1.5.5.2 PROFESSIONAL INFORMATION - CLEAN

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

STRATEX 10 Capsules

STRATEX 18 Capsules

STRATEX 25 Capsules

STRATEX 40 Capsules

STRATEX 60 Capsules

STRATEX 80 Capsules

WARNING:

SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

Atomoxetine (contained in STRATEX) 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 STRATEX 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. STRATEX is

Registered 21 February 2021

Sign:

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains atomoxetine hydrochloride equivalent to 10 mg, 18 mg, 25 mg, 40 mg, 60 mg or 80 mg atomoxetine.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gelatin capsules

STRATEX 10 is presented as a white powder in a hard gelatin capsule of size no. 3, opaque white cap imprinted with ‘10’ and opaque white body imprinted with ‘mg’.

STRATEX 18 is presented as white powder in a hard gelatin capsule of size no. 3, opaque rich yellow cap imprinted with ‘18’ and opaque white body imprinted with ‘mg’.

STRATEX 25 is presented as white powder in a hard gelatin capsule of size no. 3, opaque blue cap imprinted with ‘25’ and opaque white body imprinted with ‘mg’.

STRATEX 40 is presented as white powder in a hard gelatin capsule of size no. 3, opaque blue cap imprinted with ‘40’ and opaque blue body imprinted with ‘mg.’

STRATEX 60 is presented as white powder in a hard gelatin capsule of size no. 2, opaque blue cap imprinted with '60' and opaque rich yellow body imprinted with 'mg'.

STRATEX 80 is presented as white powder in a hard gelatin capsule of size no. 2, opaque brown cap imprinted with '80' and opaque white body imprinted with 'mg'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

STRATEX capsules are not intended to be opened. STRATEX is an eye irritant. See section 6.6 and *Method of administration* for instructions what to do if capsule content comes into contact with the eye.

Dosing of children older than 6 years and adolescents up to 70 kg body mass

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

Dosing of children and adolescents over 70 kg body mass and adults

STRATEX 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.

STRATEX may be discontinued without tapering the dose.

Long-term use

No fixed dose 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 daily amount of STRATEX in any 24-hour period.

Special populations

Elderly population:

The use of atomoxetine in patients over 65 years of age has not been systematically evaluated.

Paediatric population under six years of age:

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

Hepatic and renal insufficiency

For those ADHD patients who have hepatic insufficiency or end-stage renal disease, cautious titration of STRATEX to the desired clinical response is recommended. STRATEX clearance may be reduced in patients with hepatic insufficiency. For patients with moderate hepatic insufficiency (Child-Pugh Class B), initial and target doses should be reduced to 50 % of the usual dose. For patients with severe hepatic insufficiency (Child-Pugh Class C), initial dose and target doses should be reduced to 25 % of usual dose (see section 5.2).

STRATEX may exacerbate hypertension in patients with end-stage renal disease (see section 4.8).

Method of administration

For oral use.

STRATEX capsules should not be opened (see section 6.6), but swallowed whole with water.

It may be taken with or without food.

4.3 Contraindications

- Hypersensitivity to atomoxetine or to any of the excipients of STRATEX.
- STRATEX should not be used in patients with uncontrolled hypertension or impairment of liver function.
- Monoamine oxidase inhibitors**:** STRATEX should not be taken in combination with monoamine oxidase inhibitors (MAOI), including linezolid. STRATEX should not be taken within a minimum of 2 weeks after discontinuing therapy with MAOI. Treatment with MAOI should not be initiated within 2 weeks after discontinuing STRATEX.
- Severe cardiovascular disorders**:** STRATEX 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 heartrate 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: STRATEX should not be used in patients with pheochromocytoma or a history of pheochromocytoma (see section 4.4 - *Cardiovascular effects*).
- Narrow angle glaucoma: The use of atomoxetine was associated with an increased incidence of mydriasis, therefore the use of STRATEX is not recommended in patients with narrow angle glaucoma.

4.4 Special warnings and precautions for use

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. a paediatrician or child/adolescent psychiatrist).

Suicide-related behaviour, hostility

Suicidal behaviour, suicidal ideation, hostility (predominantly aggression, oppositional behaviour and anger) and emotional lability were more frequently observed among patients treated with atomoxetine (as in STRATEX), 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 at usual doses. Although some serious structural cardiac abnormalities alone carry an increased risk of sudden death, STRATEX should only be used with caution in patients with known serious structural cardiac abnormalities, and in consultation with a cardiac specialist.

Cardiovascular effects

STRATEX can significantly increase the heart rate and blood pressure. Most patients experience a modest increase in heart rate (mean < 10 bpm) and/or increase in blood pressure (mean < 5 mm Hg) (see section 4.8).

However, combined data from controlled and uncontrolled ADHD clinical trials show that approximately 8-12 % of children and adolescents, and 6-10 % of adults experience more pronounced changes in heart rate (20 beats per minute or greater) and blood pressure (15-20 mmHg or greater). Analysis of these clinical trial data showed that approximately 15-26 % of children and adolescents, and 27-32 % of adults experiencing such changes in blood pressure and heart rate during treatment with atomoxetine 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 STRATEX 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.

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

STRATEX 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 treatment with STRATEX should undergo a prompt specialist cardiac evaluation.

STRATEX should also 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, STRATEX 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 STRATEX.

Hepatic effects

Spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported, in some cases associated with severe liver injury, including acute liver failure, have also been reported. STRATEX should be discontinued in patients with jaundice or laboratory evidence of liver injury and it 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 STRATEX at usual doses. If such symptoms occur, consideration should be given to a possible causal role of STRATEX, and discontinuation of treatment should be considered. The possibility that STRATEX 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 (contained in STRATEX) 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, angioedema and urticaria have been reported in patients taking atomoxetine (as in STRATEX) (see section 4.8).

Seizures

Seizures are a potential risk with atomoxetine. STRATEX should be introduced with caution in patients with a history of seizure. Discontinuation of STRATEX 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

Weight gain and longitudinal growth should be monitored during treatment with STRATEX. Reportedly, paediatric patients treated with atomoxetine in ADHD clinical trials had a mean initial decrease in weight and height gain. Subsequently, over the long-term period, patients recovered to the mean weight and height predicted by group baseline data.

The amount of available long-term data is limited. Therefore, patients requiring long-term therapy should be carefully monitored.

Effects on micturition

In adult ADHD controlled trials, the rates of urinary retention and urinary hesitation were increased among the patients given atomoxetine, compared with patients on placebo. A complaint of urinary retention or urinary hesitancy should be considered potentially related to STRATEX.

Raynaud's phenomenon

STRATEX should not be used in patients with Raynaud's phenomenon.

New-onset or worsening of co-morbid depression, anxiety and tics

STRATEX 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 and children).

There have less frequently been reports of anxiety, depression or depressed mood and tics (see section 4.8). Patients who are being treated for ADHD with STRATEX should be monitored for the appearance

or worsening of anxiety symptoms, depressed mood and depression or tics.

Special populations

Paediatric population under six years of age

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

Elderly patients (65 years and older)

The safety and efficacy of STRATEX in elderly persons have not been established.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on STRATEX

MAOIs

Concomitant use of STRATEX and MAOIs is contraindicated (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 $C_{ss\ max}$ 3 to 4 times higher, because it is metabolised by the CYP2D6 pathway. Slower titration and final lower dosage of STRATEX may be necessary in patients who are already taking CYP2D6 inhibitors. If a CYP2D6 inhibitor is prescribed or discontinued after titration to the appropriate STRATEX 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 STRATEX 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-adrenergic receptor agonists)

STRATEX should be administered with caution to patients treated with high dose inhaled, nebulised or systemically administered salbutamol (or other beta2-agonists) because the action of salbutamol on the cardiovascular effects can be potentiated.

Attention should be paid to monitoring heart rate and blood pressure, and dose adjustments may be justified for either STRATEX 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.

Medicines that may increase prolonged QT-interval

There is a potential for an increased risk of QT-interval prolongation when STRATEX is administered with other QT prolonging medicines (such as neuroleptics, class IA and III anti-dysrhythmic medicines, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium, or cisapride), medicines that cause electrolyte imbalance (such as thiazide diuretics), and medicines that inhibit CYP2D6.

Medicines that may lower the seizure threshold

Seizures are a potential risk with STRATEX. Caution is advised with concomitant use of medicines which are known to lower the seizure threshold (such as tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), neuroleptics, phenothiazines, butyrophenone, mefloquine, chloroquine, bupropion or tramadol - see section 4.4). Caution is also advised when stopping concomitant treatment with benzodiazepines, due to potential withdrawal seizures.

Anti-hypertensive medicines

STRATEX should be used cautiously with anti-hypertensive medicines. Because of a possible increase in blood pressure, STRATEX may decrease the effectiveness of anti-hypertensive medicines. Attention should be paid to monitoring of blood pressure and review of treatment of STRATEX or anti-hypertensive medicines may be justified in the case of significant changes of blood pressure.

Pressor substances or medicines that increase blood pressure

Because of possible increase in effects on blood pressure, STRATEX should be used cautiously with pressor substances or medicines that may increase blood pressure. Blood pressure should be monitored. A review of treatment for either STRATEX or pressor substances may be justified in the case of significant change in blood pressure.

Medicines that affect norepinephrine (noradrenaline)

Medicines that affect norepinephrine should be used cautiously when co-administered with STRATEX 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.

Methylphenidate

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

Medicinal products that affect gastric pH

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

Midazolam

Co-administration of 60 mg atomoxetine 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.

Medicines highly bound to plasma protein

In vitro medicine-displacement studies with atomoxetine and other highly-bound medicines at therapeutic concentrations showed that warfarin, acetylsalicylic acid, phenytoin, or diazepam do not affect the binding of atomoxetine to human albumin. Similarly, atomoxetine does not affect the binding of these compounds to human albumin.

4.6 Fertility, pregnancy and lactation

Pregnancy

Clinical data on exposed pregnancies are limited for atomoxetine. Such data are insufficient to indicate either an association or a lack of association between atomoxetine and adverse pregnancy outcomes. STRATEX should not be used during pregnancy.

Breastfeeding

Atomoxetine and/or its metabolites are excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Because of the lack of data, STRATEX should be avoided during breastfeeding.

4.7 Effects on ability to drive and use machines

STRATEX may cause fatigue, somnolence and dizziness. 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 STRATEX.

4.8 Undesirable effects

Paediatric population:

Summary of the safety profile

In paediatric trials, headache, abdominal pain and decreased appetite are the adverse events most commonly associated with atomoxetine but seldom lead to discontinuation of the medicine. Abdominal pain and decreased appetite are usually transient.

Associated with decreased appetite, some patients experienced growth retardation early in therapy in terms of both weight and height gain. On average, after an initial decrease in weight and height gain, patients treated with atomoxetine recovered to mean weight and height as predicted by group baseline data over the long-term treatment.

Nausea, vomiting and somnolence can occur in patients, particularly during the first month of therapy. However, these episodes were usually mild to moderate in severity and transient and did not result in a significant number of discontinuations from therapy.

In both paediatric and adult 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.

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 list of adverse reactions - child and adolescent patients:

System Organ Class/ Frequency	**Adverse reaction**
Infections and infestations	
Frequent:	Sinusitis

Immune system disorders

Less frequent: Hypersensitivity reactions, anaphylactic reactions, angioedema

Metabolism and nutrition disorders

Frequent: Decreased appetite, anorexia

Psychiatric disorders

Frequent: Irritability, mood swings, insomnia, agitation, anxiety, depression and depressed mood, tics (see section 4.4)

Less frequent: Suicide-related events, anger, aggression, hostility, emotional lability, psychosis (including hallucinations) (see section 4.4)

Frequency unknown: Suicidal ideation

Nervous system disorders

Frequent: Headache, somnolence, sedation, dizziness

Less frequent: Syncope, tremor, migraine, paraesthesia, hypoaesthesia, seizure (see section 4.4 and 4.5)

Eye disorders

Frequent: Mydriasis

Less frequent: Vision blurred, conjunctivitis

Cardiac disorders

Less frequent: Palpitations, sinus tachycardia, QT-interval prolongation (see section 4.4 and 4.5)

Vascular disorders

Less frequent: Raynaud's phenomenon

Frequency unknown: Peripheral vascular instability

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea (see section 4.4)

Gastrointestinal disorders

Frequent: Abdominal pain, stomach discomfort, abdominal discomfort, epigastric discomfort, vomiting, nausea, constipation, dyspepsia

Hepatobiliary disorders

Less frequent: Increased blood bilirubin, abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure (see section 4.4)

Skin and subcutaneous tissue disorders

Frequent: Dermatitis, pruritus, rash

Less frequent: Hyperhidrosis, allergic reactions

Renal and urinary disorders

Less frequent: Urinary hesitation, urinary retention

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Sign:

Reproductive system and breast disorders	
Less frequent:	Priapism, male genital pain
General disorders and administrative site conditions	
Frequent:	Fatigue, lethargy, chest pain (see section 4.4)
Less frequent:	Asthenia
Investigations	
Frequent:	Increased blood pressure, increased heart rate, decreased weight

CYP2D6 poor metabolisers

The following adverse events occurred in at least 2 % of child and adolescent CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: weight decreased, constipation, insomnia, depression, tremor; middle insomnia; syncope; conjunctivitis; early morning awakening; mydriasis; sedation. The following event did not meet the above criteria but is noteworthy: generalised anxiety disorder. In addition, in trials lasting up to 10 weeks, weight loss was more pronounced in PM patients.

Adults:

Summary of the safety profile

In adult ADHD clinical trials, the following system organ classes had the highest frequency of adverse events during treatment with atomoxetine: gastrointestinal, nervous system and psychiatric disorders. The most frequent adverse events reported were decreased appetite, insomnia, headache, dry mouth and nausea. The majority of these events were mild or moderate in severity and the events most frequently reported as severe were nausea, insomnia, fatigue and headache. A complaint of urinary retention or urinary hesitancy in adults should be considered potentially related to atomoxetine.

The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials and post-marketing spontaneous reports in adults:

Tabulated list of adverse reactions - adult patients:

System Organ Class/ Frequency	Adverse reaction
Infections and infestations	
Frequent:	Sinusitis
Immune system disorders	
Less frequent:	Allergic reactions, anaphylactic reactions, angioedema
Metabolism and nutrition disorders	
Frequent:	Decreased appetite
Psychiatric disorders	
Frequent:	Insomnia, agitation, libido decreased, sleep disorders, depression and depressed mood, anxiety (see section 4.4)
Less frequent:	Suicide-related events, suicidal ideation, aggression, anger, hostility, emotional lability, restlessness, psychosis (including hallucinations) (see section 4.4)
Nervous system disorders	
Frequent:	Headache, dizziness, dysgeusia, paraesthesia, sedation, tremor

Less frequent:	Syncope, migraine, hypoaesthesia, seizures (see section 4.4 and 4.5)
Eye disorders	
Less frequent:	Vision blurred
Cardiac disorders	
Frequent:	Palpitations, tachycardia
Less frequent:	QT-interval prolongation, stroke, myocardial infarction, sudden death (see section 4.4 and 4.5)
Vascular disorders	
Frequent:	Flushing, hot flushes
Less frequent:	Raynaud's phenomenon, peripheral coldness
Frequency unknown:	Peripheral vascular instability
Respiratory, thoracic and mediastinal disorders	
Less frequent:	Dyspnoea (see section 4.4), rhinorrhoea
Gastrointestinal disorders	
Frequent:	Dry mouth, nausea, abdominal pain, abdominal discomfort, epigastric discomfort, vomiting, constipation, dyspepsia, flatulence
Hepatobiliary disorders	

Less frequent:	Increased blood bilirubin, abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure (see section 4.4)
Skin and subcutaneous tissue disorders	
Frequent:	Dermatitis, hyperhidrosis, rash
Less frequent:	Allergic reactions and angioneurotic oedema, urticaria, pruritus
Musculoskeletal and connective tissue disorders	
Less frequent:	Muscle spasms
Renal and urinary disorders	
Frequent:	Dysuria, pollakiuria, urinary hesitation, urinary retention
Less frequent:	Micturition urgency
Reproductive system and breast disorders	
Frequent:	Dysmenorrhoea, ejaculation disorders, erectile dysfunction, prostatitis, male genital pain
Less frequent:	Priapism, ejaculation failure, irregular menstruation, abnormal orgasm
General disorders and administrative site conditions	
Frequent:	Asthenia, fatigue, lethargy, chills, feeling jittery, irritability, thirst

Less frequent:	Feeling cold, chest pain (see section 4.4)
Investigations	
Frequent:	Increased blood pressure, increased heart rate, decreased weight

CYP2D6 poor metabolisers (PM)

The following adverse events occurred in at least 2 % of adult CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared to CYP2D6 extensive metaboliser (EM) patients: vision blurred; dry mouth; constipation; feeling jittery; decreased appetite; tremor; insomnia; sleep disorder; middle insomnia; terminal insomnia; urinary retention; erectile dysfunction; ejaculation disorder; hyperhidrosis; peripheral coldness.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Signs and symptoms

There have been post-marketing reports of non-fatal acute and chronic overdoses of atomoxetine (as in STRATEX) 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, increased blood pressure, mydriasis, dry mouth) were also observed.

In some cases of overdose involving atomoxetine, seizures and less frequently QT prolongation have been reported (see section 5.1). There have also been reports of fatal, acute overdoses involving a mixed ingestion of atomoxetine 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. The patient should be observed for a minimum of 6 hours. Activated charcoal may be useful in limiting absorption if the patient presents within one hour of ingestion. Because STRATEX is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 1.2 Psychoanaleptics

Pharmacotherapeutic group: Psychoanaleptics, centrally acting sympathomimetics, ATC code: N06BA09

Mechanism of action

Atomoxetine is a selective inhibitor of the pre-synaptic norepinephrine (noradrenaline) 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.

Absorption

Atomoxetine is well absorbed after oral administration. The mean maximal observed plasma concentration (C_{max}) is reached within 1 to 2 hours after dosing. Atomoxetine can be taken with or without food.

Distribution

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

Biotransformation

Atomoxetine is mainly metabolised 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 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 the CYP2D6 pathway.

Other Cytochrome P450 Enzymes: Atomoxetine did not cause clinically significant inhibition or induction of other cytochrome P450 enzymes, including CYP1A2, CYP3A, 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 mainly in the urine, primarily as 4-hydroxyatomoxetine-*O*-glucuronide.

Linearity/non-linearity

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

Special populations

Hepatic impairment

Hepatic impairment results in a reduced atomoxetine clearance, increased atomoxetine exposure (AUC can increase 2-fold in moderate impairment and 4-fold in severe impairment) and a prolonged half-life of the parent substance.

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).

Renal impairment

Atomoxetine mean plasma concentrations for end-stage renal disease patients are generally higher than the mean for healthy persons. After adjustment for body weight, the differences between the two groups may be minimised and dose adjustment may not be required. See section 4.2.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules content

Maize starch, pregelatinised

Silica, colloidal anhydrous

Dimethicone (350)

Capsule shell

STRATEX 10 mg capsules

Gelatin

Sodium lauryl sulphate (E487)

Titanium dioxide (E171)

STRATEX 18 mg capsules

Gelatin

Sodium lauryl sulphate (E487)

Titanium dioxide (E171)

Iron oxide yellow (E172)

STRATEX 25 mg capsules

Gelatin

Sodium lauryl sulphate (E487)

Titanium dioxide (E171)

Indigo carmine (E132)

STRATEX 40 mg capsules

Gelatin

Sodium lauryl sulphate (E487)

Titanium dioxide (E171)

Indigo carmine (E132)

STRATEX 60 mg capsules

Gelatin

Sodium lauryl sulphate (E487)

Titanium dioxide (E171)

Indigo carmine (E132)

Registered 21 February 2021

Sign:

Iron oxide yellow (E172)

STRATEX 80 mg capsules

Gelatin

Sodium lauryl sulphate (E487)

Titanium dioxide (E171)

Iron oxide red (E172)

Iron oxide yellow (E172)

Printing ink (black)

Shellac Glaze-45 % (20 % esterified) in ethanol

Iron oxide black (E172)

Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C, in the original packaging. Keep blisters in the carton until required for use.

6.5 Nature and contents of container

A cardboard box containing transparent PVC/PE/PCTFE-aluminium foil blisters or PA/AL/PVC-aluminium foil blisters.

Packs of 7, 14, 28 or 30 hard capsules.

Not all pack sizes are necessarily marketed at any one time.

6.6 Special precautions for disposal and other handling

The capsules are not intended to be opened. Atomoxetine is an ocular irritant. In the event of the capsules content coming in contact with the eye, the affected eye should be flushed immediately with water, and medical advice obtained. Hands and any potentially contaminated surfaces should be washed as soon as possible.

7. HOLDER OF REGISTRATION CERTIFICATES

Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle and Pontac Streets

Cape Town

8001

enquiries@unicornpharma.co.za

8. REGISTRATION NUMBER (S)

STRATEX 10: *511038*

STRATEX 18: *511039*

STRATEX 25: *511040*

STRATEX 40: *511041*

STRATEX 60: *511042*

STRATEX 80: *511043*

Registered 21 February 2021

Sign:

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 February 2021

10. DATE OF REVISION OF THE TEXT

To be confirmed.