SCHEDULING STATUS

S5

PROPRIETARY NAMES (AND DOSAGE FORM)

INIR 10 (capsule)

INIR 18 (capsule)

INIR 25 (capsule)

INIR 40 (capsule)

INIR 60 (capsule)

COMPOSITION

INIR 10: Each capsule contains atomoxetine hydrochloride equivalent to 10 mg atomoxetine.

INIR 18: Each capsule contains atomoxetine hydrochloride equivalent to 18 mg atomoxetine.

INIR 25: Each capsule contains atomoxetine hydrochloride equivalent to 25 mg atomoxetine.

INIR 40: Each capsule contains atomoxetine hydrochloride equivalent to 40 mg atomoxetine.

INIR 60: Each capsule contains atomoxetine hydrochloride equivalent to 60 mg atomoxetine.

The other ingredients are dimethicone and pregelatinised starch.

PHARMACOLOGICAL CLASSIFICATION

A1.2 Psychoanaleptics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Atomoxetine is a selective inhibitor of the presynaptic norepinephrine transporter, without directly affecting the serotonin or dopamine transporters. Atomoxetine has minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors.

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 the age of 6 years.

Absorption:

Atomoxetine is well absorbed after oral administration and reaches a mean maximal observed plasma concentration (C_{max}) approximately 1 to 2 hours after dosing.

Atomoxetine can be administered with or without food.

Distribution:

Atomoxetine is widely distributed. Atomoxetine is extensively bound to plasma proteins, primarily albumin.

Metabolism:

Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway.

4-hydroxyatomoxetine is the major oxidative metabolite formed, that is glucuronidated.

4-hydroxyatomoxetine is equipotent to atomoxetine but circulates in plasma at much lower concentrations. As 4-hydroxyatomoxetine is primarily formed by CYP2D6, in individuals that lack CYP2D6 activity, 4-hydroxyatomoxetine is still formed by several other cytochrome P450 enzymes, but at a slower rate.

The CYP2D6 pathway is not inhibited or induced by atomoxetine.

Elimination:

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

INDICATIONS

INIR is indicated for:

The treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children 6 years of age or older, adolescents and adults.

CONTRA-INDICATIONS

INIR should not be used in:

- Patients with a hypersensitivity to atomoxetine or to any of the excipients of **INIR.**
- Patients with uncontrolled hypertension or impairment of liver function.
- Combination with monoamine oxidase inhibitors (MAOIs). **INIR** 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**.
- Narrow angle glaucoma: In clinical studies, the use of **INIR** was associated with an increased risk of mydriasis and therefore its use is not recommended in patients with narrow angle glaucoma.

WARNINGS AND SPECIAL PRECAUTIONS

Allergic events: allergic reactions including rash, angioedema and urticaria, have been reported in patients taking **INIR**.

Suicide-related behaviour (suicide attempts and suicidal ideation), hostility (predominantly aggression, oppositional behaviours and anger) and emotional lability: has been reported in patients treated with **INIR.** Patients should be monitored for the appearance and worsening of such behaviours.

The possibility of serious psychiatric adverse events 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.

Mood swings: INIR may increase the risk of mood swings including hostility and emotional lability.

Hepatic effects: INIR should be discontinued in patients with jaundice or laboratory evidence of liver injury and should not be restarted. Rarely, liver toxicity manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported. Signs and symptoms likely to indicate liver involvement include, pruritus, 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 symptom 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.

Depression: INIR lacks efficacy as treatment modality in depression.

Growth and development: Weight gain and longitudinal growth should be monitored during treatment with **INIR**.

Cardiovascular effects: Many patients taking **INIR** experience a modest increase in pulse (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg). **INIR** should be used with caution in patients with hypertension, tachycardia, cardiovascular or cerebrovascular disease. Orthostatic hypotension has also been reported. Use with caution in any condition that may predispose patients to hypotension, or conditions associated with abrupt heart rate or blood pressure changes.

Paediatric use: The safety and efficacy of **INIR** in paediatric patients less than 6 years of age have not been established. The efficacy of atomoxetine beyond 18 months of treatment and safety of **INIR** beyond 2 years of treatment have not been systematically evaluated.

Geriatric use: The safety and efficacy of **INIR** in geriatric patients have not been established.

Effects on the ability to drive and use machines: 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 **INIR**.

INTERACTIONS

Monoamine oxidase inhibitors (MAOIs): See 'CONTRA-INDICATIONS'.

Interactions with other medicines and other forms of interaction:

Beta-adrenergic receptor agonists: INIR should be administered with caution to patients being treated with systemically administered (oral, inhaled or intravenous) salbutamol or other β-2 agonists, because the action of salbutamol on the cardiovascular system can be potentiated.

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

principally metabolised by the CYP2D6 pathway. In CYP2D6 extensive metabolisers, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metabolisers.

In vitro studies suggest that co-administration of cytochrome P450 inhibitors to CYP2D6 poor metabolisers will not increase the plasma concentrations of atomoxetine**.**

Slower titration of atomoxetine may be necessary. No dosage adjustment of **INIR** is required when co-administered with CYP2D6 inhibitors.

Methylphenidate: Co-administration of methylphenidate with **INIR** did not increase cardiovascular effects beyond those seen with methylphenidate administration alone.

Pressor medicines: Because of possible effects on blood pressure, **INIR** should be used cautiously with pressor medicines.

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

Alcohol: Consumption of ethanol with **INIR** did not change the intoxicating effects of ethanol.

Midazolam: Co-administration of **INIR** (60 mg BID 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 metabolized by CYP3A.

Medicines that affect norepinephrine (noradrenaline): Medicines that affect norepinephrine should be used cautiously when co-administered with **INIR** because of the potential for additive or synergistic pharmacological effects.

Medicines highly bound to plasma protein: *In vitro* medicine-displacement studies were conducted with **INIR** and other highly bound medicines at therapeutic concentrations. **INIR** did not affect the binding of warfarin, acetylsalicylic acid, phenytoin or diazepam to human albumin. Similarly, these compounds did not affect the binding of **INIR** to human albumin.

PREGNANCY AND LACTATION

Pregnancy: No adequate and well-controlled studies have been conducted with **INIR** in pregnant

women.

Lactation: **INIR** and/or its metabolites were excreted in the milk of rats. It is not known if **INIR** is excreted in human milk.

DOSAGE AND DIRECTIONS FOR USE

Do not exceed the recommended daily dose and subsequent increases, as potentially serious side effects could result with overdosing.

INIR capsules should not be opened. In the event of the capsule contents coming into contact with the eye, the eyes should be immediately flushed with water and medical advice obtained. Hands and any contaminated surfaces should be washed as soon as possible.

Dosing of children and adolescents up to 70 kg body weight: INIR should be initiated at a total 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**). No additional benefit has been demonstrated for doses higher than 1,2 mg/kg/day.

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).

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

Treatment must be initiated by or under the supervision of a medical practitioner with appropriate knowledge and experience of adult ADHD, e.g. a psychiatrist.

General dosing information:

INIR may be taken with or without food.

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

INIR 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.

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** in a 24-hour period.

SIDE- EFFECTS

Table 1: Side effects in Child and Adolescent patients

System Organ Class/Adverse Event	Frequent	Less frequent
Infections and Infestations		
Influenza	x	
Metabolism and Nutritional Disorders		
Anorexia (loss of appetite)	x	
Decreased appetite	x	
Psychiatric Disorders		
Suicidal ideation*		x
Suicidal behavior		x
Aggression/hostility*	x	
Anger*		x
Early morning awakening		x

Irritability	x	
Mood swings	x	
Agitation	x	
Anxiety	x	
Depression and depressed mood	x	
Tics	x	
Emotional lability		x
Psychosis (including hallucinations)		x
Nervous System Disorders		
Dizziness	x	
Headache	x	
Somnolence[2]	x	
Syncope		x
Tremor		x
Migraine		x
Paraesthesia		x
Hypoaesthesia		x
Seizure		x
Eye Disorders		
Mydriasis		x
Blurred vision		x
Cardiac Disorders		
Palpitations		x
Sinus tachycardia		x
QT interval prolongation		x
Vascular disorders		
Raynaud's phenomenon		x
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	x	

Gastrointestinal Disorders		
Abdominal pain[1]	x	
Constipation	x	
Dyspepsia	x	
Nausea	x	
Vomiting	x	
Hepatobiliary disorders		
Increased blood bilirubin		x
Abnormal/increased liver function tests		x
Jaundice		x
Hepatitis		x
Liver injury		x
Acute hepatic failure		x
Skin and Subcutaneous Tissue Disorders		
Dermatitis	x	
Pruritus		x
Rash	x	
Hyperhidrosis		x
Allergic reactions		x
Renal and urinary disorders		
Urinary hesitation		x
Urinary retention		x
Reproductive system and breast disorders		
Priapism		x
Male genital pain		x
General Disorders and Administration Site Conditions		
Asthenia		x
Fatigue	x	
Lethargy	x	
Chest pain	x	

Investigations		
Decreased weight	x	
Increased heart rate	x	
Increased blood pressure	x	

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

[2] Also includes sedation

Table 2: Side effects in Adult patients

System Organ Class/Adverse Event	Frequent	Less frequent
Metabolism and nutrition disorders		
Decreased weight	x	
Psychiatric Disorders		
Early morning awakening	x	
Decreased libido	x	
Sleep disorder	x	
Insomnia	x	
Suicide- related events		x
Aggression/hostility*	x	
Agitation	x	
Anxiety	x	
Depression and depressed mood	x	
Tics		x
Emotional lability		x
Restlessness		x
Psychosis (including hallucinations)		x
Nervous System Disorders		
Dizziness	x	
Insomnia[2]	x	
Paraesthesia	x	
Sinus headache	x	

Headache	x	
Dysgeusia	x	
Somnolence (including sedation)	x	
Tremor	x	
Syncope		x
Migraine		x
Hypoaesthesia		x
Seizure		x
Eye Disorders		
Blurred vision		x
Cardiac Disorders		
Palpitations	x	
Tachycardia	x	
QT interval prolongation		x
Vascular Disorders		
Hot flushes	x	
Flushing	x	
Peripheral coldness		x
Raynaud's phenomenon		x
Respiratory, thoracic and mediastinal disorders		
Dyspnoea		x
Gastrointestinal Disorders		
Abdominal pain[1]	x	
Constipation	x	
Dry mouth	x	
Dyspepsia	x	
Flatulence	x	
Nausea	x	
Hepatobiliary disorders		
Abnormal/increased liver function tests		x
Jaundice		x

Hepatitis		x
Liver injury		x
Acute hepatic failure		x
Increased blood bilirubin		x
Skin and Subcutaneous Tissue Disorders		
Rash	x	
Hyperhidrosis	x	
Dermatitis	x	
Allergic reactions		x
Pruritis		x
Urticaria		x
Musculoskeletal and connective tissue disorders		
Muscle spasms		x
Renal and Urinary Disorders		
Difficulty in micturition	x	
Urinary hesitation	x	
Urinary retention	x	
Dysuria	x	
Pollakiuria	x	
Micturition urgency		x
Reproductive System and Breast Disorders		
Dysmenorrhoea	x	
Ejaculation disorder	x	
Ejaculation failure	x	
Erectile disturbance	x	
Menstruation irregular	x	
Prostatitis	x	
Male genital pain	x	
Abnormal orgasm		x
Priapism		x
General Disorders and Administration Site Conditions		

Fatigue	x	
Chills	x	
Asthenia	x	
Lethargy	x	
Feeling jittery	x	
Irritability	x	
Thirst	x	
Feeling cold		x
Chest pain		x
Investigations		
Increased blood pressure	x	
Increased heart rate	x	
Decreased weight		x

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

[2] Also includes sedation

Post-marketing experience: The following events have been reported: aggression, hostility, suicidal ideation, anger, suicidal behavior, abnormal liver function tests, jaundice and hepatitis (see 'WARNINGS AND SPECIAL PRECAUTIONS').

Investigations: increased blood pressure.

Vascular disorders: peripheral vascular instability and/or Raynaud's phenomenon, potential to worsen pre-existing Raynaud's phenomenon.

Urogenital system: painful or prolonged penile erection, male genital pain, urinary hesitation and urinary retention in children and adolescents.

Nervous system disorders: syncope, paraesthesia in children and adolescents, hypoaesthesia.

Psychiatric disorders: sensory disturbances including hallucinations.

General disorders and administration site conditions: lethargy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Human experience:

The most commonly reported symptoms accompanying acute and chronic overdoses were

somnolence, agitation, hyperactivity, abnormal behaviour and gastrointestinal symptoms. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g. mydriasis, tachycardia, dry mouth) have also been observed. In some cases of overdose, seizures have been reported. There have also been reports of fatal acute overdose involving a mixed ingestion of **INIR** and at least one other medicine.

Management of overdose: An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion. Activated charcoal may be useful in limiting absorption. Because **INIR** is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

IDENTIFICATION

INIR 10: White to off- white powder filled in size '4' hard gelatin capsules with opaque white coloured cap and opaque white coloured body imprinted "RDY" on cap and "519"on body with black ink.

INIR 18: White to off-white powder filled in size '3' hard gelatin capsules with opaque dark gold coloured cap and opaque white coloured body imprinted 'RDY' on cap and '520' on body with black ink.

INIR 25: White to off-white powder filled in size '3' hard gelatin capsules with opaque dark blue coloured cap and opaque white coloured body imprinted 'RDY' on cap and '528' on body with black ink.

INIR 40: White to off-white powder filled in size '1' hard gelatin capsules with opaque dark blue coloured cap and opaque dark blue coloured body imprinted 'RDY' on cap and '521' on body with black ink.

INIR 60: White to off-white powder filled in size '1' hard gelatin capsules with opaque dark blue coloured cap and opaque dark gold coloured body imprinted 'RDY' on cap and '522' on body with black ink.

PRESENTATION

HDPE containers: The capsules will be packaged in white plastic containers with white plastic caps containing 30 or 500 capsules.

PVC-PVdC/Alu pack: The capsules are packed in blister strips of clear transparent PVC film coated with PVdC on one side and paper backed aluminium foil with heat seal coating on the other side. The blister strips will be packaged in a cardboard box containing 7, 10, or 14 capsules.

STORAGE INSTRUCTIONS

Store at or below 25 ºC. Store in the original blister packs.

Keep the blisters in the carton until required for use. Store protected from light and moisture.

Keep the HDPE containers tightly closed.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

INIR 10: 43/1.2/0809

INIR 18: 43/1.2/0810

INIR 25: 43/1.2/0811

INIR 40: 43/1.2/0812

INIR 60: 43/1.2/0813

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Dr. Reddy's Laboratories (Pty) Ltd

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DATE OF PUBLICATIONOF THE PACKAGE INSERT