PROFESSIONAL INFORMATION

**SCHEDULING STATUS:** S5

## 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.

**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).

### 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.

**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 increases 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) |
| **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. 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**
3 Gwen Lane, 4th Floor, Sandton, 2031.
Contact No.: +27 (0)10 594 5610
PV Email Address: pv@trinitypharma.co.za

## 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
ATOXTRIN 60 mg: 55/1.2/0747
ATOXTRIN 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
24 March 2023.

PROFESSIONELE INLIGTING

**SKEDULERINGSSTATUS:** S5

## 1. NAAM VAN DIE GENEESMIDDEL
**ATOXTRIN 10 mg** Harde gelatienkapsules
**ATOXTRIN 18 mg** Harde gelatienkapsules
**ATOXTRIN 25 mg** Harde gelatienkapsules
**ATOXTRIN 40 mg** Harde gelatienkapsules
**ATOXTRIN 60 mg** Harde gelatienkapsules
**ATOXTRIN 80 mg** Harde gelatienkapsules

**WAARSKUWING:**
**SELFMOORDGEDAGTES BY KINDERS EN ADOLESSENTE**
**ATOXTRIN (atomoksetien) het die risiko van selfmoordgedagtes in korttermynstudies by kinders of adolessente met aandag-tekort/hiperaktiwiteitsversteuring (ADHD) verhoog. Enige een wat die gebruik van ATOXTRIN by 'n kind of adolessent oorweeg, moet hierdie risiko met die kliniese behoefte balanseer. Gepaardgaande siektes wat met ADHD voorkom, kan geassosieer word met 'n toename in die risiko van selfmoordgedagtes en/ of -gedrag. Pasiënte wat begin met terapie moet noukeurig gemonitor word vir selfmoord (selfmoordende en -gedrag), kliniese verergering of ongewone veranderinge in gedrag. Gesinne en versorgers moet ingelig word oor die behoefte aan noukeurige waarneming en kommunikasie met die voorskrywer. ATOXTRIN is goedgekeur vir ADHD by pediatriese en volwasse pasiënte. ATOXTRIN is nie goedgekeur vir ernstige depressiewe versteurings nie.**

## 2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
**ATOXTRIN 10 mg**
Elke harde gelatienkapsule bevat 10 mg atomoksetien as 11,43 mg atomoksetienhidrochloried.
**ATOXTRIN 18 mg**
Elke harde gelatienkapsule bevat 18 mg atomoksetien as 20,57 mg atomoksetienhidrochloried.
**ATOXTRIN 25 mg**
Elke harde gelatienkapsule bevat 25 mg atomoksetien as 28,57 mg atomoksetienhidrochloried.
**ATOXTRIN 40 mg**
Elke harde gelatienkapsule bevat 40 mg atomoksetien as 45,71 mg atomoksetienhidrochloried.
**ATOXTRIN 60 mg**
Elke harde gelatienkapsule bevat 60 mg atomoksetien as 68,57 mg atomoksetienhidrochloried.
**ATOXTRIN 80 mg**
Elke harde gelatienkapsule bevat 80 mg atomoksetien as 91,42 mg atomoksetienhidrochloried.

Suikervry.
Vir volledige lys van hulpstowwe, sien afdeling 6.1.

## 3. FARMASEUTIESE VORM
Harde gelatienkapsule
**ATOXTRIN 10 mg**
Wit poeier in 'n harde gelatienkapsule van No 3 grootte, ondeursigtige wit doppie met '10' in swart ink gedruk en 'n ondeursigtige wit lyf in swart ink met 'mg' gedruk.
**ATOXTRIN 18 mg**
Wit poeier in 'n harde gelatienkapsule van Nr. 3 grootte, ondeursigtige ryk geel doppie met '18' in swart ink gedruk en 'n ondeursigtige wit lyf in swart ink met 'mg' gedruk.
**ATOXTRIN 25 mg**
Wit poeier in 'n harde gelatienkapsule van Nr. 3 grootte, ondeursigtige blou doppie met '25' in swart ink gedruk en 'n ondeursigtige wit lyf in swart ink met 'mg' gedruk.
**ATOXTRIN 40 mg**
Wit poeier in 'n harde gelatienkapsule van Nr. 3 grootte, ondeursigtige blou doppie met '40' in swart ink gedruk en 'n ondeursigtige blou lyf in swart ink met 'mg' gedruk.
**ATOXTRIN 60 mg**
Wit poeier in 'n harde gelatienkapsule van Nr. 2 grootte, ondeursigtige blou doppie met '60' in swart ink gedruk en 'n ondeursigtige ryk geel lyf in swart ink met 'mg' gedruk.
**ATOXTRIN 80 mg**
Wit poeier in 'n harde gelatienkapsule van Nr. 2 grootte, ondeursigtige bruin doppie met '80' in swart ink gedruk en 'n ondeursigtige wit lyf in swart ink met 'mg' gedruk.

## 4. KLINIESE BESONDERHEDE
### 4.1. Terapeutiese indikasies
ATOXTRIN is aangedui vir die behandeling van aandag-tekort/hiperaktiwiteitsversteuring (ADHD) by kinders van 6 jaar of ouer, adolessente en volwassenes.

### 4.2. Dosering en metode van toediening
**Posologie**
Behandeling moet geïnisieer word deur of onder toesig van 'n mediese praktisyn met toepaslike kennis en ervaring van kinder- en/of adolessente gedragsafwykings (byvoorbeeld pediater of kinder/adolessente psigiater) (sien afdeling 4.4).

ATOXTRIN kan as 'n enkele daaglikse dosis in die oggend toegedien word. Pasiënte wat nie 'n bevredigende kliniese respons (verdraagsaamheid [bv. naarheid of slaperigheid] of doeltreffendheid) bereik wanneer ATOXTRIN as 'n enkele daaglikse dosis geneem word nie, kan baat vind by deur dit te neem in twee daaglikse eweredig verdeelde dosisse in die oggend en laatmiddag of vroegaand.

**Pediatriese bevolking**
**Dosering van pediatriese bevolking tot en met 70 kg liggaamsgewig:**
ATOXTRIN moet met 'n totale daaglikse dosis van ongeveer 0,5 mg/kg begin word. Die aanvanklike dosis moet vir 'n minimum van 7 dae gehandhaaf word voor opwaartse dositeitrasie volgens kliniese respons en verdraagsaamheid. Die aanbevole onderhoudsdosis is ongeveer 1,2 mg/kg/dag (afhangende van die pasiënt se gewig en beskikbare doseringssterktes van atomoksetien). Geen bykomende voordeel is getoon vir dosisse hoër as 1,2 mg/kg/dag nie.

**Dosering van pediatriese bevolking van meer as 70 kg liggaamsgewig en volwassenes:**
ATOXTRIN moet begin word met 'n totale daaglikse dosis van 40 mg. Die aanvanklike dosis moet vir 'n minimum van 7 dae gehandhaaf word voor opwaartse dositeitrasie volgens kliniese respons en verdraagsaamheid. Die aanbevole onderhoudsdosis is 80 mg. Geen bykomende voordeel is getoon vir dosisse hoër as 80 mg nie. Die maksimum aanbevole totale daaglikse dosis is 80 mg.

ATOXTRIN kan gestaak word sonder om die dosis te verminder.

**Gemisde dosis**
As pasiënte 'n dosis mis, moet hulle dit so gou as moontlik neem; hulle moet egter nie meer as die voorgeskrewe totale daaglikse hoeveelheid ATOXTRIN in enige 24-uur periode inneem nie.

**Spesiale bevolkings**
*Nier inkorting*
Vir daardie ADHD pasiënte wat lewerversaking of eindstadium niersiekte het, word versigtige titrasie van ATOXTRIN tot die verlangde kliniese respons aanbeveel. ATOXTRIN kan hipertensie by pasiënte met eindstadium niersiekte vererger.

*Lewer inkorting*
PN-opruiming kan verminder word by pasiënte met lewerversaking.

**Metode van toediening**
Vir orale gebruik.
ATOXTRIN kan met of sonder voedsel toegedien word.
Die kapsules moet nie oopgemaak word nie en die inhoud binne die kapsules moet nie verwyder en op enige ander manier geneem word nie.

ATOXTRIN is 'n okulêre-irritant. Indien kapsule-inhoud met die oog in aanraking kom, moet die aangetaste oog onmiddellik met water gespoel word en mediese advies verkry word. Hande en enige potensieel besmette oppervlaktes moet so gou as moontlik gewas word.

### 4.3. Kontraïndikasies
Hipersensitiwiteit vir atomoksetien of vir enige van die hulpstowwe gelys in afdeling 6.1.

ATOXTRIN moet nie in kombinasie met monoamienoksidase-inhibeerders (MAOI), insluitend linesolied, gebruik word nie. ATOXTRIN moet nie binne 'n minimum van 2 weke na staking van behandeling met MAOI gebruik word nie. Behandeling met MAOI moet nie binne 2 weke na staking van ATOXTRIN begin word nie. ATOXTRIN moet nie by pasiënte met nouhoek gloukoom gebruik word nie, aangesien die gebruik van atomoksetien in kliniese toetse geassosieer is met 'n verhoogde voorkoms van midriase.

ATOXTRIN moet nie by pasiënte met ernstige kardiovaskulêre of serebrovaskulêre afwykings gebruik word nie (sien afdeling 4.4 - Kardiovaskulêre effekte). Ernstige kardiovaskulêre afwykings kan ernstige hipertensie of 'n hartklop wat klinies belangrik kan wees insluit (byvoorbeeld 15 tot 20 mmHg in bloeddruk of 20 slae per minuut in hartklop) (sien afdeling 4.4 – kardiovaskulêre effekte), hartversaking, arteriële okklusiewe siekte, angina, hemodinamies beduidende aangebore hartsiekte, kardiomiopatieë, miokardiale infarksie, moontlik lewens-dreigende disritmieë en kanaalopatieë (afwykings wat veroorsaak word deur die disfunksie van ioonkanale). Ernstige serebrovaskulêre afwykings kan serebrale aneurisme of beroerte insluit.

ATOXTRIN moet nie by pasiënte met feochromositoom of 'n geskiedenis van feochromositoom gebruik word nie (sien afdeling 4.4 - Kardiovaskulêre effekte).

ATOXTRIN moet nie gebruik word by pasiënte met onbeheerde hipertensie of inkorting van lewerfunksie nie.

### 4.4. Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
**Selfmoordverwante gedrag**
Selfmoordverwante gedrag (selfmoordpogings en selfmoordgedagtes), vyandigheid (hoofsaaklik aggressie, opposisionele gedrag en woede) en emosionele labiliteit is aangemeld by pasiënte wat met atomoksetien behandel is. In dubbelblinde kliniese proewe is selfmoordverwante gedrag meer gereeld waargeneem in kinders en adolessente wat met atomoksetien behandel is in vergelyking met dié wat met die plasebo behandel is, waar daar geen gebeure was nie. In volwasse dubbelblinde kliniese proewe was daar geen verskil in die frekwensie van selfmoordverwante gedrag tussen atomoksetien en die plasebo nie. Pasiënte wat vir ADHD behandel word, moet noukeurig gemonitor word vir die voorkoms of verergering van selfmoordverwante gedrag. Die moontlikheid van ernstige psigiatriese nadelige effekte kan nie uitgesluit word nie.

Daar is bewyse dat die risiko van psigiatriese nadelige gebeurtenisse verhoog is by kinders met 'n persoonlike geskiedenis van gemoedsversteurings, of wat 'n familiegeskiedenis van gemoedsversteurings het.

**Skielike dood en voorafbestaande hartafwykings**
Skielike dood is aangemeld by pasiënte met strukturele hartafwykings wat atomoksetien teen gewone dosisse geneem het. Alhoewel sommige ernstige strukturele hartafwykings alleen 'n verhoogde risiko van skielike dood inhou, moet atomoksetien slegs met omsigtigheid gebruik word by pasiënte met bekende ernstige strukturele hartafwykings en in oorleg met 'n hartspesialis.

**Kardiovaskulêre effekte**
Atomoksetien kan hartklop en bloeddruk beïnvloed. Die meeste pasiënte wat atomoksetien neem, ervaar 'n matige toename in hartklop (gemiddeld <10 spm) en/of toename in bloeddruk (gemiddeld <5 mm Hg) (sien afdeling 4.8).

Gekombineerde data van gekontroleerde en onbeheerde ADHD kliniese proewe toon egter dat ongeveer 8-12 % van kinders en adolessente, en 6-10 % van volwassenes meer uitgesproke veranderinge in hartklop (20 slae per minuut of meer) en bloeddruk (15-20 mmHg of meer) ervaar. Ontleding van hierdie kliniese proefdata het getoon dat ongeveer 15-26 % van kinders en adolessente, en 27-32 % van volwassenes wat sulke veranderinge in bloeddruk en hartklop tydens atomoksetienbehandeling ervaar het, volgehoue of progressiewe verhogings gehad het. Langtermyn volgehoue veranderinge in bloeddruk kan moontlik bydra tot kliniese gevolge soos miokardiale hipertrofie.
As gevolg van hierdie bevindinge, moet pasiënte wat vir behandeling met atomoksetien oorweeg word, 'n noukeurige geskiedenis en fisiese ondersoek ondergaan om te bepaal of daar teenwoordigheid van hartsiekte is en moet verdere spesialis-hart-evaluering ontvang indien aanvanklike bevindinge sulke geskiedenis of siekte voorstel.

Dit word aanbeveel dat hartklop en bloeddruk gemeet en aangeteken word voordat behandeling begin word en, tydens behandeling, na elke dosisaanpassing en dan ten minste elke 6 maande om moontlike klinies belangrike verhogings op te spoor. Vir pediatriese pasiënte word die gebruik van 'n sentielkaart aanbeveel. Vir volwassenes moet huidige verwysingsriglyne vir hipertensie gevolg word.

ATOXTRIN moet nie by pasiënte met ernstige kardiovaskulêre of serebrovaskulêre afwykings gebruik word nie (sien afdeling 4.3 – Ernstige kardiovaskulêre en serebrovaskulêre afwykings). ATOXTRIN moet met omsigtigheid gebruik word by pasiënte wie se onderliggende mediese toestande vererger kan word deur verhogings in bloeddruk en hartklop, soos pasiënte met hipertensie, tagikardie of kardiovaskulêre of serebrovaskulêre siekte.

Pasiënte wat simptome soos hartkloppings, inspannende borspyn, onverklaarbare sinkopee, dyspnee of ander simptome wat op hartsiekte dui tydens atomoksetienbehandeling ontwikkel, moet 'n vinnige spesialis-hart-evaluering ondergaan.

Daarbenewens moet atomoksetien met omsigtigheid gebruik word by pasiënte met aangebore of verworwe lang QT of 'n familiegeskiedenis van QT-verlenging (sien afdelings 4.5 en 4.8).

Aangesien ortostatiese hipotensie ook aangemeld is, moet atomoksetien met omsigtigheid gebruik word in enige toestand wat pasiënte kan vatbaar maak vir hipotensie of toestande wat verband hou met skielike hartklop- of bloeddrukveranderinge.
ATOXTRIN moet nie by pasiënte met Raynaud se verskynsel gebruik word nie.

**Serebrovaskulêre effekte**
Pasiënte met bykomende risikofaktore vir serebrovaskulêre toestande (soos 'n geskiedenis van kardiovaskulêre siektes, gepaardgaande medikasie wat bloeddruk verhoog) moet by elke besoek vir neurologiese tekens en simptome geassesseer word nadat behandeling met atomoksetien begin is.

**Hepatiese effekte**
Spontane verslae van lewerbesering, gemanifesteer deur verhoogde lewerensieme en bilirubien met geelsug, is aangemeld. Ernstige lewerbesering, insluitend akute lewerversaking, is aangemeld. ATOXTRIN moet gestaak word by pasiënte met geelsug of laboratoriumbewyse van lewerbesering en moet nie weer begin word nie. Tekens en simptome wat waarskynlik lewerbetrokkenheid aandui, sluit pruritis, donker urine, geelsug, sagtheid van die regter boonste kwadrant of onverklaarbare "griepagtige" simptome in. Laboratoriumtoetse om lewerensiemvlakke en bilirubien te bepaal moet gedoen word by die eerste tekens of simptome van moontlike lewerbetrokkenheid. As gevolg van die oënskynlik eiesoortige aard van die lewerbesering, is dit onwaarskynlik dat roetine-monitering van lewerfunksie nuttig sal wees om die risiko van sulke reaksies te verminder.

**Psigotiese of maniese simptome**
Behandeling-ontluikende psigotiese of maniese simptome, bv. hallusinasies, waandenke, manie of agitasie by pasiënte sonder 'n vorige geskiedenis van psigotiese siekte of manie kan deur atomoksetien by gewone dosisse veroorsaak word. Indien sulke simptome voorkom, moet oorweging gegee word aan 'n moontlike oorsaaklike rol van atomoksetien, en staking van behandeling moet oorweeg word. Die moontlikheid dat ATOXTRIN die verergering van reeds bestaande psigotiese of maniese simptome sal veroorsaak, kan nie uitgesluit word nie.

**Aggressiewe gedrag, vyandigheid of emosionele labiliteit**
Vyandigheid (hoofsaaklik aggressie, opposisiegedrag en woede) is meer gereeld waargeneem in kliniese proewe onder kinders, adolessente en volwassenes wat met atomoksetien behandel is in vergelyking met dié wat met die plasebo behandel is. Emosionele labiliteit is meer gereeld waargeneem in kliniese proewe onder kinders wat met atomoksetien behandel is in vergelyking met dié wat met die plasebo behandel is. Pasiënte moet noukeurig gemonitor word vir die voorkoms of verergering van aggressiewe gedrag, vyandigheid of emosionele labiliteit.

**Moontlike allergiese gebeure**
Allergiese reaksies, insluitend anafilaktiese reaksies, uitslag, angioneurotiese edeem en urtikaria, is aangemeld by pasiënte wat atomoksetien gebruik.

**Okulêre irritant**
Die kapsules is nie bedoel om oopgemaak te word nie. Atomoksetien is 'n okulêre irritant. Indien die inhoud van die kapsules met die oog in aanraking kom, moet die aangetaste oog onmiddellik met water gespoel word en mediese advies verkry word. Hande en enige potensieel besmette oppervlaktes moet so gou as moontlik gewas word.

**Aanvalle**
Aanvalle is 'n potensiële risiko met atomoksetien. Atomoksetien moet met omsigtigheid gebruik word by pasiënte met 'n geskiedenis van aanvalle. Die staking van atomoksetien moet oorweeg word in enige pasiënt wat 'n aanval ontwikkel of as daar 'n toename in die frekwensie van aanvalle is waar geen ander oorsaak geïdentifiseer word nie.

**Groei en ontwikkeling**
Groei en ontwikkeling moet gemonitor word by kinders en adolessente tydens behandeling met atomoksetien. Pasiënte wat langtermyn-terapie benodig, moet gemonitor word en oorweging moet gegee word aan dosisvermindering of onderbreking van terapie by kinders en adolessente wat nie bevredigend groei of gewig optel nie.

Kliniese data dui nie op 'n nadelige effek van atomoksetien op kognisie of seksuele rypwording nie; die hoeveelheid beskikbare langtermyndata is egter beperk. Daarom moet pasiënte wat langtermynterapie benodig, noukeurig gemonitor word.

**Nuwe aanvang of verergering van Ko-morbiede Depressie, Angs en Tieke**
In 'n gekontroleerde studie van pediatriese pasiënte met ADHD en ko-morbiede chroniese motoriese tieke of Tourette se versteuring, het atomoksetien-behandelde pasiënte nie verergering van tieke ervaar in vergelyking met plasebo-behandelde pasiënte nie. In 'n gekontroleerde studie van adolessente pasiënte met ADHD en ko-morbiede Ernstige Depressiewe Versteuring, het atomoksetien-behandelde pasiënte nie verergering van depressie ervaar in vergelyking met plasebo-behandelde pasiënte nie. In twee gekontroleerde studies (een in pediatriese pasiënte en een in volwasse pasiënte) van pasiënte met ADHD en ko-morbiede angsversteurings, het atomoksetien-behandelde pasiënte nie verergering van angs ervaar in vergelyking met plasebo-behandelde pasiënte nie.

Daar was seldsame na-bemarkingsverslae van angs en depressie of depressiewe gemoed en baie seldsame verslae van tieke by pasiënte wat atomoksetien gebruik (sien afdeling 4.8).

Pasiënte wat vir ADHD met atomoksetien behandel word, moet gemonitor word vir die voorkoms of verergering van angssimptome, depressiewe gemoed en depressie of tieke.

**Effekte op mikturisie**
In volwasse ADHD-gekontroleerde proewe was die tempo van urienretensie en urinêre huiwering onder die atomoksetien verhoog, soos ATOXTRIN-proefpersone vergelyk was met plasebo-proefpersone. 'n Klag van urienretensie of urinêre huiwering moet oorweeg word wat moontlik verband hou met ATOXTRIN.

**Pediatriese bevolking onder ses jaar oud**
ATOXTRIN moet nie by pasiënte jonger as ses jaar gebruik word nie, aangesien doeltreffendheid en veiligheid nie in hierdie ouderdomsgroep vasgestel is nie. Die doeltreffendheid van ATOXTRIN na 18 maande se behandeling en veiligheid van ATOXTRIN na 2 jaar se behandeling is nie sistematies geëvalueer nie.

**Bejaardes gebruik**
Die veiligheid en doeltreffendheid van ATOXTRIN by bejaarde pasiënte is nie vasgestel nie.

**Ander terapeutiese gebruike**
Atomoksetien is nie aangedui vir die behandeling van ernstige depressiewe episodes en/of angs nie, aangesien die resultate van kliniese proewe by volwassenes in hierdie toestande, waar ADHD nie teenwoordig is nie, nie 'n effek getoon het in vergelyking met die plasebo nie (sien afdeling 5.1).

### 4.5. Interaksies met ander medisyne en ander vorme van interaksie
Effekte van ander medisyne op atomoksetien:

**MAOI's**
Atomoksetien moet nie saam met MAOI's gebruik word nie (sien afdeling 4.3).

**CYP2D6-inhibeerders (SSRI's) (bv. fluoksetien, paroksetien), kinidien, terbinafien)**
By pasiënte wat hierdie medisyne ontvang, kan blootstelling aan atomoksetien 6- tot 8-voudig verhoog word en Css-maks 3 tot 4 keer hoër, omdat dit deur die CYP2D6-weg gemetaboliseer word. Stadiger titrasie en finale laer dosis atomoksetien kan nodig wees by pasiënte wat reeds CYP2D6-inhibeerder medisyne gebruik. Indien 'n CYP2D6-inhibeerder voorgeskryf of gestaak word nadat titrasie na die toepaslike atomoksetien dosis plaasgevind het, moet die kliniese respons en verdraagsaamheid vir daardie pasiënt herevalueer word om te bepaal of dosisaanpassing nodig is.

Omsigtigheid word aangeraai wanneer atomoksetien gekombineer word met kragtige inhibeerders van sitochroom P450-ensieme anders as CYP2D6 by pasiënte wat swak CYP2D6-metaboliseerders is, aangesien die risiko van kliniese relevante verhogings in atomoksetienblootstelling *in vivo* onbekend is.

**Salbutamol (of ander beta$_2$-agoniste)**
Atomoksetien moet met omsigtigheid toegedien word aan pasiënte wat behandel word met 'n hoë dosis geneboliseerde of sistemies toegediende salbutamol (of ander beta$_2$-agoniste) omdat kardiovaskulêre effekte versterk kan word.

Teenstrydige bevindings rakende hierdie interaksie is gevind. Sistemies toegediende salbutamol (600 µg i.v. oor 2 uur) in kombinasie met atomoksetien (60 mg twee keer daagliks vir 5 dae) het verhogings in hartklop en bloeddruk geïnduseer. Hierdie effek was die meeste merkbaar na die aanvanklike gelyktydige toediening van salbutamol en atomoksetien, maar het teruggekeer na die basislyn aan die einde van 8 uur. In 'n afsonderlike studie is die uitwerking op bloeddruk en hartklop van 'n standaard ingeasemde dosis salbutamol (200 µg) egter nie verhoog deur die korttermyn gesamentlike toediening van atomoksetien (80 mg een keer daagliks vir 5 dae) in 'n studie van gesonde Asiatiese volwassenes wat uitgebreide atomoksetienmetaboliseerders was nie. Net so het hartklop na veelvuldige inaseming van salbutamol (800 µg) nie verskil in die teenwoordigheid of afwesigheid van atomoksetien nie.

Aandag moet gegee word aan die monitering van hartklop en bloeddruk, en dosisaanpassings kan geregverdig wees vir óf atomoksetien óf salbutamol (of ander beta$_2$-agoniste) in die geval van beduidende verhogings in hartklop en bloeddruk tydens gelyktydige toediening van hierdie medisyne.

Daar is die potensiaal vir 'n verhoogde risiko van verlenging van die QT-interval wanneer atomoksetien saam met ander QT-verlengende medisyne toegedien word (soos neuroleptika, klas IA en III anti-ritmies, moksifloksasien, eritromisien, metadoon, meflokien, trisikliese antidepressante, litium of sisapried), medisyne wat elektrolietwanbalans veroorsaak (soos tiasieddiuretika), en medisyne wat CYP2D6 inhibeer.

Aanvalle is 'n potensiële risiko met atomoksetien. Omsigtigheid word aangeraai met die gelyktydige gebruik van medisyne wat bekend is dat dit die aanvalsdrempel verlaag (soos trisikliese antidepressante of SSRI's, neuroleptika, fenotiasiene of butirofenoon, meflokien, chlorokien, bupropion of tramadol (sien afdeling 4.4)). Daarbenewens word omsigtigheid aangeraai wanneer gelyktydige behandeling met bensodiasepiene gestaak word as gevolg van moontlike onttrekkingsaanvalle.

**Anti-hipertensiewe medisyne**
Atomoksetien moet versigtig gebruik word saam met anti-hipertensiewe medisyne. As gevolg van 'n moontlike toename in bloeddruk, kan atomoksetien die doeltreffendheid van anti-hipertensiewe medisyne / medisyne wat gebruik word om hipertensie te behandel, verminder. Aandag moet gegee word aan monitering van bloeddruk en hersiening van behandeling van atomoksetien of anti-hipertensiewe medisyne kan geregverdig word in die geval van beduidende veranderinge in bloeddruk.

**Pressor medisyne of medisyne wat bloeddruk verhoog**
As gevolg van moontlike toename in effekte op bloeddruk, moet atomoksetien versigtig gebruik word saam met pressor medisyne of medikasie wat bloeddruk kan verhoog (soos salbutamol). Aandag moet gegee word aan die monitering van bloeddruk, en hersiening van behandeling vir óf atomoksetien óf pressor medisyne kan geregverdig word in die geval van beduidende verandering in bloeddruk.

**Medisyne wat noradrenalien beïnvloed**
Medisyne wat noradrenalien beïnvloed, moet versigtig gebruik word wanneer dit saam met atomoksetien toegedien word as gevolg van die potensiaal vir additiewe of sinergistiese farmakologiese effekte. Voorbeelde sluit in antidepressante, soos imipramien, venlafaksien en mirtazapien, of die dekongestante pseudoefedrien of fenielefrien.

**Medisyne wat gastriese pH beïnvloed**
Medisyne wat gastriese pH verhoog (magnesiumhidroksied/aluminiumhidroksied, omeprazool) het geen effek op atomoksetien biobeskikbaarheid gehad nie.

**Medisyne wat hoogs plasmaproteïen gebonde is**
In vitro medisyne-verplasingstudies is uitgevoer met atomoksetien en ander hoogs gebonde medisyne by terapeutiese konsentrasies. Warfarien, asetielsalisielsuur, fenitoïen of diasepam het nie die binding van atomoksetien aan menslike albumien beïnvloed nie. Net so het atomoksetien nie die binding van hierdie verbindings aan menslike albumien beïnvloed nie.

**Metielfenidaat**
Gesamentlike toediening van metielfenidaat met atomoksetien het nie kardiovaskulêre effekte meer verhoog as dié wat gesien is met alleenlike metielfenidaattoediening nie.

**Alkohol**
Verbruik van etanol met atomoksetien het nie die bedwelmende effekte van etanol verander nie.

**Midazolam**
Gesamentlike toediening van atomoksetien (60 mg twee keer daagliks vir 12 dae) met midazolam, 'n modelverbinding vir CYP3A4-gemetaboliseerde medisyne (enkeldosis van 5 mg), het gelei tot 'n toename van 15 % in AOK van midazolam. Geen dosisaanpassing word aanbeveel vir medisyne wat deur CYP3A gemetaboliseer word nie.

### 4.6. Vrugbaarheid, swangerskap en laktasie
**Swangerskap**
Dierestudies in die algemeen dui nie op direkte skadelike effekte met betrekking tot swangerskap, embrionale/fetale ontwikkeling, bevalling of postnatale ontwikkeling nie. Vir atomoksetien is kliniese data oor blootgestelde swangerskappe beperk. Sulke data is onvoldoende om óf 'n assosiasie óf 'n gebrek aan assosiasie tussen atomoksetien en ongunstige swangerskap en/of laktasie-uitkomste aan te dui. ATOXTRIN moet nie tydens swangerskap gebruik word nie.

**Borsvoeding**
Atomoksetien en/of sy metaboliete was in die melk van rotte uitgeskei. Dit is nie bekend of atomoksetien in menslike melk uitgeskei word nie. As gevolg van die gebrek aan data, moet atomoksetien tydens borsvoeding vermy word.

### 4.7. Effekte op die vermoë om te bestuur en masjiene te gebruik
Atomoksetien is geassosieer met verhoogde vlakke van moegheid, slaperigheid en duiseligheid by pediatriese en volwasse pasiënte. Pasiënte moet aangeraai word om versigtig te wees wanneer hulle 'n motor bestuur of gevaarlike masjinerie bedryf totdat hulle redelik seker is dat hul werkverrigting nie deur ATOXTRIN beïnvloed word nie.

### 4.8. Ongewenste effekte
**Pediatriese populasie**
**Opsomming van die veiligheidsprofiel:**
In pediatriese plasebo-beheerde proewe is hoofpyn, abdominale pyn[1] en verminderde eetlus die nadelige gebeurtenisse wat die meeste met atomoksetien geassosieer word, maar lei selde tot staking van atomoksetien. Buikpyn en verminderde eetlus is gewoonlik verbygaande.

Sommige pasiënte het groeivertraging vroeg in terapie in terme van beide gewig en lengtetoename ervaar wat geassosieer is met verminderde eetlus. Gemiddeld, na 'n aanvanklike afname in gewig en lengtetoename, het pasiënte wat met atomoksetien behandel is, herstel tot gemiddelde gewig en lengte soos voorspel deur groepsbasislyndata oor die langtermynbehandeling.

Naarheid, braking en slaperigheid kan voorkom, veral gedurende die eerste maand van terapie. Hierdie episodes was egter gewoonlik lig tot matig in erns en verbygaande en het nie gelei tot 'n beduidende aantal stakings van terapie nie. In beide pediatriese en volwasse plasebo-gekontroleerde proewe het pasiënte wat atomoksetien geneem het, toenames in hartklop, sistoliese en diastoliese bloeddruk ervaar (sien afdeling 4.4).

As gevolg van die effek daarvan op noradrenergiese toon, is ortostatiese hipotensie en sinkopee aangemeld by pasiënte wat atomoksetien neem. ATOXTRIN moet met omsigtigheid gebruik word in enige toestand wat pasiënte vir hipotensie kan vatbaar maak.

Die volgende tabel van ongewenste effekte is gebaseer op verslagdoening van nadelige gebeurtenisse en laboratoriumondersoeke van kliniese proewe en spontane na-bemarkingsverslae by kinders en adolessente:
**Getabelleerde opsomming van nadelige reaksies**

| Stelselorgaanklas | Frekwensie | Ongewenste effek |
|---|---|---|
| **Metabolisme en voedingafwykings** | Gereeld | Eetlus verminder, anoreksie (verlies van eetlus) |
| **Psigiatriese afwykings** | Gereeld | Prikkelbaarheid, buierigheid, slapeloosheid, agitasie, angs, depressie en depressiewe bui, tieke |
| | Minder gereeld | Selfmoordverwante gebeure (sien afdeling 4.4), aggressie, vyandigheid, emosionele labiliteit, psigose (insluitend hallusinasies) |
| **Senuweestelselafwykings** | Gereeld | Hoofpyn, slaperigheid, duiseligheid |
| | Minder gereeld | Sinkopee, bewing, migraine, parestesie, hipoestesie, aanvalle |
| **Oogafwykings** | Gereeld | Midriasis |
| | Minder gereeld | Vervaagde visie, konjunktivitis |
| **Hartafwykings** | Minder gereeld | Palpitasies, sinus tagikardie, QT-interval verlenging |
| **Vaskulêre afwykings** | Minder gereeld | Raynaud se verskynsel |
| **Respiratoriese, torakale en mediastinale afwykings** | Minder gereeld | Dispnee (sien afdeling 4.4) |
| **Gastrointestinale afwykings** | Gereeld | Buikpyn, braking, naarheid, hardlywigheid, dispepsie |
| **Hepatobiliêre afwykings** | Minder gereeld | Verhoogde bloedbilirubien, abnormale/ verhoogde lewerfunksietoetse, geelsug, hepatitis, lewerbesering, akute lewerversaking |
| **Vel- en subkutane weefselafwykings** | Gereeld | Dermatitis, pruritus, uitslag |
| | Minder gereeld | Hiperhidrose, allergiese reaksies |
| **Nier- en urienêre afwykings** | Minder gereeld | Urinêre huiwering, urienretensie |
| **Voortplantingstelsel- en borsafwykings** | Minder gereeld | Priapisme, manlike genitale pyn |
| **Algemene afwykings en toedieningsplektoestande** | Gereeld | Moegheid, lusteloosheid, borspyn (sien afdeling 4.4), prikkelbaarheid |
| | Minder gereeld | Astenie |
| **Ondersoeke** | Gereeld | Verhoogde bloeddruk, verhoogde hartklop, gewig afname |

**CYP2D6 swak metaboliseerders (SM):**
Die volgende nadelige gebeurtenisse het voorgekom in CYP2D6 swak metaboliseerder (SM) pasiënte en was statisties beduidend meer gereeld in SM pasiënte in vergelyking met CYP2D6 ekstensiewe metaboliseerder (EM) pasiënte: eetlus het afgeneem; slapeloosheid gekombineer (insluitend slapeloosheid, middelslapeloosheid en aanvanklike slapeloosheid); depressie gekombineer (insluitend depressie, ernstige depressie, depressiewe simptoom, depressiewe bui en disforie), gewig verminder, hardlywigheid; bewing; sedasie; ekskoriasie; enuresis; konjunktivitis; sinkopee; vroeggoggend wakker word; midriase. Die volgende gebeurtenis het nie aan bogenoemde kriteria voldoen nie, maar is opmerklik: veralgemeende angsversteuring. Daarbenewens, in proewe wat tot 10 weke geduur het, was gewigsverlies meer uitgesproke by SM-pasiënte.

**Volwassenes**
**Opsomming van die veiligheidsprofiel:**
In volwasse ADHD kliniese proewe het die volgende stelselorgaanklasse die hoogste frekwensie van nadelige gebeurtenisse tydens behandeling met atomoksetien gehad: gastrointestinale, senuweestelsel en psigiatriese afwykings. Die mees algemene newe-effekte wat aangemeld is, was verminderde eetlus, slapeloosheid, hoofpyn, droë mond en naarheid. Die meerderheid van hierdie gebeure was lig of matig in erns en die gebeure wat die meeste as ernstig aangemeld is, was naarheid, slapeloosheid, moegheid en hoofpyn. 'n Klag van urienretensie of urinêre huiwering by volwassenes moet beskou word as moontlik verwant aan atomoksetien. Die volgende tabel van ongewenste effekte is gebaseer op newe-gebeurtenisrapportering en laboratoriumondersoeke van kliniese proewe en spontane na-bemarkingsverslae by volwassenes.

**Getabelleerde opsomming van nadelige reaksies:**

| Stelselorgaanklas | Frekwensie | Ongewenste effek |
|---|---|---|
| **Metabolisme en voedingafwykings** | Gereeld | Eetlus verminder |
| **Psigiatriese afwykings** | Gereeld | Slapeloosheid, agitasie, libido verminder, slaapversteuring, depressie en depressiewe bui, angs |
| | Minder gereeld | Selfmoordverwante gebeure, aggressie, vyandigheid en emosionele labiliteit, rusteloosheid, tieke, abnormale orgasme, psigose (insluitend hallusinasies) |
| **Senuweestelselafwykings** | Gereeld | Hoofpyn, duiseligheid, disgesie parestesie, slaperigheid (insluitend sedasie), bewing |
| | Minder gereeld | Sinkopee, migraine, hipoestesie, aanvalle |
| **Oogafwykings** | Minder gereeld | Vervaagde visie |
| **Hartafwykings** | Gereeld | Palpitasies, tagikardie |
| | Minder gereeld | QT-interval verlenging |
| **Vaskulêre afwykings** | Gereeld | Gloede, warm gloede |
| | Minder gereeld | Perifere koue, Raynaud se verskynsel |
| **Respiratoriese, torakale en mediastinale afwykings** | Minder gereeld | Dispnee (sien afdeling 4.4) |
| **Gastrointestinale afwykings** | Gereeld | Droë mond, naarheid, buikpyn, hardlywigheid, dispepsie, winderigheid, braking |
| **Hepatobiliêre afwykings** | Minder gereeld | Abnormale/verhoogde lewerfunksietoetse, geelsug, hepatitis, lewerbesering, akute lewerversaking, verhoogde bloedbilirubien |
| **Vel- en subkutaneuse afwykings** | Gereeld | Dermatitis, hiperhidrose, uitslag |
| | Minder gereeld | Allergiese reaksies, pruritis, urtikaria |
| **Muskuloskeletale en bindingsweefselafwykings** | Minder gereeld | Spierspasmas |
| **Nier- en urienêre afwykings** | Gereeld | Disurie, pollakurie, urinêre huiwering, urienretensie |
| | Minder gereeld | Mikturasie dringendheid |
| **Voortplantingstelsel- en borsafwykings** | Gereeld | Dismenorree, ejakulasieversteuring, erektiele disfunksie, prostatitis, manlike genitale pyn |
| | Minder gereeld | Ejakulasie mislukking, onreëlmatige menstruasie, abnormale orgasme, priapisme |
| **Algemene afwykings en toedieningsplektoestande** | Gereeld | Astenie, moegheid, lusteloosheid, kouekoors, angstigheid, prikkelbaarheid, dors |
| | Minder gereeld | Koue gevoel, borspyn (sien afdeling 4.4) |
| **Ondersoeke** | Gereeld | Verhoogde bloeddruk, verhoogde hartklop, gewig afname |

**CYP2D6 swak metaboliseerders (SM):**
Die volgende nadelige gebeurtenisse het voorgekom by CYP2D6 swak metaboliseerder (SM) pasiënte en was statisties beduidend meer gereeld in SM pasiënte in vergelyking met CYP2D6 ekstensiewe metaboliseerder (EM) pasiënte: versteurde visie, droë mond, hardlywigheid, gevoel van wanhoop, verminderde eetlus, bewing, slapeloosheid, slaapversteuring, middelslapeloosheid, terminale slapeloosheid, urienretensie, erektiele disfunksie, ejakulasieversteuring, hiperhidrose, perifere koue.

**Na-bemarking ervaring**
Die volgende gebeure is aangemeld:
**Psigiatriese versteurings:**
Aggressie/vyandigheid. Selfmoordgedagtes en woede. Selfmoordgedrag. Sensoriese versteurings insluitend hallusinasies, depressie en depressiewe bui, angs.
**Hepatobiliêre afwykings:**
Abnormale lewerfunksietoetse, geelsug en hepatitis (sien afdeling 4.4).
**Ondersoeke:**
Bloeddruk het toegeneem.
**Vel- en subkutane weefselafwykings:**
Hiperhidrose.
**Vaskulêre afwykings:**
Perifere vaskulêre onstabiliteit en/of Raynaud se verskynsel, potensiaal om reeds bestaande Raynaud se verskynsel te vererger.
**Urogenitale stelsel:**
Pynlike of langdurige penis ereksie, manlike genitale pyn, urinêre huiwering by kinders en adolessente, urienretensie by kinders en adolessente.
**Senuweestelselafwykings:**
Sinkope, parestesie by kinders en adolessente, hipoestesie, tieke.
**Algemene afwykings en toedieningsplektoestande:**
Lusteloosheid.

**Rapportering van vermoedelike nadelige reaksies**
Dit is belangrik om vermoedelike nadelige reaksies aan te meld na goedkeuring van die medisyne. Dit laat voortgesette monitering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgpersoneel word gevra om enige vermoedelike nadelige reaksies by SAHPRA aan te meld via die "6.04 Adverse Drug Reaksieverslagdoeningsvorm", aanlyn gevind onder SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8

### 4.9. Oordosering
**Tekens en simptome**
Tydens nabemarking was daar verslae van nie-dodelike akute en chroniese oordosis van atomoksetien alleenlik. Die mees algemeen gerapporteerde simptome wat gepaard gaan met akute en chroniese oordosis was gastrointestinale simptome, slaperigheid, duiseligheid, bewing en abnormale gedrag. Hiperaktiwiteit en agitasie is ook aangemeld. Tekens en simptome wat ooreenstem met ligte tot matige simpatiese senuweestelselaktivering (bv. tagikardie, verhoogde bloeddruk, midriase, droë mond) is ook waargeneem en verslae van pruritus en uitslag is ontvang. Die meeste gebeure was lig tot matig. In sommige gevalle van oordosis wat atomoksetien behels, is aanvalle aangemeld en baie seldsame QT-verlenging. Daar was ook verslae van noodlottige, akute oordosis wat 'n gemengde inname van atomoksetien en ten minste een ander medisyne behels. Daar is beperkte kliniese proefervaring met atomoksetien oordosis.

**Bestuur**
'n Lugweg moet gevestig word. Geaktiveerde houtskool kan nuttig wees om absorpsie te beperk as die pasiënt binne 1 uur na inname presenteer. Monitering van kardiale en vitale tekens word aanbeveel, tesame met toepaslike simptomatiese en ondersteunende maatreëls. Die pasiënt moet vir 'n minimum van 6 uur waargeneem word. Omdat atomoksetien hoogs proteïengebonde is, sal dialise waarskynlik nie nuttig wees in die behandeling van oordosis nie.

## 5. FARMAKOLOGIESE EIENSKAPPE
### 6.1 Farmakodinamiese eienskappe
Farmakoterapeutiese groep: Psigoanaleptika; sentraalwerkende simpatomimetika. ATC-kode: N06BA09.

**Werkingsmeganisme en farmakodinamiese effekte**
Atomoksetien is 'n hoogs selektiewe en kragtige inhibeerder van die pre-sinaptiese noradrenalien-transporter, sy veronderstelde werkingsmeganisme, sonder om die serotonien- of dopamien-transporter direk te beïnvloed. Atomoksetien het minimale affiniteit vir ander noradrenergiese reseptore of vir ander neurotransmitter transporters of reseptore. Atomoksetien het twee hoof oksidatiewe metaboliete: 4-hidroksiatomoksetien en N-desmetielatomoksetien. 4-hidroksiatomoksetien is ekwipotent aan atomoksetien as 'n inhibeerder van die noradrenalientransporter, maar, anders as atomoksetien, oefen hierdie metaboliet ook 'n mate van inhiberende aktiwiteit by die serotonientransporter uit. Enige effek op hierdie transporter sal waarskynlik minimaal wees, aangesien die meerderheid van 4-hidroksiatomoksetien verder gemetaboliseer word sodat dit teen baie laer konsentrasies in plasma sirkuleer (1 % van atomoksetienkonsentrasie in ekstensiewe metaboliseerders en 0,1 % van atomoksetienkonsentrasie by swak metaboliseerders). N-desmetielatomoksetien het aansienlik minder farmakologiese aktiwiteit in vergelyking met atomoksetien. Dit sirkuleer in plasma teen laer konsentrasies by ekstensiewe metaboliseerders en teen vergelykbare konsentrasies as die moedermedisyne by swak metaboliseerders by ewewigstoestand.

Atomoksetien is nie 'n psigostimulant nie en is nie 'n amfetamienderivaat nie. In 'n gerandomiseerde, dubbelblinde, plasebo-beheerde, misbruik-potensiaal studie in volwassenes wat die effekte van atomoksetien en plasebo vergelyk, was atomoksetien nie geassosieer met 'n patroon van respons wat stimulante of euforiese eienskappe voorgestel het nie.

### 6.2 Farmakokinetiese eienskappe
Die farmakokinetika van atomoksetien by kinders en adolessente is soortgelyk aan dié by volwassenes. Die farmakokinetika van atomoksetien is nie by kinders jonger as ses jaar geëvalueer nie. Farmakokinetiese studies het getoon dat atomoksetienkapsules en orale oplossing bio-ekwivalent is.

**Absorpsie**
Atomoksetien word geabsorbeer na orale toediening en bereik die gemiddelde maksimum waargenome plasmakonsentrasie ($C_{max}$) ongeveer 1 tot 2 uur na toediening. Die absolute biobeskikbaarheid van atomoksetien na orale toediening het gewissel van 63 % tot 94 %, afhangende van inter-individuele verskille in die beskeie eerste-deurgangse metabolisme. Atomoksetien kan met of sonder kos toegedien word.

**Verspreiding**
Atomoksetien is wydversprei en is omvattend (98%) gebind aan plasmaproteïene, hoofsaaklik albumien.

**Biotransformasie**
Atomoksetien ondergaan biotransformasie hoofsaaklik deur die sitochroom P450 2D6 (CYP2D6) ensiematiese weg. Individue met verminderde aktiwiteit van hierdie weg (swak metaboliseerders) verteenwoordig ongeveer 7 % van die Kaukasiese bevolking en het hoër plasmakonsentrasies atomoksetien in vergelyking met mense met normale aktiwiteit (ekstensiewe metaboliseerders). Vir swak metaboliseerders is AOK van atomoksetien ongeveer 10 keer groter, en Css-max is ongeveer 5 keer groter as ekstensiewe metaboliseerders. Die belangrikste oksidatiewe metaboliet wat gevorm word, is 4-hidroksiatomoksetien wat vinnig geglukuronideer word. 4-hidroksiatomoksetien is ekwipotent aan atomoksetien, maar sirkuleer in plasma teen baie laer konsentrasies. Alhoewel 4-hidroksiatomoksetien hoofsaaklik deur CYP2D6 gevorm word, kan 4-hidroksiatomoksetien by individue wat nie CYP2D6-aktiwiteit het nie, deur verskeie ander sitochroom P450-ensieme gevorm word, maar teen 'n stadiger tempo. Atomoksetien inhibeer of induseer nie CYP2D6 by terapeutiese dosisse nie.
Sitochroom P450-ensieme: Atomoksetien het nie klinies betekenisvolle inhibisie of induksie van sitochroom P450-ensieme veroorsaak nie, insluitend CYP1A2, CYP3A, CYP2D6 en CYP2C9, veroorsaak nie.

**Eliminasie**
Die gemiddelde eliminasie-halfleeftyd van atomoksetien na orale toediening is 3,6 uur by ekstensiewe metaboliseerders en 21 uur by swak metaboliseerders. Atomoksetien word hoofsaaklik as 4-hidroksiatomoksetien-O-glukuronied uitgeskei, hoofsaaklik in die urine.

**Lineariteit/nie-lineariteit**
Farmakokinetika van atomoksetien is lineêr oor die reeks dosisse wat bestudeer is in beide ekstensiewe en swak metaboliseerders.

**Spesiale bevolkings**
Lewerinkorting lei tot 'n verminderde atomoksetienopruiming, verhoogde atomoksetienblootstelling (AOK het 2-voudig toegeneem in matige inkorting en 4-voudig in ernstige inkorting), en 'n verlengde halfleeftyd van ouer-medisinale produk in vergelyking met gesonde kontroles met dieselfde CYP2D6 ekstensiewe metaboliseerder genotipe. By pasiënte met matige tot ernstige lewerinkorting (Child-Pugh klas B en C) moet aanvanklike en teiken dosisse aangepas word (sien afdeling 4.2).
Gemiddelde atomoksetien plasmakonsentrasies vir eindstadium niersiekte (ESRD) proefpersone was oor die algemeen hoër as die gemiddelde vir gesonde kontrole proefpersone, getoon deur $C_{max}$ (7 % verskil) en $AOK_{0-\infty}$ (ongeveer 65 % verskil) toenames. Na aanpassing vir liggaamsgewig word die verskille tussen die twee groepe tot die minimum beperk. Farmakokinetika van atomoksetien en sy metaboliete by individue met ESRD dui daarop dat geen dosisaanpassing nodig sal wees nie (sien afdeling 4.2).

## 7. FARMASEUTIESE BESONDERHEDE
### 7.1. Lys van hulpstowwe
**ATOXTRIN 10 mg** harde gelatienkapsules:
Voorgegelatineerde mieliestysel, kolloïdale watervrye silika, dimetikoon, gelatien, natriumlaurielsulfaat (E487), titaandioksied (E171), swart drukink.
**ATOXTRIN 18 mg** harde gelatienkapsules:
Voorgegelatineerde mieliestysel, kolloïdale watervrye silika, dimetikoon, gelatien, natriumlaurielsulfaat (E487), titaandioksied (E171), ysteroksied geel (E172), swart drukink.
**ATOXTRIN 25 mg** harde gelatienkapsules:
Voorgegelatineerde mieliestysel, kolloïdale watervrye silika, dimetikoon, gelatien, natriumlaurielsulfaat (E487), titaandioksied (E171), indigokarmien (E132), swart drukink.
**ATOXTRIN 40 mg** harde gelatienkapsules:
Voorgegelatineerde mieliestysel, kolloïdale watervrye silika, dimetikoon, gelatien, natriumlaurielsulfaat (E487), titaandioksied (E171), indigokarmien (E132), swart drukink.
**ATOXTRIN 60 mg** harde gelatienkapsules:
Voorgegelatineerde mieliestysel, kolloïdale watervrye silika, dimetikoon, gelatien, natriumlaurielsulfaat (E487), titaandioksied (E171), indigokarmien (E132), ysteroksied geel (E172), swart drukink.
**ATOXTRIN 80 mg** harde gelatienkapsules:
Voorgegelatineerde mieliestysel, kolloïdale watervrye silika, dimetikoon, gelatien, natriumlaurielsulfaat (E487), titaandioksied (E171), indigokarmien (E132), ysteroksied geel (E172), swart drukink.

### 7.2. Onversoenbaarheid
Nie van toepassing nie.

### 7.3. Raklewe
36 maande.

### 7.4. Spesiale voorsorgmaatreëls vir berging
Berg by of onder 25 °C.

### 7.5. Aard en inhoud van houer
'n Kartondoos wat deursigtige PVC/PE/PCTFE-Aluminiumfoelie stulpstroke of PA/AL/PVC-Aluminiumfoelie stulpstroke bevat.
Pakgroottes: 7, 14, 28,30 en 56 harde gelatienkapsules.
Nie alle verpakkings en pakgroottes word dalk bemark nie.

### 7.6. Spesiale voorsorgmaatreëls vir wegdoening van 'n gebruikte medisyne of afvalmateriaal afkomstig van sodanige medisyne en ander hantering van die produk
Geen spesiale vereistes nie.

## 8. BEMARKINGSMAGTIGING HOUER
**TRINITY PHARMA (EDMS.) BPK**
3 Gwen Lane, 4de vloer, Sandton, 2031.
Kontaknommer: +27 (0)10 594 5610
PV E-posadres: pv@trinitypharma.co.za

## 9. BEMARKINGSMAGTIGING NOMMER(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
ATOXTRIN 60 mg: 55/1.2/0747
ATOXTRIN 80 mg: 55/1.2/0748

## 10. DATUM VAN EERSTE MAGTIGING/HERNUWING VAN DIE MAGTIGING
24 Maart 2023.

## 11. DATUM VAN HERSIENING VAN DIE TEKS
24 Maart 2023.

TRINITY PHARMA