SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

STRATTERA 10 mg (Capsules)

STRATTERA 18 mg (Capsules)

STRATTERA 25 mg (Capsules)

STRATTERA 40 mg (Capsules)

STRATTERA 60 mg (Capsules)

STRATTERA 80 mg (Capsules)

WARNING: SUICIDAL IDEATION IN CHILDREN AND ADOLESCENTS

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

COMPOSITION

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

STRATTERA capsules contain the following inactive ingredients: black ink, dimethicone, FD&C blue 2 (25 mg, 40 mg and 60 mg only), gelatin, pregelatinised starch, red iron oxide (80 mg only), sodium laurilsulfate, titanium dioxide, yellow iron oxide (18 mg, 60 mg and 80 mg only).

Lactose Free.

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 6 years of age.

Absorption

Atomoxetine is well absorbed after oral administration reaching 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.

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.

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.

INDICATIONS

STRATTERA is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children 6 years of age or older, adolescents and adults.

CONTRAINDICATIONS

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

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

Monoamine oxidase inhibitors: STRATTERA should not be used in combination with monoamine oxidase inhibitors (MAOIs), including linezolid.

STRATTERA 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 STRATTERA.

Severe Cardiovascular Disorders: STRATTERA 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 WARNINGS AND SPECIAL PRECAUTIONS – Cardiovascular Effects).

Phaeochromocytoma: STRATTERA should not be used in patients with phaeochromocytoma or a history of phaeochromocytoma (see WARNINGS AND SPECIAL PRECAUTIONS – Cardiovascular Effects).

Narrow angle glaucoma: In clinical studies, the use of STRATTERA 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

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 STRATTERA.

Suicidal behavior, 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 STRATTERA 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.

Hepatic effects: STRATTERA should be discontinued in patients with jaundice or laboratory evidence of liver injury and should never be restarted. 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 and acute liver failure. 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: STRATTERA lacks efficacy as treatment modality in depression and should not be used for the treatment of depression.

Growth: Weight gain and longitudinal growth should be monitored during treatment with STRATTERA. Paediatric patients treated with STRATTERA 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.

Cardiovascular effects: STRATTERA can significantly increase heart rate and blood pressure. It is recommended that the heart rate and blood pressure be measured before treatment is started and periodically during treatment to detect possible clinically important increases.

Most patients taking STRATTERA experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg (see SIDE EFFECTS). However, data from ADHD clinical trials show that some patients (approximately 5 to 10 % of children and adults) do experience clinically important changes in heart rate (20 beats per minute or greater) or blood

pressure (15 to 20 mm Hg or greater). STRATTERA should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease. It 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 heart rate that could be clinically important (see CONTRAINDICATIONS – Severe Cardiovascular Disorders).

In addition, STRATTERA should be used with caution in patients with congenital long QT syndrome, acquired long QT syndrome (for example, due to concomitant use of a medicine that prolongs the QT), or a family history of QT prolongation. Because orthostatic hypotension has also been reported, STRATTERA 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.

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

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

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

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

Special Populations: STRATTERA 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).

Effects on the ability to drive and use machines

As STRATTERA may cause 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 STRATTERA.

INTERACTIONS

Interaction with other medicaments and other forms of interaction:

Beta-adrenergic receptor agonists STRATTERA should be administered with caution to patients treated with high dose inhaled, nebulised or systemically administered salbutamol (or other beta2 agonists) because cardiovascular effects can be potentiated.

Cytochrome P450 enzyme: STRATTERA did not cause clinically significant inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6 and CYP2C9. STRATTERA is principally metabolised by the CYP2D6 pathway. In CYP2D6 extensive metabolisers, inhibitors of CYP2D6 increase STRATTERA 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 STRATTERA. Slower titration of STRATTERA may be necessary in those patients who are also taking CYP2D6 inhibitor medicines as the side effects are increased in frequency in patients who are poor CYP2D6 metabolisers (See SIDE EFFECTS).

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

Pressor agents: Because of possible effects on blood pressure, STRATTERA should be used cautiously with anti-hypertensive medicines and pressor agents or other medicines that increase blood pressure.

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

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

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

Midazolam: Co-administration of STRATTERA (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.

Medicines highly bound to plasma protein: *In vitro* drug-displacement studies were conducted with STRATTERA and other highly bound medicines at therapeutic concentrations. STRATTERA

did not affect the binding of warfarin, aspirin, phenytoin or diazepam to human albumin. Similarly, these medicines did not affect the binding of STRATTERA to human albumin.

PREGNANCY AND LACTATION

Pregnancy: Safety and efficacy have not been demonstrated in pregnancy.

Lactation

STRATTERA and/or its metabolites were excreted in the milk of rats. It is not known if STRATTERA is excreted in human milk. Women using STRATTERA should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE

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 WARNINGS AND SPECIAL PRECAUTIONS).

The recommended initial dose and subsequent dosage escalations of
STRATTERA should not be exceeded because of potential side effects (See SIDE EFFECTS).

STRATTERA capsules are not intended to be opened. STRATTERA 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: STRATTERA 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 STRATTERA). 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:

STRATTERA should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is 80 mg. No additional benefit has been demonstrated for doses higher than 80 mg. The maximum recommended total daily dose for adults is 80 mg.

General dosing information:

STRATTERA may be taken with or without food.

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

STRATTERA may be discontinued without tapering the dose.

Long-term use:

No fixed dose-response studies have been conducted in adults. The recommended daily dose of 80 mg reflects the optimal daily dose of 1,2 mg/kg/day demonstrated in children and adolescents.

No controlled long-term studies have been conducted in adults. Open-label study data from 384 patients with up to 97 weeks of treatment with STRATTERA are consistent with maintenance of efficacy in long-term treatment.

Missing a dose:

If patients miss a dose, they should take it as soon as possible; however, they should not take more than the prescribed total daily amount of STRATTERA in any 24-hour period.

SIDE EFFECTS

Clinical Trial Data:

Child and Adolescent Patients	**Frequency of Occurrence**		
System Organ Class/Adverse Event	**Very common ≥1:10 (≥10 %)**	**Common ≥1:100 and <1:10 (≥1 % and <10 %)**	**Uncommon ≥1:1000 and <1:100 (≥0,1 % and <1 %)**
Metabolism and Nutritional Disorders	Appetite decreased	Anorexia	

Psychiatric Disorders		Insomnia[1] Depression[2] Mood swings	
Nervous System Disorders	Headache Somnolence[3]	Dizziness	Syncope[4] Tremor
Eye disorders		Mydriasis	Conjunctivitis
Cardiac disorders			Palpitations Sinus Tachycardia
Gastrointestinal Disorders	Abdominal pain[5] Nausea Vomiting	Constipation Dyspepsia	
Skin and Subcutaneous Tissue Disorders		Pruritus Rash	
General Disorders and Administration Site Conditions		Fatigue Irritability	Asthenia
Investigations	Blood pressure increased[6] Heart rate increased[6]	Weight decreased	

[1]Also includes initial insomnia, middle insomnia and terminal insomnia

[2]Also includes major depression, depressive symptoms, depressed mood and dysphoria

[3]Also includes sedation

[4]Also includes syncope vasovagal

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

[6]Heart rate and blood pressure data are based on measured vital signs

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 (7,3 % of PMs, 4,4 % of EMs), constipation (6,8 % of PMs, 4,3 % of EMs), insomnia (11 % of PMs, 6,1 % of EMs), depression (6,5 % of PMs, 4,1 % of EMs), tremor (4,5 % of PMs, 0,9 % of EMs); middle insomnia (2,8 % of PMs, 1,3 % of EMs); syncope (2,5 % of PMs, 0,7 % of EMs); conjunctivitis (2,5 % of PMs, 1,2 % of EMs); early morning awakening (2,3 % of PMs, 0,8 % of EMs); mydriasis (2,0 % of PMs, 0,6 % of EMs); sedation (3,9 % of PMs, 2,1 % of EMs).

Adults	**Frequency of Occurrence**		
System Organ Class/Adverse Event	**Very common ≥1:10 (≥10 %)**	**Common ≥1:100 and <1:10 (≥1 % and <10 %)**	**Uncommon ≥1:1000 and <1:100 (≥0,1 % and <1 %)**
Metabolism and Nutritional Disorders	Appetite decreased		
Psychiatric disorders	Insomnia[1]	Agitation Libido decreased Sleep disorder	Orgasm abnormal Restlessness
Nervous System Disorders	Headache	Dizziness Dysgeusia	

		Paraesthesia Somnolence[2] Tremor	
Eye Disorders			Vision blurred
Cardiac disorders		Palpitations Tachycardia	
Vascular disorders		Flushing Hot flushes	Peripheral coldness
Gastrointestinal disorders	Dry mouth Nausea	Abdominal pain[3] Constipation Dyspepsia Flatulence Vomiting	
Skin and subcutaneous disorders		Rash Hyperhydrosis	Pruritus Urticaria
Musculoskeletal and connective tissue disorders			Muscle spasms
Renal and urinary disorders		Dysuria Pollakiuria Urinary hesitation[4] Urinary retention	Micturition urgency
Reproductive System and Breast Disorders		Dysmmenorrhoea[5] Ejaculation disorder[6]	Ejaculation failure Menstruration disorder

		Erectile dysfunction[6] Prostatitis[6] Testicular pain[6]	
General Disorders and Administration Site Conditions		Asthenia Fatigue Chills Feeling jittery Irritability Thirst	Feeling cold
Investigations	Blood pressure increased[7] Heart rate increased[7]	Weight decreased	

[1]Also includes initial insomnia, middle insomnia and terminal insomnia

[2]Also includes sedation

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

[4]Also includes urine flow decreased

[5]Frequency percentage based on female patients only

[6]Frequency percentage based on male patients only

[7]Heart rate and blood pressure data are based on measured vital signs

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 (3,9 % of PMs, 1,3 % of EMs); dry mouth (34,5 % of PMs, 17,4 % of EMs); constipation (11,3 % of PMs, 6,7 % of EMs); feeling jittery (4,9 % of PMs,

1,9 % of EMs); decreased appetite (23,2 % of PMs, 14,7 % of EMs); tremor (5,4 % of PMs, 1,2 % of EMs); insomnia (19,2 % of PMs, 11,3 % of EMs); sleep disorder (6,9 % of PMs, 3,4 % of EMs); middle insomnia (5,4 % of PMs, 2,7 % of EMs); terminal insomnia (3,0 % of PMs, 0,9 % of EMs); urinary retention (5,9 % of PMs, 1,2 % of EMs); erectile dysfunction (20,9 % of PMs, 8,9 % of EMs); ejaculation disorder (6,1 % of PMs, 2,2 % of EMs); hyperhidrosis (14,8 % of PMs, 6,8 % of EMs); peripheral coldness (3,0 % of PMs, 0,5 % of EMs).

Post-marketing experience: The following events have been been reported:

Aggression/hostility

Suicidal ideation, anger

Suicidal behaviour

Abnormal liver function tests, jaundice and hepatitis (see WARNINGS and SPECIAL PRECAUTIONS).

Investigations: blood pressure increased.

Skin and Subcutaneous Tissue Disorders: hyperhidrosis

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

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

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

Psychiatric Disorders: sensory disturbances including hallucinations, depression and depressed mood, anxiety.

General disorders and administration site conditions: lethargy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Human experience:

During post-marketing, there have been reports of non-fatal acute and chronic overdoses of STRATTERA 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.

In some cases of overdose involving STRATTERA, seizures and very rarely QT prolongation have been reported (see Pharmacodynamic properties). There have also been reports of fatal, acute overdoses involving a mixed ingestion of STRATTERA and at least one other medicine. There is limited clinical trial experience with STRATTERA overdose. ~~No fatal overdoses occurred in clinical trials~~.

Management of overdose: An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Activated charcoal may be useful in limiting absorption. Because STRATTERA is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

IDENTIFICATION

STRATTERA 10 mg (Capsule, size 3) has an opaque white body and opaque white cap and is imprinted with "Lilly 3227" and "10 mg" in black ink.

STRATTERA 18 mg (Capsule, size 3) has an opaque white body and gold cap and is imprinted with "Lilly 3238" and "18 mg" in black ink.

STRATTERA 25 mg (Capsule, size 3) has an opaque white body and opaque blue cap and is imprinted with "Lilly 3228" and "25 mg" in black ink.

STRATTERA 40 mg (Capsule, size 3) has an opaque blue body and opaque blue cap and is imprinted with "Lilly 3229" and "40 mg" in black ink.

STRATTERA 60 mg (Capsule, size 2) has a gold body and opaque blue cap and is imprinted with "Lilly 3239" and "60 mg" in black ink.

STRATTERA 80 mg (Capsule, size 2) has an opaque white body and opaque brown cap and is imprinted with "Lilly 3250" and "80 mg" in black ink.

PRESENTATION

STRATTERA 10 mg capsules, PU3227, are supplied in opaque white or clear plastic web film and aluminium foil blister packs of 28.

STRATTERA 18 mg capsules, PU3238, are supplied in opaque white or clear plastic web film and aluminium foil blister packs of 28.

STRATTERA 25 mg capsules, PU3228, are supplied in opaque white or clear plastic web film and aluminium foil blister packs of 28.

STRATTERA 40 mg capsules, PU3229, are supplied in opaque white or clear plastic web film and aluminium foil blister packs of 28.

STRATTERA 60 mg capsules, PU3239, are supplied in opaque white or clear plastic web film and aluminium foil blister packs of 28.

STRATTERA 80 mg capsules, PU3250, are supplied in opaque white or clear plastic web film and aluminium foil blister packs of 28.

STORAGE INSTRUCTIONS

Store at or below 25 °C in blister packs.

Keep out of reach of children.

REGISTRATION NUMBERS

STRATTERA 10 mg capsules: 38/1.2/0520

STRATTERA 18 mg capsules: 38/1.2/0521

STRATTERA 25 mg capsules: 38/1.2/0522

STRATTERA 40 mg capsules: 38/1.2/0523

STRATTERA 60 mg capsules: 38/1.2/0524

STRATTERA 80 mg capsules: 42/1.2/0789

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

Eli Lilly (S.A.) (Pty) Limited

Private Bag X119, 2021

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Bryanston, 2191

DATE OF PUBLICATION OF THE PACKAGE INSERT

Date of initial Registration:

STRATTERA 10 mg , 18 mg , 25 mg, 40 mg , 60 mg: 03/06/2005

STRATTERA 80 mg: 05/08/2011

Date of the most recently revised package insert approved by council: 20 March 2018