Direct Healthcare Professional Communication

February 2026

Potential Risk of The Unavailability of Patient Information Leaflet within the product packaging for INTAS's Axepta 5 mg and 10 mg Axepta 5 mg & 10 mg (atomoxetine), Batches No. K2500051 & K2500272.

Dear Healthcare professional,

Spectropharma in agreement with The Saudi Food and Drug Authority [SFDA] would like to inform you of the following:

Summary:

INTAS's Axepta 5 mg & 10 mg (atomoxetine), was distributed to hospitals with no patient information leaflet (PIL) within the product packaging.

Background on the safety concern:

Spectropharma's quality department initiated an investigation report with the findings below:

- INTAS's Axepta 5 mg & 10 mg (atomoxetine): No impact on the chemical, physical, or microbiological quality of the product.
- Safety impact of missing PIL within product packaging: Potential risk due to patients or healthcare professionals being unable to have clear instructions on the clear use of the medication.

Recommendations to healthcare professionals:

- Inform relevant hospital staff (including nurses, pharmacists, allied health professionals, and any other personnel who may handle, dispense, or administer the product) that the original package of Axepta 5 mg & 10 mg (Atomoxetine) may be missing the Patient Information Leaflet (PIL).
- Ensure the availability of Patient Information Leaflet (PIL), enclosed with this Direct Healthcare Professional Communication, is made available and distributed together with the affected product.
- Verify the affected batch, noting that this DHPC applies to Batches No. K2500051 & K2500272 only.
- Report any suspected adverse events associated with the use of this product in accordance with SFDA requirements, using the contact details provided below

CALL FOR REPORTING

Healthcare professionals should report any adverse events, which are suspected to be associated with the use of INTAS's Axepta 5 mg & 10 mg (atomoxetine) batches No. K2500051 & K2500272, in accordance with the requirements via the national spontaneous reporting systems to:

National Pharmacovigilance Centre (NPC)	Spectropharma reporting channels
Landline: 19999.	Mobile: +966 53 688 1702.
Email: npc.drug@sfda.gov.sa.	Email: pharmacovigilance@spectropharma.com.
Webpage:https://ade.sfda.gov.sa/.	Webpage:https://spectropharma.com/Pharmacovigilance.html.

COMPANY CONTACT POINT

Should you have any questions regarding the use of INTAS's Axepta 5 mg & 10 mg (atomoxetine), please feel free to contact us at m.alsaif@spectropharma.com

For Spectropharma,

Modhi A. Alsaif, QPPV

Patient information Leaflet (PIL):

Axepta

Atomoxetine 10, 18, 25, 40 & 60mg Tabs.

INDIA'S NO.1 ATOMOXETINE BRAND

PRODUCT MONOGRAPH

ATOMOXETINE

- **Synonyms**

  - Atomoxetine
  - Atomoxetine HCl
  - Atomoxetine Hydrochloride
  - Tomoxetine

- **Class**
  - a) This drug is a member of the following class(es):
    - Central Nervous System Agent
    - Norepinephrine Reuptake Inhibitor

- **Drug Properties**
  - Physicochemical Properties
    - 1) Molecular Weight
      - a) 291.82
    - 2) Solubility
      - a) 27.8 mg/mL in water.

- **Place in Therapy**

- A) **ADHD**
- 1) Atomoxetine is promoted as an equally efficacious form of ADHD therapy as conventional agents (eg, methylphenidate, dextroamphetamine, pemoline, bupropion, tricyclic antidepressants). Controlled studies, essential for evaluation of this agent, have shown evidence of efficacy; direct comparisons are lacking. Unpublished data suggest that the frequency and severity of some adverse effects are similar to those of methylphenidate (eg, cardiovascular effects, weight loss).
- 2) At the very least, prospective comparisons with short- and long-acting forms of methylphenidate (usual agent of choice) are indicated before the place in therapy of atomoxetine can be addressed.
- 3) Until additional data for atomoxetine are made available, it should not be considered over conventional therapy.

- B) **DEPRESSION**
- 1) Clinical data for atomoxetine in major depression are limited to small, uncontrolled studies. Placebo-controlled studies are required to confirm efficacy; comparisons with selective serotonin reuptake inhibitors (SSRIs)/other antidepressants are needed to assess its role in therapy.

• Dosing Information

◆ Adult Dosage

- **Normal Dosage**
  - **A) Atomoxetine Hydrochloride**
    - **1) Oral route**
      - **a) Attention deficit hyperactivity disorder**
        - 1) In adult patients (18 years or older), the manufacturer recommends a starting dose of 40 milligrams (mg) daily, increasing after a minimum of 3 days to a target dose of approximately 80 mg daily; the drug can be given either as a single daily dose (morning) or two divided doses in the morning and late afternoon/evening. An increase in dosage to a maximum of 100 mg daily can be considered after 2 to 4 additional weeks in patients who have not achieved adequate response on lower doses; there are no data to suggest greater efficacy with higher doses. Atomoxetine may be taken with or without food. Guidelines regarding the duration of treatment are unavailable. Tapering of the dose is not required on discontinuation of therapy.
        - 2) Patients exhibiting marked responses or significant adverse effects on lower doses may be of the poor-metabolizer phenotype; maintenance of lower doses in these patients may be required. At present, DNA-genotyping is not recommended prior to therapy.
        - 3) Concomitant Cytochrome P450 (CYP) 2D6-Inhibitor Therapy
        - a) In adult patients (18 years or older) also receiving strong CYP 2D6 inhibitors (eg, quinidine, paroxetine), the manufacturer recommends a starting dose of 40 milligrams (mg) daily; an increase to the usual target dose of 80 mg daily is indicated only if symptoms do not improve after 4 weeks, and the initial dose is well tolerated

- **Dosage in Renal Failure**
  - A) Atomoxetine Hydrochloride
    - 1) No dose adjustment is necessary.

- **Dosage in Hepatic Insufficiency**
  - A) Atomoxetine Hydrochloride
    - 1) Atomoxetine is metabolized in the liver; accumulation of the drug can occur in patients with hepatic insufficiency.

- **Dosage in Renal Failure**
  - A) Atomoxetine Hydrochloride
    - 1) No dose adjustment is necessary.

- **Dosage in Hepatic Insufficiency**

  - A) Atomoxetine Hydrochloride
    - 1) The manufacturer recommends the following dose adjustments in patients with hepatic insufficiency :
      - a) Moderate hepatic insufficiency (Child-Pugh class B): starting and target doses should be half of normal doses.
      - b) Severe hepatic insufficiency (Child-Pugh class C): starting and target doses should be reduced to 25% of normal doses.

Pharmacokinetics

- **Onset and Duration**

  - A) Onset
    - 1) Initial Response
      - a) ATTENTION-DEFICIT/HYPERACTIVITY DISORDER, ORAL: 1 week
        - 1) Based on data from children with ADHD in an open study (twice-daily dosing).
        - 2) In adults with ADHD, a significant reduction in symptoms versus placebo was seen after 2 weeks of treatment.

- **Drug Concentration Levels**

  - A) Therapeutic Drug Concentration
    - 1) Not established in any indication.
  - B) Time to Peak Concentration
    - 1) ORAL: 1 to 2 hours.
      - a) In children ages 7 to 14 years with attention deficit hyperactivity disorder and classified as extensive metabolizers, maximal concentration was achieved in 2 hours after either a single dose of atomoxetine 10 milligrams (mg) or steady-state dosing (20 to 45 mg twice daily).
      - b) Following single 90-mg oral doses in healthy subjects (extensive metabolizers), peak plasma levels of atomoxetine varied considerably, ranging from 315 to 1231 ng/mL. Plasma levels fell to undetectable levels at 36 hours postdosing. In poor metabolizers, peak levels tended to be higher, and occurred later.
      - c) With administration of 20 and 40 mg twice daily for 7 days in extensive metabolizers (healthy subjects), peak levels on day 1 were approximately 100 and 250 ng/mL, respectively; there was no significant accumulation on days 2 through 7. Plasma concentrations of the metabolite, noratomoxetine, were low in these subjects (less than 10 ng/mL). In subjects who were poor metabolizers in this study (n=2), significant accumulation of both atomoxetine and noratomoxetine was observed during repeat dosing.
  - C) Area Under the Curve

- 1) mean 2766 ng x hr/mL after 90-mg single dose (extensive metabolizers).
  - a) In children ages 7 to 14 years with attention deficit disorder and classified as extensive metabolizers, plasma concentrations of the active metabolite 4-hydroxyatomoxetine were 26 to 35 times less than those for atomoxetine.
  - b) During repeat dosing in extensive metabolizers (healthy subjects), AUC data indicated no significant accumulation of atomoxetine; in subjects receiving 20 mg and 40 mg twice daily for one week, AUC(0-24) values at steady-state (last dose) were 975 to 1126 ng x hr/mL and 2460 to 3710 ng x hr/mL, respectively. In poor metabolizers receiving these doses, accumulation was significant, with corresponding values of 10,490 ng x hr/mL and 29,330 ng x hr/mL (based on data from two subjects).

ADME

Absorption

- A) Bioavailability
  - 1) ORAL: 63% in extensive metabolizers; 94% in poor metabolizers.
- B) Effects of Food
  - 1) extent of absorption unaffected.
    - a) The rate of absorption is reduced when given with food in adults (by 37%) and time to peak levels prolonged (by about 3 hours); however, AUC is unaffected.

Distribution

- A) Distribution Sites
  - 1) Protein Binding
    - a) 98% (albumin).
- B) Distribution Kinetics
  - 1) Volume of Distribution
    - a) Approximately 74 to 250 liters (extensive metabolizers).
      - 1) Volume of distribution was similar (74 to 328 liters) between single oral doses (10 to 90 milligrams (mg)), and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects). In poor metabolizers (data limited), a slightly lower volume of distribution was reported (about 90 L).

Metabolism

- A) Metabolism Sites and Kinetics
  - 1) LIVER, extensive.
    - a) Cytochrome P450 (CYP)-2D6 is involved in the metabolism of atomoxetine. An active metabolite, 4-hydroxyatomoxetine, undergoes significant glucuronidation and renal excretion.
    - b) Some patients are poor metabolizers of atomoxetine and will have significantly higher AUC values (10-fold) and plasma levels compared to extensive metabolizers; lab tests are available to identify poor metabolizers.
- B) Metabolites
  - 1) 4-Hydroxyatomoxetine (active).

- a) Equipotent to the parent compound as a norepinephrine transporter inhibitor; however, it is present in low concentrations in plasma relative to the parent compound (about 1%). Its contribution to clinical effects is unknown.
- 2) Noratomoxetine (inactive).
- 3) N-desmethylatomoxetine (inactive).

Excretion

- A) Kidney
  - 1) Renal Excretion (%)
    - a) less than 3% unchanged.
      - 1) Most of an oral dose of atomoxetine is excreted in the urine as 4-hydroxyatomoxetine-O-glucuronide (80%).

- B) Total Body Clearance
  - 1) 0.3 to 0.5 L/hr/kg (extensive metabolizers).
    - a) Clearance is about 10-fold lower in poor metabolizers (0.03 to 0.04 L/hr/kg).
    - b) Plasma clearance was similar (17 to 62 liters/hour; average, 36 to 40 liters/ hour) between single oral doses (10 to 90 mg) and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects); there was no evidence of dose-dependency. In poor metabolizers receiving repeat doses, a substantially lower clearance was observed (about 3 L/hr).

- C) Other
  - 1) OTHER EXCRETION
    - a) FECES
      - 1) Less than 17% of a dose is excreted in feces as 4-hydroxyatomoxetine-O-glucuronide.

Elimination Half-life

- A) Parent Compound
  - 1) ELIMINATION HALF-LIFE
    - a) 4 to 5 hours (in extensive metabolizers; 22 hours in poor metabolizers.
      - 1) Half-life was similar (3 to 6 hours) between single oral doses (10 to 90 milligrams (mg)), and repeat dosing (20 to 45 mg twice daily) in extensive metabolizers (healthy subjects); there was no evidence of dose-dependency. In poor metabolizers receiving the same repeat doses, a substantially longer half-life was observed (17 to 21 hours).

Mechanism of Action/Pharmacology

- A) MECHANISM OF ACTION
- 1) Atomoxetine is a methylphenoxy-benzene propanamine derivative with antidepressant activity; its structure is unlike that of other antidepressants. The drug is under investigation as a "nonstimulant" treatment of attention-deficit/hyperactivity disorder (ADHD) in both adults and children, and for treatment of adult depression.

- 2) Atomoxetine purportedly enhances noradrenergic function via selective inhibition of the presynaptic norepinephrine transporter. It has minimal-to-no affinity for other neuronal transporters or neurotransmitter receptor sites (eg, muscarinic, histaminic, dopaminergic, serotonergic, alpha-adrenergic).
- 3) Animal and human studies suggest a low propensity for anticholinergic and adverse cardiovascular effects with atomoxetine. No significant hypertensive effects were seen in healthy subjects given single doses of 20 or 40 mg twice daily for one week in one study.

Cautions

- A) Black Box WARNING
  - 1) Atomoxetine Hydrochloride
    - a) Suicidal ideation in children and adolescents: atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of atomoxetine in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Atomoxetine is approved for ADHD in pediatric and adult patients. Atomoxetine is not approved for major depressive disorder.
    - b) Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of atomoxetine in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials.

- **Contraindications**
  - A) Atomoxetine Hydrochloride
    - 1) hypersensitivity to atomoxetine or to other components of the product.
    - 2) MAO inhibitors; atomoxetine should not be administered during therapy with or within 2 weeks of discontinuing an MAO inhibitor.
    - 3) narrow angle glaucoma; increased risk of mydriasis.

- **Precautions**
  - A) Atomoxetine Hydrochloride
    - 1) suicidal ideation or clinical worsening; increased risk in children and adolescents during the first few months of therapy or following a dosage adjustment.
    - 2) behavioral changes including aggression and hostility; may be precursor to emerging suicidality.
    - 3) bipolar disorder; mixed/manic episode may be induced.
    - 4) cardiovascular disease, cerebrovascular disease, hypertension, tachycardia; risk of increased blood pressure and heart rate.
    - 5) jaundice or liver injury; risk of acute liver failure or liver transplant.
    - 6) orthostatic hypotension; use cautiously in conditions predisposing patient to orthostatic hypotension.

- 7) psychotic or manic symptoms, hallucinations, delusional thinking or mania; may emerge in children and adolescents without a prior history of psychotic illness or mania at usual doses, discontinuation of therapy may be necessary.
- 8) structural cardiac abnormalities; risk of sudden death at usual doses, should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems.