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

ATONCY (atomoxetine) oral solution
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 pediatric patients 6 years of age and older treated with ATONCY 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 ATONCY in patients who experience emergent suicidal thoughts and behavior. (5.1)**
- **ATONCY (atomoxetine) increased the risk of suicidal ideation in pediatric patients 6 years of age and older with attention-deficit/hyperactivity disorder (ADHD) in short-term studies. (5.1)**

----------INDICATIONS AND USAGE----------
ATONCY is 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 ATONCY:
  - Screen patients for a personal or family history of bipolar disorder, mania, or hypomania. (2.1, 5.6)
  - Consider genetic testing to determine the patient's CYP2D6 metabolizer status prior to dosing. (2.1, 2.5)
- See table below for the recommended ATONCY 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----------
Oral solution: Each mL contains 4 mg of atomoxetine

----------CONTRAINDICATIONS----------
Contraindicated in patients (4):
- With known hypersensitivity to ATONCY or other components of ATONCY
- 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:* ATONCY should be discontinued and not restarted in patients with jaundice or laboratory evidence of liver injury. (5.2)
- *Serious Cardiovascular Reactions:* Prior to ATONCY treatment, patients should have a careful history and physical exam to assess for presence of cardiovascular (CV) disease. ATONCY generally should not be used in pediatric patients with known serious cardiac abnormalities, cardiomyopathy, serious arrhythmias. Consideration should be given to not using ATONCY in adults with clinically significant cardiac abnormalities. Patients who develop symptoms suggestive of cardiac disease during ATONCY treatment should stop ATONCY 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 ATONCY dosage increases, and periodically while on therapy. (5.4)
- *New Psychotic or Manic Symptoms and Activation of Mania:* If psychotic or manic symptoms occur, consider discontinuing ATONCY. (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. (5.8)
- *Priapism:* Prompt medical attention is required in the event of suspected priapism. (5.9)
- *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 ATONCY (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Validus Pharmaceuticals LLC at 1-866-982-5438 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 of ATONCY and strong CYP2D6 inhibitors, increase the titration intervals. (7)
- *Antihypertensives:* Increase the frequency of monitoring blood pressure and adjust ATONCY dosage as clinically appropriate. (7)
- *Albuterol (or other beta$_2$ 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. (8.6 and 12.3)
- *Use in Genomic Subgroups:* CYP2D6 poor metabolizers may have a greater risk of atomoxetine-related adverse reactions compared to other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2026

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 pediatric patients 6 years of age or older treated with ATONCY should be monitored and observed closely for suicidal thoughts and behaviors, 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 ATONCY in patients who experience emergent suicidal thoughts and behavior *[see Warnings and Precautions (5.1)]*.

Atomoxetine increased the risk of suicidal ideation in pediatric patients 6 years of age and older with attention-deficit/hyperactivity disorder (ADHD) in short-term studies *[see Warnings and Precautions (5.1)*.

1 INDICATIONS AND USAGE

ATONCY is indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in adult and pediatric patients 6 years of age and older. ATONCY is 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 ATONCY Treatment

Prior to initiating treatment with ATONCY:

- Screen patients for a personal or family history of bipolar disorder, mania, or hypomania *[see Warnings and Precautions (5.6)].*
- Consider genetic testing to determine the patient's CYP2D6 metabolizer status *[see Dosage and Administration (2.5)].*

2.2 Administration Instructions

ATONCY may be taken with or without food. Instruct patients to only use the supplied syringe and bottle adapter to measure and take ATONCY *[see Instructions for Use].*

2.3 Recommended Dosage

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

Table 1: Recommended Dosage of ATONCY for the Treatment of ADHD

Age and Body Weight	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] Administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening.
[b] No additional benefit has been demonstrated with atomoxetine 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 dosage to a maximum of 100 mg/day. There are no data that support increased effectiveness at a dosage higher than 100 mg/day *[see Clinical Studies (14)]*.

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

2.4 Recommended Dosage in Patients with Hepatic Impairment

For patients 6 years of age or older with:

- Severe hepatic impairment (HI) (Child-Pugh Class C), the recommended initial and target 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 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 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

Table 2 includes the recommended ATONCY dosage in adult patients and pediatric patients aged 6 years of age or older with concomitant use of a strong CYP2D6 inhibitor or in CYP2D6 poor metabolizers *[see Drug Interactions (7) and Use in Specific Populations (8.7)]*. The recommended titration interval in these patients is every four weeks (if ADHD symptoms fail to improve and the initial dosage is well tolerated).

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)]*.

Table 2: Recommended Dosage of ATONCY with Concomitant Use of a Strong CYP2D6 Inhibitor or in CYP2D6 Poor Metabolizers

Age and Body Weight	Starting Dosage	Titration Interval[a]	Target Dosage[d]
Pediatric patients who weigh less than 70 kg	0.5 mg/kg/day	4 weeks	1.2 mg/kg/day[b,c]
Pediatric patients who weigh 70 kg or more and adult patients	40 mg/day	4 weeks	80 mg/day[b]

[a] Titrate if ADHD symptoms fail to improve and the initial dosage is well tolerated.
[b] Administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening.
[c] No additional benefit has been demonstrated with atomoxetine dosages higher than 1.2 mg/kg/day *[see Clinical Studies (14)]*.
[d] Maximum dosage has not been established with concomitant use of a strong CYP2D6 inhibitor or in CYP2D6 poor metabolizers.

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 ATONCY. In addition, at least 14 days must elapse after stopping ATONCY before starting an MAOI antidepressant.

2.7 Recommendations for a Missed Dose

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

2.8 Recommendations for Discontinuation

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

3 DOSAGE FORMS AND STRENGTHS

Oral Solution: Each mL contains 4 mg of atomoxetine (equivalent to 4.57 mg of atomoxetine hydrochloride), clear colorless solution, free from any visible foreign and particulate matter, free of precipitation and hazy mass. Supplied with a 10 mL oral syringe and a bottle adapter.

4 CONTRAINDICATIONS

ATONCY is contraindicated in patients:

- With known hypersensitivity reaction to ATONCY or other components of ATONCY. Hypersensitivity reactions that occurred with ATONCY use 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, ATONCY 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 ATONCY.
- With severe cardiac or vascular disorders whose condition would be expected to deteriorate if they had 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 pediatric patients 6 years of age and older treated with ATONCY should be monitored observed closely for clinical worsening, suicidal thoughts and behavior, and unusual changes in behavior, especially during the initial few months of ATONCY therapy, or at times of dose changes, either increases or decreases.
- Families and caregivers of pediatric patients 6 years of age and older treated with ATONCY 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 ATONCY, 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 increased the risk of suicidal ideation in pediatric patients 6 years of age 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 in another clinical study) with over 2,200 pediatric patients, the mean incidence of suicidal ideation in pediatric patients treated with another atomoxetine product was 0.4% (5/1357) (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 treatment with the other atomoxetine product. It is unknown whether the risk of suicidal ideation in pediatric patients extends to longer-term use. A similar analysis in adult patients treated with atomoxetine for ADHD did not reveal an increased risk of suicidal ideation or behavior.

The following psychiatric symptoms have been reported with the use of atomoxetine: 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

ATONCY 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 ATONCY is started, but laboratory abnormalities may continue to worsen for several weeks after ATONCY is stopped.

5.3 Serious Cardiovascular Reactions

Risk Management Recommendations for Serious Cardiovascular Reactions

Prior to ATONCY 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, ATONCY 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 ATONCY 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 treatment should stop ATONCY 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 Increases in Blood Pressure and Heart Rate

ATONCY is 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. ATONCY 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. ATONCY 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 ATONCY 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 patients treated with another atomoxetine product, 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 patients treated with another atomoxetine product compared with 0% (0/934) of placebo-treated patients.

- In placebo-controlled adult ADHD studies, tachycardia was identified as an adverse reaction for 1.5% (8/540) of patients treated with another atomoxetine product 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 patients treated with another atomoxetine product 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 patients treated with another atomoxetine product 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 treated with another atomoxetine product, 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, for patients treated with another atomoxetine product 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, for patients treated with another atomoxetine product 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 ATONCY.

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 ATONCY at the recommended dosage.

5.6 Screening Patients for Bipolar Disorder

Before initiating treatment with ATONCY, 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 ATONCY. It may not be possible to determine whether a manic or mixed episode that appears during treatment with ATONCY is due to an adverse reaction to ATONCY or a patient's underlying bipolar disorder.

5.7 Aggressive Behavior or Hostility

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

There is evidence that ATONCY 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 ATONCY 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 ATONCY.

5.8 Hypersensitivity Reactions

ATONCY is contraindicated in patients with a known hypersensitivity reaction to ATONCY or other components of ATONCY.

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 ATONCY.

In adult ADHD controlled studies, the incidence of urinary retention (1.7% (9/540)) and urinary hesitation (5.6% (30/540)) were increased among patients treated with another atomoxetine product compared with placebo-treated patients (0% (0/402); 0.5% (2/402), respectively). Two adult patients treated with another atomoxetine product 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 ATONCY-treated patients.

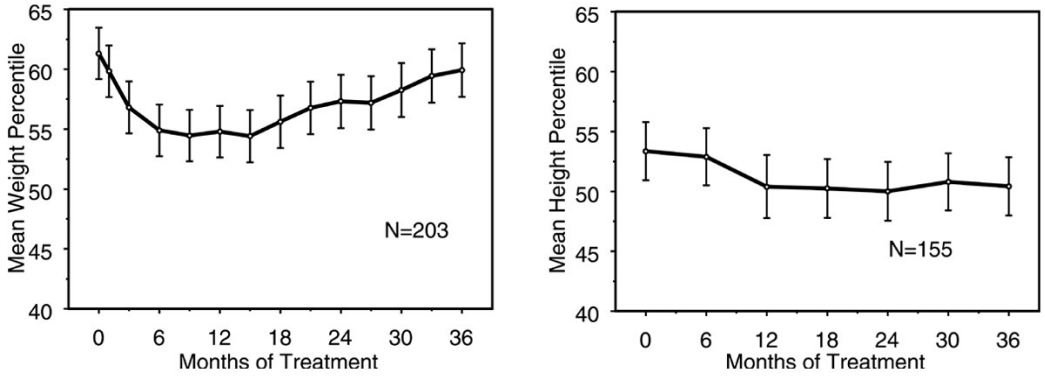
Rare postmarketing cases of priapism, defined as painful and nonpainful penile erection lasting more than 4 hours, have been reported for pediatric and adult patients treated with atomoxetine. The erections resolved in cases in which follow-up information was available, some following discontinuation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

5.11 Effect on Growth in Pediatric Patients
Closely monitor growth (e.g., weight, height) in pediatric patients during ATONCY treatment.

Weight and Height in Long-Term Open-Label Studies in Pediatric Patients
Data on the long-term effects of another atomoxetine product on growth in pediatric patients from open-label studies in which weight and height changes were compared to normative pediatric population data are presented below. In general, the weight and height gain of atomoxetine-treated pediatric patients treated with another atomoxetine product lagged behind that predicted by normative population data for about the first 9-12 months of treatment, and subsequently (see Figure 1 below):

- Weight gain rebounded. At about 3 years of treatment with another atomoxetine product, 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 treatment with another atomoxetine product, 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 treatment with another atomoxetine product 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 another atomoxetine product 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 treatment initiation with another atomoxetine product.

Weight and Height in Short-Term, Placebo-Controlled Studies in Pediatric Patients
In short-term, placebo-controlled studies (up to 9 weeks), patients treated with another atomoxetine product 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 other atomoxetine product 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.

The safety of ATONCY has been established from adequate and well-controlled studies of atomoxetine capsules (also referred to as another atomoxetine product) in patients 6 years of age and older with ADHD *[see Clinical Studies (14)].* Below is a display of the adverse reactions of [atomoxetine capsules in these adequate and well-controlled studies.

Atomoxetine capsules were 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 capsules-treated pediatric patients and 1.4% (13/945) of placebo-treated pediatric patients discontinued due to an adverse reaction. Among atomoxetine capsules-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 capsules-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 capsules-treated patients and with a higher incidence in atomoxetine capsules-treated patients compared to placebo-treated patients) in pediatric patients 6 years of age and older with ADHD are listed in Table 3. The most commonly observed

adverse reactions in atomoxetine capsules-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 3 and 4).

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

	Atomoxetine Capsules (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%
Decrease weight	3%	0%
Anorexia	3%	1%
Rash	2%	1%

[a] Adverse reactions reported by at least 2% of atomoxetine capsules-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 capsules-treated patients who received twice daily, and once daily dosing are shown in Table 4 (adverse reactions based on statistically significant Breslow-Day tests).

Table 4: Common Adverse Reactions in Acute studies (up to 18 weeks) in Pediatric Patients 6 Years and Older with ADHD

	ADHD Studies with Twice Daily Dosing		ADHD Studies with Once Daily Dosing	
	Atomoxetine Capsules (N=715)	Placebo (N=434)	Atomoxetine Capsules (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 includes the terms: upper abdominal pain upper, 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 5 displays adverse reactions occurred in at least 2% of atomoxetine capsules-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 5: Common Adverse Reactions[a] in Acute Studies (up to 18 weeks) in Atomoxetine Capsules-Treated Pediatric Patients 6 Years and Older with ADHD by CYP2D6 Metabolizer Types

	Atomoxetine Capsules CYP2D6 Poor	Atomoxetine Capsules Other CYP2D6 Metabolizer Types

	Metabolizers (N=355)	(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 capsules-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 capsules-treated patients than placebo-treated patients and are possibly related to atomoxetine capsules 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 clinical studies in the atomoxetine capsules studies. In the clinical development program, seizures were reported in 0.2% (12/5,073) of atomoxetine capsules-treated pediatric patients whose average age was 10 years old (range 6 to 16 years of age). In these clinical trials, for atomoxetine capsules-treated pediatric patients 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 treated with atomoxetine capsules 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 Studies 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% (61/541) atomoxetine capsules-treated pediatric patients and 3% (12/405) of placebo-treated patients discontinued for adverse reactions. Among atomoxetine capsules-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 one patient.

Common Adverse Reactions in the Clinical Studies of Adults: Commonly observed adverse reactions associated with the use of atomoxetine capsules (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (atomoxetine capsules incidence greater than placebo) are listed in Table 6. The most commonly observed adverse reactions in patients treated with atomoxetine capsules (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 6).

Table 6: Common Adverse Reactions[a] Associated in Acute Studies (up to 25 weeks) of Adult Patients with ADHD

	Atomoxetine Capsules (N=1697)	Placebo (N=1560)
Nausea	26%	6%
Dry mouth	20%	5%
Decreased appetite	16%	3%
Insomnia[d]	15%	8%
Fatigue	10%	6%
Erectile dysfunction[f]	8%	1%
Constipation	8%	3%
Dizziness	8%	3%
Somnolence[c]	8%	5%
Abdominal pain[b]	7%	4%
Urinary hesitation[e]	6%	1%
Irritability	5%	3%
Ejaculation delayed[f] and/or ejaculation disorder[f]	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 capsules, 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] Abdominal pain includes the terms: abdominal pain upper, abdominal pain, stomach discomfort, abdominal discomfort, epigastric discomfort.

[c] Somnolence includes the term sedation.

[d] Insomnia includes the terms: insomnia, initial insomnia, middle insomnia, and terminal insomnia.

[e] Urinary hesitation includes the terms: urinary hesitation, urine flow decreased.

[f] Based on total number of males (atomoxetine capsules, N=943; placebo, N=869).

[g] Based on total number of females (atomoxetine capsules, N=754; placebo, N=691).

Common Adverse Reactions by CYP2D6 Metabolizer Status in the Clinical Studies of Adults: Table 7 displays adverse reactions that occurred in at least 2% of atomoxetine capsules-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 7: Common Adverse Reactions[a] in Acute Studies (up to 18 weeks) in Atomoxetine Capsules-Treated Adults with ADHD by CYP2D6 Metabolizer Types

	Atomoxetine Capsules CYP2D6 Poor Metabolizers (N=203)	Atomoxetine Capsules 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 capsules-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).

Less Common Adverse Reactions in the Clinical Studies of Adults: The following reactions did not meet this criterion but were reported by more atomoxetine capsules-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 has not been systematically evaluated in adult patients with a seizure disorder as these patients were excluded from clinical studies during the product's premarket testing. In the clinical development program, seizures were reported on 0.1% (1/748) of adult patients treated with atomoxetine capsules. 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 8 displays the proportion of atomoxetine capsules-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 of in pediatric and adult patients with ADHD *[see Warnings and Precautions (5.4)].*

Table 8: Proportion of ADHD Patients With an Increase ≥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 Capsules	Placebo	Atomoxetine Capsules	Placebo	Atomoxetine Capsules	Placebo	Atomoxetine Capsules	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 treated with atomoxetine capsules 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 capsules 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. Sexual adverse reactions reported by at least 2% of atomoxetine capsules-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 9 for clinically significant drug interactions with ATONCY and other drugs.

Table 9: Clinically Significant Drug Interactions with ATONCY and Other Drugs

Monoamine Oxidase Inhibitors (MAOIs)	
Prevention or Management	ATONCY 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 ATONCY and an MAOI. Some cases presented with features resembling neuroleptic

	malignant syndrome.
Strong CYP2D6 Inhibitors	
Prevention or Management	With concomitant use of ATONCY and a strong CYP2D6 inhibitor[1], 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. Concomitant use of ATONCY and a strong CYP2D6 inhibitor increases atomoxetine exposure *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.
Antihypertensive Drugs	
Prevention or Management	Increase the frequency of monitoring blood pressure and adjust ATONCY dosage as clinically appropriate.
Mechanism and Clinical Effect(s)	Because of increased risk of increased blood pressure, ATONCY should be used cautiously with antihypertensive drugs, other drugs that increase blood pressure or pressor drugs (e.g., dopamine, dobutamine).
Albuterol or Other Beta 2 (β2) Agonists	
Prevention or Management	Increase the frequency of monitoring blood pressure and heart rate and adjust ATONCY dosage as clinically appropriate.
Mechanism and Clinical Effect(s)	Systemically administered albuterol (e.g., oral) can be potentiated by ATONCY, resulting in increases in heart rate and blood pressure *[see Clinical Pharmacology (12.3)]*.

[1]See www.fda.gov/CYPandTransporterInteractingDrugs for examples of strong CYP2D6 inhibitors.

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 ATONCY, 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 2-4% and 15- 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 of atomoxetine (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 ATONCY and any potential adverse effects on the breastfed child from atomoxetine hydrochloride or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ATONCY for the treatment of ADHD have been established in pediatric patients 6 years of age and older. Use of ATONCY for this indication is supported by evidence from another atomoxetine product in seven clinical trials in outpatients with ADHD: four acute treatment 6 to 9-week trials in pediatric subjects (ages 6 to 18 years), two acute treatment 10-week trials in adults, and one maintenance trial in pediatric subjects (ages 6 to 15 years) *[see Clinical Studies (14)]*.

ATONCY increases the risk of suicidal ideation in pediatric patients. Anyone considering the use of ATONCY in a pediatric patient must balance the potential risks with the clinical need *[see Boxed Warning and Warnings and Precautions (5.1, 5.3, 5.4, 5.10)]*.

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

Juvenile Animal Toxicity 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)]*.

8.7 Use in Genomic Subgroups

The recommended titration interval (before increasing the ATONCY 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 for patients treated with another atomoxetine product 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

ATONCY 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 another atomoxetine product and placebo, the other atomoxetine product 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 (ATONCY 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 discontinuation, there was no evidence of symptom rebound or adverse reactions suggesting an atomoxetine-discontinuation or withdrawal syndrome.

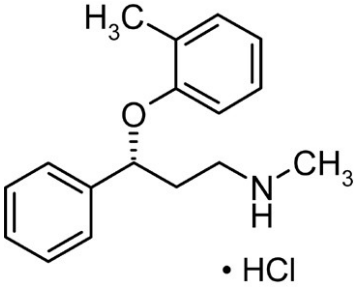
10 OVERDOSAGE

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 overdose of ATONCY.

11 DESCRIPTION

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



Atomoxetine hydrochloride is a white to almost white powder, which has a solubility of 27.8 mg/mL in water.

ATONCY oral solution is for oral administration only. Each mL contains 4 mg of atomoxetine (equivalent to 4.57 mg of atomoxetine hydrochloride) and the following inactive ingredients: grape flavor, maltitol solution, monobasic sodium phosphate, phosphoric acid, purified water, sodium benzoate, sodium hydroxide, sorbitol crystallizing solution, sucralose, and xylitol. ATONCY is a clear colorless solution, free from any visible foreign and particulate matter, free of precipitation and hazy mass with pH 3.0-5.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism by which ATONCY produces its therapeutic effects in the treatment of ADHD in adults and pediatric patients 6 years of age and older 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 the treatment of the signs and symptoms of ADHD as measured by the ADHD Rating Scale (ADHDRS)-IV-Parent Version (investigator administered and scored). At the observed median area under the plasma-concentration curve (AUC) after administration of atomoxetine 0.5 mg/kg/day, 1.2 mg/kg/day, and 1.8 mg/kg/day, 62%, 78% and 85%, respectively, of the maximum improvement over baseline for the ADHDRS scores are expected.

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 another atomoxetine product (i.e., atomoxetine capsules) (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 the other atomoxetine product did not change the intoxicating effects of ethanol.
- Concomitant use of the other atomoxetine product 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 the other atomoxetine product (60 mg twice daily for 5 days), particularly initially *[see Drug Interactions (7)].*

12.3 Pharmacokinetics

No clinically significant differences in pharmacokinetics of atomoxetine were observed after administration of ATONCY and immediate-release atomoxetine capsules under fasted conditions.

Pharmacokinetic parameters for atomoxetine and its metabolites in CYP2D6 poor metabolizers and other CYP2D6 metabolizer types (ultrarapid, normal, and intermediate) from studies of another atomoxetine product (i.e., atomoxetine capsules) are presented in **Error! Reference source not found.**11.

Table 11*:* 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	10-120 mg	
Accumulation	1.1-fold	3.3-fold
Absolute bioavailability	63%	94%
T_{max}	1 hour	-
Effect of Food	AUC: Unchanged; Cmax: Decreased 21% T_{max}: Delayed 1 hour	
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 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	

Values shown in the table are average values; Tmax is represented as median values.
Abbreviations: $C_{max,ss}$: maximum plasma concentration at steady state; T_{max}: time to peak concentration
[a] In this analysis, other CYP2D6 metabolizers were defined as individuals who are 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 status, which is 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

The pharmacokinetics of atomoxetine after administration of ATONCY in specific populations is based on the pharmacokinetics of atomoxetine after administration of another atomoxetine product (i.e., atomoxetine capsules) and these results are presented below.

Hepatic Impairment: Atomoxetine exposure (AUC) was increased by 2-fold in patients with moderate

(Child-Pugh Class B) hepatic impairment and 4-fold in patients with severe (Child-Pugh Class C) hepatic impairment compared to patients 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) 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 have been evaluated in more than 400 pediatric patients treated with another atomoxetine product (i.e., atomoxetine capsules) in clinical studies, primarily using population pharmacokinetic studies. 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

The pharmacokinetics of atomoxetine after administration of ATONCY with concomitant drugs is based on the pharmacokinetics of atomoxetine after administration of another atomoxetine product (i.e., atomoxetine capsules) and these results are presented below.

Clinical Studies

Strong CYP2D6 Inhibitors: Concomitant use of another atomoxetine product (i.e., atomoxetine capsules) (20 mg twice daily for 5 days) with paroxetine (20 mg once daily 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 the other atomoxetine product (at sequential dosing of 10, 45, and 75 mg twice daily for up to 5 days of each dosage) with fluoxetine (20 mg once daily 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 the other atomoxetine product alone.

After concomitant use of the other atomoxetine product 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 the other atomoxetine product (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 the other atomoxetine product (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 another atomoxetine product (i.e., atomoxetine capsules) 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.

In a study of another atomoxetine product (i.e., atomoxetine capsules), 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 (ultrarapid, normal, and intermediate) *[see Dosage and Administration (2.5), Warnings and Precautions (5.4), Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

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 pediatric patients 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 pediatric patients 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

The effectiveness of ATONCY has been established for the treatment of ADHD in pediatric patients 6 years of age and older based on adequate and well-controlled studies of atomoxetine capsules in pediatric patients 6 years of age and older with ADHD. Below is a display of the efficacy results of the adequate and well-controlled studies of atomoxetine capsules in pediatric patients 6 years of age and older with ADHD.

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

In four randomized, double-blind, placebo-controlled studies of pediatric patients 6 to 18 years of age (Studies 1, 2, 3, and 4) with ADHD, approximately one-third of the patients met DSM-IV criteria for inattentive ADHD subtype and two-thirds met criteria for both inattentive and hyperactive/impulsive ADHD 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 capsules (0.25, 0.6, or 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 capsules dosages compared with patients treated with placebo as measured on the ADHDRS scale. The 0.9 mg/kg twice daily atomoxetine capsules dosage did not provide any additional benefit over that observed with the 0.6 mg/kg twice daily atomoxetine capsules dosage. The 0.25 mg/kg twice daily atomoxetine capsules 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 capsules or placebo. Atomoxetine capsules was administered as a once daily dosage 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 capsules was approximately 1.3 mg/kg once daily. ADHD symptoms were statistically significantly improved in the atomoxetine capsules group compared to the placebo group, as measured on the ADHDRS scale. Study 2 showed that atomoxetine capsules 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 capsules, methylphenidate, or placebo. In Studies 3 and 4, atomoxetine capsules 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 a maximum recommended atomoxetine capsules dosage of 1 mg/kg twice daily. The mean final dosage of atomoxetine capsules in Studies 3 and 4 was approximately 0.8 mg/kg twice daily. In both Studies 3 and 4, ADHD symptoms statistically significantly improved more in the atomoxetine capsules group than in 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 capsules in the maintenance treatment of ADHD in pediatric patients 6 years of age and older was studied in an outpatient randomized withdrawal study of pediatric patients 6-15 years of age (Study 5). In this study, patients who met DSM-IV criteria for ADHD who showed continuous response for about 4 weeks during an initial 10 week open-label treatment phase with atomoxetine capsules (1.2 to 1.8 mg/kg/day) were randomized to continue their current atomoxetine capsules dosage (N=292) or 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 capsules 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 of their current atomoxetine capsules 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:Inv total score returns to ≥90% of study entry score for 2 consecutive visits.

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

14.2 ADHD Studies in Adults

The effectiveness of ATONCY has been established for the treatment of ADHD in adults based on adequate and well-controlled studies of atomoxetine capsules in adult patients with ADHD. Below is a display of the efficacy results of the adequate and well-controlled studies of atomoxetine capsules in adult patients with ADHD.

The effectiveness of atomoxetine capsules for the treatment of ADHD in adults was evaluated 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 capsules or placebo. Patients in the atomoxetine capsules group received 30 mg to 60 mg twice a day (in the early morning and late afternoon/early evening) of atomoxetine capsules which was titrated according to clinical response. The mean final atomoxetine capsules dosage in these studies was approximately 48 mg twice daily. In both studies, ADHD symptoms were statistically significantly improved in the atomoxetine capsules 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 exposure of number of patients in racial and ethnic groups to determine 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

The safety of ATONCY has been established from adequate and well-controlled studies of atomoxetine capsules (also referred to as another atomoxetine product) in patients 6 years of age and older with ADHD. Below is a display of the adverse reactions of atomoxetine capsules in two safety studies.

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, the effect of atomoxetine capsules on tic severity was assessed. Patients in the atomoxetine capsules 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 capsules 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 capsules 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 capsules or placebo. In the atomoxetine capsules group, following a 2-week double-blind placebo lead-in, atomoxetine capsules was initiated at 0.8 mg/kg/day with increase to a target dosage of 1.2 mg/kg/day (median dosage 1.3 mg/kg/day +/- 0.29 mg/kg/day). Atomoxetine capsules 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 capsules or placebo. In the atomoxetine capsules group, following a 2-week double-blind placebo lead-in, atomoxetine capsules was initiated at 40 mg/day to a maximum dosage of 100 mg/day (mean daily dosage 83 mg/day +/- 19.5 mg/day). Atomoxetine capsules 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 in atomoxetine-treated patients *[see Adverse Reactions (6.2)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ATONCY™ (atomoxetine) oral solution is supplied in a 100 mL, amber glass bottles with child-resistant cap, and is co-packaged with a 10 mL calibrated oral dosing syringe and bottle adapter: NDC 30698-456-02. Each mL contains 4 mg of atomoxetine (equivalent to 4.57 mg of atomoxetine hydrochloride), clear colorless solution, free from any visible foreign and particulate matter, free of precipitation and hazy mass. Supplied with a 10 mL syringe and a bottle adapter.

16.2 Storage and Handling

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

Discard unused ATONCY remaining in the bottle, 45 days after first opening the bottle.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

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 ATONCY 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 ATONCY 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 ATONCY treatment should stop ATONCY and contact a health care provider *[see Warnings and Precautions (5.3)]*.

Increased Blood Pressure or Heart Rate

Atomoxetine can increase the 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 ATONCY 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. In the event ATONCY comes in contact with an 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 ATONCY 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 ATONCY with or without food.

Missed Dose
If patients miss an ATONCY dose, they should be instructed to take it as soon as possible, but should not take more than the prescribed total daily amount of ATONCY 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 ATONCY.

Manufactured by:
Rubicon Research Limited,
Satara, 415004, India

Distributed by:
Validus Pharmaceuticals LLC
Parsippany, NJ 08520
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1-866-982-5438

MEDICATION GUIDE
ATONCY™ (ah TON see)
(atomoxetine) oral solution

What is the most important information I should know about ATONCY?
ATONCY can cause serious side effects, including:

- **Suicidal thoughts and actions in children 6 years of age and older.** ATONCY increases 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 ATONCY 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 ATONCY?"** for more information about side effects.

What is ATONCY?
ATONCY is a prescription medicine used to treat ADHD in adults and children 6 years of age and older. ATONCY may help increase attention and decrease impulsiveness and hyperactivity in people with ADHD.
ATONCY 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 ATONCY is safe and effective in children less than 6 years old.

Who should not take ATONCY?
Do not take ATONCY if you or your child:

- are allergic to atomoxetine or any of the ingredients in ATONCY. See the end of this Medication Guide for a complete list of ingredients in ATONCY.
- 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 ATONCY, 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 ATONCY 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 ATONCY.
  - There is a pregnancy exposure registry for women who are exposed to ADHD medicines, including ATONCY, during pregnancy. The purpose of the registry is to collect information about the health of women exposed to ATONCY and their baby. If you or your child become pregnant during treatment with ATONCY, 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 ATONCY passes into the breast milk. Talk to your healthcare provider about the best way to feed the baby during treatment with ATONCY.

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. ATONCY and some medicines may interact with each other and cause serious side effects. Your healthcare provider will decide whether ATONCY 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 that you or your child take. Keep a list of your medicines with you to show your healthcare provider and pharmacist. **Do not start any new medicines during treatment with ATONCY without talking to your healthcare provider first.**

How should I take ATONCY?

- Take ATONCY exactly as your healthcare provider tells you. Your healthcare provider may adjust the dose until it is right for you or your child.
- See the detailed "**Instructions for Use**" for more information on how to prepare and take ATONCY.
- Take ATONCY with or without food.
- ATONCY is 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 ATONCY, take the dose as soon as possible. Do not take more ATONCY than your healthcare provider prescribes in a 24-hour period.
- Use only the oral dosing syringe and bottle adapter that come with ATONCY to measure and take the dose.
- If you take too much ATONCY, 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 ATONCY?

- **Do not** drive or operate heavy machinery until you know how ATONCY affects you. ATONCY can cause sleepiness.
- **Do not** get ATONCY in or near the eyes. ATONCY can irritate the eyes. If ATONCY gets into the eyes, rinse them with water right away and tell your healthcare provider. Avoid touching ATONCY. Wash your hands and any surfaces that ATONCY comes in contact with as soon as possible.

What are possible side effects of ATONCY?
ATONCY can cause serious side effects, including:

- See **"What is the most important information I should know about ATONCY?"**
- **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
  - dark urine
- **Serious heart-related side effects.** ATONCY 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 ATONCY. Stop taking ATONCY 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.** ATONCY 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 medicines. 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 priapism develops 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 ATONCY in children include:

- nausea
- vomiting
- tiredness
- decreased appetite
- stomach (abdominal) pain
- sleepiness

The most common side effects of ATONCY in adults include:

- constipation
- dry mouth
- nausea
- decreased appetite
- dizziness
- erectile dysfunction
- urinary hesitation

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

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 ATONCY treatment if serious side effects develop during treatment.

These are not all of the possible side effects of ATONCY. 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 ATONCY?

- Store ATONCY at room temperature between 68°F to 77°F (20°C to 25°C).
- Throw away (discard) any unused ATONCY 45 days after first opening the bottle. Write the discard date in the space provided on the bottle and carton.

Keep ATONCY and all medicines out of the reach of children.

General information about the safe and effective use of ATONCY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ATONCY for a condition for which it was not prescribed. Do not give ATONCY 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 ATONCY that is written for health professionals.

What are the ingredients in ATONCY?

Active ingredient: atomoxetine hydrochloride

Inactive ingredients: grape flavor, maltitol solution, monobasic sodium phosphate, phosphoric acid, purified water, sodium benzoate, sodium hydroxide, sorbitol crystallizing solution, sucralose, and xylitol

Manufactured by:
Rubicon Research Limited,
Satara, 415004, India

Distributed by:
Validus Pharmaceuticals LLC
Parsippany, NJ 08520
www.validuspharma.com

For more information about ATONCY call Validus Pharmaceutical at 1-866-982-5438.

This Medication Guide has been approved by the US Food and Drug Administration. Issued: 3/2026

INSTRUCTIONS FOR USE
ATONCY™ (ah TON see)
(atomoxetine) oral solution

This Instructions for Use contains information on how to take ATONCY.

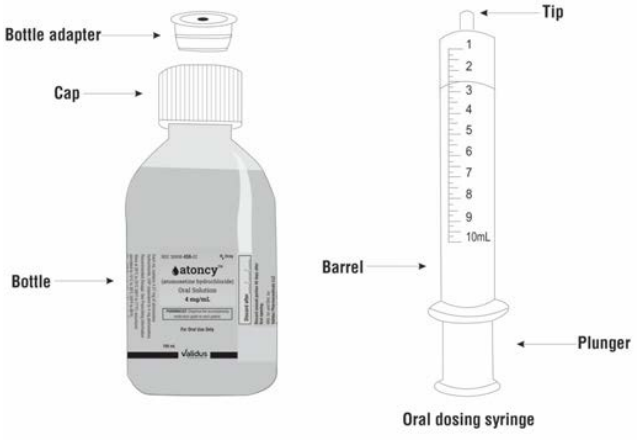
Important Information You Need to Know Before Taking ATONCY:

- Read these instructions carefully to learn how to prepare and take ATONCY the right way.
- ATONCY is for oral use only (taken by mouth).
- Take ATONCY with or without food.
- Use only the oral dosing syringe and bottle adapter that come with ATONCY to measure and take a dose of the medicine.
- Do not get ATONCY in or near the eyes. If ATONCY gets into the eyes, rinse them with water right away and tell the healthcare provider.
- Check the expiration date on the ATONCY bottle and carton. Do not take ATONCY after the expiration date has passed.
- Throw away (discard) any unused ATONCY 45 days after first opening the bottle. Write the discard date in the space provided on the bottle and carton. See "**Disposing of ATONCY**."

Storing ATONCY

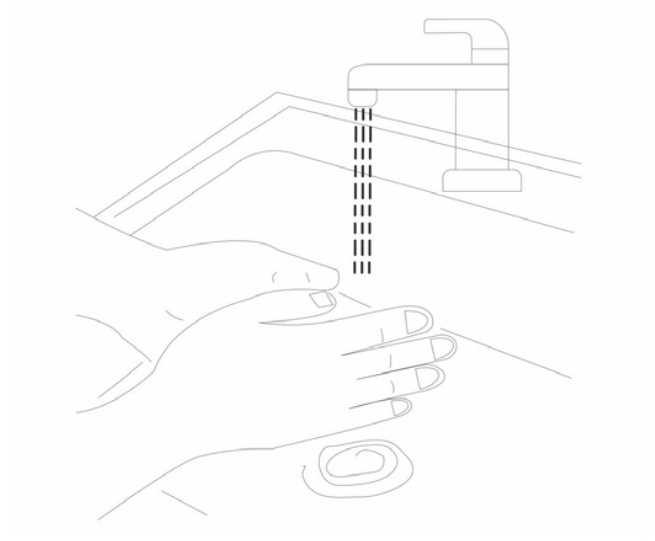
- Store ATONCY at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the child-resistant cap tightly closed.
- **Keep ATONCY and all medicines out of the reach of children.**

Supplies included in the ATONCY Carton



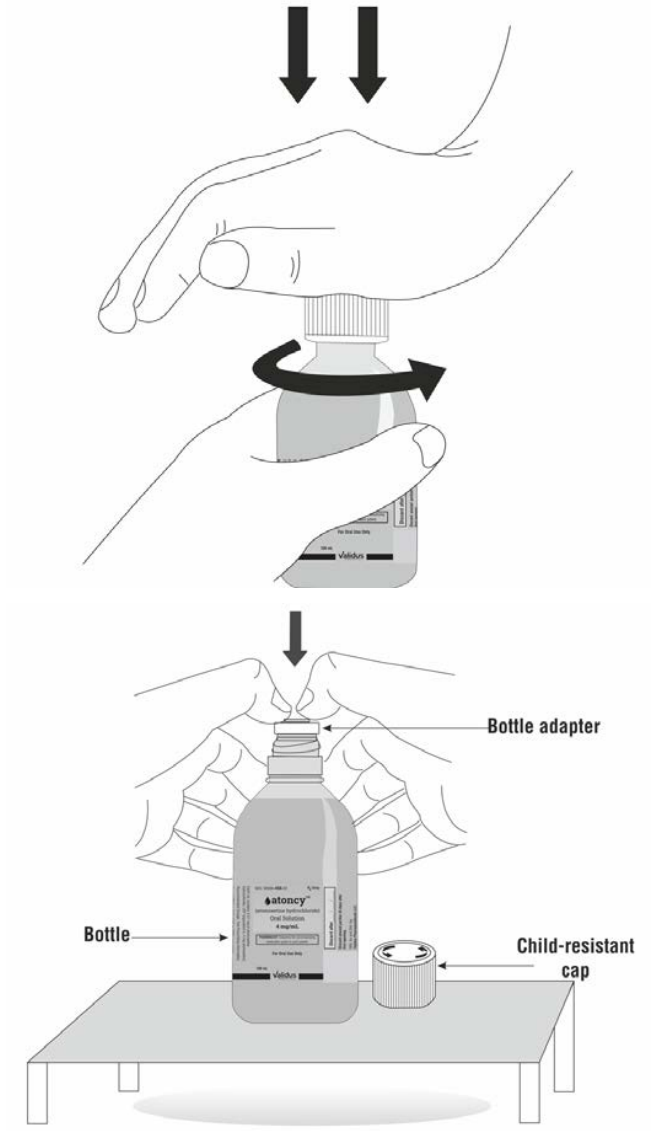
- A **press-in bottle adapter** that you push into the neck of the bottle. After it is inserted, the bottle adapter must always stay in the bottle.
- A **bottle** containing medicine, with a child-resistant cap. Always put the child-resistant cap back on the bottle and close it tightly after use.
- A 10 milliliter (mL) **oral dosing syringe** that fits into the bottle adapter to withdraw and measure the prescribed dose of medicine from the bottle.

Hand Washing



- Wash and dry your hands.
- Remove the ATONCY bottle and bottle adapter from the carton.
- Tell your pharmacist right away if you are missing supplies from the carton.

Step 1: Preparing the Bottle

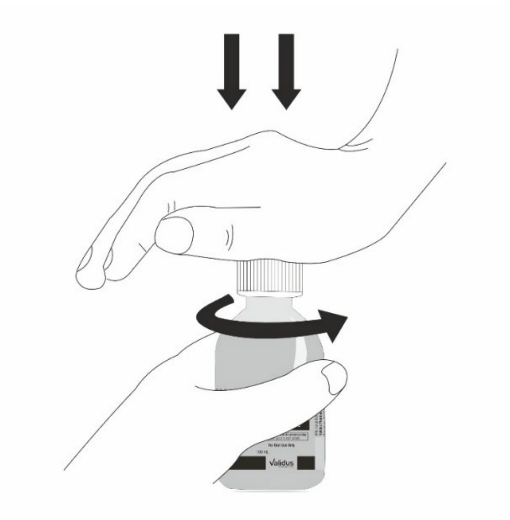


- Remove the child-resistant cap by pushing it **firmly** down and turning it to the left (counterclockwise) as shown on the top of the child-resistant cap.
  Note: Save the child-resistant cap so you can close the bottle after each use.
- Hold the open bottle upright on a table and push the bottle adapter **firmly** into the neck of the bottle as far as you can.
- **Put the child-resistant cap back on the bottle and close it tightly by turning it to the right (clockwise) to make sure that the bottle adapter has been fully forced into the neck of the bottle.**

  Note: You may not be able to push the bottle adapter fully down, but it will be forced into the bottle when you screw the child-resistant cap back on.

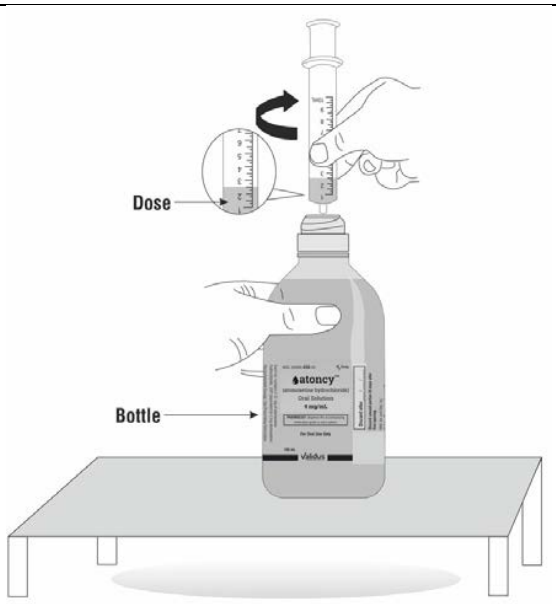
  Now the bottle is ready to use with the syringe. The bottle adapter must always stay in the bottle. **Do not** remove the bottle adapter. The child-resistant cap should seal the bottle in between use.

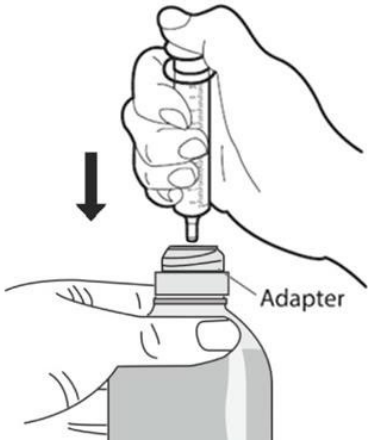
Step 2: Measuring the Dose of ATONCY



- Push and turn the child-resistant cap counterclockwise to open the bottle.

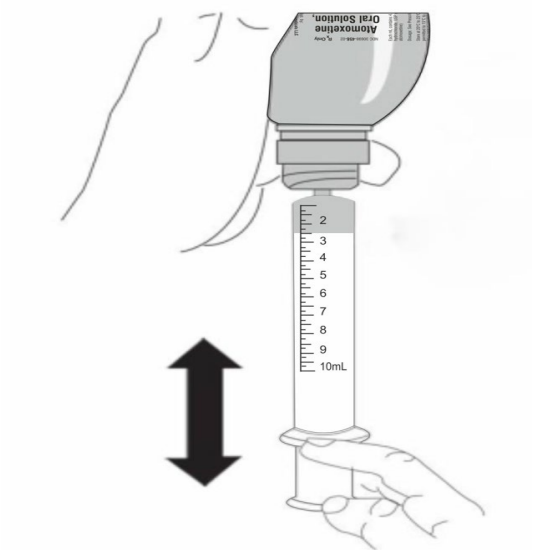
  Note: Always put the child-resistant cap tightly back on the bottle after use.





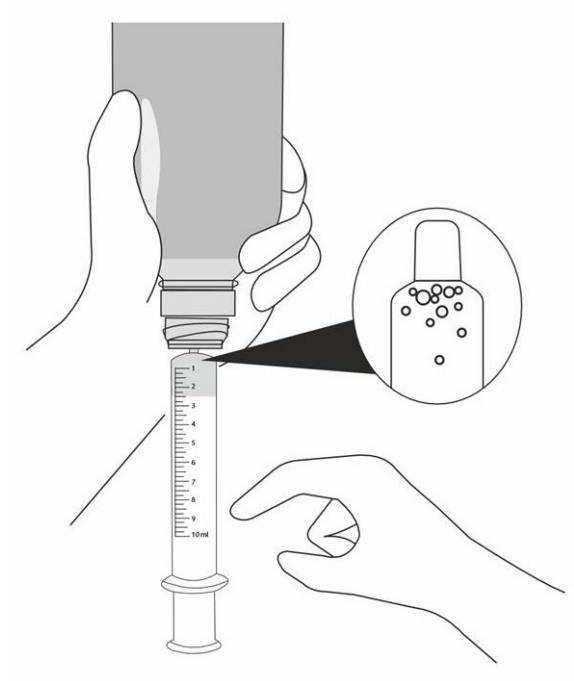
- Check that the plunger is pushed all the way down inside the barrel of the syringe.
- Keep the bottle upright and push the tip of the syringe **firmly** into the hole in the bottle adapter.

Step 3:



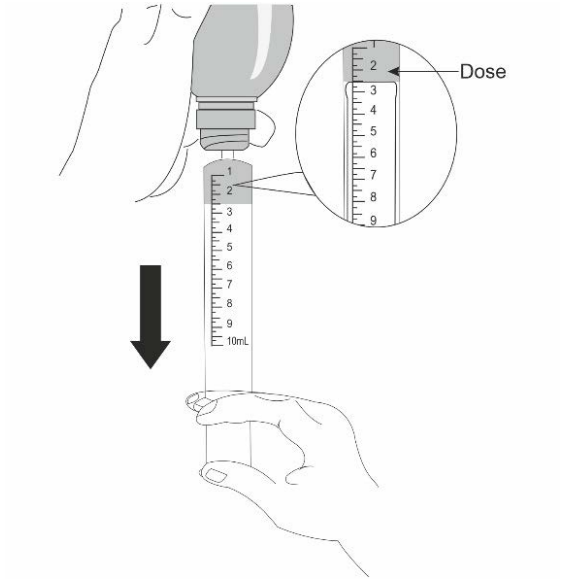
- Hold the syringe in place and carefully turn the bottle upside down.
- Check the oral dosing syringe to find the right dose in milliliters (mL) that has been prescribed by the healthcare provider.
- Slowly pull the plunger out to fill the oral dosing syringe so that the top edge of the plunger is slightly past the prescribed dose line to help remove any air bubbles.

Step 4:



- Tap the syringe barrel to move air bubbles to the top. Doing this helps set the correct dose.
- Push the plunger down slowly just far enough to completely push out any large or small air bubbles that may be trapped in the syringe.

Step 5:

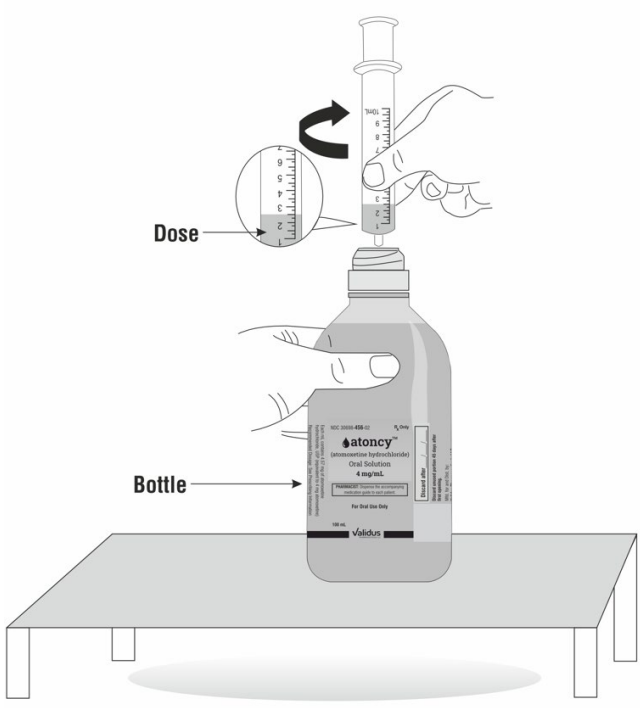


- Slowly pull the plunger out until the top edge of the plunger is exactly level with the marker on the syringe barrel for the prescribed dose.
  See the Figure for an example of a dose of 2.5 mL. **The prescribed dose may be different.**

  Note: If the prescribed dose is more than 10 mL, you will need to repeat steps 2 through 7 to refill the syringe and to take the full dose.

  Ask your pharmacist or healthcare provider to show you how to measure the dose if you are not sure.

Step 6:



- Carefully turn the bottle upright.
- Place the bottle on the table.
- Take out the syringe by gently twisting it out of the bottle adapter. The bottle adapter should stay in the bottle.
- Check that the correct dose in mL is in the oral dosing syringe.
- If the correct dose is not in the oral dosing syringe:
  - Put the tip of the syringe back into the bottle adapter and push the plunger to the bottom of the barrel to empty the contents of the syringe.
  - Repeat steps 2 through 6.

Step 7: Taking the dose of ATONCY

- **Important: Sit in an upright position when taking ATONCY.**
- Place the oral dosing syringe gently into the mouth and close the mouth tightly around the barrel of the syringe.
- Push the plunger down **slowly** to make sure that all the medicine is swallowed.
- Check to make sure that there is no medicine left in the oral dosing syringe.
- If the prescribed dose is more than 10 mL, repeat steps 2 through 7.
- Put the child-resistant cap tightly back on the bottle to close the bottle after use.

Step 8: Cleaning up

- After the dose of medicine is taken, rinse the syringe with warm water and allow it to dry thoroughly before you use it again.
- After touching ATONCY, wash your hands and any surfaces that ATONCY comes in contact with as soon as possible.

Step 9: Disposing of ATONCY

- Throw away any unused ATONCY 45 days after first opening the bottle.
- Throw away medicine that is expired or no longer needed.
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Manufactured by:

Rubicon Research Private Limited,
Satara, 415004, India.

Distributed by:

Validus Pharmaceuticals LLC
Parsippany, NJ 07054

This Instructions for Use has been approved by the U.S. Food and Drug Administration. Issued 3/2026