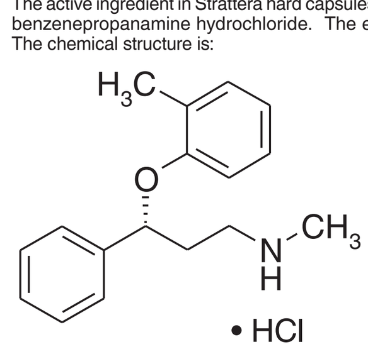
NAME OF THE MEDICINE

Strattera 10mg, 18mg, 25mg, 40mg or 60mg Hard Capsule

The active ingredient in Strattera hard capsules is atomoxetine hydrochloride. Chemically, Strattera is (*R*)-(-)-N-Methyl-gamma-(2-methylphenoxy)-benzenepropanamine hydrochloride. The empirical formula is $C_{17}H_{21}NO•HCl$ which corresponds to a molecular weight of 291.82 daltons. The chemical structure is:



The CAS number for atomoxetine hydrochloride is 82248-59-7.

DESCRIPTION

Atomoxetine hydrochloride is a white to practically white solid which has a solubility of 27.8 mg/mL in water.

Strattera is available as hard capsules for oral administration. Each hard capsule contains 10, 18, 25, 40 or 60mg of atomoxetine (as hydrochloride). The hard capsules also contain pregelatinised maize starch, dimethicone 350, gelatin, sodium lauryl sulfate, titanium dioxide, edible black ink (TekPrint SW-9008 or SW-9010), indigo carmine CI73015 (25mg, 40mg and 60mg only), yellow iron oxide CI77492 (18mg and 60mg only).

PHARMACOLOGY

Pharmacodynamics

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

Strattera is a treatment for Attention-Deficit/Hyperactivity Disorder (ADHD). ADHD was formerly known as Attention Deficit Disorder (ADD) with or without hyperactivity. Atomoxetine is a relatively potent inhibitor of the presynaptic noradrenaline transporter (K_i 4.5nM), a moderate inhibitor of 5HT uptake (K_i 152nM) and a weak inhibitor of dopamine uptake (K_i 658nM), with minimal affinity for the other noradrenergic receptors. Atomoxetine has moderate affinity for $5HT_2$ and $GABA_A$ receptors but poor affinity for most other receptors. The main hydroxyatomoxetine metabolite is equipotent to the parent compound at the noradrenaline transporter (K_i 3.0nM), and a more potent inhibitor of the 5HT transporter (K_i 43nM) than the parent compound.

A thorough QT/QTc study, conducted in healthy adult CYP2D6 poor metaboliser (PM) subjects dosed up to 60mg of atomoxetine twice daily, demonstrated that at maximum expected concentrations the effect of atomoxetine on QTc interval was not significantly different from placebo. There was a slight increase in QTc interval with increased atomoxetine concentration (see *Clinical Trials - Cardiac Electrophysiology, Precautions - Cardiovascular Effects, Interaction with Other Medicines).*

Pharmacokinetics

Single-dose and steady-state individual pharmacokinetic data were obtained in children, adolescents and adults. After administration of the same mg/kg dose to children, adolescents and adults, similar half-life, C_{max} and AUC values were observed. Clearance and volume of distribution after adjustment for body weight were also similar.

Absorption: Atomoxetine is rapidly and almost completely absorbed after oral dosing reaching mean maximal observed plasma concentration (C_{max}) approximately 1 to 2 hours after dosing. The C_{max} observed after a single 1 mg/kg dose of atomoxetine is 568 ng/mL (range of 92 to 1544 ng/mL).

Strattera can be administered with or without food. In clinical trials with children and adolescents, administration of Strattera with food resulted in a 9% lower C_{max}. Administration of Strattera with a standard high-fat meal in adults did not affect the extent of oral absorption of atomoxetine (AUC), but did decrease the rate of absorption resulting in a 37% lower C_{max}. After a high-fat meal, the T_{max} was approximately 4 hours after dosing (range of 0.5-16 hours for high-fat; 0.5-6 hours for fasting).

Following oral administration of Strattera, a lower absolute bioavailability (63%) after modest first pass metabolism was observed in extensive CYP2D6 metabolisers, while a higher absolute bioavailability (94%) was observed in poor CYP2D6 metabolisers.

Distribution: The steady-state volume of distribution after intravenous administration was approximately 0.85 L/kg indicating atomoxetine distributes primarily into total body water. In children and adolescents, volume of distribution increased nearly proportionally to increases in body weight. Volume of distribution was similar across the patient weight range after normalising for body weight.

At therapeutic concentrations, 98.5% of atomoxetine in plasma is bound to protein, primarily albumin.

Metabolism: Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway. There are two major phenotypes associated with CYP2D6: extensive metabolisers (EMs) (93% of Caucasians and 98% of African Americans) and PMs (7% of Caucasians and 2% of African Americans). The major oxidative metabolite formed, regardless of CY2D6 status, is 4-hydroxyatomoxetine, which is rapidly glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine at inhibiting noradrenaline uptake and is slightly more potent at inhibiting 5HT uptake than the parent compound (see *Pharmacology*). This metabolite circulates in plasma at much lower concentrations but it is also less plasma protein bound (66%) than the parent compound (98.5%), so that in EMs the exposure to unbound 4-hydroxyatomoxetine exceeds exposure to unbound atomoxetine. 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. N-Desmethylatomoxetine is formed by CYP2C19 and other cytochrome P450 enzymes, but has a much less pharmacological activity than atomoxetine and plasma concentrations are lower (5% of atomoxetine concentration in EMs and 45% of atomoxetine concentration in PMs).

People with reduced activity in the CYP2D6 pathway (PMs) have higher plasma concentrations of atomoxetine compared with people with normal activity (EMs). Drugs that inhibit CYP2D6, such as fluoxetine, paroxetine and quinidine also cause increases in exposure. Atomoxetine does not inhibit or induce the CYP2D6 pathway.

Co-administration of Strattera with known inhibitors of CYP2D6 does not result in an increased sensitivity to Strattera, although it may result in higher atomoxetine plasma exposure.

Adjustment of dosing regimens based on metabolism through the CYP2D6 pathway is not necessary.

Elimination: The mean elimination half-life of atomoxetine after oral administration is 3.6 hours in EMs and 21 hours in PMs. Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-O-glucuronide, mainly in the urine.

Mean apparent plasma clearance of atomoxetine after oral administration in adult EMs is 0.35 L/hr/kg and the mean half-life is 5.2 hours. Following oral administration of atomoxetine to PMs, mean apparent plasma clearance is 0.03 L/hr/kg and mean half-life is 21.6 hours. For PMs, AUC of atomoxetine is approximately 10-fold and $C_{ss,max}$ is about 5-fold greater than EMs. The elimination half-life of 4-hydroxyatomoxetine is similar to that of N-desmethylatomoxetine (6 to 8 hours) in EM subjects, while the half-life of N-desmethylatomoxetine is much longer in PM subjects (34 to 40 hours).

Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-O-glucuronide, mainly in the urine (greater than 80% of the dose) and to a lesser extent in the faeces (less than 17% of the dose). Only a small fraction of the Strattera dose is excreted as unchanged atomoxetine (less than 3% of the dose), indicating extensive biotransformation.

Hepatic Impairment: Single doses of Strattera were administered to subjects with moderate to severe hepatic impairment (Child-Pugh Class B and C) resulting in reduced atomoxetine clearance, increased atomoxetine exposure (AUC) (2-fold increase for Child-Pugh Class B and 4-fold increase for Child-Pugh Class C) and prolonged half-life of parent drug compared with healthy subjects. However, the maximum exposure observed in subjects with hepatic impairment did not exceed that observed in the population of healthy CYP2D6 PMs. Dosage adjustment is recommended for patients with moderate or severe hepatic impairment (see *Dosage and Administration, Hepatic Impairment*).

Renal Impairment: Single doses of Strattera were administered to subjects with end stage renal disease, resulting in higher atomoxetine exposure (AUC) than in healthy subjects (about a 65% increase). However, the maximum exposure observed in subjects with end stage renal disease did not exceed that observed in the population of healthy CYP2D6 PMs. Strattera may exacerbate hypertension in patients with end stage renal disease. For those ADHD patients who have end stage renal disease, cautious titration of Strattera to the desired clinical response is recommended, with particular attention to those with hypertension who may experience deterioration in the control of their blood pressure.

Elderly: The pharmacokinetics of atomoxetine have not been evaluated in the elderly population (over 65).

Children and Adolescents: 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.

Gender: Gender did not influence atomoxetine disposition.

Ethnic origin: Ethnic origin did not influence atomoxetine disposition (except that PMs are more common in Caucasians than in African Americans).

CLINICAL TRIALS

The efficacy of Strattera for the treatment of ADHD in children and adolescents (age 6 to 17 years) meeting the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria was satisfactorily established in four, short-term (6-9 weeks), randomised, double-blind, placebo-controlled studies; one long-term (9 months), randomised, double-blind, placebo-controlled study; and one long-term (2 years), open-label study. The efficacy of Strattera for the treatment of ADHD in adults (18 years of age and older) meeting DSM-IV criteria and with a childhood history of ADHD was established in two, short-term (10 weeks), randomised, double-blind, placebo-controlled studies; and one, long-term (up to 2 years), open-label study. There are no long term, randomised, double-blind, placebo-controlled studies in adults.

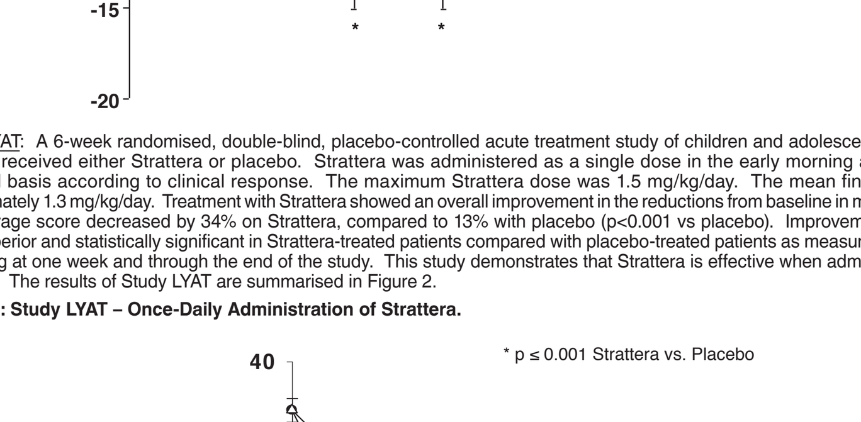
Children and Adolescents

The efficacy of Strattera in the treatment of ADHD was established in four acute, randomised, double-blind, placebo-controlled studies of paediatric patients (ages 6 to 17) who met DSM-IV criteria for ADHD (studies LYAC, LYAT, HFBD, HFBK). Approximately one third of the patients met DSM-IV criteria for inattentive subtype and two thirds met criteria for both inattentive and hyperactive/impulsive subtypes.

Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for Strattera-treated and placebo-treated patients using an intent-to-treat analysis. The primary outcome measure was the investigator administered and scored ADHD Rating Scale-IV-Parent Version (ADHDRS) total score including hyperactive/impulsive and inattentive sub-scales. Each item on the ADHDRS maps directly to one symptom criterion for ADHD in the DSM-IV.

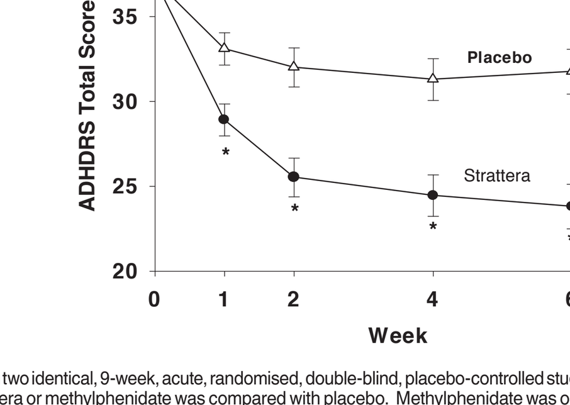
Study LYAC: An 8-week randomised, double-blind, placebo-controlled acute treatment study of children and adolescents aged 8 to 18 (N=297), patients received either a fixed dose of Strattera (0.5 mg/kg/day, 1.2 mg/kg/day or 1.8 mg/kg/day) or placebo. Strattera was administered as a divided dose in the early morning and late afternoon/early evening. Treatment with Strattera showed an overall improvement in the reductions from baseline in mean ADHDRS total score. The average score decreased by 25% on 0.5mg/kg/day, 35% on 1.2 mg/kg/day and 34% on 1.8 mg/kg/day Strattera, compared to 15% with placebo. At the two higher doses, improvements in ADHD symptoms were superior and statistically significant (p<0.001 vs placebo) in Strattera-treated patients compared with placebo-treated patients as measured on the ADHDRS scale. The results of Study LYAC are summarised in Figure 1.

Figure 1: Study LYAC – Strattera Response by Dose.



Study LYAT: A 6-week randomised, double-blind, placebo-controlled acute treatment study of children and adolescents aged 6 to 16 (N=171), patients received either Strattera or placebo. Strattera was administered as a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response. The maximum Strattera dose was 1.5 mg/kg/day. The mean final dose of Strattera was approximately 1.3 mg/kg/day. Treatment with Strattera showed an overall improvement in the reductions from baseline in mean ADHDRS total score. The average score decreased by 34% on Strattera, compared to 13% with placebo (p<0.001 vs placebo). Improvements in ADHD symptoms were superior and statistically significant in Strattera-treated patients compared with placebo-treated patients as measured on the ADHDRS scale beginning at one week and through the end of the study. This study demonstrates that Strattera is effective when administered once daily in the morning. The results of Study LYAT are summarised in Figure 2.

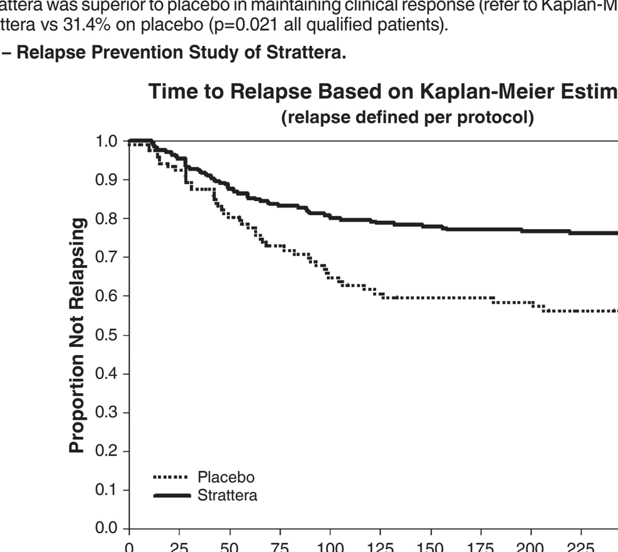
Figure 2: Study LYAT – Once-Daily Administration of Strattera.



Studies HFBD and HFBK: In two identical, 9-week, acute, randomised, double-blind, placebo-controlled studies of children aged 7 to 13 (Study HFBD, N=147; Study HFBK, N=144), Strattera or methylphenidate was compared with placebo. Methylphenidate was only used to show that the study design was valid (i.e. by its separation from placebo). These studies were not statistically powered to provide a comparative analysis between Strattera and methylphenidate (patient numbers per treatment Study HFBD, Strattera N=65, methylphenidate N=20, placebo N=62; Study HFBK, Strattera N=64, methylphenidate N=18, placebo N=62). The primary comparison of interest in both studies was Strattera vs placebo. Strattera was administered as a divided dose in the early morning and late afternoon (after school) and titrated on a weight-adjusted basis according to clinical response. The maximum recommended Strattera dose was 2.0 mg/kg/day. The mean final dose of Strattera for both studies was approximately 1.6 mg/kg/day. Treatment with Strattera showed an overall improvement from baseline in mean ADHDRS total score. The average score decreased by 38% on Strattera, compared to 13% with placebo (p<0.0001 vs placebo) in study HFBD and 38% on Strattera, compared to 16% with placebo (p<0.0003 vs placebo) in study HFBK.

Study LYAF: A two-stage relapse prevention study in children and adolescents who met DSM-IV criteria for ADHD. In this study, patients were treated for 12 weeks with Strattera and responders were randomised to a further 40 weeks of treatment discontinuation phase (N=292 Strattera, N=124 placebo). At endpoint (1 year), Strattera was superior to placebo in maintaining clinical response (refer to Kaplan-Meier plot provided as Figure 3). The relapse rate was 18.7% on Strattera vs 31.4% on placebo (p=0.021 all qualified patients).

Figure 3: Study LYAF – Relapse Prevention Study of Strattera.



Study LYAB: A multi-centre open label safety and efficacy study in children and adolescents who met DSM-IV criteria for ADHD. In this study patients were treated for 10 weeks with Strattera (study period II) and responders were eligible to enter a long term treatment phase of up to 2 years (study period III) (N=301 completing long term treatment). On average, symptoms of ADHD in Strattera-treated patients decreased by 48.5% as measured by the ADHD rating scale total score for study periods II and III. Strattera was well tolerated in this long-term safety study and adverse events did not increase over time. The adverse event profile for PM patients was similar to that for EM patients with a similar tolerability profile as described in the short-term studies.

Examination of population subsets (gender, age, or prior stimulant treatment) did not reveal any differential responsiveness on the basis of these subgroupings.

Adults

The efficacy of Strattera in the treatment of ADHD was established in two randomised, double-blind, placebo-controlled clinical studies of adult patients, age 18 and older who met DSM-IV criteria for ADHD.

Signs and symptoms of ADHD were evaluated using the investigator administered Conners Adult ADHD Rating Scale Screening Version (CAARS), a 30-item scale. The primary efficacy measure was the 18-item Total ADHD Symptom score (the sum of the inattentive and hyperactivity/impulsivity subscales) evaluated by a comparison of mean change from baseline to endpoint using an intent-to-treat analysis.

Studies LYAA and LYAO: In two identical, 10-week, randomised, double-blind, placebo-controlled acute treatment studies (Study LYAA, N=280; Study LYAO, N=256), patients received either Strattera or placebo. Strattera was administered as a divided dose in the early morning and late afternoon/early evening and titrated according to clinical response. The maximum Strattera dose was 120 mg/day. The mean final dose of Strattera for both studies was approximately 95 mg/day. Treatment with Strattera showed an overall improvement from baseline in mean CAARS total score. The average score decreased by 28% on Strattera, compared to 18% with placebo (p<0.001 vs placebo) in study LYAA and 30% on Strattera, compared to 20% with placebo (p<0.001 vs placebo) in study LYAO. In both studies, improvements in ADHD symptoms were superior and statistically significant in Strattera-treated patients compared with placebo-treated patients as measured on the CAARS scale.

Study LYAR: An open-label, multi-centre investigation of the long-term safety and tolerability of Strattera in patients aged 18 years or older who meet the DSM-IV criteria for ADHD. This was an open label extension of the LYAA and LYAO studies. Average symptom severity decreased by 30.6% (p<0.001) as measured by the CAARS investigator rated scale for 18 item total ADHD symptoms. The adverse event profile was similar to that observed in short-term studies with most treatment emergent adverse events reported to be of mild or moderate severity.

Examination of population subsets (gender, age, prior stimulant treatment, or CYP2D6 metabolic status) did not reveal any differential responsiveness on the basis of these subgroupings.

Cardiac Electrophysiology
The effect of atomoxetine on QTc prolongation was evaluated in a randomised, double-blinded, positive-(moxifloxacin 400mg) and placebo-controlled, cross-over study in healthy male CYP2D6 PMs. A total of 120 healthy subjects were administered atomoxetine (20mg and 60mg) twice daily for 7 days. Although a statistically significant increase in QTc was associated with increasing plasma concentrations, atomoxetine was not associated with a clinically significant change in QTc (see *Pharmacodynamics, Precautions – Cardiovascular Effects, Interactions with Other Medicines*).

INDICATIONS

Strattera is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) as defined by DSM-IV criteria or the guidelines in ICD-10 in children 6 years of age and older, adolescents and adults.

CONTRAINDICATIONS

Strattera is contraindicated in patients with:

- Known hypersensitivity to atomoxetine or any excipients in Strattera
- Symptomatic cardiovascular disease – moderate to severe hypertension, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, or ventricular flutter, advanced arteriosclerosis (see *Precautions*)
- Severe cardiac or vascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate that could be clinically important (for example, 15 to 20 mmHg in blood pressure or 20 beats per minute in heart rate) (see *Precautions - Cardiovascular Effects)*
- Uncontrolled hyperthyroidism
- Phaeochromocytoma or a history of phaeochromocytoma (see *Precautions - Cardiovascular Effects*)
- Monoamine Oxidase Inhibitors (MAOI) – Strattera should not be taken with MAOI or within 2 weeks after discontinuing MAOI. Treatment with MAOI should not be initiated within 2 weeks after discontinuing Strattera.
  With other drugs that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal, reactions when taken in combination with MAOI. These reactions include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to delirium and coma, some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity.
- Narrow Angle Glaucoma – In clinical studies, the use of Strattera was associated with an increased risk of mydriasis and therefore its use is not recommended in patients with narrow angle glaucoma.

PRECAUTIONS

Suicidal Ideation and Behaviour

Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials of Strattera in children and adolescents showed a greater risk of suicidal ideation during treatment in those receiving Strattera. There were a total of 12 trials (11 in ADHD and 1 in enuresis) involving over 2200 patients. The average risk of suicidal ideation in patients treated with Strattera was 0.4% (5/1357) compared with 0% (0/851) in patients treated with placebo. There was 1 suicide attempt in patients treated with Strattera and none in patients treated with placebo. No suicides occurred in these trials. All events of suicidal ideation and behaviour associated with Strattera occurred in children 12 years of age and younger. It is unknown whether the risk of suicidality in children extends to longer-term use of Strattera. A similar meta-analysis in adult patients treated with Strattera for either ADHD or major depressive disorder (MDD) did not reveal an increased risk of suicidal ideation or behaviour in association with the use of Strattera.

All children being treated with Strattera should be monitored closely for suicidality, clinical worsening, and unusual changes of behaviour, especially during the first few months of treatment or at times of dose change. The following symptoms have been reported with Strattera: anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania. Although a causal link between the emergence of such symptoms and the emergence of suicidal ideation and behaviour has not been established, there is a concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including discontinuing Strattera, in patients who are experiencing emergent suicidality or symptoms that might be precursors to emerging suicidality, especially if these symptoms are severe or abrupt in onset, or were not part of the patients' presenting symptoms. These patients should be referred to a paediatric psychiatrist for assessment and supervision.

Families and caregivers of children and adolescents being treated with Strattera should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behaviour, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers.

Based on clinical trials conducted in children and adolescents (< 18 years of age) to establish the efficacy of the drug over placebo for the treatment of ADHD, the number needed to treat calculations suggest that a clinician should expect to treat 2 to 3 patients to see one patient respond and 4 to 5 patients to see one patient respond that would not have with placebo treatment. This is balanced against suicidal ideation occurring in 1 out of about every 271-272 patients treated.

Aggressive Behaviour or Hostility

Hostility (predominantly aggression, oppositional behaviour and anger) and emotional lability are often observed in patients with ADHD and has been reported in clinical trials and the post-marketing experience of some medications indicated for the treatment of ADHD. Although there is no conclusive evidence that atomoxetine causes aggressive behaviour or hostility, aggressive behaviour or hostility was more frequently observed in clinical trials among children, adolescents and adults treated with atomoxetine compared to placebo (not statistically significant). Patients beginning treatment for ADHD should be monitored for the appearance or worsening of aggressive behaviour or hostility. Referral of patients to a psychiatrist for regular assessment and supervision during treatment should also be considered.

Possible Allergic Events

Although uncommon, allergic reactions, including anaphylactic reactions, rash, angioneurotic oedema and urticaria, have been reported in patients taking Strattera.

Seizures

The pre-clinical and clinical trial data for Strattera do not suggest that Strattera is proconvulsive. However, seizures have been very rarely reported in post-marketing spontaneous reports. Strattera should be used with caution in patients with a history of seizures. Discontinuation of Strattera should be considered in any patient developing seizures or if there is an increase in seizure frequency where no other cause is identified.

Cardiovascular Effects

Patients should be screened for pre-existing or underlying cardiovascular or cerebrovascular conditions before initiation of treatment with atomoxetine and monitored for new conditions of the heart or brain during the course of treatment.

Strattera can affect heart rate and blood pressure. It is recommended that the heart rate and blood pressure be measured before treatment is started, after the dose is increased or decreased and periodically during treatment to detect possible clinically important increases.

Most patients taking Strattera experience a modest increase in heart rate (mean < 10 bpm) and/or increase in blood pressure (mean < 5mmHg) that are not clinically important (see *Adverse Effects*). However, data from ADHD clinical trials show that some patients (approximately 5 to 10% of children and adults) do experience clinically important changes in heart rate (20 beats per minute or greater) or blood pressure (15 to 20 mm Hg or greater).

Strattera should be used with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate, such as patients with hypertension, tachycardia or cardiovascular or cerebrovascular disease.

Strattera should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or heart rate that could be clinically important (see *Contraindications*).

In addition, Strattera should be used with caution in patients with congenital QT prolongation, acquired QT prolongation (for example, due to concomitant use of a drug that prolongs the QT), or a family history of QT prolongation (see *Clinical Trials – Cardiac Electrophysiology*).

Because orthostatic hypotension has also been reported, Strattera should be used with caution in any condition that may predispose patients to orthostatic hypotension or conditions associated with abrupt heart rate or blood pressure changes (see *Contraindications*).

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

A pharmacological potential exists for all ADHD drugs to increase the risk of sudden/cardiac death. Although confirmation of an incremental risk for adverse cardiac events arising from treatment with ADHD medications is lacking, prescribers should consider this potential risk.

All drugs with sympathomimetic effects prescribed in the management of ADHD should be used with caution in patients who are: a) involved in strenuous exercise or activities, b) use stimulants, or c) have a family history of sudden/cardiac death. Strattera is a drug with peripheral sympathomimetic effects and should not generally be used in children, adolescents, or adults with known structural cardiac abnormalities. Prior to the initiation of treatment, a personal and family cardiac and psychiatric history should be obtained. In patients with relevant risk factors and based on the clinician's judgment, further evaluation by a specialist should be considered.

Children and adolescents: Sudden death has been reported in association with atomoxetine treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, Strattera generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the noradrenergic effects of atomoxetine.

Adults: Sudden deaths, stroke, and myocardial infarction have been reported in adults taking atomoxetine at usual doses for ADHD. Although the role of atomoxetine in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Consideration should be given to not treating adults with clinically significant cardiac abnormalities.

Effects on Urine Outflow from the Bladder

In adult ADHD controlled trials, the rates of urinary retention (3%, 7/269) and urinary hesitation (3%, 7/269) were increased among Strattera subjects compared with placebo subjects (0%, 0/263). A complaint of urinary retention or urinary hesitancy should be considered potentially related to Strattera. Use with caution in patients with enlarged prostates or other conditions predisposing to urinary retention.

Priapism

Rare post-marketing cases of priapism, defined as painful and non-painful penile erection lasting more than 4 hours, have been reported for paediatric and adult patients treated with Strattera. The erections resolved in cases in which follow-up information was available, some following discontinuation of Strattera. Prompt medical attention is required in the event of suspected priapism.

Effects on Growth (Height and Weight)

Data from longer-term trials (≥2 years) suggest that any effect of Strattera on growth is minimal and is most strongly associated with initiation of treatment. At 24 months, patients displayed a marked absolute mean weight gain (approximately 10.7kg), which corresponded to a slight decrease relative to baseline normative weights (-2.8 percentiles). The decrease at endpoint from the weight that would have been reached had the baseline normative weight been maintained was 0.9kg. At 24 months, there was also marked absolute mean height gain (approximately 13.1cm), which corresponded to a slight decrease relative to baseline normative heights (-2.2 percentiles). The decrease at endpoint from the height predicted by baseline normative height and the mean observed height was approximately 0.5cm.

In the placebo-controlled study, LYAF, a statistically significant effect was seen for both height and weight corresponding to decreases relative to baseline normative heights (-2.68 percentiles for atomoxetine group vs 0.76 for placebo group) and normative weights (-3.93 percentiles for atomoxetine group vs 5.44 percentiles for placebo group). A similar response was seen in the open-label study LYAB with weight and height increases lower than normative rates (-2.0 percentile for height and -3 percentiles for weight). Analysis of effects by baseline weight and height shows that patients in the lowest quartile for weight and height are the least affected by Strattera. The potential effect of treatment with Strattera on final adult stature is unknown. Periodic monitoring of height and weight are recommended for patients requiring long-term therapy.

Hepatic Effects

Very rarely, spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported. In some very rare cases, severe liver injury, including acute liver failure, has also been reported. Strattera should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.

Hepatic or Renal Impairment (see *Pharmacology – Pharmacokinetics, Dosage and Administration*)

Carcinogenicity and Mutagenicity

Atomoxetine hydrochloride was not carcinogenic in rats and mice when given in the diet for 2 years. The time-weighted average doses of up to 47 and 458 mg/kg/day were approximately 6 (rat) and 30 (mouse) times the maximum recommended daily oral dose in children and approximately 4 (rat) and 17 (mouse) times the maximum recommended daily oral dose in adults, on a mg/m^2 basis. Systemic exposure (plasma AUC) to active moiety (atomoxetine + 4-hydroxyatomoxetine) in rats was estimated to be less than that in EMs or PMs receiving the maximum dose, and exposure in mice was estimated to be 1 to 3 times that in EMs but less than that in PMs.

Atomoxetine hydrochloride was not genotoxic in a battery of tests including bacterial reverse mutation assays, a mouse lymphoma assay, a chromosomal aberration test in Chinese hamster ovary cells, *in vivo* micronucleus test in mice, unscheduled DNA synthesis test in rat hepatocytes and *in vivo* sister chromatid exchange test in bone marrow of Chinese hamsters. However, there was a slight increase in the percentage of Chinese hamster ovary cells with diplochromosomes, suggesting endoreduplication (numerical aberration). The metabolite N-desmethylatomoxetine hydrochloride was negative in the Ames test, mouse lymphoma assay and unscheduled DNA synthesis test.

Impairment of Fertility

Atomoxetine hydrochloride did not impair fertility when administered to rats from 10 days of age through adulthood at oral doses up to 50 mg/kg/day (up to 7 times the maximum recommended daily oral dose in children and 4 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis). In addition, there was no evidence of impaired fertility in two studies in adult rats given atomoxetine in the diet at time-weighted average doses up to 57 mg/kg/day in males and 46 mg/kg/day in females (up to 6-8 times the maximum recommended daily oral dose in children and 4 times the maximum recommended daily oral dose in adults, on a mg/m^2 basis).

Use in Pregnancy - Pregnancy Category B3

Pregnant rabbits were treated orally with up to 100 mg/kg/day atomoxetine throughout the period of organogenesis. At this dose, a decrease in live foetuses and/or an increase in early resorptions were observed, along with evidence of slight maternal toxicity. Slight increases in the incidences of major blood vessel variations were observed in 1 of 3 studies; the no-effect dose for the cardiovascular findings was 30 mg/kg/day. The 100 mg/kg/day dose is 14 times the maximum human dose on a mg/m^2 basis; exposure (plasma AUC) to active moiety (atomoxetine + 4-hydroxyatomoxetine) at this dose is estimated to be less than that in EMs or PMs receiving the maximum human adult dose.

Rats were treated with up to 57 (males) and 46 (females) mg/kg/day of atomoxetine (4 times the maximum human adult dose on a mg/m^2 basis) in the diet from 2 (females) or 10 (males) weeks prior to mating through the periods of organogenesis and lactation. In one study, decreases in fetal and pup body weight and fetal skeletal anomalies were seen at 41-98 mg/kg/day (3-7 times the maximum tolerated human adult dose on a mg/m^2 basis) along with maternal toxicity and incisor overgrowth/teeth clipped was seen at 7 mg/kg/day or greater. In a second study, decreases in pup weight were seen at 46-70 mg/kg/day (4-5 times the maximum human adult dose on a mg/m^2 basis) and reduced pup survival at 23-39 mg/kg/day (2-3 times the maximum adult dose on a mg/m^2 basis) along with maternal toxicity. No adverse fetal effects were seen when pregnant rats were treated with up to 150 mg/kg/day (11 times the maximum human dose on a mg/m^2 basis) by gavage during the period of organogenesis only.

No adequate and well-controlled studies have been conducted in pregnant women. Strattera should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Labour and Delivery

Parturition (gestational length or live birth indices) in rats was not affected by atomoxetine. The effect of Strattera on labour and delivery in humans is unknown.

Use in Lactation

Atomoxetine and/or its metabolites are excreted in the milk of rats. It is not known if atomoxetine is excreted in human milk. Treatment of rats with atomoxetine prior to mating through the periods of organogenesis and lactation was associated with adverse effects on pups (see *Use in Pregnancy*). Caution should be exercised if Strattera is administered to a nursing woman.

Children and Adolescents

The safety and efficacy of Strattera in paediatric patients less than 6 years of age have not been established. The safety and efficacy of Strattera has been established in acute studies (up to 9 weeks) and long-term studies (up to 2 years). The efficacy of Strattera beyond 18 months of treatment and safety of Strattera beyond 2 years of treatment have not been systematically evaluated. When considering treatment with Strattera for extended periods, physicians should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see *Dosage and Administration - Maintenance/Extended Treatment*).

Young rats were treated with atomoxetine to evaluate effects on growth and neurobehavioural and sexual development. Rats were treated with 1, 10 and 50 mg/kg/day atomoxetine (0.1, 1 and 6 times, respectively, the maximum paediatric dose on a mg/m^2 basis) by gavage from the early post-natal period (day 10 of age) through adulthood (day 85 of age). Slight delays in onset of vaginal patency (all doses) and preputial separation (10 and 50 mg/kg), slight decreases in epididymal weight and sperm number (10 and 50 mg/kg) and a slight decrease in corpora lutea (50 mg/kg) were noted, but there were no effects on fertility or reproductive performance. A slight delay in onset of incisor eruption was seen at 50 mg/kg. A slight increase in motor activity was seen on day 15 (males given 10 and 50 mg/kg) and on day 30 (females at 50 mg/kg) but not on day 60 of age. There were no effects on learning and memory tests. The significance of these findings in humans is unknown.

Elderly Use

The safety and efficacy of Strattera in elderly patients (over 65) have not been established.

Patients with Concomitant Illness

In a controlled study of paediatric patients with ADHD and comorbid chronic motor tics or Tourette's Disorder, Strattera-treated patients did not experience worsening of tics compared to placebo-treated patients. In a controlled study of adolescent patients with ADHD and comorbid Major Depressive Disorder, Strattera-treated patients did not experience worsening of depression compared to placebo-treated patients. In two controlled studies (one in paediatric patients and one in adult patients) of patients with ADHD and comorbid anxiety disorders, Strattera-treated patients did not experience worsening of anxiety compared to placebo-treated patients. There have been rare post-marketing reports of anxiety and depression or depressed mood and very rare reports of tics (see *Adverse Effects*).

INTERACTIONS WITH OTHER MEDICINES

Cytochrome P450 Enzymes: Atomoxetine did not cause clinically significant inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6 and CYP2C9. Using *in vitro* preparations, atomoxetine and N-desmethylatomoxetine are predicted to inhibit the activities of cytochrome P450 enzymes CYP2D6, CYP3A and CYP2C9 (predicted inhibition is 65%, 73% and 16% at maximum dose, respectively). However, in clinical studies evaluating the co-administration of atomoxetine with desipramine, a model compound for CYP2D6 metabolised drugs, or midazolam, a model compound for CYP3A4 metabolised drugs, atomoxetine did not significantly alter the pharmacokinetics of these model compounds. Atomoxetine is principally metabolised by the CYP2D6 pathway. In CYP2D6 EMs, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 PMs. In EMs, selective inhibitors of CYP2D6 increased atomoxetine steady-state plasma concentrations to exposures less than or similar to those observed in PMs. This pharmacokinetic interaction did not result in an increased sensitivity to Strattera.

In vitro studies suggest that several CYP isoforms are involved in the formation of 4-hydroxyatomoxetine in CYP2D6 PMs (including CYP2B6, CYP2C19 and CYP2E1) and therefore co-administration of cytochrome P450 inhibitors may not markedly increase the circulating plasma concentration of atomoxetine.

Fluoxetine, Paroxetine or Quinidine: Administration of Strattera to patients taking fluoxetine, paroxetine or quinidine, known inhibitors of CYP2D6, resulted in a higher plasma exposure to atomoxetine. In EM individuals treated with paroxetine or fluoxetine, the AUC of atomoxetine is approximately 6- to 8-fold and $C_{ss,max}$ is about 3- to 4-fold greater than atomoxetine alone.

In post-marketing reports, QT prolongation has been very rarely reported amongst patients taking Strattera in overdose, and in conjunction with CYP2D6 inhibitors such as fluoxetine, paroxetine or quinidine. Concomitant administration of Strattera with drugs that prolong QT interval, drugs that cause electrolyte disturbance and drugs that inhibit CYP2D6 is cautioned (See *Clinical Trials – Cardiac Electrophysiology).*

Dosage adjustment of Strattera may be necessary in those patients who are also taking CYP2D6 inhibitor drugs (see *Dosage and Administration, CYP2D6 inhibitors*).

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

Midazolam: Co-administration of Strattera with midazolam resulted in small increases in midazolam plasma concentrations. These changes were smaller than those caused by weak inhibitors of CYP3A and therefore, no dose adjustment is recommended for drugs metabolised by CYP3A.

Monoamine Oxidase Inhibitors: (see *Contraindications).*

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

Drugs that Affect Noradrenaline: Drugs that affect noradrenaline such as α1 agonists or those that inhibit the reuptake of noradrenaline should be used cautiously when co-administered with Strattera because of the potential for additive or synergistic pharmacological effects.

Beta-Adrenergic Receptor Agonists: Strattera should be administered with caution to patients being treated with systemically-administered (oral or intravenous) salbutamol (or other $beta_2$ agonists) because the action of salbutamol on the cardiovascular system can be potentiated.

Tricyclic Antidepressants: Strattera can increase the adverse cardiovascular effects of tricyclic antidepressants if co-administered.

Desipramine (a tricyclic antidepressant) pharmacokinetics, which is dependent on CYP2D6 metabolism, were not altered by steady-state atomoxetine concentrations. However these drugs should not be used in combination because one of desipramine's effects is to block noradrenaline reuptake.

Drugs Highly Bound to Plasma Protein: *In vitro* drug-displacement studies were conducted with atomoxetine and other highly bound drugs at therapeutic concentrations. Atomoxetine did not affect plasma protein binding of acetylsalicylic acid, desipramine or warfarin to human plasma proteins. However, atomoxetine increased the fraction of unbound diazepam (by 60%), paroxetine (by 19%) and phenytoin (by 11%). Desipramine, diazepam, paroxetine, phenytoin, midazolam and warfarin did not change the fraction of atomoxetine bound to plasma proteins. High concentrations of acetylsalicylic acid (≥ 300 μg/mL) caused up to a 3-fold increase in the unbound fraction of Strattera.

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

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

Effects on Ability to Drive and Use Machinery

Patients should be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by Strattera.

Drug Abuse and Dependence

Physical and Psychological Dependence: A randomised, double-blind, placebo-controlled, abuse-potential study was conducted in recreational drug users (n=16) of the ages 18 to 36 who did not meet DSM-IV criteria for substance abuse. Atomoxetine was administered in single doses. The study results suggest that Strattera does not have a significant potential for abuse.

Clinical study data in over 3000 children, adolescents and adults with ADHD and over 1200 adults with depression did not demonstrate any pattern of drug diversion or inappropriate self-administration associated with Strattera. There was no evidence of symptom rebound or adverse events suggesting a drug-discontinuation or withdrawal syndrome.

Animal Experience: Drug discrimination studies in rats and monkeys showed inconsistent stimulus generalisation between atomoxetine and cocaine. Atomoxetine substituted for the discriminative stimulus effect of cocaine in some monkeys (0.6-5.6 mg/kg, 0.1-0.8 times the maximum adult dose on a mg/m^2 basis) and rats (at 5-50 mg/kg, 0.4-3.8 times the maximum adult dose on a mg/m^2 basis). The main 4-hydroxyatomoxetine metabolite has moderate affinity (Ki 95-422nM) for opioid receptors.

ADVERSE EFFECTS

Clinical Trial Data:

Child and Adolescent Patients	Frequency of Occurrence		
System Organ Class/Adverse Event	**≥ 10%**	**≥ 1% and < 10%**	**≥ 0.1% and < 1%**
Cardiac Disorders			
Palpitations			X
Sinus tachycardia			X
Eye Disorders			
Mydriasis		X	
Conjunctivitis			X
Gastrointestinal Disorders			
Abdominal pain[1]	X		
Constipation		X	
Dyspepsia		X	
Nausea	X		
Vomiting	X		
General Disorders and Administration Site Conditions			
Asthenia			X
Fatigue		X	
Irritability		X	
Investigations			
Blood pressure increased[2]	X		
Heart rate increased[2]	X		
Weight decreased		X	
Metabolism and Nutritional Disorders			
Anorexia		X	
Appetite decreased	X		
Nervous System Disorders			
Dizziness		X	
Headache	X		
Somnolence[3]	X		
Syncope[4]			X
Tremor			X
Psychiatric Disorders			
Insomnia[5]		X	
Mood swings		X	
Depression[6]		X	
Skin and Subcutaneous Tissue Disorders			
Pruritus		X	
Rash		X	

1 Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort.
2 Heart rate and blood pressure data are based on measured vital signs.
3 Also includes sedation.
4 Also includes syncope vasovagal.
5 Also includes initial insomnia, middle insomnia and terminal insomnia.
6 Also includes major depression, depressive symptoms, depressed mood and dysphoria.

The following adverse events occurred in at least 2% of child and adolescent CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared with CYP2D6 EM patients: weight decreased (7.3% of PMs, 4.4% of EMs); constipation (6.8% of PMs, 4.3% of EMs); insomnia (11% of PMs, 6.1% of EMs); depression (6.5% of PMs, 4.1% of EMs); tremor (4.5% of PMs, 0.9% of EMs); middle insomnia (2.8% of PMs, 1.3% of EMs); syncope (2.5% of PMs, 0.7% of EMs); conjunctivitis (2.5% of PMs, 1.2% of EMs); early morning awakening (2.3% of PMs, 0.8% of EMs); mydriasis (2.0% of PMs, 0.6% of EMs); sedation (3.9% of PMs, 2.1% of EMs).

Growth: Paediatric patients treated with Strattera in ADHD clinical trials had a mean initial decrease in weight and height gain. Subsequently, over the long-term period, patients recovered to the mean weight and height predicted by group baseline data.

Adult Patients	Frequency of Occurrence		
System Organ Class/Adverse Event	**≥ 10%**	**≥ 1% and < 10%**	**≥ 0.1% and < 1%**
Cardiac Disorders			
Palpitations		X	
Tachycardia		X	
Eye Disorders			
Vision blurred			X
Gastrointestinal Disorders			
Abdominal pain[1]		X	
Constipation		X	
Dry mouth	X		
Dyspepsia		X	
Flatulence		X	
Nausea	X		
Vomiting		X	
General Disorders and Administration Site Conditions			
Asthenia		X	
Fatigue		X	
Chills		X	
Feeling cold			X
Feeling jittery		X	
Irritability		X	
Thirst		X	
Investigations			
Blood pressure increased[2]	X		
Heart rate increased[2]	X		
Weight decreased		X	
Metabolism and Nutritional Disorders			
Appetite decreased	X		
Musculoskeletal and Connective Tissue Disorders			
Muscle spasm			X
Nervous System Disorders			
Dizziness		X	
Dysgeusia		X	
Headache	X		
Paraesthesia		X	
Somnolence[3]		X	
Tremor		X	
Psychiatric Disorders			
Agitation		X	
Insomnia[4]	X		
Libido decreased		X	
Orgasm abnormal			X
Restlessness			X
Sleep disorder		X	
Renal and Urinary Disorders			
Dysuria		X	
Micturition urgency			X
Pollakiuria		X	
Urinary hesitation[5]		X	
Urinary retention		X	
Reproductive System and Breast Disorders			
Dysmenorrhoea[6]		X	
Ejaculation disorder[7]		X	
Ejaculation failure[7]			X
Erectile dysfunction[7]		X	
Menstruation irregular[6]			X
Prostatitis[7]		X	
Testicular pain[7]		X	
Skin and Subcutaneous Tissue Disorders			
Pruritus			X
Rash		X	
Hyperhydrosis		X	
Urticaria			X
Vascular Disorders			
Flushing		X	
Hot flushes		X	
Peripheral coldness			X

1 Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort.
2 Heart rate and blood pressure data are based on measured vital signs
3 Also includes sedation.
4 Also includes initial insomnia, middle insomnia and terminal insomnia.
5 Also includes urine flow decreased.
6 Frequency percentage based on female patients only.
7 Frequency percentage based on male patients only.

The following adverse events occurred in at least 2% of adult CYP2D6 PM patients and were statistically significantly more frequent in PM patients compared to CYP2D6 EM patients: vision blurred (3.9% of PMs, 1.3% of EMs); dry mouth (34.5% of PMs, 17.4% of EMs); constipation (11.3% of PMs, 6.7% of EMs); feeling jittery (4.9% of PMs, 1.9% of EMs); decreased appetite (23.2% of PMs, 14.7% of EMs); tremor (5.4% of PMs, 1.2% of EMs); insomnia (19.2% of PMs, 11.3% of EMs); sleep disorder (6.9% of PMs, 3.4% of EMs); middle insomnia (5.4% of PMs, 2.7% of EMs); terminal insomnia (3.0% of PMs, 0.9% of EMs); urinary retention (5.9% of PMs, 1.2% of EMs); erectile dysfunction (20.9% of PMs, 8.9% of EMs); ejaculation disorder (6.1% of PMs, 2.2% of EMs); hyperhidrosis (14.8% of PMs, 6.8% of EMs); peripheral coldness (3.0% of PMs, 0.5% of EMs).

Spontaneous Data:

All Patient Unless Otherwise Specified	Frequency of Reporting	
System Organ Class/Adverse Event	**Rare** ≥ 0.01% and < 0.1%	**Very Rare** < 0.01%
General Disorders and Administration Site Conditions		
Lethargy		X
Investigations		
Blood pressure increased	X	
Nervous System Disorders		
Syncope		X
Paraesthesia *(children and adolescents)*		X
Hypoaesthesia		X
Tics		X
Psychiatric Disorders		
Sensory disturbances including hallucinations		X
Depression and depressed mood	X	
Anxiety	X	
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis		X
Urogenital System		
Painful or prolonged penile erection, male genital pain		X
Urinary hesitation *(children and adolescents)*		X
Urinary retention *(children and adolescents*		X
Vascular Disorders		
Peripheral vascular instability and/or Raynaud's phenomenon		X
Potential to exacerbate pre-existing Raynaud's phenomenon		X

DOSAGE AND ADMINISTRATION

Initial Treatment

Dosing of Children and Adolescents up to 70 kg body weight: Strattera should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After 2 to 4 additional weeks, the total daily dose may be increased to a maximum of 1.4 mg/kg in patients who have not achieved an optimal response (see *Pharmacology, Clinical Trials*).

The maximum recommended total daily dose in children and adolescents is 1.4 mg/kg or 100mg, whichever is less.

Dosing of Children and Adolescents over 70kg body weight and Adults: Strattera should be initiated at a total daily dose of 40mg and increased after a minimum of 3 days to a target total daily dose of approximately 80mg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. After 2 to 4 additional weeks, the dose may be increased to a maximum of 100mg in patients who have not achieved an optimal response (see *Pharmacology, Clinical Trials*). There are no data supporting increased effectiveness at higher doses.

The maximum recommended total daily dose in children and adolescents over 70kg and adults is 100mg.

Interrupted Treatment

If therapy is interrupted for more than 1 week, treatment should be started at the recommended starting dose – refer to Initial Treatment.

Maintenance/Extended Treatment

There is no evidence available from controlled trials to indicate how long the patient with ADHD should be treated with Strattera. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use Strattera for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

General Dosing Information

Strattera may be taken with or without food.

The safety of single doses over 120mg and total daily doses above 150mg have not been systematically evaluated.

For those ADHD patients who have end stage renal disease, cautious titration of Strattera to the desired clinical response is recommended (see *Pharmacology – Pharmacokinetics*). Atomoxetine may exacerbate hypertension in patients with end stage renal disease.

Strattera may be discontinued without tapering the dose.

Hepatic Impairment Dosage Adjustment

Atomoxetine clearance may be reduced in patients with hepatic impairment. For those ADHD patients who have hepatic impairment, dosage adjustment is recommended as follows: For patients with moderate hepatic impairment (Child-Pugh Class B), initial and target doses should be reduced to 50% of the normal dose. For patients with severe hepatic impairment (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of the normal dose.

Dosing adjustment for use with a strong CYP2D6 inhibitor

In children and adolescents up to 70kg body weight administered strong CYP2D6 inhibitors, e.g. paroxetine, fluoxetine and quinidine, Strattera should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70kg body weight and adults administered strong CYP2D6 inhibitors, e.g. paroxetine, fluoxetine and quinidine, Strattera should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

OVERDOSAGE

During post-marketing, there have been no fatalities involving overdose with Strattera alone, including intentional overdose at amounts up to or exceeding 1500mg. The most commonly reported symptoms accompanying acute and chronic overdoses were gastrointestinal symptoms, somnolence, dizziness, tremor and abnormal behaviour. Hyperactivity and agitation have also been reported. Signs and symptoms consistent with mild to moderate sympathetic nervous system activation (e.g. tachycardia, blood pressure increased, mydriasis, dry mouth) were also observed. Most events were mild to moderate. In some cases of overdose involving Strattera, seizures and QT prolongation have been reported (see *Pharmacodynamics*). There have also been reports of fatal, acute overdoses involving mixed ingestion of Strattera and at least one other drug. There is limited clinical trial experience with Strattera overdose.

No specific information is available on the treatment of overdose with Strattera. An airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion. Activated charcoal may be useful in limiting absorption. Because Strattera is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

INSTRUCTIONS FOR USE/HANDLING

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

STORAGE CONDITION AND PRESENTATION

Do not store above 30°C.

Hard capsules containing 10mg, 18mg, 25mg, 40mg and 60mg atomoxetine (as hydrochloride) in cold-form aluminium laminate blister sealed with PVC based heat seal coated aluminium foil in packs of 28's.

The hard capsule colours and markings are as follows:
10mg hard capsules: opaque white and marked with 'Lilly 3227' and '10mg'
18mg hard capsules: gold and opaque white and marked with 'Lilly 3238' and '18mg'
25mg hard capsules: opaque blue and opaque white and marked with 'Lilly 3228' and '25mg'
40mg hard capsules: opaque blue and marked with 'Lilly 3229' and '40mg'
60mg hard capsules: opaque blue and gold and marked with 'Lilly 3239' and '60mg'

PRODUCT OWNER

Eli Lilly and Company, Indianapolis, IN 46285, United States

Date of Revision of Text: 20 Oct 2017

STRATTERA®

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NL057SPNS00

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PPD Information Box		ALRP Information Box
Technical Information: BLACK	DIECUT	Translations of Variable Data Lot: N/A Exp Date: N/A Mfg Date: N/A Price: N/A GTIN: N/A Serial Number : N/A
Layout Name ALCPA0076A00	Previous Item Code *(to be destroyed)* N/A	Variable Barcode Information N/A

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