1.3.1.1 Professional Information for Medicines for Human Use

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

STRADENT 10 mg/18 mg/25 mg/40 mg/60 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

STRADENT 10 mg:

Each capsule contains atomoxetine hydrochloride equal to 10 mg atomoxetine

STRADENT 18 mg:

Each capsule contains atomoxetine hydrochloride equal to 18 mg atomoxetine

STRADENT 25 mg:

Each capsule contains atomoxetine hydrochloride equal to 25 mg atomoxetine

STRADENT 40 mg:

Each capsule contains atomoxetine hydrochloride equal to 40 mg atomoxetine

STRADENT 60 mg:

Each capsule contains atomoxetine hydrochloride equal to 60 mg atomoxetine

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

STRADENT 10 mg

Off-white opaque / off-white opaque, size '5' hard gelatin capsules filled with white to off-white powder and imprinted with 'F' on off-white opaque cap and '41' on off-white opaque body with black ink

STRADENT 18 mg

Golden opaque / off-white opaque, size '4' hard gelatin capsules filled with white to off-white powder and imprinted with 'F' on golden opaque cap and '42' on off-white opaque body with black ink

STRADENT 25 mg

Blue opaque / off-white opaque, size '4' hard gelatin capsules filled with white to off-white powder and imprinted with 'F' on blue opaque cap and '43' on off-white opaque body with black ink

STRADENT 40 mg

Blue opaque / blue opaque, size '2' hard gelatin capsules filled with white to off-white powder and imprinted with 'F' on blue opaque cap and '45' on blue opaque body with black ink.

STRADENT 60 mg

Blue opaque / golden opaque, size '1' hard gelatin capsules filled with white to off-white powder and imprinted with 'F' on blue opaque cap and '46' on golden opaque body with black ink.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

STRADENT 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

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).

Posology

The recommended initial dose and subsequent dosage escalations of **STRADENT** should not be exceeded because of potential side effects (See Section 4.8).

STRADENT are not intended to be opened. **STRADENT** 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:

STRADENT 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 **STRADENT**). 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:

STRADENT 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

Patients with renal impairment:

For those ADHD patients who have end-stage renal disease, cautious titration of **STRADENT** to the desired clinical response is recommended.

STRADENT may exacerbate hypertension in patients with end-stage renal disease.

Patients with hepatic impairment:

For those ADHD patients who have hepatic insufficiency, cautious titration of **STRADENT** to the desired clinical response is recommended. **STRADENT** clearance may be reduced in patients with hepatic insufficiency.

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. Study data from patients on treatment with atomoxetine are consistent with maintenance of efficacy in long-term treatment.

Elderly patients:

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

Paediatric populations:

The safety and efficacy of **STRADENT** in children under 6 years of age have not been established. Therefore, **STRADENT** should not be used in children under 6 years of age (see section 4.4).

Method of administration

For oral administration

STRADENT may be taken with or without food.

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 **STRADENT** in any 24-hour period.

Discontinuing STRADENT:

STRADENT may be discontinued without tapering the dose.

4.3. Contraindications

STRADENT should not be used in patients with hypersensitivity to atomoxetine or to any of its excipients.

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

Monoamine oxidase inhibitors:

STRADENT should not be used in combination with monoamine

oxidase inhibitors (MAOIs), including linezolid.

STRADENT 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 **STRADENT.**

Severe Cardiovascular Disorders:

STRADENT 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 – Cardiovascular Effects).

Phaeochromocytoma:

STRADENT should not be used in patients with phaeochromocytoma or a history of phaeochromocytoma (see Section 4.4 – Cardiovascular Effects).

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

STRADENT (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 STRADENT 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. STRADENT is approved for ADHD in paediatric and adult patients. STRADENT 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).

Possible allergic events:

Allergic reactions including anaphylactic reactions, rash, angio-oedema

and urticarial have been reported in patients taking atomoxetine as in **STRADENT.**

Suicidal behaviour, hostility:

Suicidal behaviour, suicidal ideation, hostility (predominantly aggression, oppositional behaviour and anger) and emotional lability were more frequently observed in clinical trials among patients treated with atomoxetine as in **STRADENT** compared to those treated with placebo but the differences were not statistically significant. Patients beginning treatment for ADHD should be carefully monitored for the appearance or worsening of suicide-related behaviour, hostility and emotional lability. 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 as in **STRADENT** at usual doses. Although some serious structural cardiac abnormalities alone carry an increased risk of sudden death, **STRADENT** should only be used with caution in patients with known serious structural cardiac abnormalities and in consultation with a cardiac specialist.

Cardiovascular effects:

STRADENT can affect heart rate and blood pressure. Most patients taking **STRADENT** 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 5-10 % of children and 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 **STRADENT** 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 **STRADENT** 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.

STRADENT should not be used in patients with severe cardiovascular or cerebrovascular disorders (see section 4.3 Contraindications – Severe Cardiovascular and Cerebrovascular Disorders). **STRADENT** 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, **STRADENT** 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 **STRADENT.**

Hepatic effects:

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. **STRADENT** 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 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 reaction.

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 **STRADENT** at usual doses. If such symptoms occur, consideration should be given to a possible causal role of **STRADENT**, and discontinuation of treatment should be considered. The possibility that **STRADENT** 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 a in **STRADENT** compared to those treated with placebo. Emotional lability was more frequently observed in clinical trials among children treated with atomoxetine a in **STRADENT** compared to those treated with placebo. Patients should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional lability.

Seizures:

Seizures are a potential risk with **STRADENT**. **STRADENT** should be introduced with caution in patients with a history of seizure. Discontinuation of **STRADENT** 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 **STRADENT**. 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 **STRADENT** 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 **STRADENT** should be monitored for the appearance or worsening of anxiety symptoms, depressed mood and depression or tics.

Paediatric population under six years of age:

STRADENT 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 **STRADENT** beyond 18 months of treatment and safety of **STRADENT** beyond 2 years of treatment has not been systematically evaluated.

Elderly use:

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

Other therapeutic use:

STRADENT 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).

Effects on micturition:

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

4.5. Interaction with other medicines and other forms of interaction

Effects of Other Medicines on Atomoxetine

MAOIs:

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

CYP2D6 inhibitors {SSRIs (e.g., fluoxetine, paroxetine), quinidine, terbinafine}: In patients receiving these medicines, STRADENT 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 **STRADENT** 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 **STRADENT** 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 **STRADENT** 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 **STRADENT** exposure in vivo is unknown.

Midazolam:

Co-administration of **STRADENT** (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.

Methylphenidate:

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

Salbutamol (or other beta$_2$ agonists):

STRADENT 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 **STRADENT** (60 mg twice daily for 5

days) induced increases in heart rate and blood pressure. This effect was most marked after the initial co-administration of salbutamol and **STRADENT** 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 co-administration of **STRADENT** (80 mg once daily for 5 days) in a study of healthy Asian adults who were extensive **STRADENT** metabolisers. Similarly, heart rate after multiple inhalations of salbutamol (800 µg) did not differ in the presence or absence of **STRADENT.**

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

There is the potential for an increased risk of QT interval prolongation when **STRADENT** 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 **STRADENT**. 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:

STRADENT should be used cautiously with anti-hypertensive medicines. Because of a possible increase in blood pressure, **STRADENT** may decrease the effectiveness of anti-

hypertensive medicines used to treat hypertension. Attention should be paid to monitoring of blood pressure and review of treatment of **STRADENT** or anti-hypertensive medicines may be justified in the case of significant changes of blood pressure.

Pressor medicines that increase blood pressure:

Because of possible increase in effects on blood pressure, **STRADENT** should be used cautiously with pressor medications that may increase blood pressure (such as salbutamol). Attention should be paid to monitoring of blood pressure, and review of treatment for either **STRADENT** 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 **STRADENT** 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 **STRADENT** bioavailability.

Medicines highly bound to plasma protein:

In vitro medicines-displacement studies were conducted with **STRADENT** and other highly-bound medicines at therapeutic concentrations. Warfarin, acetylsalicylic acid, phenytoin, or

diazepam did not affect the binding of **STRADENT** to human albumin. Similarly, **STRADENT** did not affect the binding of these compounds to human albumin.

Alcohol:

Consumption of ethanol with **STRADENT** did not change the intoxicating effects of ethanol.

4.6. Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy have not been demonstrated in pregnancy.

Lactation

STRADENT and/or its metabolites were excreted in the milk of rats. It is not known if atomoxetine as in **STRADENT** is excreted in human milk.

Because of the lack of data, **STRADENT** should be avoided during breast-feeding.

4.7. Effects on ability to drive and use machines

Data on the effects on the ability to drive and use machines is limited. **STRADENT** has an influence on the ability to drive and use machines. **STRADENT** 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 **STRADENT.**

4.8. Undesirable effects

<u>Paediatric population</u>

a. *Summary of the safety profile*

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:

b. *Tabulated list of adverse reactions*

System Organ Class	Frequency	Event
Metabolism and nutrition disorders	Frequent	Appetite decreased Anorexia (loss of appetite)
Psychiatric disorders	Frequent	Irritability, mood swings, insomnia[3], agitation *, anxiety, depression and depressed mood *, tics
	Less frequent	Suicide-related events, aggression, hostility, emotional lability * Psychosis (including hallucinations) *
Nervous system disorders	Frequent	Headache, somnolence[2] Dizziness
	Less frequent	Syncope, tremor, migraine, paraesthesia *, hypoaesthesia *, Seizure **

Eye disorders	Frequent	Mydriasis
	Less frequent	Vision blurred
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
Gastro-intestinal disorders	Frequent	Abdominal pain1, 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, pruritis, 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)
	Less frequent	Asthenia
Investigations	Frequent	Blood pressure increased[4] heart rate increased[4] Weight decreased

[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

Adults:

a. ***Summary of the safety profile:***

b. Tabulated list of adverse reactions

System Organ Class	Frequency	Event
Metabolism and nutrition disorders	Frequent	Appetite decreased
Psychiatric disorders	Frequent	Insomnia[2] Agitation*, libido decreased, sleep disorder, depression and depressed mood*, anxiety
	Less frequent	Suicide-related events, aggression, hostility, emotional lability * Psychosis (including hallucinations) *
Nervous system disorders	Frequent	Headache, Dizziness, dysgeusia, Paraesthesia, somnolence (Including sedation), tremor
	Less frequent	Syncope, migraine, hypoesthesia *, 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
Gastro-intestinal disorders	Frequent	Abdominal pain[1], vomiting, nausea Constipation, dyspepsia, dry mouth, nausea flatulence, vomiting
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, hyperhydrosis, rash
	Less frequent	Allergic reactions[4] , pruritis, urticarial
Musculoskeletal and connective tissue disorders	Less frequent	Muscle spasms
Renal and urinary disorders	Frequent	Dysuria, pollakuria, urinary hesitation, urinary retention
	Less frequent	Micturition 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[3] heart rate increased[3] Weight decreased

[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.

* 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8.

4.9. Overdose

Symptoms

During post-marketing, there have been reports of non-fatal acute and chronic overdoses of **STRADENT** 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 **STRADENT**, seizures have been reported and very rarely QT prolongation. There have also been reports of fatal, acute overdoses involving a mixed ingestion of **STRADENT** and at least one other medicine.

There is limited clinical trial experience with **STRADENT** overdose.

Treatment

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 **STRADENT** is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Psychoanaleptics, ATC code: N06BA09

Mechanism of action and Pharmacodynamic effects

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**.**

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 well 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 $C_{ss, max}$ 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

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

Special Populations

Renal impairment

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).

Hepatic impairment

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).

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

STRADENT capsules contain the following inactive ingredients: Starch pregelatinised, simethicone emulsion.

Composition of the capsule:

10 mg - gelatin, titanium dioxide (CI no. 77891)

18 mg – gelatin, titanium dioxide (CI no. 77891), Iron oxide yellow (CI no. 77492)

25 mg – gelatin, titanium dioxide (CI no. 77891), FD&C Blue 2 (CI no. 73015)

40 mg - gelatin, titanium dioxide (CI no. 77891), FD&C Blue 2 (CI no. 73015)

60 mg - gelatin, titanium dioxide (CI no. 77891), Iron oxide yellow (CI no. 77492), FD&C Blue 2 (CI no. 73015)

Composition of the ink:

Black iron oxide (C.I. No. 77499), butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

1. 30 capsules are packed in 25 micron PVC / 25 micron PE / 90 gsm PVdc Film - Aluminium foil blister pack. Each carton contains 3 blisters of 10 capsules each. The blisters are further packed in pre-printed cartons with leaflet
2. 30 capsules are packed in 25 micron OPA / 45 micron Al.foil / 60 micrometre PVC Film - Aluminium foil blister pack. Each carton contains 3 blisters of 10 capsules each. The blisters are further packed in pre-printed cartons with leaflet
3. 30 capsules are packed in white opaque round HDPE container closed with polypropylene stock ribbed closure with wad having induction sealing liner. Capsules shall be packed in HDPE container pack along with 1 g silica gel sachet. The HDPE container will be further packed in pre-printed carton with package leaflet.

Not all packs and pack sizes are necessarily marketed.

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

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

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF TEXT