# CLEAN PROPOSED PROFESSIONAL INFORMATION

## 1. NAME OF THE MEDICINAL PRODUCT

**ATOXTRIN 10 mg** Hard Gelatine Capsules

**ATOXTRIN 18 mg** Hard Gelatine Capsules

**ATOXTRIN 25 mg** Hard Gelatine Capsules

**ATOXTRIN 40 mg** Hard Gelatine Capsules

**ATOXTRIN 60 mg** Hard Gelatine Capsules

**ATOXTRIN 80 mg** Hard Gelatine Capsules

**WARNING:**

**SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS**

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**ATOXTRIN 10 mg**

Each hard gelatine capsule contains 10 mg atomoxetine as 11,43 mg atomoxetine hydrochloride.

**ATOXTRIN 18 mg**

Each hard gelatine capsule contains 18 mg atomoxetine as 20,57 mg atomoxetine hydrochloride.

**ATOXTRIN 25 mg**

Each hard gelatine capsule contains 25 mg atomoxetine as 28,57 mg atomoxetine hydrochloride.

**ATOXTRIN 40 mg**

Each hard gelatine capsule contains 40 mg atomoxetine as 45,71 mg atomoxetine hydrochloride.

**ATOXTRIN 60 mg**

Each hard gelatine capsule contains 60 mg atomoxetine as 68,57 mg atomoxetine hydrochloride.

**ATOXTRIN 80 mg**

Each hard gelatine capsule contains 80 mg atomoxetine as 91,42 mg atomoxetine hydrochloride.

Sugar free.

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard Gelatine Capsule

**ATOXTRIN 10 mg**

White powder in a hard gelatine capsule of size No 3, opaque white cap imprinted in black ink with ‘10’ and opaque white body imprinted in black ink with ‘mg’.

**ATOXTRIN 18 mg**

White powder in a hard gelatine capsule of size No 3, opaque rich yellow cap imprinted in black ink with ‘18’ and opaque white body imprinted in black ink with ‘mg’.

**ATOXTRIN 25 mg**

White powder in a hard gelatine capsule of size No 3, opaque blue cap imprinted in black ink with ‘25’ and opaque white body imprinted in black ink with ‘mg’

**ATOXTRIN 40 mg**

White powder in a hard gelatine capsule of size No 3, opaque blue cap imprinted in black ink with ‘40’ and opaque blue body imprinted in black ink with ‘mg.’

**ATOXTRIN 60 mg**

White powder in a hard gelatine capsule of size No 2, opaque blue cap imprinted in black ink with ‘60’ and opaque rich yellow body imprinted in black ink with ‘mg’

**ATOXTRIN 80 mg**

White powder in a hard gelatine capsule of size No 2, opaque brown cap imprinted in black ink with ‘80’ and opaque white body imprinted in black ink with ‘mg’.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

ATOXTRIN is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children 6 years of age or older, adolescents and adults.

### 4.2 Posology and method of administration

**Posology**

Treatment must be initiated by or under the supervision of a medical practitioner with appropriate knowledge and experience of childhood and/or adolescent behavioural disorders (for example, paediatrician or child/adolescent psychiatrist) (see section 4.4).

ATOXTRIN can be administered as a single daily dose in the morning. Patients who do not achieve a satisfactory clinical response (tolerability [e.g., nausea or somnolence] or efficacy) when taking ATOXTRIN as a single daily dose might benefit from taking it as twice daily evenly divided doses in the morning and late afternoon or early evening.

**Paediatric population**

**Dosing of paediatric population up to 70 kg body weight:**

ATOXTRIN should be initiated at a total daily dose of approximately 0,5 mg/kg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is approximately 1,2 mg/kg/day (depending on the patient's weight and available dosage strengths of atomoxetine). No additional benefit has been demonstrated for doses higher than 1,2 mg/kg/day.

**Dosing of paediatric population over 70 kg body weight and adults:**

ATOXTRIN should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is 80 mg. No additional benefit has been demonstrated for doses higher than 80 mg. The maximum recommended total daily dose is 80 mg.

ATOXTRIN may be discontinued without tapering the dose.

**Missing a dose**

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

**Special populations**

*Renal impairment*

For those ADHD patients who have hepatic insufficiency or end-stage renal disease, cautious titration of ATOXTRIN to the desired clinical response is recommended. ATOXTRIN may exacerbate hypertension in patients with end-stage renal disease.

*Hepatic impairment*

PN clearance may be reduced in patients with hepatic insufficiency.

**Method of administration**

For oral use.

ATOXTRIN can be administered with or without food.

The capsules should not be opened and the contents inside the capsules should not be removed and taken in any other way.

ATOXTRIN is an ocular irritant. In the event of capsule content coming into contact with the eye, the affected eye should be flushed immediately with water, and medical

advice obtained. Hands and any potentially contaminated surfaces should be washed as soon as possible.

**4.3 Contraindications**

Hypersensitivity to the atomoxetine or to any of the excipients listed in section 6.1.

ATOXTRIN should not be used in combination with monoamine oxidase inhibitors (MAOI), including linezolid. ATOXTRIN should not be used within a minimum of 2 weeks after discontinuing therapy with MAOI. Treatment with MAOI should not be initiated within 2 weeks after discontinuing ATOXTRIN. ATOXTRIN should not be used in patients with narrow-angle glaucoma, as in clinical trials the use of atomoxetine was associated with an increased incidence of mydriasis.

ATOXTRIN should not be used in patients with severe cardiovascular or cerebrovascular disorders (see section 4.4 - Cardiovascular Effects). Severe cardiovascular disorders may include severe hypertension or in heart rate that could be clinically important (for example 15 to 20 mmHg in blood pressure or 20 beats per minute in heart rate) (see section 4.4 – cardiovascular effects), heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening dysrhythmias and channelopathies (disorders caused by the dysfunction of ion channels). Severe cerebrovascular disorders may include cerebral aneurysm or stroke.

ATOXTRIN should not be used in patients with pheochromocytoma or a history of pheochromocytoma (see section 4.4 - Cardiovascular Effects).

ATOXTRIN should not be used in patients with uncontrolled hypertension or impairment of liver function.

**4.4 Special warnings and precautions for use**

**Suicide-related behaviour**

Suicide-related behaviour (suicide attempts and suicidal ideation), hostility (predominantly aggression, oppositional behaviour and anger) and emotional lability have been reported in patients treated with atomoxetine. In double-blind clinical trials, suicide-related behaviours were more frequently observed among children and adolescents treated with atomoxetine compared to those treated with placebo, where there were no events. In adult double-blind clinical trials, there was no difference in the frequency of suicide-related behaviour between atomoxetine and placebo. Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide-related behaviour. The possibility of serious psychiatric adverse effects cannot be excluded.

There is evidence that the risk of psychiatric adverse events is increased in children with a personal history of mood disorders, or who have a family history of mood disorders.

**Sudden death and pre-existing cardiac abnormalities**

Sudden death has been reported in patients with structural cardiac abnormalities who were taking atomoxetine at usual doses. Although some serious structural cardiac abnormalities alone carry an increased risk of sudden death, atomoxetine should only

be used with caution in patients with known serious structural cardiac abnormalities and in consultation with a cardiac specialist.

**Cardiovascular effects**

Atomoxetine can affect heart rate and blood pressure. Most patients taking atomoxetine experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) (see section 4.8).

However, combined data from controlled and uncontrolled ADHD clinical trials show that approximately 8-12 % of children and adolescents, and 6-10 % of adults experience more pronounced changes in heart rate (20 beats per minute or greater) and blood pressure (15-20 mmHg or greater). Analysis of these clinical trial data showed that approximately 15-26 % of children and adolescents, and 27-32 % of adults experiencing such changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases. Long-term sustained changes in blood pressure may potentially contribute to clinical consequences such as myocardial hypertrophy.

As a result of these findings, patients who are being considered for treatment with atomoxetine should have a careful history and physical exam to assess for the presence of cardiac disease and should receive further specialist cardiac evaluation if initial findings suggest such history or disease.

It is recommended that heart rate and blood pressure be measured and recorded before treatment is started and, during treatment, after each adjustment of dose and then at least every 6 months to detect possible clinically important increases. For

paediatric patients the use of a centile chart is recommended. For adults, current reference guidelines for hypertension should be followed.

ATOXTRIN should not be used in patients with severe cardiovascular or cerebrovascular disorders (see section 4.3 – Severe Cardiovascular and Cerebrovascular Disorders). ATOXTRIN should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure and heart rate, such as patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease.

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

In addition, atomoxetine should be used with caution in patients with congenital or acquired long QT or a family history of QT prolongation (see sections 4.5 and 4.8).

As orthostatic hypotension has also been reported, atomoxetine should be used with caution in any condition that may predispose patients to hypotension or conditions associated with abrupt heart rate or blood pressure changes.

ATOXTRIN should not be used in patients with Raynaud's phenomenon.

**Cerebrovascular effects**

Patients with additional risk factors for cerebrovascular conditions (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure)

should be assessed at every visit for neurological signs and symptoms after initiating treatment with atomoxetine.

**Hepatic effects**

Spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported. Severe liver injury, including acute liver failure, have been reported. ATOXTRIN should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted. Signs and symptoms likely to indicate liver involvement include pruritis, dark urine, jaundice, right upper quadrant tenderness or unexplained “flu-like” symptoms. Laboratory testing to determine liver enzyme levels and bilirubin should be done upon the first sign or symptoms of possible liver involvement. Due to the seemingly idiosyncratic nature of the liver injury, routine monitoring of liver function is unlikely to be helpful in minimising the risk of such reactions.

**Psychotic or manic symptoms**

Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, mania or agitation in patients without a prior history of psychotic illness or mania can be caused by atomoxetine at usual doses. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine, and discontinuation of treatment should be considered. The possibility that ATOXTRIN will cause the exacerbation of pre-existing psychotic or manic symptoms cannot be excluded.

**Aggressive behaviour, hostility or emotional lability**

Hostility (predominantly aggression, oppositional behaviour and anger) was more frequently observed in clinical trials among children, adolescents and adults treated with Atomoxetine compared to those treated with placebo. Emotional lability was more frequently observed in clinical trials among children treated with Atomoxetine compared to those treated with placebo. Patients should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional lability.

Severe cases have been reported concerning paediatric patients, including reports of physical assault, or threatening behaviour and thoughts of harming others. Families and caregivers of paediatric patients treated with atomoxetine should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted, particularly after starting treatment or changing the dose. Physicians should evaluate the need for dose adjustment or treatment discontinuation in patients experiencing behavioural changes.

**Possible allergic events**

Allergic reactions, including anaphylactic reactions, rash, angioneurotic oedema, and urticaria, have been reported in patients taking atomoxetine.

**Ocular Irritant**

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

**Seizures**

Seizures are a potential risk with atomoxetine. Atomoxetine should be introduced with caution in patients with a history of seizure. Discontinuation of atomoxetine should be considered in any patient developing a seizure or if there is an increase in seizure frequency where no other cause is identified.

**Growth and development**

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

Clinical data do not suggest a deleterious effect of atomoxetine on cognition or sexual maturation; however, the amount of available long-term data is limited. Therefore, patients requiring long-term therapy should be carefully monitored.

**New-onset or worsening of Comorbid Depression, Anxiety and Tics**

In a controlled study of paediatric patients with ADHD and comorbid chronic motor tics or Tourette's Disorder, atomoxetine-treated patients did not experience worsening of tics compared to placebo-treated patients. In a controlled study of adolescent patients with ADHD and comorbid Major Depressive Disorder, atomoxetine-treated patients did not experience worsening of depression compared to placebo-treated patients. In two controlled studies (one in paediatric patients and one in adult patients) of patients with ADHD and comorbid anxiety disorders, atomoxetine-treated patients did not experience worsening of anxiety compared to placebo-treated patients.

There have been rare post-marketing reports of anxiety and depression or depressed mood and very rare reports of tics in patients taking atomoxetine (see section 4.8).

Patients who are being treated for ADHD with atomoxetine should be monitored for the appearance or worsening of anxiety symptoms, depressed mood and depression or tics.

**Effects on micturition**

In adult ADHD controlled trials, the rates of urinary retention and urinary hesitation were increased among the atomoxetine, as ATOXTRIN subjects compared with placebo subjects. A complaint of urinary retention or urinary hesitancy should be considered potentially related to ATOXTRIN.

**Paediatric population under six years of age**

ATOXTRIN should not be used in patients less than six years of age as efficacy and safety have not been established in this age group. The efficacy of ATOXTRIN beyond 18 months of treatment and safety of ATOXTRIN beyond 2 years of treatment has not been systematically evaluated.

**Elderly use**

The safety and efficacy of ATOXTRIN in elderly patients have not been established.

**Other therapeutic use**

Atomoxetine is not indicated for the treatment of major depressive episodes and/or anxiety as the results of clinical trials in adults in these conditions, where ADHD is not present, did not show an effect compared to placebo (see section 5.1).

**Serotonin syndrome:**

Serotonin syndrome has been reported following concomitant use of atomoxetine with other serotonergic medicinal products (e.g. serotonin-norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs], other SNRIs, triptans, opioids, and tricyclic and tetracyclic antidepressants). If concomitant use of atomoxetine with a serotonergic medicinal product is warranted, prompt recognition of the symptoms of serotonin syndrome is important. These symptoms may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

**4.5 Interactions with other medicines and other forms of interaction**

Effects of other medicinal products on atomoxetine:

**MAOIs**

Atomoxetine should not be used with MAOIs (see section 4.3).

**CYP2D6 inhibitors (SSRIs (e.g., fluoxetine, paroxetine), quinidine, terbinafine)**

In patients receiving these medicinal products, atomoxetine exposure may be 6-to 8-fold increased and Css-max 3 to 4 times higher, because it is metabolised by the CYP2D6 pathway. Slower titration and final lower dosage of atomoxetine may be

necessary in patients who are already taking CYP2D6 inhibitor medicinal products. If a CYP2D6 inhibitor is prescribed or discontinued after titration to the appropriate atomoxetine dose has occurred, the clinical response and tolerability should be re-evaluated for that patient to determine if dose adjustment is needed.

Caution is advised when combining atomoxetine with potent inhibitors of cytochrome P450 enzymes other than CYP2D6 in patients who are poor CYP2D6 metabolisers as the risk of clinically relevant increases in atomoxetine exposure in vivo is unknown.

**Salbutamol (or other beta$_2$ agonists)**

Atomoxetine should be administered with caution to patients treated with high dose nebulised or systemically administered salbutamol (or other beta$_2$ agonists) because cardiovascular effects can be potentiated.

Contradictory findings regarding this interaction were found. Systemically administered salbutamol (600 µg i.v. over 2 hrs) in combination with atomoxetine (60 mg twice daily for 5 days) induced increases in heart rate and blood pressure. This effect was most marked after the initial coadministration of salbutamol and atomoxetine but returned towards baseline at the end of 8 hours. However, in a separate study the effects on blood pressure and heart rate of a standard inhaled dose of salbutamol (200 µg) were not increased by the short-term coadministration of atomoxetine (80 mg once daily for 5 days) in a study of healthy Asian adults who were extensive atomoxetine metabolisers. Similarly, heart rate after multiple inhalations of salbutamol (800 µg) did not differ in the presence or absence of atomoxetine.

Attention should be paid to monitoring heart rate and blood pressure, and dose adjustments may be justified for either atomoxetine or salbutamol (or other $beta_2$ agonists) in the event of significant increases in heart rate and blood pressure during coadministration of these medicines.

There is the potential for an increased risk of QT interval prolongation when atomoxetine is administered with other QT prolonging medicines (such as neuroleptics, class IA and III anti-dysrhythmics, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium, or cisapride), medicines that cause electrolyte imbalance (such as thiazide diuretics), and medicines that inhibit CYP2D6.

Seizures are a potential risk with atomoxetine. Caution is advised with concomitant use of medicines which are known to lower the seizure threshold (such as tricyclic antidepressants or SSRIs, neuroleptics, phenothiazines or butyrophenone, mefloquine, chloroquine, bupropion or tramadol (see section 4.4)). In addition, caution is advised when stopping concomitant treatment with benzodiazepines due to potential withdrawal seizures.

**Serotoninergic medications**

Atomoxetine should be used with caution in combination with serotonergic medicinal products, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), opioids as tramadol, and tetracyclic or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

**Anti-hypertensive medicines**

Atomoxetine should be used cautiously with anti-hypertensive medicines. Because of a possible increase in blood pressure, atomoxetine may decrease the effectiveness of anti-hypertensive medicines / medicines used to treat hypertension. Attention should be paid to monitoring of blood pressure and review of treatment of atomoxetine or anti-hypertensive medicines may be justified in the case of significant changes of blood pressure.

**Pressor medicines or medicines that increase blood pressure**

Because of possible increase in effects on blood pressure, atomoxetine should be used cautiously with pressor medicines or medications that may increase blood pressure (such as salbutamol). Attention should be paid to monitoring of blood pressure, and review of treatment for either atomoxetine or pressor medicines may be justified in the case of significant change in blood pressure.

**Medicines that affect noradrenaline**

Medicines that affect noradrenaline should be used cautiously when co-administered with atomoxetine because of the potential for additive or synergistic pharmacological effects. Examples include antidepressants, such as imipramine, venlafaxine, and mirtazapine, or the decongestants pseudoephedrine or phenylephrine.

**Medicines that affect gastric pH**

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

**Medicines highly bound to plasma protein**

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

**Methylphenidate**

Co-administration of methylphenidate with atomoxetine did not increase cardiovascular effects beyond those seen with methylphenidate administration alone.

**Alcohol**

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

**Midazolam**

Co-administration of atomoxetine (60 mg twice daily for 12 days) with midazolam, a model compound for CYP3A4 metabolised medicines (single dose of 5 mg), resulted in 15 % increase in AUC of midazolam. No dose adjustment is recommended for medicines metabolised by CYP3A.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

Animal studies in general do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. For

atomoxetine clinical data on exposed pregnancies are limited. Such data are insufficient to indicate either an association or a lack of association between atomoxetine and adverse pregnancy and/or lactation outcomes. ATOXTRIN should not be used during pregnancy.

**Breastfeeding**

Atomoxetine and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Because of the lack of data, atomoxetine should be avoided during breastfeeding.

**4.7 Effects on ability to drive and use machines**

Atomoxetine has been associated with increased rates of fatigue, somnolence and dizziness in paediatric and adult patients. Patients should be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by ATOXTRIN.

**4.8 Undesirable effects**

**Paediatric population**

**Summary of the safety profile:**

In paediatric placebo-controlled trials, headache, abdominal pain[1] and decreased appetite are the adverse events most frequently associated with atomoxetine, but seldom lead to atomoxetine discontinuation. Abdominal pain and decreased appetite are usually transient.

Associated with decreased appetite, some patients experienced growth retardation early in therapy in terms of both weight and height gain. On average, after an initial

decrease in weight and height gain, patients treated with atomoxetine recovered to mean weight and height as predicted by group baseline data over the long-term treatment.

Nausea, vomiting and somnolence can occur, particularly during the first month of therapy. However, these episodes were usually mild to moderate in severity and transient and did not result in a significant number of discontinuations from therapy. In both paediatric and adult placebo-controlled trials, patients taking atomoxetine experienced increases in heart rate, systolic and diastolic blood pressure (see section 4.4).

Because of its effect on noradrenergic tone, orthostatic hypotension and syncope have been reported in patients taking atomoxetine. ATOXTRIN should be used with caution in any condition that may predispose patients to hypotension.

The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials and post-marketing spontaneous reports in children and adolescents:

**Tabulated summary of adverse reactions:**

| **System Organ Class** | **Frequency** | **Adverse Event** |
|---|---|---|
| **Metabolism and nutrition disorders** | Frequent | Appetite decreased, anorexia (loss of appetite) |
| **Psychiatric disorders** | Frequent | Irritability, mood swings, insomnia, agitation, anxiety, depression and depressed mood, tics |

| | | |
|---|---|---|
| | Less frequent | Suicide-related events (see section 4.4), aggression, hostility, emotional lability, psychosis (including hallucinations) |
| | Frequency unknown | Bruxism |
| **Nervous system disorders** | Frequent | Headache, somnolence, dizziness |
| | Less frequent | Syncope, tremor, migraine, paraesthesia, hypoaesthesia, seizure |
| **Eye disorders** | Frequent | Mydriasis |
| | Less frequent | Vision blurred, conjunctivitis |
| **Cardiac disorders** | Less frequent | Palpitations, sinus tachycardia, QT interval prolongation |
| **Vascular disorders** | Less frequent | Raynaud's phenomenon |
| **Respiratory, thoracic and mediastinal disorders** | Less frequent | Dyspnoea (see section 4.4) |
| **Gastrointestinal disorders** | Frequent | Abdominal pain, vomiting, nausea, constipation, dyspepsia |
| **Hepatobiliary disorders** | Less frequent | Blood bilirubin increased, abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure |

| | | |
|---|---|---|
| **Skin and subcutaneous tissue disorders** | Frequent | Dermatitis, pruritus, rash |
| | Less frequent | Hyperhydrosis, allergic reactions |
| **Renal and urinary disorders** | Less frequent | Urinary hesitation, urinary retention |
| **Reproductive system and breast disorders** | Less frequent | Priapism, male genital pain |
| **General disorders and administration site conditions** | Frequent | Fatigue, lethargy, chest pain (see section 4.4), irritability |
| | Less frequent | Asthenia |
| **Investigations** | Frequent | Blood pressure increased, heart rate increased, weight decreased |

**CYP2D6 poor metabolisers (PM):**

The following adverse events occurred in CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: appetite decreased; insomnia combined (including insomnia, middle insomnia and initial insomnia); depression combined (including depression, major depression, depressive symptom, depressed mood and dysphoria), weight decreased, constipation; tremor; sedation; excoriation; enuresis; conjunctivitis; syncope; early morning awakening; mydriasis. The following event did not meet the above criteria but is noteworthy: generalised anxiety disorder. In addition, in trials lasting up to 10 weeks, weight loss was more pronounced in PM patients.

**Adults**

**Summary of the safety profile:**

In adult ADHD clinical trials, the following system organ classes had the highest frequency of adverse events during treatment with atomoxetine: gastrointestinal, nervous system and psychiatric disorders. The most frequent adverse events reported were appetite decreased, insomnia, headache, dry mouth and nausea. The majority of these events were mild or moderate in severity and the events most frequently reported as severe were nausea, insomnia, fatigue and headache. A complaint of urinary retention or urinary hesitancy in adults should be considered potentially related to atomoxetine. The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials and post-marketing spontaneous reports in adults.

**Tabulated list of adverse reactions:**

| System Organ Class | Frequency | Adverse Event |
|---|---|---|
| **Metabolism and nutrition disorders** | Frequent | Appetite decreased |
| **Psychiatric disorders** | Frequent | Insomnia, agitation, libido decreased, sleep disorder, depression and depressed mood, anxiety |
| | Less frequent | Suicide-related events aggression, hostility and emotional lability, restlessness, tics, orgasm abnormal, psychosis (including hallucinations) |
| **Nervous system disorders** | Frequent | Headache, dizziness, dysgeusia paraesthesia, somnolence (including sedation), tremor |

| | | |
|---|---|---|
| | Less frequent | Syncope, migraine, hypoaesthesia, seizure |
| **Eye disorders** | Less frequent | Vision Blurred |
| **Cardiac disorders** | Frequent | Palpitations, tachycardia |
| | Less frequent | QT interval prolongation |
| **Vascular disorders** | Frequent | Flushing, hot flush |
| | Less frequent | Peripheral coldness, Raynaud's phenomenon |
| **Respiratory, thoracic and mediastinal disorders** | Less frequent | Dyspnoea (see section 4.4) |
| **Gastrointestinal disorders** | Frequent | Dry mouth, nausea, abdominal pain, Constipation, dyspepsia, flatulence, vomiting |
| **Hepatobiliary disorders** | Less frequent | Abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure, blood bilirubin increased |
| **Skin and subcutaneous tissue disorders** | Frequent | Dermatitis, hyperhidrosis, rash |
| | Less frequent | Allergic reactions, pruritis, urticaria |

| | | |
|---|---|---|
| **Musculoskeletal and connective tissue disorders** | Less frequent | Muscle spasms |
| **Renal and urinary disorders** | Frequent | Dysuria, pollakuria, urinary hesitation, urinary retention |
| | Less frequent | Micturation urgency |
| **Reproductive system and breast disorders** | Frequent | Dysmenorrhoea, ejaculation disorder, erectile dysfunction, prostatitis, male genital pain |
| | Less frequent | Ejaculation failure, menstruation irregular, orgasm abnormal, priapism |
| **General disorders and administration site conditions** | Frequent | Asthenia, fatigue, lethargy, chills, feeling, jittery, irritability, thirst |
| | Less frequent | Feeling cold, chest pain (see section 4.4) |
| **Investigations** | Frequent | Blood pressure increased, heart rate increased, weight decreased |

**CYP2D6 poor metabolisers (PM):**

The following adverse events occurred in CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: vision blurred, dry mouth, constipation, feeling jittery, decreased appetite, tremor, insomnia, sleep disorder, middle insomnia, terminal insomnia, urinary retention, erectile dysfunction, ejaculation disorder, hyperhidrosis, peripheral coldness.

**Post-marketing experience**

The following events have been reported:

**Psychiatric disorders:**

Aggression/hostility. Suicidal ideation and anger. Suicidal behaviour. Sensory disturbances including hallucinations, depression and depressed mood, anxiety.

**Hepatobiliary disorders:**

Abnormal liver function tests, jaundice and hepatitis (see section 4.4).

**Investigations:**

Blood pressure increased.

**Skin and Subcutaneous Tissue Disorders:**

Hyperhidrosis.

**Vascular disorders:**

Peripheral vascular instability and/or Raynaud's phenomenon, potential to exacerbate pre-existing Raynaud's phenomenon.

**Urogenital system:**

Painful or prolonged penile erection, male genital pain, urinary hesitation in children and adolescents, urinary retention in children and adolescents.

**Nervous system disorders:**

Syncope, paraesthesia in children and adolescents, hypoaesthesia, tics.

**General disorders and administration site conditions:**

Lethargy.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

**4.9 Overdose**

**Signs and symptoms**

During post marketing, there have been reports of non-fatal acute and chronic overdoses of atomoxetine alone. The most commonly reported symptoms accompanying acute and chronic overdoses were gastrointestinal symptoms, somnolence, dizziness, tremor and abnormal behaviour. 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) were also observed and reports of pruritus and rash have been received. Most events were mild to moderate. In some cases of overdose involving atomoxetine, seizures have been reported and very rarely QT prolongation and serotonin syndrome. There have also been reports of fatal, acute overdoses involving a mixed ingestion of atomoxetine and at least one other medicinal product. There is limited clinical trial experience with atomoxetine overdose.

**Management**

An airway should be established. Activated charcoal may be useful in limiting absorption if the patient presents within 1 hour of ingestion. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. The patient should be observed for a minimum of 6 hours. Because atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psychoanaleptics; centrally acting sympathomimetics.

ATC code: N06BA09.

**Mechanism of action and pharmacodynamic effects**

Atomoxetine is a highly selective and potent inhibitor of the pre-synaptic noradrenaline transporter, its presumed mechanism of action, without directly affecting the serotonin or dopamine transporters. Atomoxetine has minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Atomoxetine has two major oxidative metabolites: 4-hydroxyatomoxetine and N-desmethylatomoxetine. 4-hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the noradrenaline transporter but, unlike atomoxetine, this metabolite also exerts some inhibitory activity at the serotonin transporter. However, any effect on this transporter is likely to be minimal, as the majority of 4-hydroxyatomoxetine is further metabolised such that it circulates in plasma at much lower concentrations (1 % of atomoxetine concentration in extensive metabolisers and 0,1 % of atomoxetine concentration in poor metabolisers). N-desmethylatomoxetine has substantially less pharmacological activity compared with atomoxetine. It circulates in plasma at lower concentrations in extensive metabolisers and at comparable concentrations to the parent medicine in poor metabolisers at steady state.

Atomoxetine is not a psychostimulant and is not an amphetamine derivative. In a randomised, double-blind, placebo-controlled, abuse-potential study in adults

comparing effects of atomoxetine and placebo, atomoxetine was not associated with a pattern of response that suggested stimulant or euphoriant properties.

## 5.2 Pharmacokinetic properties

The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under six years of age. Pharmacokinetic studies have shown that atomoxetine capsules and oral solution are bioequivalent.

### Absorption

Atomoxetine is absorbed after oral administration, reaching mean maximal observed plasma concentration ($C_{max}$) approximately 1 to 2 hours after dosing. The absolute bioavailability of atomoxetine following oral administration ranged from 63 % to 94 %, depending upon inter-individual differences in the modest first-pass metabolism. Atomoxetine can be administered with or without food.

### Distribution

Atomoxetine is widely distributed and is extensively (98 %) bound to plasma proteins, primarily albumin.

### Biotransformation

Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway. Individuals with reduced activity of this pathway (poor metabolisers) represent about 7 % of the Caucasian population and have higher plasma concentrations of atomoxetine compared with people with normal activity

(extensive metabolisers). For poor metabolisers, AUC of atomoxetine is approximately 10-fold greater, and Css-max is about 5-fold greater than extensive metabolisers. The major oxidative metabolite formed is 4-hydroxyatomoxetine that is rapidly glucuronidated. 4-hydroxyatomoxetine is equipotent to atomoxetine but circulates in plasma at much lower concentrations. Although 4-hydroxyatomoxetine is primarily formed by CYP2D6, in individuals that lack CYP2D6 activity, 4-hydroxyatomoxetine can be formed by several other cytochrome P450 enzymes, but at a slower rate. Atomoxetine does not inhibit or induce CYP2D6 at therapeutic doses.

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

**Elimination**

The mean elimination half-life of atomoxetine after oral administration is 3,6 hours in extensive metabolisers and 21 hours in poor metabolisers. Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-O-glucuronide, mainly in the urine.

**Linearity/non-linearity**

Pharmacokinetics of atomoxetine are linear over the range of doses studied in both extensive and poor metabolisers.

**Special populations**

Hepatic impairment results in a reduced atomoxetine clearance, increased atomoxetine exposure (AUC increased 2-fold in moderate impairment and 4-fold in severe impairment), and a prolonged half-life of parent medicinal product compared to healthy controls with the same CYP2D6 extensive metaboliser genotype. In patients

with moderate to severe hepatic impairment (Child-Pugh class B and C) initial and target doses should be adjusted (see section 4.2).

Atomoxetine mean plasma concentrations for end-stage renal disease (ESRD) subjects were generally higher than the mean for healthy control subjects shown by $C_{max}$ (7 % difference) and $AUC_{0-\infty}$ (about 65 % difference) increases. After adjustment for body weight, the differences between the two groups are minimised. Pharmacokinetics of atomoxetine and its metabolites in individuals with ESRD suggest that no dose adjustment would be necessary (see section 4.2).

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**ATOXTRIN 10 mg** hard gelatine capsules:

Pregelatinized maize starch, colloidal anhydrous silica, dimeticone, gelatine, sodium lauryl sulfate (E487), titanium dioxide (E171), black imprinting ink.

**ATOXTRIN 18 mg** hard gelatine capsules:

Pregelatinized maize starch, colloidal anhydrous silica, dimeticone, gelatine, sodium lauryl sulfate (E487), titanium dioxide (E171), iron oxide yellow (E172), black imprinting ink.

**ATOXTRIN 25 mg** hard gelatine capsules:

Pregelatinized maize starch, colloidal anhydrous silica, dimeticone, gelatine, sodium lauryl sulfate (E487), titanium dioxide (E171), indigo carmine (E132), black imprinting ink.

**ATOXTRIN 40 mg** hard gelatine capsules:

Pregelatinized maize starch, colloidal anhydrous silica, dimeticone, gelatine, sodium lauryl sulfate (E487), titanium dioxide (E171), indigo carmine (E132), black imprinting ink.

**ATOXTRIN 60 mg** hard gelatine capsules:

Pregelatinized maize starch, colloidal anhydrous silica, dimeticone, gelatine, sodium lauryl sulfate (E487), titanium dioxide (E171), indigo carmine (E132), iron oxide yellow (E172), black imprinting ink.

**ATOXTRIN 80 mg** hard gelatine capsules:

Pregelatinized maize starch, colloidal anhydrous silica, dimeticone, gelatine, sodium lauryl sulfate (E487), titanium dioxide (E171), indigo carmine (E132), iron oxide yellow (E172), black imprinting ink.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

36 months.

**6.4 Special precautions for storage**

Store at or below 25 °C.

**6.5 Nature and contents of container**

A cardboard box containing transparent PVC/PE/PCTFE-Aluminium foil blisters or PA/AL/PVC- Aluminium foil blisters.

**Pack sizes:**

7, 14, 28, 30 and 56 hard gelatine capsules.

Not all packs and pack sizes may be marketed.

**6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

**TRINITY PHARMA (PTY) LTD**

106, 16th Road,

Midrand,

1686,

South Africa

**8. MARKETING AUTHORISATION NUMBER(S)**

ATOXTRIN 10 mg: 55/1.2/0743

ATOXTRIN 18 mg: 55/1.2/0744

ATOXTRIN 25 mg: 55/1.2/0745

ATOXTRIN 40 mg: 55/1.2/0746

ATROXTRIN 60 mg: 55/1.2/0747

ATROXTRIN 80 mg: 55/1.2/0748

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

24 March 2023.

**10. DATE OF REVISION OF THE TEXT**

19 August 2025.