**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

**MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007**

**(S.I. No.540 of 2007)**

**PA0047/095/001**
Case No: 2059246

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

**Eli Lilly and Company Limited**

**Lilly House, Priestley Road**, **Basingstoke**, **Hampshire**, **RG24 9NL**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

**Strattera 5 mg hard capsules.**

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **27/05/2009** until **26/05/2014**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

# Part II

# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Strattera 5 mg hard capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is atomoxetine hydrochloride.
Each Strattera 5 mg capsule contains atomoxetine hydrochloride equivalent to 5 mg of atomoxetine.
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard

Strattera 5 mg capsules are gold, imprinted with 'Lilly 3226' on the cap and '5 mg' on the body in black ink.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Strattera is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older and in adolescents as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10.

Additional information for the safe use of this product:

A comprehensive treatment programme typically includes psychological, educational and social measures and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractability, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

Pharmacological treatment is not indicated in all children with this syndrome and the decision to use the drug must be based on a very thorough assessment of the severity of the child's symptoms in relation to the child's age and the persistence of symptoms.

### 4.2 Posology and method of administration

For oral use. Strattera can be administered as a single daily dose in the morning, with or without food. Patients who do not achieve a satisfactory clinical response (tolerability or efficacy) when taking Strattera as a single daily dose might benefit from taking it as twice daily evenly divided doses in the morning and late afternoon or early evening.

Dosing of children/adolescents up to 70 kg Body Weight:

Strattera should be initiated at a total daily dose of approximately 0.5mg/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 1.2mg/kg/day (depending on the patient's weight and available dosage strengths of atomoxetine). No additional benefit has been demonstrated for doses higher than 1.2mg/kg/day. The safety of single doses over 1.8mg/kg/day and total daily doses above 1.8 mg/kg have not been systematically evaluated. In some cases it might be appropriate to continue treatment into adulthood.

Dosing of children/adolescents over 70 kg Body Weight:

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 80mg. No additional benefit has been demonstrated for doses higher than 80 mg (see section 5.1). The maximum recommended total daily dose is 100 mg. The safety of single doses over 120mg and total daily doses above 150mg have not been systematically evaluated. In some cases it might be appropriate to continue treatment into adulthood.

Additional information for the safe use of this product:

Atomoxetine should be used in accordance with national clinical guidance on treatment of ADHD where available.

In the study program no distinct withdrawal symptoms have been described. In cases of significant adverse effects, atomoxetine may be stopped abruptly; otherwise the drug may be tapered off over a suitable time period.

Where patients are continuing treatment with atomoxetine beyond 1 year, re-evaluation of the need for therapy by a specialist in the treatment of ADHD is recommended.

In adolescents whose symptoms persist into adulthood and who have shown clear benefit from treatment, it may be appropriate to continue treatment into adulthood. However, start of treatment with Strattera in adults is not appropriate.

Special Populations

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)

Renal Insufficiency: subjects with end stage renal disease had higher systemic exposure to atomoxetine than healthy subjects (about a 65% increase), but there was no difference when exposure was corrected for mg/kg dose. Strattera can therefore be administered to ADHD patients with end stage renal disease or lesser degrees of renal insufficiency using the usual dosing regimen. Atomoxetine may exacerbate hypertension in patients with end stage renal disease. ( see section 5.2)

Approximately 7% of Caucasians have a genotype corresponding to a non-functional CYP2D6 enzyme (called CYP2D6 poor metabolisers). Patients with this genotype have a several fold higher exposure to atomoxetine when compared to patients with a functional enzyme. Poor metabolisers are therefore at higher risk of adverse events (see sections 4.8 and 5.2). For patients with a known poor metaboliser genotype, a lower starting dose and slower up titration of the dose may be considered.

Elderly patients: not applicable.

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

## 4.3 Contraindications

Hypersensitivity to atomoxetine or to any of the excipients.

Atomoxetine should not be used in combination with monoamine oxidase inhibitors (MAOI). Atomoxetine should not be used within a minimum of 2 weeks after discontinuing therapy with MAOI. Treatment with MAOI should not be initiated within 2 weeks after discontinuing atomoxetine.

Atomoxetine should not be used in patients with narrow angle glaucoma, as in clinical trials the use of atomoxetine was associated with an increased incidence of mydriasis.

## 4.4 Special warnings and precautions for use

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

**Sudden death and pre-existing structural cardiac abnormalities or other serious heart problems**
Sudden death has been reported in children and adolescents with structural cardiac abnormalities who were taking atomoxetine at usual doses. Although some serious structural cardiac abnormalities alone carry an increased risk of sudden death, atomoxetine should only be used with caution in children or adolescents with known serious structural cardiac abnormalities and in consultation with a cardiac specialist.

**Cardiovascular effects**
Many patients taking atomoxetine experience a modest increase in pulse (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) (see section 4.8). For most patients, these changes are not clinically important. Atomoxetine should be used with caution in patients with hypertension, tachycardia, or cardiovascular or cerebrovascular disease. Pulse and blood pressure should be measured periodically while on therapy. Orthostatic hypotension has also been reported. Use with caution in any condition that may predispose patients to hypotension.

Atomoxetine should be used with caution in patients with congenital or acquired long QT or a family history of QT prolongation (see sections 4.5 Interactions and 4.8 Undesirable Effects).

**Hepatic effects**
Strattera should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Very rarely, liver toxicity, manifested by elevated hepatic enzymes and bilirubin with jaundice, has been reported.

**Growth and development**
Growth and development should be monitored during treatment with atomoxetine**.** Patients requiring long-term therapy should be monitored and consideration should be given to dose reduction or interrupting therapy in patients who are not growing or gaining weight satisfactorily.

Clinical data do not suggest a deleterious effect of atomoxetine on cognition or sexual maturation, however the amount of available long-term data is limited. Therefore, patients requiring long-term therapy should be carefully monitored.

**Suicide-related behaviour**
Suicide related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine. In double blind clinical trials, suicide related behaviours were uncommon but more frequently observed among children and adolescents treated with atomoxetine compared to those treated with placebo, where there were no events. Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide related behaviour.

**Psychotic or manic symptoms**
Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, mania or agitation in children and adolescents without a prior history of psychotic illness or mania can be caused by atomoxetine at usual doses. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine, and discontinuation of treatment should be considered. The possibility that Strattera 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) and emotional lability were more frequently observed in clinical trials among children and adolescents treated with Strattera 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 atomoxetine. Atomoxetine should be introduced with caution in patients with a history of seizure. Discontinuation of atomoxetine should be considered in any patient developing a seizure or if there is an increase in seizure frequency where no other cause is identified.

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

**Other indications**
Strattera is not indicated for the treatment of major depressive episodes and/or anxiety as the results of clinical trials that were conducted in adults did not show any effect compared to placebo, and therefore were negative.

## 4.5 Interaction with other medicinal products and other forms of interaction

Effects of other drugs on atomoxetine:
MAOIs: Atomoxetine should not be used with MAOIs (see section 4.3).

CYP2D6 inhibitors (SSRIs (e.g. fluoxetine, paroxetine), quinidine, terbinafine): Atomoxetine is primarily metabolised by the CYP2D6 pathway to 4-hydroxyatomoxetine. In CYP2D6 extensive metaboliser patients, potent inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metaboliser patients. In extensive metaboliser individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and Css, max is about 3- to 4- fold greater than atomoxetine alone. Dose adjustment and slower titration of atomoxetine may be necessary in those patients who are also taking CYP2D6 inhibitor drugs. If a CYP2D6 inhibitor is prescribed or discontinued after titration to the appropriate atomoxetine dose has occurred, the clinical response and tolerability should be re-evaluated for that patient to determine if dose adjustment is needed.

Caution is advised when combining atomoxetine with potent inhibitors of cytochrome P450 enzymes other than CYP2D6 in patients who are poor CYP2D6 metabolisers as the risk of clinically relevant increases in atomoxetine exposure in vivo is unknown.

Salbutamol: Atomoxetine should be administered with caution to patients being treated with high dose nebulised or systemically administered (oral or intravenous) salbutamol (or other $beta_2$ agonists) because the action of salbutamol on the cardiovascular system can be potentiated. Systemically administered Salbutamol (600 μg i.v. over 2 hrs) induced increases in heart rate and blood pressure. These effects were potentiated by atomoxetine (60 mg twice daily for 5 days) and were most marked after the initial coadministration of salbutamol and atomoxetine. In a study of healthy Asian adults who were extensive atomoxetine metabolisers, the effects on blood pressure and heart rate of a standard inhaled dose of salbutamol (200 μg) were not clinically significant compared to intravenous administration and not increased by the short term coadministration of atomoxetine (80 mg once daily for 5 days). Heart rate after multiple inhalations of salbutamol (800 μg) was similar in the presence or absence of atomoxetine.

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

Seizures are a potential risk with atomoxetine. Caution is advised with concomitant use of medicinal drugs which are known to lower the seizure threshold (such as antidepressants, neuroleptics, mefloquine, buproprion or tramadol). (see section 4.4)

Pressor Agents: Because of possible effects on blood pressure, atomoxetine should be used cautiously with pressor agents.

Drugs that Affect Noradrenaline: Drugs that affect noradrenaline should be used cautiously when co-administered with atomoxetine because of the potential for additive or synergistic pharmacological effects. Examples include antidepressants such as imipramine, venlafaxine and mirtazapine, or the decongestants pseudoephedrine or

phenylephrine.

Drugs that Affect Gastric pH: Drugs that elevate gastric pH (magnesium hydroxide/aluminum hydroxide, omeprazole) had no effect on atomoxetine bioavailability.

Drugs Highly Bound to Plasma Protein: In vitro drug-displacement studies were conducted with atomoxetine and other highly bound drugs at therapeutic concentrations. Warfarin, acetylsalicylic acid, phenytoin, or diazepam did not affect the binding of atomoxetine to human albumin. Similarly, atomoxetine did not affect the binding of these compounds to human albumin.

Effects of atomoxetine on other drugs:
Cytochrome P450 Enzymes: Atomoxetine did not cause clinically significant inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9. In vitro studies indicate that atomoxetine does not cause clinically significant induction of CYP1A2 and CYP3A.

## 4.6 Pregnancy and lactation

For atomoxetine no clinical data on exposed pregnancies are available. Animal studies in general do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Atomoxetine should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

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

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Atomoxetine was associated with increased rates of fatigue relative to placebo. In paediatric patients only, atomoxetine was associated with increased rates of somnolence relative to placebo. Patients should be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

## 4.8 Undesirable effects

Children and adolescents:
In paediatric placebo-controlled trials, headache, abdominal pain[1] and decreased appetite are the adverse events most commonly associated with atomoxetine, and are reported by about 19%, 18% and 16% of patients respectively, but seldom lead to drug discontinuation (discontinuation rates are 0.1% for headache, 0.2 % for abdominal pain and 0.0% for decreased appetite). Abdominal pain and decreased appetite are usually transient.**-**

Associated with decreased appetite, some patients lost weight early in therapy (average about 0.5 kg), and effects were greatest at the highest doses. After an initial decrease in weight, patients treated with atomoxetine showed a mean increase in weight during long-term treatment. Growth rates (weight and height) after 2 years of treatment are near normal (See section 4.4.).

Nausea, vomiting and somnolence[2] can occur in about 10% to 11% of 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 discontinuation from therapy (discontinuation rates ≤ 0.5%).

In paediatric placebo-controlled trials, patients taking atomoxetine experienced a mean increase in heart rate of about 6 beats/minute and mean increases in systolic and diastolic blood pressure of about 2 mm Hg compared with placebo. In adult placebo-controlled trials, patients taking atomoxetine experienced a mean increase in heart rate of 5 beats/minute and mean increases in systolic (about 2 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo.

Because of its effect on noradrenergic tone, orthostatic hypotension (0.2%) and syncope (0.8% ) 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 in child and adolescent patients and spontaneous reporting from children/adolescents and adults post marketing:

*Table: Adverse reactions*

Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), data from spontaneous reports (frequency not known – cannot be estimated from the available data).

| **System Organ Class** | **Very common** | **Common** | **Uncommon** | **Post marketing experience Spontaneous reports. *** |
|---|---|---|---|---|
| **Metabolism and Nutrition Disorders** | Appetite decreased. | Anorexia (loss of appetite). | | |
| **Psychiatric Disorders** | | Irritability, mood swings, insomnia[3]. | Suicide-related events, aggression, hostility, emotional lability ** Early morning awakening. | Psychosis (including hallucinations),** agitation** |
| **Nervous System Disorders** | Headache, somnolence[2] | Dizziness. | Syncope, tremor, migraine | Seizure*** |
| **Eye Disorders** | | | Mydriasis. | |
| **Cardiac Disorders** | | | Palpitations, sinus tachycardia. | QT interval prolongation*** |
| **Vascular disorders** | | | | Raynaud's phenomenon |
| **Gastrointestinal Disorders** | Abdominal pain[1], vomiting, nausea. | Constipation, dyspepsia, | | |
| **Hepatobiliary disorders** | | | | Abnormal liver function tests, jaundice, hepatitis. ** |
| **Skin and Subcutaneous Tissue Disorders** | | Dermatitis, Rash | Pruritus, hyperhidrosis, Allergic reactions | |
| **Renal and urinary disorders** | | | | Urinary hesitation, urinary retention |
| **Reproductive System and Breast Disorders** | | | | Priapism, male genital pain. |
| **General Disorders and Administration Site Conditions** | | Fatigue, lethargy | Asthenia | |
| **Investigations** | | Weight decreased, | | |

| | | | | |
|---|---|---|---|---|
| | | blood pressure increased. | | |

[1]Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort.
[2] Also includes sedation
[3] Also includes initial insomnia and middle insomnia
* These reports are derived from spontaneous event reporting and it is not possible to determine frequency accurately.
** See section 4.4
*** See section 4.4 and section 4.5

CYP2D6 poor metabolisers (PM)

The following adverse events occurred in at least 2% of CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: appetite decreased (24.1% of PMs, 17.0% of EMs); insomnia combined (including insomnia, middle insomnia and initial insomnia, 14.9% of PMs, 9.7% of EMs); depression combined (including depression, major depression, depressive symptom, depressed mood and dysphoria, 6.5% of PMs and 4.1% of EMs), weight decreased (7.3% of PMs, 4.4% of EMs), constipation 6.8% of PMs, 4.3% of EMs); tremor (4.5% of PMs, 0.9% of EMs); sedation (3.9% of PMs, 2.1% of EMs); excoriation (3.9% of PMs, 1.7% of EMs); enuresis (3.0% of PMs, 1.2% of EMs); conjunctivitis (2.5% of PMs, 1.2% of EMs); syncope (2.5% of PMs, 0.7% of EMs); early morning awakening (2.3% of PMs, 0.8% of EMs); mydriasis (2.0% of PMs, 0.6% of EMs). The following event did not meet above criteria but is noteworthy: generalised anxiety disorder (0.8% of PMs and 0.1% of EMs). In addition, in trials lasting up to 10 weeks, weight loss was more pronounced in PM patients (mean of 0.6 kg in EM and 1.1kg in PM).

Adults:

In adults, the adverse events reported most frequently with atomoxetine treatment were gastrointestinal and insomnia. A complaint of urinary retention or urinary hesitancy in adults should be considered potentially related to atomoxetine. No serious safety concerns were observed during acute or long term treatment.
The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials in adults and spontaneous reporting from children/adolescents and adults post marketing.

*Table: Adverse reactions*
Frequency estimate: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), data from spontaneous reports (frequency not known – cannot be estimated from the available data).

| **System Organ Class** | **Very common** | **Common** | **Uncommon** | **Post-marketing experience Spontaneous reports. *** |
|---|---|---|---|---|
| **Metabolism and Nutrition Disorders** | Appetite decreased. | | | |
| **Psychiatric Disorders** | Insomnia[2] | Libido decreased, sleep disorder. | Early morning awakening, | Suicide-related events, aggression, hostility and emotional lability,** psychosis (including hallucinations),** agitation** |
| **Nervous System** | | Dizziness, sinus | Syncope, migraine | Seizure*** |

| | | | | |
|---|---|---|---|---|
| **Disorders** | | headache, paraesthesia, tremor. | | |
| **Cardiac Disorders** | | Palpitations, tachycardia. | | QT interval prolongation, *** |
| **Vascular disorders** | | Hot flushes. | Peripheral coldness | Raynaud's phenomenon |
| **Gastrointestinal Disorders** | Dry mouth, nausea. | Abdominal pain[1], constipation, dyspepsia, flatulence | | |
| **Hepato-biliary disorders** | | | | Abnormal liver function tests, jaundice, hepatitis. ** |
| **Skin and Subcutaneous Tissue Disorders** | | Dermatitis,hyperhidrosis, rash. | Allergic reactions | |
| **Renal and urinary disorders** | | Dysuria, urinary hesitation, urinary retention | | |
| **Reproductive System and Breast Disorders** | | Dysmenorrhoea, ejaculation disorder, erectile dysfunction, menstruation irregular, orgasm abnormal, prostatitis, male genital pain. | Ejaculation failure | Priapism |
| **General Disorders and Administration Site Conditions** | | Fatigue, lethargy, chills. | | |
| **Investigations** | | Weight decreased | Blood pressure increased | |

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

[2] Also includes initial insomnia and middle insomnia

* These reports are derived from spontaneous event reporting and it is not possible to determine frequency accurately

** See section 4.4

*** See section 4.4 and section 4.5

## 4.9 Overdose

Signs and symptoms:

During postmarketing, there have been reports of non-fatal acute and chronic overdoses of atomoxetine alone. The most commonly reported symptoms accompanying acute and chronic overdoses were somnolence, agitation, hyperactivity, abnormal behaviour, and gastrointestinal symptoms. Most events were mild to moderate. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g., mydriasis, tachycardia, dry mouth) were also observed and reports of pruritis and rash have been received. All patients recovered from these events. In some cases of overdose involving atomoxetine, seizures have been reported and very rarely QT prolongation. There have also been reports of fatal, acute overdoses involving a mixed ingestion of atomoxetine and at least one other drug.

There is limited clinical trial experience with atomoxetine overdose. No fatal overdoses occurred in clinical trials.

Management of Overdose:
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 atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Centrally acting sympathomimetics
ATC code: N06BA09

Atomoxetine is a highly selective and potent inhibitor of the pre-synaptic noradrenaline transporter, its presumed mechanism of action, without directly affecting the serotonin or dopamine transporters. Atomoxetine has minimal affinity for other noradrenergic receptors or for other neurotransmitter transporters or receptors. Atomoxetine has two major oxidative metabolites: 4-hydroxyatomoxetine and N-desmethylatomoxetine. 4-Hydroxyatomoxetine is equipotent to atomoxetine as an inhibitor of the noradrenaline transporter but unlike atomoxetine, this metabolite also exerts some inhibitory activity at the serotonin transporter. However, any effect on this transporter is likely to be minimal as the majority of 4-hydroxyatomoxetine is further metabolised such that it circulates in plasma at much lower concentrations (1% of atomoxetine concentration in extensive metabolisers and 0.1% of atomoxetine concentration in poor metabolisers). N-Desmethylatomoxetine has substantially less pharmacological activity compared with atomoxetine. It circulates in plasma at lower concentrations in extensive metabolisers and at comparable concentrations to the parent drug in poor metabolisers at steady state.

Atomoxetine is not a psychostimulant and is not an amphetamine derivative. In a randomised, double-blind, placebo-controlled, abuse-potential study in adults comparing effects of atomoxetine and placebo, atomoxetine was not associated with a pattern of response that suggested stimulant or euphoriant properties.

Strattera has been studied in trials in over 5000 children and adolescents with ADHD. The acute efficacy of Strattera in the treatment of ADHD was initially established in six randomised, double-blind, placebo-controlled trials of six to nine weeks duration. Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for Strattera treated and placebo treated patients. In each of the six trials, atomoxetine was statistically significantly superior to placebo in reducing ADHD signs and symptoms.

Additionally, the efficacy of atomoxetine in maintaining symptom response was demonstrated in a 1 year, placebo-controlled trial with over 400 patients, primarily conducted in Europe (approximately 3 months of open label acute treatment followed by 9 months of double-blind, placebo-controlled maintenance treatment). The proportion of patients relapsing after 1 year was 18.7% and 31.4% (atomoxetine and placebo, respectively). After 1 year of atomoxetine treatment, patients who continued atomoxetine for 6 additional months were less likely to relapse or to experience partial symptom return compared with patients who discontinued active treatment and switched to placebo (2% vs. 12% respectively). For children and adolescents periodic assessment of the value of ongoing treatment during long-term treatment should be performed.

Strattera was effective as a single daily dose and as a divided dose administered in the morning, and late afternoon/early evening. Strattera administered once daily demonstrated statistically significantly greater reduction in severity of ADHD symptoms compared with placebo as judged by teachers and parents.

Atomoxetine does not worsen tics in patients with ADHD and comorbid chronic motor tics or Tourette's Disorder.

536 adult patients with ADHD were enrolled in 2 randomised, double-blind, placebo-controlled clinical studies of 10 weeks duration.
Patients received STRATTERA twice daily titrated according to clinical response in a range of 60 to 120 mg/day. The mean final dose of STRATTERA for both studies was approximately 95 mg/day. In both studies, ADHD symptoms were statistically significantly improved on STRATTERA, as measured on the ADHD Symptom score from the CAARS scale. Magnitude of symptom improvement in adults was less than that observed in children. Long-term

maintenance of effect in adults has not been shown.

## 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 6 years of age.

Absorption: Atomoxetine is rapidly and almost completely absorbed after oral administration, reaching mean maximal observed plasma concentration ($C_{max}$) approximately 1 to 2 hours after dosing. The absolute bioavailability of atomoxetine following oral administration ranged from 63% to 94% depending upon inter-individual differences in the modest first pass metabolism. Atomoxetine can be administered with or without food.

Distribution: Atomoxetine is widely distributed and is extensively (98%) bound to plasma proteins, primarily albumin.

Biotransformation: Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway. Individuals with reduced activity of this pathway (poor metabolisers) represent about 7% of the Caucasian population and, have higher plasma concentrations of atomoxetine compared with people with normal activity (extensive metabolisers). For poor metabolisers, AUC of atomoxetine is approximately 10-fold greater and Css, max is about 5- fold greater than extensive metabolisers. The major oxidative metabolite formed is 4-hydroxyatomoxetine that is rapidly glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine but circulates in plasma at much lower concentrations. Although 4-hydroxyatomoxetine is primarily formed by CYP2D6, in individuals that lack CYP2D6 activity, 4-hydroxyatomoxetine can be formed by several other cytochrome P450 enzymes, but at a slower rate. Atomoxetine does not inhibit or induce CYP2D6 at therapeutic doses.

Elimination: The mean elimination half-life of atomoxetine after oral administration is 3.6 hours in extensive metabolisers and 21 hours in poor metabolisers. Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-*O*-glucuronide, mainly in the urine.
Linearity/non-linearity: pharmacokinetics of atomoxetine are linear over the range of doses studied in both extensive and poor metabolisers.

Special populations.

Hepatic impairment results in a reduced atomoxetine clearance, increased atomoxetine exposure (AUC increased 2-fold in moderate impairment and 4-fold in severe impairment), and a prolonged half-life of parent drug compared to healthy controls with the same CYP2D6 extensive metaboliser genotype. In patients with moderate to severe hepatic impairment (Child Pugh Class B and C) initial and target doses should be adjusted (see section 4.2).

Atomoxetine mean plasma concentrations for end stage renal disease (ESRD) subjects were generally higher than the mean for healthy control subjects shown by $C_{max}$ (7% difference) and $AUC_{0-\infty}$ (about 65% difference) increases. After adjustment for body weight, the differences between the two groups are minimized. Pharmacokinetics of atomoxetine and its metabolites in individuals with ESRD suggest that no dose adjustment would be necessary (see section 4.2)**.**

## 5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, or reproduction and development. Due to the dose limitation imposed by the clinical (or exaggerated pharmacological) response of the animals to the drug combined with metabolic differences among species, maximum tolerated doses in animals used in nonclinical studies produced atomoxetine exposures similar to or slightly above those that are achieved in CYP2D6 poor metabolizing patients at the maximum recommended daily dose.
A study was conducted in young rats to evaluate the effects of atomoxetine on growth and neurobehavioral and sexual development. Slight delays in onset of vaginal patency (all doses) and preputial separation (≥10mg/kg/day) and slight decreases in epididymal weight and sperm number (≥10mg/kg/day) were seen; however, there were no effects on fertility or reproductive performance. The significance of these findings to humans is unknown.

Pregnant rabbits were treated with up to 100 mg/kg/day of atomoxetine by gavage throughout the period of organogenesis. At this dose, in 1 of 3 studies, decrease in live fetuses, increase in early resorption, slight increases in the incidences of atypical origin of carotid artery and absent subclavian artery were observed. These findings were observed at doses that caused slight maternal toxicity. The incidence of these findings is within historical control values. The no-effect dose for these findings was 30 mg/kg/day. Exposure (AUC) to unbound atomoxetine in rabbits, at 100mg/kg/day was approximately 3.3 times (CYP2D6 extensive metabolisers) and 0.4 times (CYP2D6 poor metabolisers) those in humans at the maximum daily dose of 1.4mg/kg/day. The findings in one of three rabbit studies were equivocal and the relevance to man is unknown.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

The capsules contain:
Starch, pregelatinised (Maize)
Dimeticone

Capsule shell:
Sodium laurilsulfate
Gelatin
Edible Black Ink SW-9008 or Edible Black Ink SW-9010
(containing Shellac and Black Iron Oxide (E172))

Capsule Shell Cap colourants:
Yellow iron oxide (E172)

Capsule Shell Body colourants:
Yellow iron oxide (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf Life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

Polyvinyl chloride (PVC)/polyethylene (PE)/Polychlorotrifluoroethylene (PCTFE) blister sealed with aluminium foil lid.
Available in pack sizes of 7, 14, 28 and 56 capsules.
Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Atomoxetine capsules are not intended to be opened. Atomoxetine is an ocular irritant. In the event of capsule 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 MARKETING AUTHORISATION HOLDER

Eli Lilly and Company Limited
Lilly House
Priestley Road
Basingstoke
Hampshire RG24 9NL
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER

PA 47/95/1

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th February 2006

Date of last renewal: 27th May 2009

## 10 DATE OF REVISION OF THE TEXT

October 2009