TABLE OF CONTENTS – APPROVED PROFESSIONAL INFORMATION

JULY 2025

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APPROVED PROFESSIONAL INFORMATION JULY 2025

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

ATOMAKTIN 10 (capsule)

ATOMAKTIN 18 (capsule)

ATOMAKTIN 25 (capsule)

ATOMAKTIN 40 (capsule)

ATOMAKTIN 60 (capsule)

ATOMAKTIN 80 (capsule)

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

ATOMAKTIN (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 ATOMAKTIN 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. ATOMAKTIN is approved for ADHD in paediatric and adult patients. ATOMAKTIN is not approved for major depressive disorder.

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2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ATOMAKTIN 10: Each capsule contains atomoxetine hydrochloride equivalent to 10 mg of atomoxetine.

ATOMAKTIN 18: Each capsule contains atomoxetine hydrochloride equivalent to 18 mg of atomoxetine.

ATOMAKTIN 25: Each capsule contains atomoxetine hydrochloride equivalent to 25 mg of atomoxetine.

ATOMAKTIN 40: Each capsule contains atomoxetine hydrochloride equivalent to 40 mg of atomoxetine.

ATOMAKTIN 60: Each capsule contains atomoxetine hydrochloride equivalent to 60 mg of atomoxetine.

ATOMAKTIN 80: Each capsule contains atomoxetine hydrochloride equivalent to 80 mg of atomoxetine.

Sugar free

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules

ATOMAKTIN 10: Opaque white cap/ opaque white body size “3” capsules containing white to off white powder, with ‘I 23’ on body imprinted with black ink.

ATOMAKTIN 18: Gold cap/ opaque white body size “3” capsules containing white to off white powder, with ‘I 24’ on body imprinted with black ink.

ATOMAKTIN 25: Opaque blue cap/ opaque white body size “3” capsules containing white to off white powder, with ‘I 25’ on body imprinted with black ink.

ATOMAKTIN 40: Opaque blue cap/ opaque blue body size “3” capsules containing white to off white powder, with ‘I 26’ on body imprinted with black ink.

ATOMAKTIN 60: Opaque blue cap/ gold body size “2” capsules containing white to off white powder, with ‘I 27’ on body imprinted with black ink.

ATOMAKTIN 80: Opaque brown cap/ opaque white body size “2” capsules containing white to off white powder, with ‘I 28’ on body imprinted with black ink.

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4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ATOMAKTIN 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).

The recommended initial dose and subsequent dosage escalations of **ATOMAKTIN** should not be exceeded because of potential side effects (see section 4.8).

ATOMAKTIN capsules are not intended to be opened. **ATOMAKTIN** 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.

Dosing of children and adolescents up to 70 kg body weight:

ATOMAKTIN 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 **ATOMAKTIN**). No additional benefit has been demonstrated for doses higher than 1,2 mg/kg/day.

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Dosing of children and adolescents over 70 kg body weight and adults:

ATOMAKTIN 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 for adults is 80 mg.

Special populations

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

ATOMAKTIN may be discontinued without tapering the dose.

Long term use:

No fixed dose-response studies have been conducted in adults. The recommended daily dose of 80 mg reflects the optimal daily dose of 1,2 mg/kg/day demonstrated in children and adolescents.
No controlled long-term studies have been conducted in adults. Open-label study data from 384 patients with up to 97 weeks of treatment with atomoxetine are consistent with maintenance of efficacy in long-term treatment.

Method of administration

For oral use.

ATOMAKTIN may be taken with or without food.

4.3 Contraindications

ATOMAKTIN is contraindicated:

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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- **ATOMAKTIN** should not be used in patients with uncontrolled hypertension or impairment of liver function.
- Atomoxetine should not be used in combination with monoamine oxidase inhibitors (MAOI) including linezolid. Atomoxetine 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 atomoxetine.
- Atomoxetine 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.
- Atomoxetine should not be used in patients with severe cardiovascular or cerebrovascular disorders (see section 4.4). Severe cardiovascular disorders may include severe hypertension, 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.
- Atomoxetine should not be used in patients with pheochromocytoma or a history of pheochromocytoma (see section 4.4).

4.4 Special warnings and precautions for use

Suicide-related behaviour

Suicide related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine. In double blind clinical trials, suicide related behaviours were uncommon but 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.

Sudden death and pre-existing cardiac abnormalities

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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% 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 **ATOMAKTIN** 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.

ATOMAKTIN should not be used in patients with severe cardiovascular or cerebrovascular disorders (see section 4.3). **ATOMAKTIN** 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.

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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, **ATOMAKTIN** 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, **ATOMAKTIN** 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.

ATOMAKTIN 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. **ATOMAKTIN** should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.

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 **ATOMAKTIN** 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 as in **ATOMAKTIN**

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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.

Seizures

Seizures are a potential risk with atomoxetine. **ATOMAKTIN** 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 co morbid 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 co morbid 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 co-morbid anxiety disorders, atomoxetine-treated patients did not experience worsening of anxiety compared to placebo-treated patients.

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

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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 adults ADHD controlled trias, the rates of urinary retention and urinary hesitation were increased among the atomoxetine subjects compared with placebo subjects. A complaint of urinary retention or urinary hesitancy should be considered potentially related to **ATOMAKTIN**.

Elderly use

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

Paediatric population under six years of age

ATOMAKTIN should not be used in patients less than six years of age as efficacy and safety have not been established in this age group.

Special populations

ATOMAKTIN has been used in patients with ADHD without deterioration of conditions of motor tics. Tourette syndrome (children), co-morbid major depressive disorder (adolescents) and anxiety disorders (adults).

Other therapeutic use

ATOMAKTIN 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 Interaction with other medicines and other forms of interaction

*Effects of other medicines on **ATOMAKTIN***

MAOIs

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

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

In patients receiving these medicines, 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

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medicines. 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)

ATOMAKTIN 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 2hrs) 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 beta2 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).

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In addition, caution is advised when stopping concomitant treatment with benzodiazepines due to potential withdrawal seizures.

Anti-hypertensive medicines

ATOMAKTIN should be used cautiously with antihypertensive drugs. Because of a possible increase in blood pressure, **ATOMAKTIN** may decrease the effectiveness of antihypertensive medicines / medicines used to treat hypertension. Attention should be paid to monitoring of blood pressure and review of treatment of **ATOMAKTIN** or antihypertensive medicines may be justified in the case of significant changes of blood pressure.

Pressor agents or medicines that increase blood pressure

Because of possible increase in effects on blood pressure, **ATOMAKTIN** should be used cautiously with pressor agents 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 **ATOMAKTIN** or pressor agents may be justified in the case of significant change in blood pressure.

Medicines that Affect Noradrenaline

Drugs that affect noradrenaline should be used cautiously when co-administered with **ATOMAKTIN** 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.

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4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy have not been demonstrated in pregnancy.

Breastfeeding

Women using **ATOMAKTIN** should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

Atomoxetine, as in **ATOMAKTIN** has been associated with increased rates of fatigue, somnolence, and dizziness relative to placebo 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 **ATOMAKTIN**.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions in paediatric patients, during placebo-controlled clinical trials with atomoxetine were headache, abdominal pain and decreased appetite. 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 may occur.

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. Atomoxetine should be used with caution in any condition that may predispose patients to hypotension.

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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	Frequent	Less frequent	Frequency unknown
Metabolism and nutrition disorders	Appetite decreased Anorexia (loss of appetite)		
Psychiatric disorders	Irritability, mood swings, insomnia, agitation, libido decreased, sleep disorder anxiety, depression and depressed mood, tics	Suicide-related events, aggression, hostility, emotional lability, restlessness, psychosis (including hallucinations), orgasm abnormal	
Nervous system disorders	Headache Somnolence (including sedation), Dizziness, tremor, dysgeusia,	Syncope, migraine, hypoaesthesia, Seizure.	

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	parasthesia, tremor		
Eye disorders	Mydriasis	Vision blurred Conjunctivitis	
Cardiac disorders	Palpitations Tachycardia	Sinus QT interval prolongation	
Vascular disorders	Flushing, hot flush	Peripheral coldness, Raynaud's phenomenon	
Respiratory, thoracic and mediastinal disorders		Dyspnoea	
Gastrointestinal disorders	Dry mouth, Vomiting Nausea Abdominal pain Constipation Dyspepsia, Flatulence		
Hepatobiliary disorders		Blood bilirubin increased, Abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute	

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		hepatic failure	
Skin and subcutaneous tissue disorders	Dermatitis, pruritis, rash, hyperhidrosis	allergic reactions, urticaria	
Musculoskeletal and connective tissue disorders		Muscle spasms	
Renal and urinary disorders	Dysuria, pollakuria, urinary hesitation, urinary retention	Urinary hesitation, urinary retention, micturition urgency	
Reproductive system and breast disorders	Dysmenorrhoea, ejaculation disorder, erectile dysfunction, prostatitis, male genital pain	Ejaculation failure, menstruation irregular, orgasm abnormal, Priapism,	
General disorders and administration site conditions	Fatigue, Asthenia lethargy, chest pain, chills, feeling jittery,	Feeling cold, chest pain	

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	irritability, thirst		
Investigations	Blood pressure increased, heart rate increased, weight decreased		

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or report to safety@macleodspharma.com.

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

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atomoxetine and at least one other medicine.

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 1hour 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

Category and class: A 1.2 Psychoanaleptics

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-desmethyl atomoxetine. 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

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to the parent drug 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 notassociated 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 has not been evaluated in children under 6 years of age.

Pharmacokinetic studies have shown that atomoxetine capsules and oral solution are bioequivalent.

Absorption

Atomoxetine is rapidly and almost completely 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

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

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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 P450enzymes, 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 drug 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 minimized. 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

Pregelatinized starch,

Colloidal silicon dioxide

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ATOMAKTIN 10 contains gelatin, SLS, titanium dioxide

ATOMAKTIN 18 contains gelatin, SLS, iron oxide yellow, titanium dioxide

ATOMAKTIN 25 contains gelatin, SLS, iron oxide yellow, titanium dioxide

ATOMAKTIN 40 contains gelatin, SLS, iron oxide yellow, titanium dioxide

ATOMAKTIN 60 contains gelatin, SLS, iron oxide yellow, Indigo carmine, titanium dioxide

ATOMAKTIN 80 contains gelatin, SLS, iron oxide yellow, Indigo carmine, titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months for blister pack.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

Clear PVC/PVdC – Al blister pack: Blister pack consist of Clear PVC/PVdC (250µ/90 GSM) as the forming material and plain 25µ Aluminium foil with 6-8 GSM heat seal lacquer coating as the lidding material.

Pack sizes include 14s 28s & 30s capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

8. REGISTRATION NUMBERS

ATOMAKTIN 10: 56/1.2/1141

ATOMAKTIN 18: 56/1.2/1142

ATOMAKTIN 25: 56/1.2/1143

ATOMAKTIN 40: 56/1.2/1144

ATOMAKTIN 60: 56/1.2/1145

ATOMAKTIN 80: 56/1.2/1146

9. DATE OF FIRST AUTHORISATION

29 July 2025

10. DATE OF REVISION OF THE TEXT

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