Public Assessment Report

Decentralised

Strattera 80mg hard capsules
Strattera 100mg hard capsules

Atomoxetine hydrochloride

UK/H/0686/07-08/DC

Eli Lilly and Company Limited UK
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Eli Lilly and Company UK Ltd, Strattera 80mg and 100mg Hard Capsules
# Module 1

| **Product Name** | Strattera 80mg Hard Capsules  
|                 | Strattera 100mg Hard Capsules |
| **Type of Application** | Standard Abridged Decentralised (Article 8.3) |
| **Active Substance (INN)** | Amtonoxetine hydrochloride |
| **Pharmacotherapeutic Classification (ATC)** | Centrally acting sympathomimetics ATC-code N06BA9 |
| **Pharmaceutica Form and Strength** | Capsules, hard  
|                | 80 and 100mg |
| **Procedure Numbers** | UK/H/686/07-08/DC |
| **RMS** | UK |
| **CMS** | AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, HU, IE, IS, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK. |
| **Start Date** | 15/10/2007 |
| **End Date** | 05/06/2008 |
| **MA Number** | PL 00006/0615-6 |
| **Name and address of MA holder** | Eli Lilly and Company Limited  
| | Lilly House, Priestley Road  
| | Basingstoke, Hampshire  
| | RG24 9NL  
| | United Kingdom |
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
STRATTERA 80 mg hard capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
The active substance is atomoxetine hydrochloride. Each STRATTERA 80 mg capsule contains atomoxetine hydrochloride equivalent to 80 mg of atomoxetine. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard
STRATTERA 80 mg capsules are opaque brown (cap) and opaque white (body), imprinted with “Lilly 3250” and “80 mg” 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 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. 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. Elderly patients: not applicable.

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.

Many patients taking atomoxetine experience a modest increase in pulse (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) (see 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 section 4.5 Interactions and 4.8 Undesirable 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 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 attempts and suicidal ideation) has been reported in patients treated with atomoxetine. In double blind clinical trials, suicide related behaviours occurred at a frequency of 0.44% in atomoxetine treated patients (6 out of 1357 patients treated, one case of suicide attempt and five of suicidal ideation). There were no events in the placebo group (n=851). The age range of children experiencing these events was 7 to 12 years. It should be noted that the number of adolescent patients included in the clinical trials was low. 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 who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide related behaviour, hostility and emotional lability.
As with other psychotropic medication, the possibility of rare, serious psychiatric adverse effects cannot be excluded. 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. 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 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 beta₂ agonists) because the action of salbutamol on the cardiovascular system can be potentiated.

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 antiarrhythmics, 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, bupropion 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 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:
Abdominal pain and decreased appetite are the adverse events most commonly associated with atomoxetine, and are reported by about 18% and 16% of patients respectively, but seldom lead to drug discontinuation (discontinuation rates are 0.3% for abdominal pain and 0.0% for decreased appetite). These effects 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 4.4.).

Nausea or vomiting can occur in about 9% and 11% of patients respectively, 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 rate 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 6 beats/minute and mean increases in systolic (about 3 mm Hg) and
diastolic (about 1 mm Hg) blood pressures compared with placebo.

Because of its effect on noradrenergic tone, orthostatic hypotension (0.2%, N=7) and
syncope (0.8%, N=26) 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 (≥10%), common (≥1% and <10%), uncommon
(≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%), data from
spontaneous reports (frequency not known)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Post marketing experience Spontaneous reports. *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td>Influenza (ie, cold/flu symptoms).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Appetite decreased.</td>
<td>Anorexia (loss of appetite).</td>
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<tr>
<td>Psychiatric Disorders</td>
<td>Early morning awakening, irritability, mood swings.</td>
<td>Suicide-related events, aggression, hostility, emotional lability **</td>
<td></td>
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</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Dizziness, somnolence.</td>
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<tr>
<td>Eye Disorders</td>
<td>Mydriasis.</td>
<td>Palpitations, sinus tachycardia.</td>
<td>QT interval prolongation***</td>
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<tr>
<td>Cardiac Disorders</td>
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<td></td>
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<tr>
<td>Vascular disorders</td>
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<td></td>
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<td></td>
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<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain, vomiting.</td>
<td>Constipation, dyspepsia, nausea.</td>
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<tr>
<td>Hepatobiliary disorders</td>
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<td></td>
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<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
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<td>Dermatitis, pruritus, rash.</td>
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<td>Reproductive System and Breast Disorders</td>
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Eli Lilly and Company UK Ltd, Strattera 80mg and 100mg Hard Capsules
General Disorders and Administration Site Conditions

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Fatigue.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
</tr>
</tbody>
</table>

* 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 either twice as frequent or 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 (10.5% of PMs, 6.8% of EMs);
- Middle insomnia (3.8% of PMs, 1.5% of EMs);
- Enuresis (3.0% of PMs, 1.2% of EMs);
- Depressed mood (3.0% of PMs, 1.0% of EMs);
- Tremor (5.1% of PMs, 1.1% of EMs);
- Early morning awakening (3.0% of PMs, 1.1% of EMs);
- Conjunctivitis (3.0% of PMs, 1.5% of EMs);
- Syncope (2.1% of PMs, 0.7% of EMs);
- Mydriasis (2.5% of PMs, 0.7% of EMs).

The following events did not meet above criteria but were reported by more PM patients than EM patients:
- Anxiety (2.5% of PMs, 2.2% of EMs);
- Depression (2.5% of PMs, 1.9% 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 1.1 kg in PM).

**Adults:**

In adults, the adverse events reported most frequently with atomoxetine treatment were gastrointestinal or genitourinary. 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 (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%), data from spontaneous reports (frequency not known)
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Post-marketing experience Spontaneous reports. *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Appetite decreased.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Early morning awakening, libido decreased, sleep disorder.</td>
<td></td>
<td>Suicide-related events, aggression, hostility and emotional lability**</td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Insomnia.</td>
<td>Dizziness, middle insomnia, sinus headache.</td>
<td></td>
<td>Seizure***</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Palpitations, tachycardia.</td>
<td></td>
<td>QT interval prolongation** ***</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flushes.</td>
<td>Peripheral coldness</td>
<td>Raynaud’s phenomenon</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Dry mouth, nausea.</td>
<td>Abdominal pain, constipation, dyspepsia, flatulence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
<td>Abnormal liver function tests, jaundice, hepatitis. **</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Dermatitis, sweating increased.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Difficulty in micturition, urinary hesitation, urinary retention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>Dysmenorrhoea, ejaculation disorder, ejaculation failure, erectile disturbance, impotence, menstruation irregular, orgasm abnormal, prostatitis,</td>
<td></td>
<td>Priapism</td>
<td></td>
</tr>
</tbody>
</table>
**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 pruritus 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.

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**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).
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 involving over 4000 children and adolescents with ADHD. The acute efficacy of Strattera in the treatment of ADHD was 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 Cmax (7% difference) and AUC0-∞ (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 (≥10mg/kg/day) 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:
80 mg: Yellow iron oxide E172, Red iron oxide E172, Titanium dioxide E171

Capsule Shell Body colourants:
80 mg: Titanium dioxide E 171

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**
Atomoxetine capsules are not intended to be opened. Atomoxetine is an ocular irritant. In the event of 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 **MARKETING AUTHORISATION HOLDER**
Eli Lilly and Company Limited
Lilly House, Priestley Road,
Basingstoke, Hampshire,
RG24 9NL,
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 00006/0615

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
05/06/2008

10 **DATE OF REVISION OF THE TEXT**
05/06/2008
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
STRATTERA 100 mg hard capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
The active substance is atomoxetine hydrochloride. Each STRATTERA 100 mg capsule contains atomoxetine hydrochloride equivalent to 100 mg of atomoxetine. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard
STRATTERA 100 mg capsules are opaque brown, imprinted with “Lilly 3251” and “100 mg” 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 1.2 mg/kg/day. The safety of single doses over 1.8 mg/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 80 mg. No additional benefit has been demonstrated for doses higher than 80 mg (see 5.1). The maximum recommended total daily dose is 100 mg. The safety of single doses over 120 mg and total daily doses above 150 mg 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.

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.

Elderly patients: not applicable.
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.

Many patients taking atomoxetine experience a modest increase in pulse (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) (see 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 section 4.5 Interactions and 4.8 Undesirable 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 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 attempts and suicidal ideation) has been reported in patients treated with atomoxetine. In double blind clinical trials, suicide related behaviours occurred at a frequency of 0.44% in atomoxetine treated patients (6 out of 1357 patients treated, one case of suicide attempt and five of suicidal ideation). There were no events in the placebo group (n=851). The age range of children experiencing these events was 7 to 12 years. It should be noted that the number of adolescent patients included in the clinical trials was low. 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 who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide related behaviour, hostility and emotional lability. As with other psychotropic medication, the possibility of rare, serious psychiatric adverse effects cannot be excluded. 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.
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 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 beta2 agonists) because the action of salbutamol on the cardiovascular system can be potentiated.

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 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:
Abdominal pain and decreased appetite are the adverse events most commonly associated with atomoxetine, and are reported by about 18% and 16% of patients respectively, but seldom lead to drug discontinuation (discontinuation rates are 0.3% for abdominal pain and 0.0% for decreased appetite). These effects 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 4.4.).

Nausea or vomiting can occur in about 9% and 11% of patients respectively, 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 rate 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 6 beats/minute and mean increases in systolic (about 3 mm Hg) and diastolic (about 1 mm Hg) blood pressures compared with placebo.

Because of its effect on noradrenergic tone, orthostatic hypotension (0.2%, N=7) and syncope (0.8%, N=26) 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 (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%), data from spontaneous reports (frequency not known)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Post marketing experience Spontaneous reports. *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td>Influenza (ie, cold/flu symptoms).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Appetite decreased.</td>
<td>Anorexia (loss of appetite).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Early morning awakening, irritability, mood swings.</td>
<td>Suicide-related events, aggression, hostility, emotional lability **</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Dizziness, somnolence.</td>
<td></td>
<td>Seizure***</td>
<td></td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Mydriasis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td>Palpitations, sinus tachycardia.</td>
<td>QT interval prolongation***</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td>Raynaud’s phenomenon</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Abdominal pain, vomiting.</td>
<td>Constipation, dyspepsia, nausea.</td>
<td>Abnormal liver function tests, jaundice, hepatitis. **</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Dermatitis, pruritus, rash.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td></td>
<td></td>
<td>Priapism</td>
<td></td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
* 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 either twice as frequent or 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 (10.5% of PMs, 6.8% of EMs); middle insomnia (3.8% of PMs, 1.5% of EMs); enuresis (3.0% of PMs, 1.2% of EMs); depressed mood (3.0% of PMs, 1.0% of EMs); tremor (5.1% of PMs, 1.1% of EMs); early morning awakening (3.0% of PMs, 1.1% of EMs); conjunctivitis (3.0% of PMs, 1.5% of EMs); syncope (2.1% of PMs, 0.7% of EMs); mydriasis (2.5% of PMs, 0.7% of EMs). The following events did not meet above criteria but were reported by more PM patients than EM patients: anxiety (2.5% of PMs, 2.2% of EMs); depression (2.5% of PMs, 1.9% 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 1.1 kg in PM).

**Adults:**
In adults, the adverse events reported most frequently with atomoxetine treatment were gastrointestinal or genitourinary. 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 (≥10%), common (≥1% and <10%), uncommon (≥0.1% and <1%), rare (≥0.01% and <0.1%), very rare (<0.01%), data from spontaneous reports (frequency not known)
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Post-marketing experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Appetite decreased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Early morning awakening, libido decreased, sleep disorder.</td>
<td></td>
<td></td>
<td>Suicide-related events, aggression, hostility and emotional instability**</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Insomnia.</td>
<td>Dizziness, middle insomnia, sinus headache.</td>
<td></td>
<td>Seizure***</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Palpitations, tachycardia.</td>
<td></td>
<td></td>
<td>QT interval prolongation**, ***</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flushes.</td>
<td>Peripheral coldness</td>
<td></td>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Dry mouth, nausea.</td>
<td>Abdominal pain, constipation, dyspepsia, flatulence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td></td>
<td></td>
<td>Abnormal liver function tests, jaundice, hepatitis. **</td>
<td></td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td></td>
<td>Dermatitis, sweating increased.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td>Difficulty in micturition, urinary hesitation, urinary retention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>Dysmenorrhoea, ejaculation disorder, ejaculation failure, erectile disturbance, impotence, menstruation irregular, orgasm abnormal, prostatitis,</td>
<td></td>
<td></td>
<td>Priapism</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue, lethargy, rigors.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* These reports are derived from spontaneous event reporting and it is not possible to determine frequency accurately
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 involving over 4000 children and adolescents with ADHD. The acute efficacy of Strattera in the treatment of ADHD was 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 Cmax (7% difference) and AUC0-∞ (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:
100 mg: Yellow iron oxide E172, Red iron oxide E172, Titanium dioxide E171

Capsule Shell Body colourants:
100 mg: Yellow iron oxide E172, Red iron oxide E172, Titanium dioxide E171

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
Atomoxetine capsules are not intended to be opened. Atomoxetine is an ocular irritant. In the event of 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 MARKETING AUTHORISATION HOLDER
Eli Lilly and Company Limited
Lilly House, Priestley Road,
Basingstoke, Hampshire,
RG24 9NL,
United Kingdom

8  MARKETING AUTHORISATION NUMBER(S)
   PL 00006/0616

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE
    AUTHORISATION
   05/06/2008

10 DATE OF REVISION OF THE TEXT
    05/06/2008
Module 3

Product Information Leaflet
PACKAGE LEAFLET: INFORMATION FOR THE USER

Strattera 5, 10, 18, 25, 40, 60, 80 and 100 mg hard capsules
Atomoxetine Hydrochloride

Read all of this leaflet carefully before you (or a child in your care) starts taking this medicine.
- Keep this leaflet in a safe place. You may need to read it again.
- If you have any further questions, please ask your doctor or pharmacist.
- This medicine has been prescribed for you or your child. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In the next sections, the word You means You or a child in your care.

In this leaflet:
1. What Strattera is and what it is used for
2. Before you take Strattera
3. How to take Strattera
4. Possible side effects
5. How to store Strattera
6. Further information

1. WHAT STRATTERA IS AND WHAT IT IS USED FOR

Strattera is a non-stimulant medicine used to treat attention-deficit and hyperactivity disorder (ADHD) in children over six years of age and in adolescents, as part of a comprehensive treatment programme which can include psychological, educational and social measures.

Strattera contains atomoxetine, which increases the amount of noradrenaline in the brain. This is a chemical in the brain that is produced naturally, which increases attention and decreases impulsiveness and hyperactivity in patients with ADHD. This medicine has been prescribed to help control the symptoms of ADHD. Strattera has not been shown to be addictive.

It may take a few weeks after you start Strattera for your symptoms to fully improve.

When treatment has started already at a younger age it might be appropriate to continue taking Strattera when you become an adult. Your specialist will advise you about this.

2. BEFORE YOU TAKE STRATTERA

Do not take Strattera
- if you are allergic (hypersensitive) to atomoxetine or any of the other ingredients of Strattera
- if you took a medicine known as a monoamine oxidase inhibitor (MAOI), for example phenelzine, in the last two weeks. An MAOI is sometimes used for depression and other
mental-health problems; taking Strattera with an MAOI could cause serious side effects or be life-threatening. (You also need to wait at least 14 days after you stop taking Strattera before you take an MAOI).
- if you have an eye disease called narrow-angle glaucoma (increased pressure in your eye).

**Take special care with Strattera**

Talk to your doctor before taking Strattera
- if you have or had liver problems. You may need a lower dose.
- if you have high blood pressure. Strattera can increase blood pressure.
- if you have problems with your heart or an increased heartbeat. Strattera can increase your heart rate (pulse).
- if you have low blood pressure. Strattera can cause dizziness or fainting in people with low blood pressure.
- if you have a cardiovascular disease or past medical history of stroke.
- if you have a history of epilepsy or have had seizures for any other reason. Strattera might lead to an increase in seizure frequency.

**Taking other medicines**

Please tell your doctor or pharmacist about all the medicines you are taking, have recently taken or plan to take, including prescription and non-prescription medicines, dietary supplements and herbal remedies. Your doctor will decide if you can take Strattera with your other medicines.

Strattera should not be used with medicines called MAOI’s (monoamine oxidase inhibitors). See section “Do not take Strattera”.

If you take Strattera at the same time as some other medicines (see examples below), the treatment with these medicines or Strattera may be affected and so caution is needed.
- medicines that increase blood pressure. Strattera can alter blood pressure.
- medicines that alter noradrenaline such as antidepressants, for example imipramine, venlafaxine and mirtazapine, or decongestants such as pseudoephedrine or phenylephrine. Strattera also alters noradrenaline.
- some medicines used to treat mental health conditions (such as antipsychotics, lithium for manic depression and tricyclic antidepressants), medicines used to control the rhythm of the heart (such as quinidine and amiodarone), medicines which change the concentration of salts in the blood (water pills such as thiazide diuretics), meclofenoxate, mefloquine (for malaria prevention and treatment) and some antibiotics (such as erythromycin and moxifloxacin). These medicines may lead to an increased risk of an abnormal rhythm of the heart when taken with Strattera.
- medications that are known to increase the risk of seizures. These can include antidepressants, some antipsychotic medicines, bupropion (for smoking cessation), antimalarial tablets and some painkillers (such as tramadol). Taking Strattera might lead to an increase in seizure frequency.

The way in which Strattera is broken down in the body can be affected by other medicines and can mean that Strattera can stay in the body for longer than normal. Examples of medications that can do this include some antidepressants e.g fluoxetine and paroxetine or other medications such
as quinidine and terbinafine. Your doctor may need to adjust your dose or increase your dose much more slowly.

Strattera may change the way your body reacts to salbutamol (a medicine to treat asthma) and other similar medicines. If you are taking salbutamol by a nebuliser, or by mouth (for example syrps or tablets), or having a salbutamol injection together with Strattera, you may feel as if your heart is racing, but this will not make your asthma worse. Talk to your doctor before taking Strattera if you are taking salbutamol by a nebuliser or by mouth, or having salbutamol injections. You do not need to worry if you are using only an inhaler.

**Pregnancy and breastfeeding**
- If you think you might be pregnant or are planning to become pregnant, speak to your doctor or pharmacist before you take Strattera.
- Strattera should not be used during pregnancy, unless your doctor has advised you to do so.
- It is not known if Strattera can pass into breast milk. Therefore you should either avoid taking Strattera if you are breastfeeding or discontinue breastfeeding. If you are breastfeeding or planning to breastfeed your baby, ask your doctor or pharmacist for advice before taking Strattera.

**Driving and using machines**
You may feel tired or sleepy after taking Strattera. You should be careful if you are driving a car or operating heavy machinery until you know how Strattera affects you. If you feel tired or sleepy you should not drive or operate hazardous machinery.

**Important information about the content of the capsules**
Strattera capsules are not intended to be opened. Strattera can irritate the eye. In the event of the contents of the capsules coming into contact with the eye, the affected eye should be flushed immediately with water, and medical advice obtained. Hands and any other part of the body that may have come into contact with the capsule contents should also be washed as soon as possible.

3. **HOW TO TAKE STRATTERA**
- You should take Strattera as your doctor has instructed you. This is usually one or two times a day (morning and late afternoon or early evening).
- You can take Strattera with or without food.
- Taking Strattera at the same time each day may help you remember to take it.

Your doctor will tell you how much Strattera you should take and will calculate this according to your weight. He/she will normally start you on a lower dose before increasing the amount of Strattera you need to take according to the instructions below:

**Children (6 years of age and older) and adolescents:**
- Body weight up to 70kg: Strattera should be started at a total daily dose of approximately 0.5mg per kilogram of body weight. This dose should be continued for a minimum of 7 days. Your doctor may then decide to increase this to a usual maintenance dose of approximately 1.2mg per kilogram of body weight daily.
- Body weight over 70kg: Strattera should be started at a total daily dose of 40 mg. This dose should be continued for a minimum of 7 days. Your doctor may then decide to
increase this to a usual maintenance dose of 80mg daily. The maximum daily dose your 
doctor will prescribe is 100 mg.

If you have problems with your liver your doctor may prescribe a smaller dose.

A child taking Strattera may start to lose a little weight after starting treatment. Your doctor will 
watch your child’s height and weight. If your child is not growing or gaining weight as expected, 
your doctor may change your child’s dose or decide to stop Strattera temporarily.

Strattera is not recommended for children under six years of age.

**If you take more Strattera than you should** contact your doctor or the nearest hospital casualty 
department immediately and tell them how many capsules you have taken. The most commonly 
reported symptoms accompanying overdoses were sleepiness, agitation, hyperactivity, abnormal 
behaviour and gastrointestinal symptoms.

**If you forget to take Strattera**
If you miss a dose, you should take it as soon as possible, but you should not take more than your 
total daily dose in any 24-hour period. Do not take a double dose to make up for forgotten doses.

**If you stop taking Strattera**
If you stop taking Strattera there are not normally any side effects, but you should talk to your 
doctor first before you stop treatment.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Strattera can cause side effects, although not everybody gets them.

Although uncommon (less than 1 in 100 patients) Strattera can cause a serious allergic 
reaction. You should stop taking Strattera and call your doctor or hospital immediately if 
you have any of the following:
- swelling of the face and throat
- difficulty breathing
- hives (small raised, itchy patches of skin)

Very rarely (less than 1 in 10,000 patients), there have been reports of liver injury. You 
should stop taking Strattera and call your doctor immediately if you have any of the 
following:
- dark urine
- yellow skin or yellow eyes
- tummy pain which is sore when you press it (tenderness) on the right side just below your 
ribs
- a feeling of sickness (nausea) that is unexplained
- tiredness
- itching
- feeling that you are coming down with flu.

These symptoms should not be ignored as they may be the start of something more serious.

Patients under 18 have an increased risk of side effects such as:
- suicidal thoughts
- hostility (predominantly aggression, oppositional behaviour and anger)
- emotional lability

You should inform your doctor if any of the symptoms listed above develop or worsen after treatment has begun. Also you should know that as with other psychotropic medication, there is a possibility of rare, serious psychiatric adverse effects. The long-term effects on growth, maturation and cognitive and behavioural development of Strattera in this age group have not yet been demonstrated.

There have been reports in some patients of abnormal rhythms of the heart, which can be serious, and also seizures. You should contact your doctor if you suspect a heart problem or have a seizure.

**Side effects reported in clinical trials of Strattera in teenagers and children over six years old**

Very common side effects (in more than 1 in 10 patients) are:
- decreased appetite (not feeling hungry)
- being sick (vomiting)
- pain in the stomach (abdomen)

These effects usually disappear after a while.

Other common side effects (in more than 1 in 100 patients) may be:
- cold/flu like-symptoms
- loss of appetite
- waking early
- being irritable
- mood swings
- dizziness
- sleepiness
- large pupils (the dark centre of the eye)
- constipation
- upset stomach
- feeling sick (nausea)
- swollen, reddened and itchy skin
- tiredness
- weight loss

**Side effects which have been seen, but are uncommon (in less than 1 in 100 patients), are:**
- feeling or having a very fast heartbeat.
- suicidal thoughts or suicidal attempt
- aggression
- hostility
- emotional lability

Please see the advice above on what to do if these side effects should occur.

**Side effects reported in clinical trials of Strattera in adults**

Very common side effects (in more than 1 in 10 patients) are:
- decreased appetite (not feeling hungry)
- problems sleeping
- dry mouth
Other common side effects (in more than 1 in 100 patients) may be:
- feeling sick (nausea)
- waking early
- sleep disturbance
- dizziness
- headaches
- constipation
- stomach ache
- indigestion
- flatulence
- hot flushes
- feeling or having a very fast heartbeat
- swollen, reddened and itchy skin
- increased sweating
- problems going to the toilet (urinating)
- inflammation of the prostate gland (prostatitis)
- failure to obtain an erection
- difficulty maintaining an erection
- absence of orgasm
- abnormal orgasm
- menstrual cramps and irregular menstruation
- tiredness
- lethargy
- stiffness
- weight loss

A side effect which has been seen, but is uncommon (less than 1 in 100 patients), is:
- cold fingers and toes.

Other possible side effects:
- prolonged and painful erections
- poor blood circulation which makes toes and fingers numb and pale (Raynaud’s)

If you experience any of these side effects and they become troublesome or get worse, or if you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE STRATTERA

This medicinal product does not require any special storage conditions.

Do not use after the expiry date stated on the carton and blister after ‘Exp’. The expiry date refers to the last day of that month.

Keep out of the reach and sight of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. FURTHER INFORMATION

What Strattera 5, 10, 18, 25, 40, 60, 80 and 100 mg hard capsules contain
- The active substance in Strattera capsules is atomoxetine hydrochloride. Each capsule contains atomoxetine hydrochloride equivalent to 5 mg, 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg or 100 mg of atomoxetine.
- The other ingredients are pregelatinised starch and dimeticone.
- The capsule shells contain sodium laurilsulfate, gelatin and edible black ink (containing shellac and black iron oxide E172). The capsule shell colourants are:
  - Yellow iron oxide E172 (5 mg, 18 mg, 60 mg, 80 mg and 100 mg)
  - Titanium dioxide E171 (10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg)
  - FD&C blue 2 (indigo carmine) E132 (25 mg, 40 mg and 60 mg)
  - Red iron oxide E172 (80 mg and 100mg)

What Strattera looks like and contents of the pack
Capsules 5 mg (gold, imprinted Lilly 3226/5 mg)
Capsules 10 mg (white, imprinted Lilly 3227/10 mg)
Capsules 18 mg (gold/white, imprinted Lilly 3238/18 mg)
Capsules 25 mg (blue/white, imprinted Lilly 3228/25 mg)
Capsules 40 mg (blue, imprinted Lilly 3229/40 mg)
Capsules 60 mg (blue/gold, imprinted Lilly 3239/60 mg)
Capsules 80 mg (brown/white, imprinted Lilly 3250/80 mg)
Capsules 100 mg (brown, imprinted Lilly 3251/100 mg)

Strattera capsules are available in packs of 7, 14, 28 or 56 capsules but not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
The marketing authorisation holder is:
Eli Lilly and Company Limited, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL, U.K.

The manufacturer is:
Eli Lilly and Company Limited, Kingsclere Road, Basingstoke, Hampshire, RG21 6XA, U.K. or Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

Strattera is a trademark of Eli Lilly and Company Limited.

This leaflet was last approved in
For information about this product, please contact:
Eli Lilly and Company Limited, Lilly House, Priestley Road, Basingstoke, Hampshire, RG24 9NL, United Kingdom
Phone: +44 (0) 1256 315999
Module 4

Labelling
Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Strattera 80 mg and 100 mg hard capsules in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) is approvable.

EXECUTIVE SUMMARY

Problem statement

These two marketing authorisation applications for atomoxetine hydrochloride are submitted by Eli Lilly and Company Ltd under EC Article 8.3 (i) of the Directive 2001/83/EC as line extensions to existing six strengths of Strattera (atomoxetine hydrochloride) 5,10,18,25,40, and 60mg hard capsules. They are for two new strengths of Strattera hard capsules, 80 mg and 100 mg, containing the active substance atomoxetine hydrochloride. The two higher strengths are to accommodate once daily dosing in larger patients.

Strattera was previously licensed in the UK as 5 mg, 10 mg, 18 mg, 25 mg, 40 mg and 60 mg hard capsules on May 27th 2004 (PL 00006/0374-0379). It was subsequently approved in the European Union via the Mutual Recognition Procedure with UK as the RMS (UK/H/0686/001-006). The applicant is now seeking a line extension to add two new strengths (80 mg and 100 mg – PL 00006/0615-0616; UK/H/686/007-008/DC) with cross reference to the lower strength capsules. These applications are submitted under Article 8.3 (known active substance) of Directive 2001/83/EC as amended by 2004/27/EC.

Strattera capsules are currently approved 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, with daily doses of 10 to 100 mg (based on body weight). These line-extension applications to include higher strengths are intended to allow for once-daily dosing in larger patients. The approved maximum recommended daily dose is currently 100 mg for patients over 70 kg. Therefore these additional doses are within the currently approved dosage range for atomoxetine hydrochloride. Thus, the applicant has not conducted any further clinical studies. Currently, multiple capsules must be taken to achieve the highest doses. By providing 80- and 100-mg capsule strengths, compliance with taking medication is expected to increase by the convenience of a single capsule to be taken once daily.

About the product

Unlike current products to treat ADHD, atomoxetine is not a stimulant, but a potent, selective and specific inhibitor of the presynaptic norepinephrine transporter (NET). It is this specific inhibition of the NET which is believed to be the mechanism for the efficacy of atomoxetine in ADHD. Atomoxetine is rapidly and completely absorbed after oral administration.
Atomoxetine has been the subject of a long development programme going back to the early 1980s for initial toxicology studies when atomoxetine was under clinical development for the treatment of depression and urinary incontinence, indications that were abandoned.

General comments on the submitted dossier

The dossier is of good quality. No new clinical or preclinical studies were submitted with this application. A single bioequivalence study is submitted.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The bioequivalence study is stated to be GCP compliant.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

The chemical-pharmaceutical documentation and Expert Report in relation to Strattera (atomoxetine) 80mg and 100mg Capsules are of sufficient quality in view of the present European regulatory requirements.

Atomoxetine hydrochloride is a white powder that is sparingly soluble in water. The INN name is atomoxetine with chemical name being (3R) –N-methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine-hydrochloride. Synthetic route, manufacturing process and in-process controls and control of materials is adequately described. Enantiomeric purity is controlled during synthesis bearing in mind that R-enantiomer is the active drug.

The active, atomoxetine hydrochloride is suitably characterised including the evidence of chemical structure from the route of synthesis, elemental analysis consistent with molecular formula, X-ray diffraction, NMR spectroscopy, mass spectroscopy, IR and Raman spectroscopy, UV spectroscopy, ionisation constant and specific rotations of atomoxetine hydrochloride along with control of impurities that include a limit for the S-enantiomer. The control tests and specifications for the atomoxetine hydrochloride drug substance are adequately drawn up with tests for atomoxetine identity, chloride identity, polymorphism, enantiomeric identity, assay, related substances/impurities including isomers, loss on drying, heavy metals, residue on ignition and particle size. This is supported by batch analyses on commercial batches of atomoxetine hydrochloride produced at the named manufacturing site.
Stability studies have been performed with the drug substance in line with ICH requirements. No significant changes in any parameters were observed. The proposed retest period of 36 months is justified.

**Drug Product**
The product is a hard gelatine capsule.

**Other Ingredients**

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)

The colours used on the two strengths are

**Capsule Shell Cap colourants:**
- 80 mg: Yellow iron oxide E172, Red iron oxide E172, Titanium dioxide E171

**Capsule Shell Body colourants:**
- 80 mg: Titanium dioxide E171

**Capsule Shell Cap colourants:**
- 100 mg: Yellow iron oxide E172, Red iron oxide E172, Titanium dioxide E171

**Capsule Shell Body colourants:**
- 100 mg: Yellow iron oxide E172, Red iron oxide E172, Titanium dioxide E171

The development of the product has been described, the choice of excipients is justified and their functions explained. As the active is water soluble drug dissolution is rapid and is not considered the rate-limiting step for absorption. Similarly as the active is water soluble the particle size of the active drug substance is not considered critical.

The manufacturing process is a direct blend followed by encapsulation and is consistent with the process used for the lower strengths of Strattera Capsules currently licensed. Process validation at the named manufacturing site has been performed on full-scale manufacturing process validation batches of capsules successfully.

Excipients are compendial grade being PhEur. Gelatin used in the manufacture of hard gelatin capsules is sourced from suppliers possessing the PhEur Certificates of Suitability in compliance with BSE/TSE guidelines.
The product specifications cover appropriate parameters for this dosage form including tests for appearance, identity by IR, assay, uniformity of dosage units, related substances, dissolution and microbial control. Validations of the analytical methods have been presented including control of limit of detection (LOD) and quantification (LOQ) for related substances. Batch analyses are provided for several batches of both strengths ranging from pilot to commercial scale batches. The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guidelines in that conditions of 25°C/60% RH, 30°C/60%RH and 40°C/75%RH have been used for storage with further data from stress testing stability studies. The control tests and specifications for drug product are adequately drawn up. No significant changes are noted during storage.

The proposed shelf-life of 36 months with no specific storage conditions for the drug product is considered acceptable in the commercial blister packaging.

The application is approvable from a quality point of view.

Non-clinical aspects

No new preclinical studies were submitted with this application. This is acceptable as atomoxetine is a well known active ingredient and the higher dose strengths are within the currently approved dosage range for atomoxetine hydrochloride. No new preclinical issues are considered to arise as a result of its inclusion in the proposed product.

Clinical aspects

The pharmacokinetics of atomoxetine are linear and dose proportional over this dosage range. As the formulations for atomoxetine 80mg and 100mg capsules are proportionally similar to the formulation for the approved atomoxetine 60-mg capsules and other multi dose biowaiver criteria appear to be met it seems likely than an additional bioequivalence study to support the present applications is not required. Nevertheless a bioequivalence study is submitted, evaluating the bioequivalence of each of the proposed dose strengths with equivalent doses administered by a combination of the currently approved 40- and 60-mg dose strengths. This study confirmed that the two new strengths of Strattera hard capsules, 80 mg and 100 mg are bioequivalent to the currently approved Strattera 40 mg and 60 mg hard capsules.

Bioequivalence Study B4Z-LC-LYCM

Study design

An open-label, four-period randomized, Latin-square design study with intermittent confinement for approximately 4 weeks in 76 healthy men and women. There was a minimum washout of at least 96 hours (4 days) between each atomoxetine dose.

Test and reference products

The following treatments were administered:
Treatment A: one 80-mg market-image capsule (“test”); supplied from package lot CT507238.
Treatment B: two 40-mg marketed capsules (“reference”); supplied from package lot 7EG32A.
Treatment C: one 100-mg market-image capsule (“test”); supplied from package lot CT507239.
Treatment D: one 40-mg marketed capsule (“reference”) and one 60-mg marketed (“reference”) capsule, from package lots 7EG32A and 7EJ06A, respectively.
Population(s) studied

76 healthy fasted adult male volunteers with extensive metabolizer CYP2D6 genotype were randomised.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>80-mg Capsule Test (N=62)</th>
<th>2x40-mg Capsules Reference (N=63)</th>
<th>100-mg Capsule Test (N=62)</th>
<th>40+60-mg Capsules Reference (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (mg/mL)</td>
<td>677 (42.2)</td>
<td>703 (36.7)</td>
<td>910 (41.6)</td>
<td>834 (38.1)</td>
</tr>
<tr>
<td>$T_{max}$ (h)</td>
<td>0.75 (0.50-6.00)</td>
<td>0.75 (0.33-6.00)</td>
<td>0.75 (0.33-12.0)</td>
<td>0.75 (0.50-12.2)</td>
</tr>
<tr>
<td>$AUC_{0-t,obs}$ (µg h/mL)</td>
<td>3.22 (50.0)</td>
<td>3.30 (46.7)</td>
<td>4.35 (50.4)</td>
<td>4.32 (47.7)</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (µg h/mL)</td>
<td>3.15 (47.8)</td>
<td>3.22 (43.9)</td>
<td>4.26 (48.7)</td>
<td>4.20 (44.8)</td>
</tr>
</tbody>
</table>

Table LYCM.7.2. Statistical Comparison of Pharmacokinetic Parameters Following 80-mg and 100-mg Doses of Atomoxetine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Treatment</th>
<th>Least-Square Mean</th>
<th>Treatment Comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{max}$ (mg/mL)</td>
<td>62</td>
<td>A</td>
<td>626.29</td>
<td>A/B 95.1 (88.2, 102.5)</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>B</td>
<td>658.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>C</td>
<td>531.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>D</td>
<td>771.17</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0,t,obs}$ (µg h/mL)</td>
<td>62</td>
<td>A</td>
<td>3.02</td>
<td>A/B 99.3 (96.2, 102.5)</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>B</td>
<td>3.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>C</td>
<td>3.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>D</td>
<td>3.01</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-t}$ (µg h/mL)</td>
<td>62</td>
<td>A</td>
<td>2.97</td>
<td>A/B 99.3 (96.2, 102.5)</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>B</td>
<td>2.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>C</td>
<td>3.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>D</td>
<td>3.83</td>
<td></td>
</tr>
<tr>
<td>$CL/F$ (L/h)</td>
<td>62</td>
<td>A</td>
<td>3.34</td>
<td>A/B 100.2 (97.6, 104.0)</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>B</td>
<td>3.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>C</td>
<td>3.32</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>D</td>
<td>3.33</td>
<td></td>
</tr>
<tr>
<td>$Vz/F$ (L/kg)</td>
<td>62</td>
<td>A</td>
<td>1.60</td>
<td>A/B 100.5 (94.7, 106.7)</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>B</td>
<td>1.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>C</td>
<td>1.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59</td>
<td>D</td>
<td>1.63</td>
<td></td>
</tr>
</tbody>
</table>

A = 1x80-mg atomoxetine (Test)
B = 2x40-mg atomoxetine (Reference)
C = 1x100-mg atomoxetine (Test)
D = 40+60-mg atomoxetine (Reference)
Pharmacokinetic conclusion

Based on the submitted bioequivalence study the two new strengths of Strattera hard capsules, 80 mg and 100 mg are considered bioequivalent to the currently approved Strattera 40 mg and 60 mg hard capsules.
Pharmacovigilance system and Risk Management Plan

The Pharmacovigilance system and proposed risk minimisation activities will be as approved for the other strengths. There are potential issues regarding the higher tablet strength but are adequately covered by the company’s existing plan.

Package Leaflet

A combined leaflet is provided including the strengths already licensed. Harmonisation of the PIL with that approved for the existing strengths is appropriate. There is a Type II Variation procedure to harmonise the PIL for the lower strength capsules for Strattera, UK/H/0686/001-006/II/15. The company has provided a commitment to submit a variation application to make changes to the PIL requested in the current procedure, applied to all strengths of the product. This is satisfactory.

Assessment of User Testing

A report on user testing of the package leaflet is provided.

“User consultation” has been conducted on a “harmonised” version of the package leaflet for the already licensed and launched strengths of Strattera hard capsules (10 mg, 18 mg, 25 mg, 40 mg and 60 mg). This “harmonised” version of the package leaflet takes into account the requirements of the October 2006 QRD template and feedback from Member States when these lower strengths were subjected to MRP. Further consultation has not been conducted for Strattera 80 mg and 100 mg hard capsules as the changes to the package leaflet are minimal and the 80 mg and 100 mg strengths have incorporated into this “harmonised” package leaflet.

The package leaflet user testing confirmed that 90% of the participants were able to find the information on each point and 90% of those were able to express the information in their own words.

BENEFIT RISK ASSESSMENT

Approval is recommended from the preclinical and clinical point of view.
Module 6

Steps taken after procedure

No non-confidential changes have been made to the marketing authorisation.