SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

INIR 80

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 80 mg atomoxetine hydrochloride equivalent to 80 mg atomoxetine.

Sugar free.

3 PHARMACEUTICAL FORM

Capsule.

White to off-white powder filled in size '1' hard gelatin capsules with opaque dark brown coloured cap and opaque white coloured body imprinted 'RDY' on cap and '563' on body with black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

INIR 80 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 INIR 80 should not be exceeded because of potential side effects (see section 4.8).

INIR 80 capsules are not intended to be opened. INIR 80 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:

INIR 80 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 INIR 80). No additional benefit has been demonstrated for doses higher than 1,2 mg/kg/day.

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

INIR 80 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.

General dosing information:

For those ADHD patients who have hepatic insufficiency or end-stage renal disease, cautious titration of INIR 80 to the desired clinical response is recommended. INIR 80 clearance may be reduced in patients with hepatic insufficiency. INIR 80 may exacerbate hypertension in patients with end-stage renal disease. INIR 80 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. Clinical data from study participants with up to 97 weeks of treatment with atomoxetine are consistent with maintenance of efficacy in long-term treatment.

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 INIR 80 in any 24-hour period.

Method of administration

For oral use.

INIR 80 may be taken with or without food.

4.3 Contraindications

INIR 80 is contraindicated in:

- Hypersensitivity to the active substance (atomoxetine) or to any of the excipients listed in section 6.1.
- INIR 80 should not be used in patients with uncontrolled hypertension or impairment of liver function.
- **Monoamine oxidase inhibitors:**

  INIR 80 should not be used in combination with monoamine oxidase inhibitors (MAOIs), including linezolid.
- INIR 80 should not be used within a minimum of 2 weeks after discontinuing therapy with MAOIs. Treatment with MAOIs should not be initiated within 2 weeks after discontinuing INIR 80.
- **Severe Cardiovascular Disorders:**

  INIR 80 should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate that could be clinically important (for example 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate) (see section 4.4).
- **Phaeochromocytoma:**

  INIR 80 should not be used in patients with phaeochromocytoma or a history of phaeochromocytoma (see section 4.4).
- **Narrow angle glaucoma:**

In clinical studies, the use of atomoxetine was associated with an increased risk of mydriasis and therefore its use is not recommended in patients with narrow angle glaucoma.

4.4 Special warnings and precautions for use

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of INIR 80 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. INIR 80 is approved for ADHD in paediatric and adult patients. INIR 80 is not approved for major depressive disorder.

Treatment must only be initiated by or under the supervision of a medical practitioner with appropriate knowledge and experience of childhood and adolescent behaviour disorders (e.g., paediatrician or child/adolescent psychiatrist).

Suicide-related behaviour

Suicide related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine. Anyone considering the use of INIR 80 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. INIR 80 is approved for ADHD in paediatric and adult patients, INIR 80 is not approved for major depressive disorder.

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 INIR 80 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.

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 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.

Possible allergic events

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

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 to 12 % of children and adolescents, and 6 to 10 % adults experience more pronounced changes in heart rate (20 beats per minute or greater) and blood pressure (15 to 20 mmHg or greater). Analysis of these clinical trial data showed that approximately 15 to 26 % of children and adolescents, and 27 to 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.

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

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.

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.

Hepatic effects

Very rarely, spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported. Also very rarely, severe liver injury, including acute liver failure, have been reported. INIR 80 should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.

Effects on micturition

In adult ADHD controlled trials, 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 atomoxetine.

Paediatric population under six years of age

INIR 80 should not be used in patients less than six years of age as efficacy and safety have not been established in this age group.

Geriatric use

The safety and efficacy of INIR 80 in geriatric patients have not been established**.**

Other therapeutic use

INIR 80 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 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 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 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)

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 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 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-arrhythmics, 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 medicinal drugs 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 antihypertensive medicines. Because of a possible increase in blood pressure, atomoxetine 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 atomoxetine 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, atomoxetine 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 atomoxetine or pressor agents 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 drugs 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 INIR 80 did not increase cardiovascular effects beyond those seen with methylphenidate administration alone.

Alcohol

Consumption of ethanol with INIR 80 did not change the intoxicating effects of ethanol.

Midazolam

Co-administration of INIR (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

Safety and efficacy have not been demonstrated in pregnancy.

INIR 80 should not be used during pregnancy.

Breast-feeding

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

Data on the effects on the ability to drive and use machines are limited. INIR 80 has a minor influence on the ability to drive and use machines. Atomoxetine 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 atomoxetine.

4.8 Undesirable effects

Tabulated list of adverse reactions experienced in children and adolescents:

System Organ Class	Frequent	Less frequent
Metabolism and nutrition disorders	Appetite decreased, anorexia (loss of appetite).	
Psychiatric disorders	Irritability, mood swings, insomnia[3], agitation*, anxiety, depression and depressed mood*, tics*.	Suicide-related events, aggression, hostility, emotional lability*, psychosis (including hallucinations)*.
Nervous system disorders	Headache, somnolence[2], dizziness.	Syncope, tremor, migraine, paraesthesia*, hypoaesthesia*, seizure**.
Eye disorders	Mydriasis.	Vision blurred, conjunctivitis.
Cardiac disorders		Palpitations, sinus tachycardia, QT interval prolongation**.
Vascular disorders		Raynaud's phenomenon.
Respiratory, thoracic and mediastinal disorders		Dyspnoea*.
Gastrointestinal disorders	Abdominal pain[1], vomiting, nausea, constipation, dyspepsia.	
Hepato-biliary disorders		Blood bilirubin increased*, abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure*.
Skin and subcutaneous tissue disorders	Dermatitis, pruritus, rash.	Hyperhidrosis, allergic reactions.

Renal and urinary disorders		Urinary hesitation, urinary retention.
Reproductive system and breast disorders		Priapism, male genital pain.
General disorders and administration site conditions	Fatigue, lethargy, chest pain*	Asthenia.
Investigations	Blood pressure increased[4], heart rate increased[4], weight decreased.	

Foot notes:

[1] Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort.

[2] Also includes sedation

[3] Includes initial, middle and terminal (early morning wakening) insomnia

[4] Heart rate and blood pressure findings are based on measured vital signs

* See section 4.4

** See section 4.4 and section 4.5

Tabulated list of adverse reactions experienced in adults:

System Organ Class	Frequent	Less frequent
Metabolism and nutrition disorders	Appetite decreased.	
Psychiatric disorders	Insomnia[2], agitation*, libido decreased, sleep disorder, depression and depressed	Suicide-related events*, aggression, hostility, emotional lability*, restlessness, tics*,

	mood*, anxiety.	psychosis (including hallucinations)*, orgasm abnormal, restlessness.
Nervous system disorders	Headache, dizziness, dysgeusia, paraesthesia, somnolence (including sedation), tremor.	Syncope, migraine, hypoaesthesia*, seizure**.
Eye disorders		Vision blurred.
Cardiac disorders	Palpitations, tachycardia.	QT interval prolongation**.
Vascular disorders	Flushing, hot flushes	Raynaud's phenomenon, peripheral coldness.
Respiratory, thoracic and mediastinal disorders		Dyspnoea*.
Gastro-intestinal disorders	Dry mouth, nausea abdominal pain[1], constipation, dyspepsia, flatulence, vomiting,	
Hepato-biliary disorders		Abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure, blood bilirubin increased*.
Skin and subcutaneous tissue disorders	Dermatitis, hyperhidrosis, rash.	Allergic reactions[4], pruritus, urticaria.
Musculoskeletal and connective tissue disorders		Muscle spasms
Renal and urinary disorders	Dysuria, pollakiuria urinary hesitation, urinary	Micturition urgency.

	retention.	
Reproductive system and breast disorders	Dysmenorrhoea[5], ejaculation disorder[6], erectile dysfunction[6], prostatitis[6], testicular pain[6]	Priapism, male genital pain, ejaculation failure, menstruation disorder.
General disorders and administration site conditions	Fatigue, lethargy, chest pain*, asthenia, chills, feeling jittery, irritability, thirst	Feeling cold, chest pain.
Investigations	Blood pressure increased[3], heart rate increased[3], weight decreased.	

Foot notes:

[1] Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort.

[2] Also includes initial insomnia, middle insomnia and terminal (early morning wakening) insomnia.

[3] Heart rate and blood pressure findings are based on measured vital signs.

[4] Includes anaphylactic reactions and angioneurotic oedema.

[5] Frequency percentage based on female patients only

[6] Frequency percentage based on male patients only

* See section 4.4

** See section 4.4 and section 4.5

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.

4.9 Overdose

Signs and symptoms

Frequently 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 less frequently QT prolongation. There have also been reports of fatal, acute overdoses involving a mixed ingestion of atomoxetine and at least one other drug.

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

A1.2 Psychoanaleptics

Pharmacotherapeutic group: Psychoanaleptics, centrally acting sympathomimetics

ATC code: N06BA09

Mechanism of action

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-Desmethyl atomoxetine 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 drug in poor metabolisers at steady state.

Pharmacodynamic effects

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 Pharmacokinetics 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 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

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 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).

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, or reproduction and development. Due to the dose limitation imposed by the clinical (or exaggerated pharmacological) response of the animals to the drug combined with metabolic differences among species, maximum tolerated doses in animals used in nonclinical studies produced atomoxetine exposures similar to or slightly above those that are achieved in CYP2D6 poor metabolizing patients at the maximum recommended daily dose.

A study was conducted in young rats to evaluate the effects of atomoxetine on growth and neurobehavioral and sexual development. Slight delays in onset of vaginal patency (all doses) and preputial separation (≥10 mg/kg/day) and slight decreases in epididymal weight and sperm number (≥10 mg/kg/day) were seen; however, there were no effects on fertility or reproductive performance. The significance of these findings to humans is unknown.

Pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, decrease in live foetuses, increase in early resorption, slight increases in the incidences of atypical origin of carotid artery and absent subclavian artery were observed. These findings were observed at doses that caused slight maternal toxicity. The incidence of these findings is within historical control values. The no-effect dose for these findings was 30 mg/kg/day. Exposure (AUC) to unbound atomoxetine in rabbits, at 100mg/kg/day was approximately 3,3 times (CYP2D6 extensive metabolisers) and 0,4 times (CYP2D6 poor metabolisers) those in humans at the maximum daily dose of 1,4 mg/kg/day. The findings in one of three rabbit studies were equivocal and the relevance to man is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethicone

Pregelatinised Starch (starch 1500 partially pregelatinised maize starch)

Capsule shell:

Gelatin

Iron oxide red

Iron oxide yellow

Titanium dioxide

Sodium lauryl sulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened bottle: 3 years

Do not use more than 30 days after first opening.

6.4 Special precautions for storage

Store at or below 25 ºC.

Store protected from light and moisture.

Keep the HDPE container tightly closed.

Keep out of reach of children.

6.5 Nature and contents of container

The capsules are packed in white plastic containers with white plastic caps containing 30 capsules.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBER

57/1.2/0370

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 June 2025

10 DATE OF REVISION OF THE TEXT