most cases and some patients presented with markedly elevated liver enzymes (>20 times upper limit of normal (ULN)), and jaundice with significantly elevated bilirubin levels (>2 times ULN), followed by recovery upon atomoxetine discontinuation. In one patient, liver injury, manifested by elevated hepatic enzymes up to 40 times ULN and jaundice with bilirubin up to 12 times ULN, recurred upon rechallenge, and was followed by recovery upon atomoxetine discontinuation, providing evidence that atomoxetine likely caused the liver injury. Such reactions may occur several months after atomoxetine is started, but laboratory abnormalities may continue to worsen for several weeks after atomoxetine is stopped.

5.3 Serious Cardiovascular Reactions

Risk Management Recommendations for Serious Cardiovascular Reactions

Prior to atomoxetine capsules treatment, adults or pediatric patients 6 years of age or older 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 cardiovascular disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram, echocardiogram).

- Although some serious heart problems alone carry an increased risk of sudden death, atomoxetine capsules generally should not be used in pediatric patients with known serious structural cardiac abnormalities, cardiomyopathy, serious arrhythmias, or other serious cardiac problems.
- Consideration should be given to not treating adults with atomoxetine capsules with clinically significant cardiac abnormalities.

Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during atomoxetine capsules treatment should stop atomoxetine capsules and undergo a prompt cardiac evaluation.

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

*Pediatric Patients 6 Years of Age and Older:*Sudden death has been reported in

association with atomoxetine treatment at the recommended dosage in pediatric patients 6 years of age and older with structural cardiac abnormalities or other serious heart problems.

*Adults:*Sudden deaths, stroke, and myocardial infarction have been reported in atomoxetine-treated adults at the recommended ADHD dosage. Although the role of atomoxetine in these adult cases is also unknown, adults have a greater likelihood than pediatric patients of having serious structural cardiac abnormalities, cardiomyopathy, serious arrhythmias, coronary artery disease, or other serious cardiac problems.

5.4 Increase in Blood Pressure and Heart Rate

Atomoxetine capsules are contraindicated in patients with severe cardiac or vascular disorders whose condition would be expected to deteriorate if they had a clinically important increase in blood pressure or heart rate. Atomoxetine capsules 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. 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. Heart rate and blood pressure should be measured at baseline, following atomoxetine dosage increases, and periodically while on therapy to detect possible clinically important increases in heart rate and blood pressure.

In the pediatric and adult patients in short-term, placebo-controlled clinical studies of ADHD, there were a greater proportion of atomoxetine-treated patients, compared to placebo-treated patients, who had an increase in diastolic blood pressure (DBP) ≥15 mm Hg, systolic blood pressure (SBP) ≥20 mm Hg and heart rate ≥20 bpm *[see Adverse Reactions (6.1)].*

Increase in Blood Pressure and Heart Rate

- In placebo-controlled studies of pediatric patients 6 years of age and older with ADHD, tachycardia was identified as an adverse reaction in 0.3% (5/1,597) of atomoxetine-treated patients compared with 0% (0/934) of placebo-treated patients.
- In placebo-controlled adult ADHD studies, tachycardia was identified as an adverse reaction in 1.5% (8/540) of atomoxetine-treated patients compared with 0.5% (2/402) of placebo-treated patients.
- Orthostatic hypotension and syncope have been reported in atomoxetine-treated patients. In ADHD studies in pediatric patients 6 years of age and older, 0.2% (12/5,596) of atomoxetine-treated patients had orthostatic hypotension and 0.8% (46/5,596) had syncope. In short-term ADHD studies in pediatric patients 6 years of age and older, 1.8% (6/340) of atomoxetine-treated patients had orthostatic hypotension compared with 0.5% (1/207) of placebo-treated patients. Syncope was not reported during these studies.

Increase in Blood Pressure and Heart Rate in CYP2D6 Poor Metabolizers

- In placebo-controlled studies of pediatric patients 6 years of age and older with ADHD, the mean heart rate increase was 9.4 beats/minute in CYP2D6 poor metabolizers and was 5 beats/minute in other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate).
- In adult clinical trials where CYP2D6 metabolizer status was available, the mean heart rate increase in CYP2D6 poor metabolizers was significantly higher than in other CYP2D6 metabolizer types (11 beats/minute versus 7.5 beats/minute, respectively).

In adult clinical trials where CYP2D6 metabolizer status was available, the mean change from baseline in DBP in CYP2D6 poor metabolizers was higher than in other CYP2D6 metabolizer types (4.2 versus 2.1 mm Hg) as was the mean change from baseline in SBP (CYP2D6 poor metabolizers: 2.8 versus other CYP2D6 metabolizer types: 2.4 mm

Hg).

5.5 New Psychotic or Manic Symptoms and Activation of Mania

If psychotic or manic symptoms occur, consider discontinuing atomoxetine capsules.

Psychotic symptoms (e.g., hallucinations, delusional thinking) manic symptoms (e.g., mania) in patients without a prior history of psychotic illness or mania can be caused by atomoxetine capsules at the recommended dosage.

5.6 Screening Patients for Bipolar Disorder

Before initiating treatment with atomoxetine capsules, patients should be adequately screened for risk factors for bipolar disorder such as a personal or family history of mania and depression.

Patients with bipolar disorder or risk factors for bipolar disorder may be at increased risk of developing mania or mixed episodes during treatment with atomoxetine. It may not be possible to determine whether a manic or mixed episode that appears during treatment with atomoxetine is due to an adverse reaction to atomoxetine or a patient's underlying bipolar disorder.

5.7 Aggressive Behavior or Hostility

Patients beginning treatment with atomoxetine should be monitored for the appearance or worsening of aggressive behavior or hostility.

There is evidence that atomoxetine may cause the emergence or worsening of aggressive behavior or hostility. ADHD and other mental illnesses can be associated with irritability, which can make it difficult to determine if atomoxetine or the underlying psychiatric condition is causing the emergence or worsening of aggressive behavior or hostility in specific patients. If such symptoms occur during treatment, consider a possible causal role of atomoxetine.

5.8 Hypersensitivity Reactions

Atomoxetine capsules are contraindicated in patients with known hypersensitivity reaction to atomoxetine or other constituents of atomoxetine capsules.

Although uncommon, hypersensitivity reactions, including anaphylaxis, angioneurotic edema, urticaria, and rash, have been reported in atomoxetine-treated patients.

5.9 Effects on Urine Outflow

A complaint of urinary retention or urinary hesitancy should be considered potentially related to atomoxetine.

In adult ADHD controlled studies, the incidence of urinary retention (1.7%, 9/540) and urinary hesitation (5.6%, 30/540) were increased among atomoxetine-treated patients compared with placebo-treated patients (0%, 0/402; 0.5%, 2/402, respectively). Two atomoxetine-treated adult patients and no placebo-treated patients discontinued from controlled clinical studies because of urinary retention.

5.10 Priapism

Prompt medical attention is required in the event of suspected priapism in atomoxetine-treated patients.

Rare postmarketing cases of priapism, defined as painful and nonpainful penile erection lasting more than 4 hours, have been reported for pediatric and adult patients treated with atomoxetine. The erections resolved in cases in which follow-up information was

available, some following discontinuation of atomoxetine.

5.11 Effect on Growth in Pediatric Patients

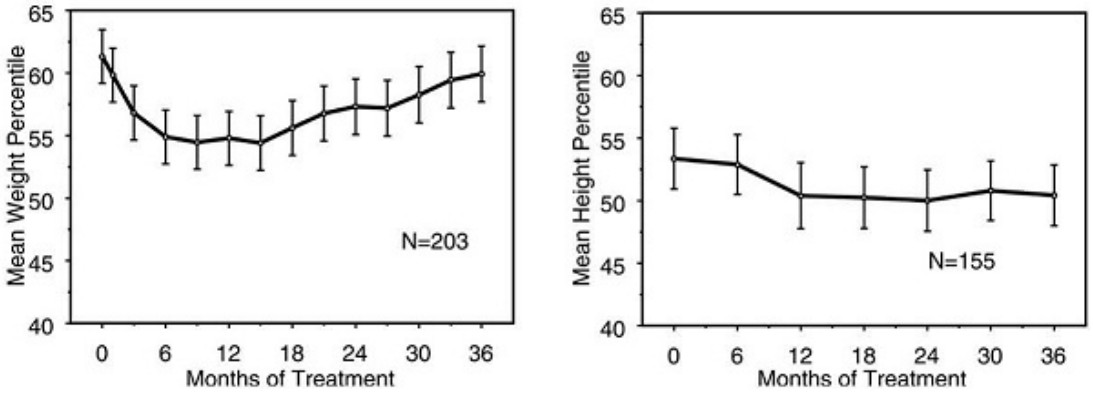
Closely monitor growth (e.g., weight, height) in pediatric patients during atomoxetine treatment.

Weight and Height in Long-Term Open-Label Studies in Pediatric Patients

Data on the long-term effects of atomoxetine on growth in pediatric patients from open-label studies in which weight and height changes were compared to normative pediatric population data. In general, the weight and height gain of atomoxetine-treated pediatric patients lagged behind that predicted by normative population data for about the first 9 to 12 months of treatment and subsequently (see Figure 1 below):

- Weight gain rebounded. At about 3 years of atomoxetine treatment, patients gained a mean of 17.9 kg, which was 0.5 kg more than predicted by their baseline data.
- Height gain stabilized. At 3 years of atomoxetine treatment, patients gained a mean of 19.4 cm, which was 0.4 cm less than predicted by their baseline data .

Figure 1:Mean Weight and Height Percentiles Over Time for Atomoxetine-Treated Pediatric Patients in Comparison to Normative Pediatric Population Values



After three years of atomoxetine treatment in the long-term open-label studies, patients who were:

- Pre-pubertal at the start of treatment (girls ≤8 years old, boys ≤9 years old) gained weight and height; however, the mean weight gain was 2.1 kg less than predicted and the mean height gain was 1.2 cm less than predicted.
- Pubertal (girls >8 to ≤13 years old, boys >9 to ≤14 years old) or late pubertal (girls >13 years old, boys >14 years old), the mean weight and height gains were close to or exceeded predicted weight and height gains.
  CYP2D6 poor metabolizers and other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) treated with atomoxetine for at least two years gained weight and height. However, in:
- CYP2D6 poor metabolizers the mean weight gain was 2.4 kg less than predicted and the mean height gain was 1.1 cm less than predicted
- Other CYP2D6 metabolizer types the mean weight gain was 0.2 kg less than predicted and the mean height gain was 0.4 cm less than predicted.

In the long-term open-label studies, the growth pattern was generally similar regardless of pubertal status at the time of atomoxetine treatment initiation.

Weight and Height in Short-Term, Placebo-Controlled Studies in Pediatric Patients

In short-term, placebo-controlled studies (up to 9 weeks), atomoxetine-treated patients lost an average of 0.4 kg in weight and gained an average of 0.9 cm in height, compared to a gain of 1.5 kg in weight and 1.1 cm in height in the placebo-treated patients.

In a fixed-dose controlled trial, 1.3%, 7.1%, 19.3%, and 29.1% of patients in the placebo, 0.5, 1.2, and 1.8 mg/kg/day atomoxetine groups, respectively, lost at least 3.5% of their body weight.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Atomoxetine was administered to 5,382 pediatric patients 6 years of age and older in clinical ADHD studies (Studies 1, 2, 3, 4, and 5) *[see Clinical Studies (14.1)]* and 1,007 adults in clinical ADHD studies (Studies 6 and 7) *[see Clinical Studies (14.2)]* . In the ADHD clinical trials, 2,529 pediatric patients were treated for over 6 months which included 1,625 pediatric patients who were treated for longer than 1 year.

Adverse Reactions in the Clinical Trials of Pediatric Patients 6 Years of Age and Older with ADHD

Discontinuation of Treatment Due to Adverse Reactions in the Clinical Studies of Pediatric Patients 6 Years of Age and Older:

In the acute placebo-controlled studies of pediatric patients 6 years of age and older with ADHD, 3% (48/1,613) of atomoxetine-treated pediatric patients and 1.4% (13/945) of placebo-treated pediatric patients discontinued due to an adverse reaction. Among atomoxetine-treated patients, irritability (0.3%, N=5); somnolence (0.3%, N=5); aggression (0.2%, N=4); nausea (0.2%, N=4); vomiting (0.2%, N=4); abdominal pain (0.2%, N=4); constipation (0.1%, N=2); fatigue (0.1%, N=2); feeling abnormal (0.1%, N=2); and headache (0.1%, N=2) were the reasons for discontinuation reported by more than one patient.

For all studies, (including open-label and long-term studies), 6% of atomoxetine-treated pediatric patients who were other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) and 11% of those who were CYP2D6 poor metabolizers discontinued due to an adverse reaction.

*Common Adverse Reactions in the Clinical Studies of Pediatric Patients 6 Years of Age and Older:*Common adverse reactions (incidence of 2% or greater in atomoxetine-treated patients and with a higher incidence in atomoxetine-treated patients compared to placebo-treated patients) in pediatric patients 6 years of age and older with ADHD are listed in Table 2. The most commonly observed adverse reactions in atomoxetine-treated patients (incidence of ≥5% and ≥ twice the incidence in placebo-treated patients), for either twice daily or once daily dosing were: nausea, vomiting, fatigue, decreased appetite, abdominal pain, and somnolence (see Tables 2 and 3).

Table 2: Common Adverse Reactions [a]in Acute Studies (up to 18 weeks) in Pediatric Patients 6 Years and Older with ADHD

Adverse Reaction	Atomoxetine (N=1,597)	Placebo (N=934)
Headache	19%	15%
Abdominal pain [b]	18%	10%

Decreased appetite	16%	4%
Somnolence [c]	11%	4%
Vomiting	11%	6%
Nausea	10%	5%
Fatigue	8%	3%
Irritability	6%	3%
Dizziness	5%	2%
Decreased weight	3%	0%
Anorexia	3%	1%
Rash	2%	1%

[a] Adverse reactions reported by at least 2% of atomoxetine-treated patients and greater than placebo-treated patients.

[b]Abdominal pain includes the terms: upper abdominal pain, and epigastric discomfort.

[c]Somnolence includes the term sedation.

Adverse reaction in the atomoxetine-treated patients who received twice daily, and once daily dosing are shown in Table 3 (adverse reactions based on statistically significant Breslow-Day tests).

Table 3: Common Adverse Reactions in Acute Studies (up to 18 weeks) in Pediatric Patients 6 Years and Older with ADHD

Adverse Reaction	ADHD Studies with Twice Daily Dosing		ADHD Studies with Once Daily Dosing	
	Atomoxetine (N=715)	Placebo (N=434)	Atomoxetine (N=882)	Placebo (N=500)
Abdominal pain [a]	17%	13%	18%	7%
Vomiting	11%	8%	11%	4%
Nausea	7%	6%	13%	4%
Fatigue	6%	4%	9%	2%
Mood swings [b]	2%	0%	1%	1%
Constipation [c]	2%	1%	1%	0%

[a]Abdominal pain included the terms: upper abdominal pain, and epigastric discomfort.
[b]Mood swings didn't meet the statistical significance on Breslow-Day test at 0.05 level, but p-value was <0.1 (trend).
[c]Constipation didn't meet the statistical significance on Breslow-Day test but is included in the table because of pharmacologic plausibility.

*Common Adverse Reactions by CYP2D6 Metabolizer Status in the Clinical Studies of Pediatric Patients 6 Years of Age and Older:*Table 4 displays adverse reactions that occurred in at least 2% of atomoxetine-treated pediatric patients who were CYP2D6 poor metabolizers and were statistically significantly more frequent in CYP2D6 poor metabolizers compared with other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate).

Table 4: Common Adverse Reactions [a]in Atomoxetine-treated Pediatric Patients 6 Years and Older with ADHD by CYP2D6 Metabolizer Types

	Atomoxetine CYP2D6	Atomoxetine Other CYP2D6

Adverse Reaction	CYP2D6 Poor Metabolizers (N=355)	Other CYP2D6 Metabolizer Types (N=5,019)
Insomnia	11%	6%
Decreased weight	7%	4%
Constipation	7%	4%
Depression [b]	7%	4%
Tremor	5%	1%
Excoriation	4%	2%
Sedation	4%	2%
Middle insomnia	3%	1%
Conjunctivitis	3%	1%
Syncope	3%	1%
Early morning awakening	2%	1%
Mydriasis	2%	1%

[a] Adverse reactions that occurred in at least 2% of atomoxetine-treated pediatric patients who were CYP2D6 poor metabolizers and were statistically significantly more frequent in poor metabolizers compared with other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate).
[b]Depression included the following terms: major depression, depressive symptoms, depressed mood, dysphoria.

*Less Common Adverse Reactions in the Clinical Studies of Pediatric Patients 6 Years of Age and Older:*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: blood pressure increased, early morning awakening (terminal insomnia), flushing, mydriasis, sinus tachycardia, asthenia, palpitations, mood swings, constipation, and dyspepsia. The following reactions were reported by at least 2% of patients treated with atomoxetine, and equal to or less than placebo: pharyngolaryngeal pain, insomnia (insomnia includes the terms, insomnia, initial insomnia, middle insomnia). The following reaction did not meet this criterion but shows a statistically significant dose relationship: pruritus.

*Seizures in the Clinical Studies of Pediatric Patients 6 Years of Age and Older:*Atomoxetine has not been systematically evaluated in pediatric patients with seizure disorder as these patients were excluded from atomoxetine studies. In the clinical development program, seizures were reported in 0.2% (12/5,073) of atomoxetine-treated pediatric patients whose average age was 10 years old (range 6 to 16 years of age). In these clinical trials, the seizure incidence among CYP2D6 poor metabolizers was 0.3% (1/293) compared to 0.2% (11/4,741) for other CYP2D6 metabolizer types.

*Heart Rate and Blood Pressure Increases in the Clinical Studies of Pediatric Patients 6 Years of Age and Older:*Additional data from ADHD clinical trials (controlled and uncontrolled) has shown that approximately 5 to 10% of pediatric patients experienced potentially clinically important changes in heart rate (≥20 beats per minute) or blood pressure (≥15 to 20 mm Hg) *[see Contraindications (4) and Warnings and Precautions (5.4)].*

Adverse Reactions in the Clinical Trials of Adults with ADHD
*Discontinuation of Treatment Due to Adverse Reactions in the Clinical Studies of Adults:*In the acute adult placebo-controlled trials, 11.3% (61/541) atomoxetine-treated patients and 3% (12/405) placebo-treated patients discontinued for adverse reactions. Among atomoxetine-treated patients, insomnia (0.9%, N=5); nausea (0.9%, N=5); chest pain (0.6%, N=3); fatigue (0.6%, N=3); anxiety (0.4%, N=2); erectile dysfunction (0.4%, N=2); mood swings (0.4%, N=2); nervousness (0.4%, N=2); palpitations (0.4%, N=2);

and urinary retention (0.4%, N=2) were the reasons for discontinuation reported by more than 1 patient.

*Common Adverse Reactions in the Clinical Studies of Adults:*Commonly observed adverse reactions associated with the use of atomoxetine (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (atomoxetine incidence greater than placebo) are listed in Table 5. The most commonly observed adverse reactions in patients treated with atomoxetine (incidence of 5% or greater and at least twice the incidence in placebo patients) were: constipation, dry mouth, nausea, decreased appetite, dizziness, erectile dysfunction, and urinary hesitation (see Table 5).

Table 5: Common Adverse Reactions [a]Associated in Acute Studies (up to 25 weeks) of Adult Patients with ADHD

Adverse Reaction	**Atomoxetine (N=1,697)**	**Placebo (N=1,560)**
Nausea	26%	6%
Dry mouth	20%	5%
Decreased appetite	16%	3%
Insomnia [b]	15%	8%
Fatigue	10%	6%
Erectile dysfunction [c]	8%	1%
Constipation	8%	3%
Dizziness	8%	3%
Somnolence [d]	8%	5%
Abdominal pain [e]	7%	4%
Urinary hesitation [f]	6%	1%
Irritability	5%	3%
Ejaculation delayed [c]and/or ejaculation disorder [c]	4%	1%
Hyperhidrosis	4%	1%
Dyspepsia	4%	2%
Vomiting	4%	2%
Abnormal dreams	4%	3%
Chills	3%	0%
Paraesthesia	3%	0%
Hot flush	3%	0%
Palpitations	3%	1%
Libido decreased	3%	1%
Sleep disorder	3%	1%
Dysmenorrhea [g]	3%	2%
Dysuria	2%	0%
Thirst	2%	1%
Weight decreased	2%	1%
Feeling jittery	2%	1%

[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, dysgeusia, agitation, restlessness, micturition urgency, pollakiuria, pruritus, urticaria, flushing, tremor, menstruation irregular, rash, and urinary retention.

[b]Insomnia includes the terms initial insomnia, middle insomnia, terminal insomnia and other related terms.
[c]Based on total number of males (atomoxetine group, N=943; placebo group, N=869).
[d]Somnolence includes related terms.
[e]Abdominal pain includes the terms: upper abdominal pain and other related terms.
[f] Urinary hesitation includes the term decreased urine flow.
[g] Based on total number of females (atomoxetine, N=754; placebo, N=691).

*Common Adverse Reactions by CYP2D6 Metabolizer Status in the Clinical Studies of Adults:*Table 6 displays adverse reactions that occurred in at least 2% of atomoxetine-treated adult patients who were CYP2D6 poor metabolizers and were statistically significantly more frequent compared to other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate).

Table 6: Common Adverse Reactions [a]in Atomoxetine-treated Adult Patients with ADHD by CYP2D6 Metabolizer Types

Adverse Reaction	Atomoxetine CYP2D6 Poor Metabolizers (N=203)	Atomoxetine Other CYP2D6 Metabolizer Types (N=3,599)
Dry mouth	35%	17%
Decreased appetite	23%	15%
Erectile dysfunction	21%	9%
Insomnia	19%	11%
Hyperhidrosis	15%	7%
Constipation	11%	7%
Sleep disorder	7%	3%
Urinary retention	6%	1%
Ejaculation disorder	6%	2%
Tremor	5%	1%
Feeling jittery	5%	2%
Middle insomnia	5%	3%
Blurred vision	4%	1%
Terminal insomnia	3%	1%
Peripheral coldness	3%	1%

[a]Adverse reactions that occurred in at least 2% of atomoxetine-treated adult patients who were CYP2D6 poor metabolizers and were statistically significantly more frequent in CYP2D6 poor metabolizers compared with other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate).

*Less Common Adverse Reactions in the Clinical Studies of Adults:*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, dysgeusia, agitation, restlessness, micturition urgency, pollakiuria, pruritus, urticaria, flushing, tremor, menstruation irregular, rash, and urinary retention.

*Seizures in the Clinical Studies of Adults:*Atomoxetine capsules have not been systematically evaluated in adult patients with a seizure disorder as these patients were excluded from clinical studies during the product’s premarket testing. In the clinical

development program, seizures were reported on 0.1% (1/748) of adult patients. In these clinical trials, no CYP2D6 poor metabolizers (0/43) reported seizures compared to 0.1% (1/705) for other CYP2D6 metabolizer types.

*Heart Rate and Blood Pressure Increases in the Clinical Studies of Adults:*Table 7 displays the proportion of atomoxetine-treated and placebo-treated patients who had an increase in diastolic blood pressure (DBP) ≥15 mm Hg, systolic blood pressure (SBP) ≥20 mm Hg, or heart rate ≥ 20 bpm in short-term, placebo-controlled clinical studies in pediatric and adult patients with ADHD *[see Warnings and Precautions (5.4)].*

Table 7: Proportion of ADHD Patients With an Increase of ≥ 15 mm Hg in DBP, ≥20 mm Hg in SBP, or ≥ 20 bpm in Heart Rate [a]

	Pediatric Acute ADHD Studies				**Adult Acute ADHD Studies**			
	Maximum [b]		**Endpoint**		**Maximum [b]**		**Endpoint**	
	Atomoxetine	**Placebo**	**Atomoxetine**	**Placebo**	**Atomoxetine**	**Placebo**	**Atomoxetine**	**Placebo**
DBP (≥15 mm Hg)	22%	14%	9%	5%	13%	9%	5%	4%
SBP (≥20 mm Hg)	13%	9%	5%	3%	12%	8%	4%	3%
HR (≥20 bpm)	23%	12%	12%	4%	22%	8%	10%	2%

[a]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 the clinical studies.

Additional data from ADHD clinical trials (controlled and uncontrolled) showed that approximately 5 to 10% of adult patients had potentially clinically important changes in heart rate (≥20 beats per minute) or blood pressure (≥15 to 20 mm Hg) *[see Contraindications (4) and Warnings and Precautions (5.4)]* .

*Male and Female Sexual Dysfunction in the Clinical Studies of Adults:*Atomoxetine impaired sexual function in some patients. Estimates of the incidence of untoward sexual experience and performance in these studies are likely to underestimate their actual incidence because patients and health care providers may be reluctant to discuss them. Table 5 displays the incidence of sexual adverse reactions (reported by at least 2% of atomoxetine-treated adult patients in the placebo-controlled studies of adults with ADHD (i.e., erectile dysfunction, dysmenorrhea, and ejaculation delayed and/or ejaculation disorder).

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, health care providers should routinely inquire about sexual dysfunction.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of atomoxetine. Unless otherwise specified, these adverse reactions have occurred in adults and pediatric patients. 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.
- Peripheral vascular effects: Raynaud's phenomenon.
- General disorders and administration site conditions: Lethargy.
- Musculoskeletal system: Rhabdomyolysis.
- Nervous system disorders: Hypoaesthesia; paraesthesia in pediatric patients; sensory disturbances; tics.
- Psychiatric disorders: Depression and depressed mood; anxiety, libido changes.
- Seizures: Seizures have been reported and included patients with pre-existing seizure disorders, those with identified risk factors for seizures, and 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 pediatric patients; urinary retention in pediatric patients.

7 DRUG INTERACTIONS

See Table 8 for clinically significant drug interactions with atomoxetine and other drugs.

Table 8: Clinically Significant Drug Interactions with Atomoxetine and Other Drugs

Monoamine Oxidase Inhibitors (MAOIs)	
Prevention or Management	Atomoxetine is contraindicated in patients taking MAOIs, including MAOIs such as linezolid or intravenous methylene blue, or in patients who stopped an MAOI within 14 days.
Mechanism and Clinical Effect(s)	As with other drugs affecting brain monoamine concentrations, there have been reports of serious, sometimes fatal reactions (hyperthermia, rigidity, myoclonus, autonomic instability with fluctuations of vital signs, extreme agitation progressing to delirium/coma) with concomitant use of atomoxetine and an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.
Strong CYP2D6 Inhibitors	
Prevention or Management	With concomitant use of atomoxetine and a strong CYP2D6 inhibitor, increase the titration interval *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)].*
Mechanism and Clinical Effect(s)	Atomoxetine is a CYP2D6 substrate. The concomitant use of atomoxetine and a strong CYP2D6 inhibitor increases atomoxetine exposure *[see Clinical Pharmacology (12.3)].*
Antihypertensive Drugs	
Prevention or Management	Increase the frequency of monitoring blood pressure and adjust atomoxetine dosage as clinically appropriate.
Mechanism and Clinical Effect(s)	Because of increased risk of increased blood pressure, atomoxetine should be used cautiously with antihypertensive drugs, other drugs that increase blood pressure or pressor drugs (e.g., dopamine, dobutamine).
Albuterol or Other Beta2 Agonists	
Prevention or Management	Increase the frequency of monitoring blood pressure and heart rate and adjust atomoxetine dosage as clinically appropriate.
Mechanism	Systemically administered albuterol (e.g., oral) can be potentiated by

and Clinical Effect(s)	atomoxetine, resulting in increases in heart rate and blood pressure *[see Clinical Pharmacology (12.3)]* .

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD drugs, including atomoxetine, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visiting https://womensmentalhealth.org/adhd-medications/

Risk Summary

Available published studies with atomoxetine use in pregnant women are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

Some animal reproduction studies of atomoxetine had adverse developmental outcomes. One of 3 studies in pregnant rabbits dosed during organogenesis resulted in decreased live fetuses and an increase in early resorptions, as well as slight increases in the incidences of atypical origin of carotid artery and absent subclavian artery. These effects were observed at plasma levels (AUC) 3 times and 0.4 times the human plasma levels in other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) and poor metabolizers receiving the maximum recommended human dose (MRHD), respectively. In rats dosed prior to mating and during 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 a dose approximately 5 times the MRHD on a mg/m ^{2}basis. In one of 2 studies in which rats were dosed prior to mating through the periods of organogenesis and lactation, decreased pup weight and decreased pup survival were observed at doses corresponding to 5-6 times the MRHD on a mg/m ^{2}basis. No adverse fetal effects were seen in pregnant rats dosed during the organogenesis period *(see Data).*

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

Data

*Animal Data:*Pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, a decrease in live fetuses and an increase in early resorptions was observed. Slight increases in the incidences of atypical origin of carotid artery and absent subclavian artery were observed. These findings were observed at doses that caused slight maternal toxicity. The no-effect dose for these findings was 30 mg/kg/day. The 100 mg/kg dose is approximately 23 times the MRHD on a mg/m ^{2}basis; plasma levels (AUC) of atomoxetine at this dose in rabbits are estimated to be 3.3 times (other CYP2D6 metabolizer types) or 0.4 times (CYP2D6 poor metabolizers) those in humans receiving the MRHD.

Rats were treated with up to approximately 50 mg/kg/day of atomoxetine (approximately 6 times the MRHD on a mg/m ^{2}basis) in the diet from 2 weeks (females) or 10 weeks (males) prior to mating through the periods of organogenesis and lactation. In 1 of 2 studies, decreases in pup weight and pup survival were observed. The

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

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

8.2 Lactation

Risk Summary

There are no data on the presence of atomoxetine or its metabolite in human milk, the effects on the breastfed child, or the effects on milk production. Atomoxetine is present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for atomoxetine and any potential adverse effects on the breastfed child from atomoxetine or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of atomoxetine for the treatment of ADHD have been established in pediatric patients 6 years of age and older. Anyone considering the use of atomoxetine in a pediatric patient should balance the potential risks with the clinical need *[see Boxed Warning and Warnings and Precautions (5.1, 5.3, 5.4, 5.10)].*

The atomoxetine pharmacokinetics in pediatric patients 6 years of age and older were similar to those in adults.

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

Juvenile Toxicity Animal Data

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.

8.5 Geriatric Use

The safety, efficacy and pharmacokinetics of atomoxetine in geriatric patients have not been evaluated. Clinical studies of atomoxetine did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

8.6 Patients with Hepatic Impairment

Compared with patients with normal hepatic function atomoxetine exposure (AUC) was

increased in patients with moderate (Child-Pugh Class B) (2-fold increase) and in patients with severe hepatic impairment (Child-Pugh Class C) (4-fold increase). The recommended dosage in patients with moderate or severe hepatic impairment is lower than in patients with normal hepatic function *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)].*

8.7 Use in Genomic Subgroups

The recommended titration interval (before increasing the atomoxetine dosage) is longer in CYP2D6 poor metabolizers than other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) *[see Dosage and Administration (2.5)].*

Atomoxetine plasma concentrations were higher in CYP2D6 poor metabolizers which may increase the risk of atomoxetine-related adverse reactions. In pediatric and adult patients, the mean heart rate was higher in CYP2D6 poor metabolizers compared to other CYP2D6 metabolizer types. In adult patients, the mean change from baseline in diastolic and systolic blood pressure was higher in CYP2D6 poor metabolizers compared to other CYP2D6 metabolizer types *[see Warnings and Precautions (5.4), Clinical Pharmacology (12.3, 12.5)].*

The prevalence of CYP2D6 poor metabolizers is approximately 7% in White populations, 2% in Asian populations, and 2% in Black or African American populations.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Atomoxetine capsules contains atomoxetine which is not a controlled substance.

9.2 Abuse

In a randomized, double-blind, placebo-controlled, abuse-potential study in adults that compared effects of atomoxetine capsules and placebo, atomoxetine was not associated with stimulant or euphoriant properties. Clinical study data in over 2,000 adults and pediatric patients with ADHD and over 1,200 adults with depression (atomoxetine capsules is not indicated for the treatment of depression) showed only isolated incidents of inappropriate atomoxetine self-administration.

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

9.3 Dependence

After atomoxetine capsules discontinuation, there was no evidence of symptom rebound or adverse reactions suggesting an atomoxetine capsules-discontinuation or withdrawal syndrome.

10 OVERDOSAGE

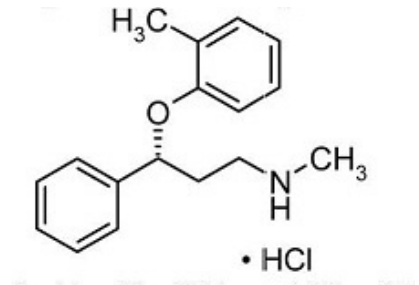
During postmarketing use, there have been fatalities reported involving a mixed ingestion overdose of atomoxetine and at least one other drug. There have been no reports of death involving overdose of atomoxetine alone, including intentional overdoses at amounts up to 1,400 mg (14 times the maximum recommended dosage). The most commonly reported symptoms with 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. In some cases of overdose involving atomoxetine, seizures have been reported. Less commonly, there have been reports of QT prolongation and mental changes, including disorientation and hallucinations *[see Clinical Pharmacology (12.2)].*

If an overdose occurs, consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations. Because atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of atomoxetine overdose.

11 DESCRIPTION

Atomoxetine is a selective norepinephrine reuptake inhibitor. Atomoxetine hydrochloride, USP is the *R*(-) isomer as determined by x-ray diffraction. The chemical designation is (-)-*N*-Methyl-3-phenyl-3-(*o*-tolyloxy)- propylamine hydrochloride. The molecular formula is $C_{17}H_{21}NO \cdot HCl$, 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 for oral administration only.

Each capsule contains atomoxetine hydrochloride, USP equivalent to 10, 18, 25, 40, 60, 80, or 100 mg of atomoxetine. The capsules also contain pregelatinized starch. The capsule shells contain gelatin and titanium dioxide. The capsule shells may also contain one or more of the following: FD&C Blue No. 2 (25 mg, 40 mg, and 60 mg), iron oxide red (80 mg and 100 mg), and iron oxide yellow (18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg). The capsules are imprinted with edible black ink (comprised of ammonia solution, iron oxide black, potassium hydroxide, propylene glycol, and shellac).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

An exposure-response analysis of atomoxetine (0.5, 1.2 or 1.8 mg/kg/day) or placebo demonstrated atomoxetine exposure correlates with efficacy as measured by the ADHD Rating Scale-IV-Parent Version: Investigator administered and scored. The exposure-efficacy relationship was similar to that observed between atomoxetine dosage and efficacy with median atomoxetine 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 interval prolongation was evaluated in a randomized, double-blinded, 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 this study, because the study failed to demonstrate assay sensitivity. There was a slight increase in QTc interval with increased atomoxetine concentration.

Pharmacodynamic Drug Interaction Studies

- Consumption of ethanol with atomoxetine did not change the intoxicating effects of ethanol.
- Concomitant use of atomoxetine with methylphenidate did not increase cardiovascular effects beyond those seen with methylphenidate alone.
- Albuterol 600 mcg given intravenously over 2 hours (albuterol is not approved for intravenous use) induced heart rate and blood pressure increases; these effects were potentiated when co-administered with atomoxetine (60 mg twice daily for 5 days), particularly initially *[see Drug Interactions (7)].*

12.3 Pharmacokinetics

Pharmacokinetic parameters for atomoxetine and its metabolites in CYP2D6 poor metabolizers and other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) are presented in Table 9.

Table 9: Atomoxetine and Metabolite Pharmacokinetics in Adult CYP2D6 Poor Metabolizers and Other CYP2D6 Metabolizer Types

Parameter	Other CYP2D6 Metabolizer Types [a]	CYP2D6 Poor Metabolizers [b]
Absorption		
Dose proportionality	10 to 120 mg	
Accumulation	1.1-fold	3.3-fold
Absolute bioavailability	63%	94%
T_{max} median	1 hour	2.5 hour
Effect of Food	AUC: Unchanged; C_{max}: Decreased 37%; T_{max}: Delayed 3 hours	
Distribution		
Protein Binding	98%	
Volume of distribution	0.85 L/kg	
Elimination		
Atomoxetine half-life	5.2 hours	21.6 hours
Atomoxetine apparent oral clearance	0.35 L/hr/kg	0.03 L/hr/kg
4-Hydroxyatomoxetine half-life	6 to 8 hours	--
N-Desmethylatomoxetine half-life	6 to 8 hours	34 to 40 hours
Metabolism		
Primary metabolic		

Primary metabolic pathways	CYP2D6	Other CYP enzymes
4-Hydroxyatomoxetine[c] concentration	1% of atomoxetine	0.1% of atomoxetine [d]
N-Desmethylatomoxetine[e] concentration	5% of atomoxetine	45% of atomoxetine
Excretion		
Urine	Greater than 80% of the administered dose excreted as 4-hydroxyatomoxetine-O-glucuronide; Less than 3% as unchanged drug	
Feces	Less than 17% of the administered dose	

Abbreviations: $C_{max,ss}$= maximum atomoxetine plasma concentration at steady state; T_{max}= time to peak concentration

[a]In this analysis, other CYP2D6 metabolizer types were defined as individuals who were not CYP2D6 poor metabolizers and included CYP2D6 ultrarapid, normal, and intermediate metabolizers.

[b]CYP2D6 poor metabolizers were defined as individuals with two nonfunctional alleles (e.g., CYP2D6*3/*4, CYP2D6*5/*5), and as a result no CYP2D6 enzyme activity.

[c]Primarily formed by CYP2D6.The major oxidative metabolite formed, regardless of CYP2D6 metabolizer type, and is further glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the norepinephrine transporter.

[d]4-hydroxyatomoxetine is formed at a slower rate by several other cytochrome P450 enzymes.

[e]Formed by CYP2C19 and other cytochrome P450 enzymes but has substantially (20-fold) less pharmacological activity compared with atomoxetine.

Specific Populations

*Hepatic Impairment:*Atomoxetine exposure (AUC) was increased in subjects with moderate (Child-Pugh Class B) (2-fold increase) and severe (Child-Pugh Class C) (4-fold increase) hepatic impairment compared to subjects with normal hepatic function in other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) *[see Dosage and Administration (2.4) and Use in Specific Populations (8.6)].*

*Renal Impairment:*Patients with severe renal impairment (end stage renal disease requiring hemodialysis) had higher systemic atomoxetine exposure (about a 65% increase) than patients with normal renal function (CrCl ≥ 90 ml/minute) in other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate), but there was no difference when exposure was corrected for mg/kg dose. Thus, the differences in exposure were not clinically significant.

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

*Sex:*Sex did not influence atomoxetine disposition.

*Ethnic Origin:*Ethnic origin did not influence atomoxetine disposition.

Drug Interaction Studies

Clinical Studies:

*Strong CYP2D6 Inhibitors:*Concomitant use of atomoxetine (20 mg BID for 5 days) with paroxetine (20 mg QD for 17 days), a known inhibitor of CYP2D6, in subjects who were not CYP2D6 poor metabolizers resulted in a 6.5-fold higher plasma exposure (AUC) to atomoxetine at steady state.

Concomitant use of atomoxetine (at sequential dosing of 10, 45, and 75 mg BID for up to 5 days of each dosage) with fluoxetine (20 mg QD for 36 days) a known inhibitor of CYP2D6, in subjects who were not CYP2D6 poor metabolizers resulted in 6- to 8-fold increases of plasma atomoxetine exposure (AUC) at steady state compared to taking atomoxetine alone.

After concomitant use of atomoxetine with paroxetine or fluoxetine, the $C_{ss,max}$of atomoxetine was about 3-to 4-fold greater than the use of atomoxetine alone *[see Drug Interactions (7)].*

*CYP3A Substrates:*Concomitant use of atomoxetine (60 mg twice daily for 12 days) with midazolam (CYP3A substrate) (single dose of 5 mg), resulted in 15% increase in the midazolam AUC. This pharmacokinetic change is not clinically significant.

*CYP2D6 Substrates:*Concomitant use of atomoxetine (40 or 60 mg twice daily for 13 days) with desipramine, (CYP2D6 substrate) (single dose of 50 mg), did not alter the desipramine pharmacokinetics.

*Drugs that Affect Gastric pH:*Drugs that elevate gastric pH had no effect on atomoxetine bioavailability.

In Vitro Studies:

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

*CYP Inhibition/induction:*Atomoxetine did not cause clinically important inhibition or induction of cytochrome P450 enzymes (including CYP1A2, CYP3A, CYP2D6, and CYP2C9).

12.5 Pharmacogenomics

Atomoxetine is metabolized by CYP2D6 *[see Clinical Pharmacology (12.3)].* The gene encoding CYP2D6 has variants that affect CYP2D6 metabolic function. CYP2D6 poor metabolizers are individuals with two nonfunctional alleles (e.g., CYP2D6*5/*5), and as a result have no CYP2D6 enzyme activity.

Atomoxetine AUC was approximately 10-fold higher and atomoxetine C_{ss}, max was approximately 5-fold higher in CYP2D6 poor metabolizers compared to other CYP2D6 metabolizer types [*see Dosage and Administration (2.5), Warnings and Precautions (5.4), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]* . In this analysis, other CYP2D6 metabolizer types were defined as individuals who were not CYP2D6 poor metabolizers and included CYP2D6 ultrarapid, normal, and intermediate metabolizers (e.g., CYP2D6*1/*2xN, CYP2D6*1/*1, CYP2D6*1/*5, respectively).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis— Atomoxetine HCl was not carcinogenic in rats and mice when given in the diet for 2 years at time-weighted average doses up to 47 and 458 mg/kg/day, respectively. The highest dose used in rats is approximately 8 and 5 times the maximum recommended human dose (MRHD) 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 (other CYP2D6 metabolizer types) or 0.2 times (CYP2D6 poor metabolizers) those in humans receiving the maximum human dose. The highest dose used in mice is approximately 39 and 26 times the MRHD in children and adults, respectively, on a mg/m ^{2}basis.

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

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

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

14 CLINICAL STUDIES

14.1 ADHD Studies in Pediatric Patients 6 Years of Age and Older

Acute Studies in Pediatric Patients 6 Years of Age and Older with ADHD:

The effectiveness of atomoxetine in the treatment of ADHD was established in four randomized, double-blind, placebo-controlled studies of pediatric patients 6 to 18 years of age (Studies 1, 2, 3, and 4). In these studies, 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 these studies, signs and symptoms of ADHD were evaluated with the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive subscales by comparing the mean change from baseline to endpoint in the atomoxetine and placebo groups using an intent-to-treat (ITT) analysis (the primary endpoint). 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, pediatric patients 8 to 18 years of age (N=297) received either a fixed dosage of atomoxetine (0.25, 0.6, or 0.9 mg/kg twice daily (in the early morning and late afternoon/early evening) or placebo. Improvements in ADHD symptoms were statistically significantly superior in patients treated with either of the two higher atomoxetine dosages compared with patients treated with placebo as measured on the ADHDRS scale. The 0.9 mg/kg twice daily atomoxetine dosage did not provide any additional benefit over that observed with the 0.6 mg/kg twice daily atomoxetine dosage. The 0.25 mg/kg twice daily atomoxetine dosage group was not superior to the placebo group.

In Study 2, a 6-week randomized, double-blind, placebo-controlled, acute treatment study, pediatric patients 6 to 16 years of age (N=171) received either atomoxetine or placebo. Atomoxetine was administered as a once daily dose in the early morning and titrated on a weight-adjusted basis according to clinical response, up to a maximum dosage of 1.5 mg/kg once daily. The mean final dosage of atomoxetine was

approximately 1.3 mg/kg once daily. ADHD symptoms were statistically significantly improved in the atomoxetine group compared to the placebo group, as measured on the ADHDRS scale. Study 2 showed that atomoxetine was effective when administered once daily in the morning.

In two identically designed, 9-week, acute, double-blind, placebo-controlled studies, pediatric patients 7 to 13 years of age (Study 3, N=147; Study 4, N=144) were randomized to receive atomoxetine, methylphenidate, or placebo. In Studies 3 and 4, atomoxetine was administered twice daily (in the early morning and late afternoon, after school) and titrated on a weight-adjusted basis according to clinical response up to the maximum recommended atomoxetine dosage of 1 mg/kg twice daily. The mean final dosage of atomoxetine in Studies 3 and 4 was approximately 0.8 mg/kg twice daily. In Studies 3 and 4, ADHD symptoms statistically significantly improved more in the atomoxetine group than the placebo group, as measured on the ADHDRS scale.

Examination of population subsets based on sex and age (<12 and 12 to 17 years of age) in these studies did not reveal any differences in response. There were not sufficient numbers of patients in racial or ethnic groups to determine if there were differences in responses in these subgroups.

Maintenance Study in Pediatric Patients 6 Years of Age and Older with ADHD

The effectiveness of atomoxetine in the maintenance treatment of ADHD in pediatric patients 6 years of age and older was established in an outpatient randomized withdrawal study of pediatric patients 6 to 15 years of age (Study 5). In this study, patients who met DSM-IV criteria for ADHD, and 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 continue of their current atomoxetine dosage (N=292) or to placebo (N=124) under double-blind treatment for observation of relapse (first double-blind phase). 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: Investigator total score.

Patients who were assigned to atomoxetine during the first double-blind phase who showed continuous response for approximately 8 months during the first double-blind treatment phase were again randomized to continue their current atomoxetine dosage (N=81) or placebo (N=82) under double-blind treatment for observation of relapse (second double-blind phase). Relapse during each of the double-blind phases was defined as CGI-ADHD-S score increases of at least 2 from the end of open-label phase and ADHDRS-IV-Parent: Investigator total score returns to ≥90% of study entry score for 2 consecutive visits.

In both double-blind phases, patients who received atomoxetine treatment experienced significantly longer times to relapse than those who received placebo.

14.2 ADHD Studies in Adults

The effectiveness of atomoxetine in the treatment of ADHD in adults was established in two 10-week randomized, double-blind, placebo-controlled clinical studies of adult patients 18 years of age and older, who met DSM-IV criteria for ADHD (Study 6, N=280; Study 7, N=256).

In Studies 6 and 7, signs and symptoms of ADHD were evaluated using the 30-item investigator-administered Conners Adult ADHD Rating Scale Screening Version (CAARS). In these studies, the primary efficacy endpoint was the mean change from baseline to endpoint (using an ITT analysis) in the 18-item Total ADHD Symptom score (the sum of the inattentive and hyperactivity/impulsivity subscales from the CAARS).

In Studies 6 and 7, patients received either atomoxetine or placebo. Patients in the atomoxetine group received 30 mg to 60 mg twice a day (in the early morning and late afternoon/early evening) of atomoxetine which was titrated according to clinical

response. The mean final atomoxetine dosage in these studies was approximately 48 mg twice daily. In both studies, ADHD symptoms were statistically significantly improved in the atomoxetine group compared to the placebo group, as measured on the ADHD Symptom score from the CAARS scale.

In Studies 6, and 7, examination of population subsets based on sex and age (<42 and ≥42 years of age) did not reveal any differences in response. There was not sufficient number of patients in racial and ethnic groups to determine if there were differences in responses among these subgroups.

14.3 Safety Studies in ADHD Patients with Tourette's Disorder or Chronic Motor Tic Disorder OR Anxiety Disorder

Tics in Patients with ADHD and Tourette's Disorder or Chronic Motor Tic Disorder

In a randomized, double-blind, placebo-controlled 18-week trial in 148 pediatric patients 7 to 17 years old with a DSM-IV diagnosis of ADHD and concurrent Tourette syndrome or chronic motor tic disorder, atomoxetine affect on tic severity was assessed. Patients in the atomoxetine group received a flexible dosage range of 0.5 to 1.5 mg/kg/day (mean dose of 1.3 mg/kg/day). In this study, 80% (n=116) of patients had Tourette's Disorder and 20% (n=29) of patients had chronic motor tic disorder. 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 (YGTSS). Out of 148 patients who entered the acute treatment phase, 103 (70%) patients discontinued the study. The primary reason for discontinuation in both the atomoxetine group (50% (38/76) and placebo group (63% (45/72) was identified lack of ADHD efficacy with most of the patients discontinuing at Week 12. There have been postmarketing reports of tics in atomoxetine-treated patients *[see Adverse Reactions (6.2)].*

Anxiety in Pediatric Patients with ADHD and Anxiety Disorders

Two post-marketing, double-blind, placebo-controlled trials 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 pediatric patients 8-17 years of age, 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 to receive atomoxetine or placebo. In the atomoxetine group, following a 2-week double-blind placebo lead-in, atomoxetine was initiated at 0.8 mg/kg/day with increase to a target dose of 1.2 mg/kg/day (median dose 1.3 mg/kg/day +/- 0.29 mg/kg/day). Atomoxetine did not worsen anxiety in these patients as determined by the Pediatric Anxiety Rating Scale (PARS). Of the 158 patients who completed the double-blind placebo lead-in, 26 (16%) patients discontinued the study.

In a separate 16-week, double-blind, placebo-controlled trial, 442 patients aged 18-65, who met DSM-IV criteria for adult ADHD and social anxiety disorder (23% of whom also had Generalized Anxiety Disorder) were randomized to receive atomoxetine or placebo. In the atomoxetine group, following a 2-week double-blind placebo lead-in, atomoxetine was initiated at 40 mg/day to a maximum dosage 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, 36% (n=149) patients discontinued the study. There have been postmarketing reports of anxiety *[see Adverse Reactions (6.2)].*

16 HOW SUPPLIED/STORAGE AND HANDLING

Atomoxetine capsules, USP 10 mg are available for oral administration as hard gelatin capsules with a white opaque body and a white opaque cap, imprinted "APO AM10" in

black ink. They are supplied as follows:

NDC: 70518-4313-00

NDC: 70518-4313-01

PACKAGING: 30 in 1 BOX

PACKAGING: 1 in 1 POUCH

Store at 20°C to 25°C (68°F to 77°F) excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Repackaged and Distributed By:

Remedy Repack, Inc.

625 Kolter Dr. Suite #4 Indiana, PA 1-724-465-8762

17 PATIENT COUNSELING INFORMATION

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

Repackaged By / Distributed By: RemedyRepack Inc.

625 Kolter Drive, Indiana, PA 15701

(724) 465-8762

Suicide Risk

Patients, their families, and their caregivers should be alerted about the need to monitor patients daily for the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, depression, and suicidal ideation, especially early during atomoxetine treatment and when the dosage is adjusted. Such symptoms should be reported to the patient's health care provider immediately *[see Warnings and Precautions (5.1)].*

Severe Liver Injury

Patients initiating atomoxetine should be cautioned that severe liver injury may develop. Patients should be instructed to contact their healthcare provider immediately should they develop pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms *[see Warnings and Precautions (5.2)].*

Serious Cardiovascular Reactions

Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during atomoxetine treatment should stop atomoxetine capsules and contact a health care provider *[see Warnings and Precautions (5.3)].*

Increased Blood Pressure or Heart Rate

Atomoxetine can increase blood pressure and heart rate *[see Warnings and Precautions (5.4)]* .

Emergence of New Psychotic or Manic Symptoms and Activation of Mania

Instruct patients and their caregivers to look for signs of activation of mania/hypomania and psychosis *[see Warnings and Precautions (5.5)].*

Aggression or Hostility

Instruct patients and their caregivers to contact their healthcare provider as soon as possible should they notice an increase in aggression or hostility *[see Warnings and Precautions (5.7)].*

Priapism

The parents or guardians of pediatric patients taking atomoxetine and adult patients taking atomoxetine should be instructed that priapism requires prompt medical attention *[see Warnings and Precautions (5.10)].*

Ocular Irritant

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

Drug-Drug Interactions

Patients should be instructed to consult a healthcare provider if they are taking or plan to take any prescription or over-the-counter drugs, dietary supplements, or herbal remedies *[see Drug Interactions (7)].*

Sexual Dysfunction

Advise patients that atomoxetine capsules may impair sexual function. Advise patients if they experience sexual dysfunction, they should contact their health care provider *[see Adverse Reactions (6.1)].*

Pregnancy Registry

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to atomoxetine during pregnancy *[see Use in Specific Populations (8.1)].*

Food

Patients may take atomoxetine capsules with or without food.

Missed Dose

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

Somnolence

The incidence of somnolence was higher in atomoxetine-treated patients than placebo-treated patients *[see Adverse Reactions (6.1)]* . Patients should be instructed to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

APOTEX INC.

ATOMOXETINE CAPSULES, USP
10 mg

Revision: 13

Repackaged and Distributed By:

Remedy Repack, Inc.

625 Kolter Dr. Suite #4 Indiana, PA 1-724-465-8762

MEDICATION GUIDE
Atomoxetine(a" toe mox' e teen) Capsules, USP
for oral use
What is the most important information I should know about atomoxetine capsules?
Atomoxetine capsules can cause serious side effects, including:

Suicidal thoughts and actions in children 6 years of age and older. Atomoxetine capsules can increase the risk of suicidal thoughts and actions in children ages 6 and older with attention deficit hyperactivity disorder (ADHD), especially within the first few months of treatment or when the dose is changed.

How can I watch for and try to prevent suicidal thoughts and actions?

Pay close attention to, and tell your healthcare provider right away about, any changes, especially sudden changes, in mood, behavior, actions, thoughts, or feelings, or suicidal thoughts or actions. This is very important when atomoxetine capsules is started or when the dose is changed.
Keep all follow-up visits with the healthcare provider as scheduled. Tell your healthcare provider about symptoms between visits as needed, especially if you have concerns.

Tell your healthcare provider right away if any of the following symptoms develop during treatment, especially if they are new, worse, or worry you:

anxiety
trouble sleeping
acting aggressive
extreme increase in activity
or talking (mania)
unusual decrease in activity (hypomania)

feeling agitated or restless
irritability
impulsivity
depression
panic attacks
restlessness or feeling like you have to move

panic attacks
hostility or being angry or violent
suicide attempts
thoughts about suicide or dying
other unusual changes in mood or behavior

See "What are the possible side effects of atomoxetine capsules?"for more information about side effects.

What are atomoxetine capsules ?
Atomoxetine capsules are a prescription medicine used to treat ADHD in adults and children 6 years of age and older. Atomoxetine capsules may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.
Atomoxetine capsules should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

It is not known if atomoxetine capsules are safe and effective in children less than 6 years old.

Who should not take atomoxetine capsules?

Do not take atomoxetine capsules if you or your child:

are allergic to atomoxetine or any of the ingredients in atomoxetine capsules. See the end of this Medication Guide for a complete list of ingredients in atomoxetine capsules.
are taking or have stopped taking within the past 14 days a medicine called a monoamine oxidase inhibitor (MAOI).
have an eye problem called narrow angle glaucoma.
have or had a rare tumor called pheochromocytoma.
have severe heart or blood vessel problems that could get worse if your blood pressure or heart rate increases.

Before taking atomoxetine capsules, tell your healthcare provider about all medical conditions, including if you or your child:

have, or have a family history of, suicide thoughts or attempts, bipolar disorder, depression, mania, or hypomania.
have liver problems.
have, or have a family history of, heart problems, heart defects, irregular heartbeat, or sudden death.
have high blood pressure or low blood pressure.
have problems urinating such as trouble starting urination, weak stream, or not fully emptying the bladder.
have glaucoma.
are pregnant or plan to become pregnant. It is not known if atomoxetine will harm the unborn baby.

Tell your healthcare provider right away if you or your child become pregnant or plan to become pregnant during treatment with atomoxetine capsules.

There is a pregnancy exposure registry for women who are exposed to ADHD medicines, including atomoxetine capsules, during pregnancy. The purpose of the registry is to collect information about the health of women exposed to atomoxetine and their baby. If you or your child become pregnant during treatment with atomoxetine capsules, talk to your healthcare provider about registering with the National Pregnancy Registry of ADHD Medications at 1-866-961-2388 or visit online at https://womensmentalhealth.org/adhdmedications/.

are breastfeeding or plan to breastfeed.

It is not known if atomoxetine passes into the breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with atomoxetine capsules.

Tell your healthcare provider about all the medicines that you or your child take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.Atomoxetine capsules and some medicines may interact with each other and cause serious side effects. Your healthcare provider will decide whether atomoxetine capsules can be taken with other medicines.

Especially tell your healthcare provider if you or your child take:

a MAOI, including linezolid and intravenous methylene blue
medicines that increase or decrease blood pressure
asthma medicines

Know the medicines you or your child take. Keep a list of your medicines to show your healthcare provider and pharmacist. Do not start any new medicines during treatment with atomoxetine capsules without talking to your healthcare provider first.

How should I take atomoxetine capsules?

Take atomoxetine capsules exactly as your healthcare provider tells you. Your

healthcare provider may adjust the dose until it is right for you or your child.
Take atomoxetine capsules with or without food.
Swallow atomoxetine capsules whole. Do not open the capsules.
Atomoxetine capsules are usually taken 1 time a day in the morning, or 2 times a day, in the morning and in the late afternoon or early evening.
If you miss a dose of atomoxetine capsules, take the dose as soon as possible. Do not take more atomoxetine capsules than your healthcare provider prescribes in a 24-hour period.
If you take too much atomoxetine capsules, call your healthcare provider or Poison Help line at 1-800-222-1222 or go to the nearest emergency room right away.

What should I avoid while taking atomoxetine capsules?

Do notdrive or operate heavy machinery until you know how atomoxetine capsules affects you. Atomoxetine capsules can cause sleepiness.
Do not get atomoxetine capsules in or near the eyes. Atomoxetine capsules can irritate the eyes. If atomoxetine capsules gets into the eyes, rinse them with water right away and tell your healthcare provider. If a capsule breaks, avoid touching the contents and wash your hands and any surfaces that they come in contact with as soon as possible.

What are possible side effects of atomoxetine capsules?
Atomoxetine capsules can cause serious side effects, including:

See “What is the most important information I should know about atomoxetine capsules?”
Severe liver damage.Your healthcare provider will check the blood levels of liver enzymes if symptoms of liver damage develop. Tell your healthcare provider right away if any of the following symptoms develop at any time during treatment:

itching
the skin or the white part of the eyes turns yellow

right upper stomach pain
unexplained flu-like symptoms of the eyes turns yellow

dark urine

Serious heart-related side effects.Atomoxetine capsules may increase the risk of serious heart problems including sudden death, heart attack, and stroke in adults and children who have serious heart problems or heart defects. Your healthcare provider should check for heart problems before starting treatment with atomoxetine capsules. Stop taking atomoxetine capsules and tell your healthcare provider or get medical help right away if any of the following symptoms develop during treatment:

chest pain
loss of consciousness (fainting)
shortness of breath
heart palpitations or fast heart rate

numbness of weakness, especially on one side of the body
slurred speech
vision changes
severe headache

Increases in blood pressure and heart rate.Your healthcare provider should check blood pressure and heart rate before starting treatment, if the dose is increased, and as needed during treatment.
New psychotic problems, manic symptoms, or mania episodes.People with bipolar disorder, or who have a higher risk of developing bipolar disorder, have an increased risk of developing mania. Tell your healthcare provider if any of the following symptoms develop during treatment:

greatly increased energy
racing thoughts
unusually grand ideas
talking more or faster than usual
unusual decrease in activity

severe trouble sleeping
reckless behavior
excessive happiness or irritability
seeing or hearing things that are not real (hallucinations)
depression

Aggressive behavior or hostility.New or worsening aggressive behavior or hostility can happen during treatment.
Allergic reactions.Tell your healthcare provider right away if trouble breathing, hives, rash, or swelling of the face, eyes, lips, or throat develop during treatment.
Problems with urination.Atomoxetine capsules may cause problems with urination including decreased urine flow or trouble starting urination (urinary hesitation) or being unable to pass any urine (urinary retention). Tell your healthcare provider if any problems with urination develop during treatment.
Painful and prolonged erections (priapism).Priapism has happened in male children and adults who take atomoxetine capsules. Priapism is a serious problem that can cause lasting damage to the penis and may require surgery. Tell your healthcare provider and get medical help right away if you or your child develop priapism during treatment.
Effect on growth (height and weight) in children.Children should have their height and weight checked often during treatment.

The most common side effects of atomoxetine capsules in children include:

nausea
vomiting
tiredness

decreased appetite
stomach (abdominal) pain
sleepiness

The most common side effects of atomoxetine capsules in adults include:

constipation
dry mouth
nausea
decreased appetite

dizziness
erectile dysfunction
urinary hesitation

Atomoxetine capsules may cause sexual problems (dysfunction).Talk to your healthcare provider if any of the following symptoms develop:

Symptoms in males may include:

delayed ejaculation or inability to have an ejaculation
decreased sex drive
problems getting or keeping an erection

Symptoms in females may include:

decreased sex drive
delayed orgasm or inability to have an orgasm

Your healthcare provider may stop atomoxetine capsules treatment if serious side

effects develop during treatment.These are not all of the possible side effects atomoxetine capsules. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store atomoxetine capsules?

Store atomoxetine capsules in a safe place at 20°C to 25°C (68°F to 77°F) excursions permitted from 15°C to 30°C (59°F to 86°F).

Keep atomoxetine capsules and all medicines out of the reach of children.

General information about safe and effective use of atomoxetine capsules.
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use atomoxetine capsules for a condition for which it was not prescribed. Do not give atomoxetine capsules to other people, even if they have the same condition. It may harm them. You can ask your pharmacist or healthcare provider for information about atomoxetine capsules that is written for health professionals.
For more information call Apotex Corp. at 1-800-706-5575 or visit www.apotex.com.

What are the ingredients in atomoxetine capsules?
Active ingredient:atomoxetine hydrochloride, USP.
Inactive ingredients:The capsules also contain pregelatinized starch. The capsule shells contain gelatin and titanium dioxide. The capsule shells may also contain one or more of the following: FD&C Blue No. 2 (25 mg, 40 mg, and 60 mg), iron oxide red (80 mg and 100 mg), and iron oxide yellow (18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg). The capsules are imprinted with edible black ink (comprised of ammonia solution, iron oxide black, potassium hydroxide, propylene glycol, and shellac).

All registered trademarks in this document are the property of their respective owners.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

APOTEX INC.
ATOMOXETINE CAPSULES, USP
10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg

Revision: 13
Revised: August 2026

Repackaged By / Distributed By: RemedyRepack Inc.

625 Kolter Drive, Indiana, PA 15701

(724) 465-8762

DRUG: Atomoxetine Hydrochloride

GENERIC: atomoxetine hydrochloride

DOSAGE: CAPSULE

ADMINSTRATION: ORAL

NDC: 70518-4313-0

NDC: 70518-4313-1

COLOR: white

SHAPE: CAPSULE

SCORE: No score

SIZE: 14 mm

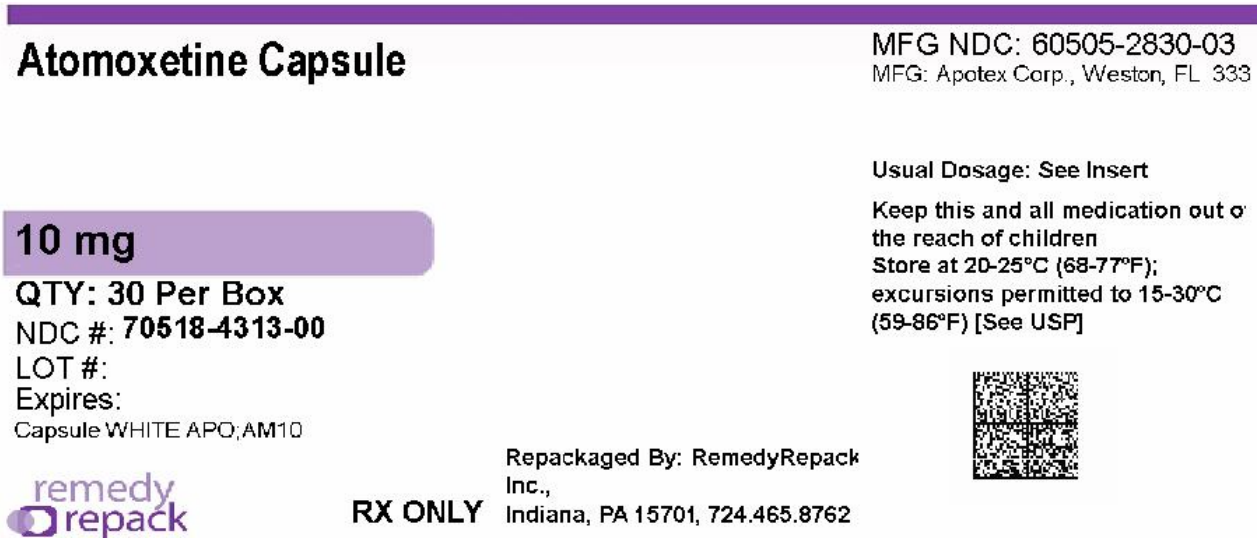
IMPRINT: APO;AM10

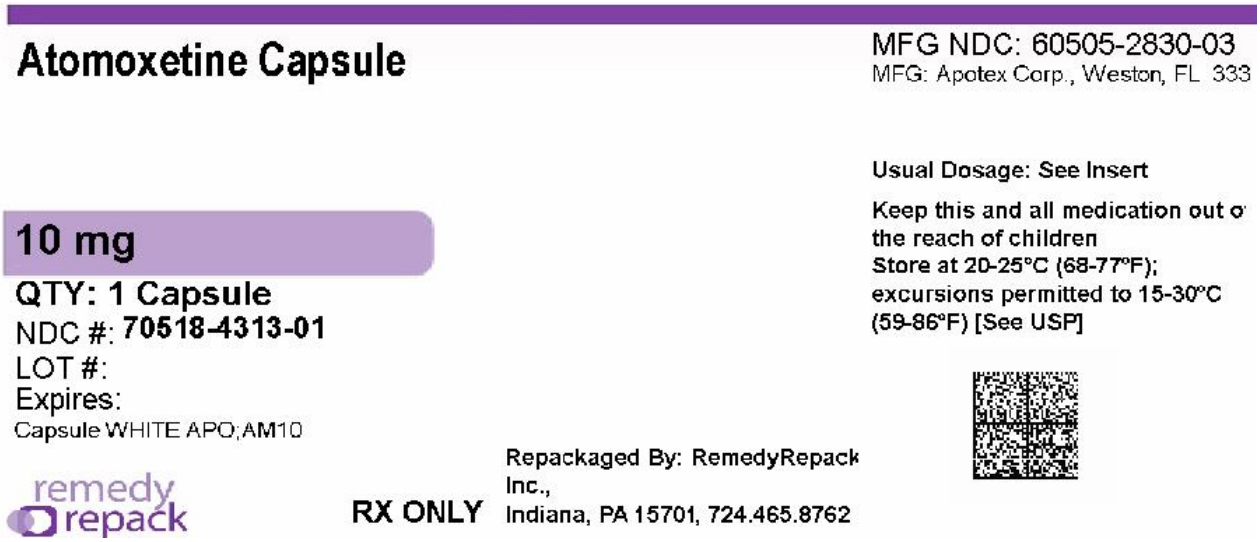
PACKAGING: 1 in 1 POUCH

OUTER PACKAGING: 30 in 1 BOX

ACTIVE INGREDIENT(S):
- ATOMOXETINE HYDROCHLORIDE 10mg in 1

INACTIVE INGREDIENT(S):
- TITANIUM DIOXIDE
- STARCH, CORN
- GELATIN, UNSPECIFIED





ATOMOXETINE HYDROCHLORIDE

atomoxetine hydrochloride capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:70518-4313(NDC:60505-2830)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		

Ingredient Name	Basis of Strength	Strength
ATOMOXETINE HYDROCHLORIDE (UNII: 57WVB6I2W0) (ATOMOXETINE - UNII:ASW034S0B8)	ATOMOXETINE	10 mg

Inactive Ingredients

Ingredient Name	Strength
STARCH, CORN (UNII: O8232NY3SJ)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	white (opaque white)	**Score**	no score
Shape	CAPSULE	**Size**	14mm
Flavor		**Imprint Code**	APO;AM10
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70518-4313-0	30 in 1 BOX	03/19/2025	
1	NDC:70518-4313-1	1 in 1 POUCH; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA078983	03/19/2025	

Labeler - REMEDYREPACK INC. (829572556)

Revised: 9/2026 REMEDYREPACK INC.