

PRODUCT INFORMATION
ATOMOXETINE SANDOZ® 10MG, 18MG, 25MG, 40MG, 60MG, 80MG, 100MG
CAPSULE

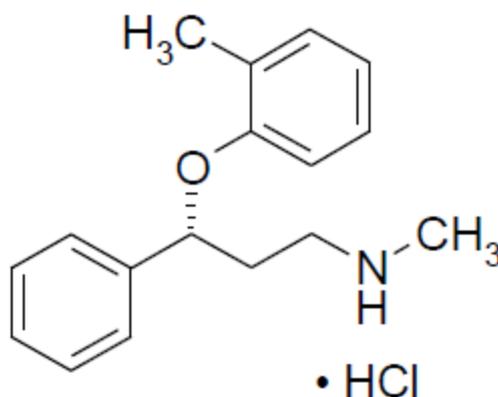
WARNINGS

Short-term placebo controlled studies evaluated over 2200 children and adolescents with Attention Deficit Hyperactivity Disorder (ADHD). Among the 1357 patients on atomoxetine, there was a positive signal for suicidal thoughts (5 patients) and behaviours (1 patient) in children 12 years of age and younger compared to placebo (0/851). No suicides occurred in these trials. Anyone considering the use of atomoxetine in children must balance the risk of suicidality (suicidal thoughts or behaviours) against the clinical need. Patients who are started on atomoxetine should be closely monitored for suicidality (see PRECAUTIONS).

NAME OF THE MEDICINE

Atomoxetine hydrochloride

The chemical structure is:



Chemical name: (3*R*)-*N*-Methyl-3-(2-methylphenoxy)-3-phenylpropan-1-amine hydrochloride.

Empirical formula: C₁₇H₂₁NO•HCl

Molecular weight: 291.82 daltons

CAS Registry Number: 82248-59-7.

DESCRIPTION

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

ATOMOXETINE SANDOZ is available as capsules for oral administration.

Each capsule contains 10, 18, 25, 40, 60, 80 or 100 mg of atomoxetine (as hydrochloride). The capsules also contain StarCap 1500 Co-Processed Starch Excipient (ARTG No. 12847), dimeticone 350, sodium starch glycolate type A.

The following details relate to the capsule shells and lids in which the capsule contents are encapsulated: Empty hard gelatin capsules size 4, 0999 White Opaque - 0999 White Opaque (ARTG No. 109783; 10 mg); Empty hard gelatin capsules size 3, 0999 White Opaque - 2306 Gold Opaque (ARTG No. 109778; 18 mg); Empty hard gelatin capsules size 3 0999 White Op - 1516 Blue Opaque (ARTG No. 109942; 25 mg); Empty hard gelatin capsules size 2, 1516 Blue Opaque - 1516 Blue Opaque (ARTG No. 109794; 40 mg); Empty hard gelatin capsules size 2, 2306 Gold Opaque - 1516 Blue Opaque (ARTG No. 109784; 60 mg); Empty hard gelatin capsules size 1, 0999 White Opaque - 1889 Brown Opaque (ARTG No. 109757; 80 mg) and Empty hard gelatin capsules size 0, 1889 Brown Opaque - 1889 Brown Opaque (ARTG No. 109785; 100 mg). These are imprinted with TekPrint SW-9008 Black Ink (ARTG No. 2328).

PHARMACOLOGY

Pharmacodynamics

Atomoxetine 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 4.5 nM), a moderate inhibitor of 5HT uptake (K_i 152 nM) and a weak inhibitor of dopamine uptake (K_i 658 nM), with minimal affinity for the other noradrenergic receptors.

Atomoxetine has moderate affinity for 5HT₂ 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 3.0 nM), and a more potent inhibitor of the 5HT transporter (K_i 43 nM) than the parent compound.

A thorough QT/QTc study, conducted in healthy adult CYP2D6 poor metabolizer (PM) subjects dosed up to 60 mg of atomoxetine BID, demonstrated that at maximum expected concentrations the effect of atomoxetine on QTc interval was not significantly different from placebo. There was an increase in QTc interval with increased atomoxetine concentration (see **CLINICAL TRIALS – Cardiac Electrophysiology, PRECAUTIONS - Cardiovascular Effects and Interactions 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).

Atomoxetine can be administered with or without food. In clinical trials with children and adolescents, administration of atomoxetine with food resulted in a 9% lower C_{max} .

Administration of atomoxetine 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 atomoxetine, 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 (93% of Caucasians and 98% of African Americans) and poor metabolisers (7% of Caucasians and 2% of African Americans). The major oxidative metabolite formed, regardless of CYP2D6 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 extensive metabolisers 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 atomoxetine with known inhibitors of CYP2D6 does not result in an increased sensitivity to atomoxetine, 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 extensive metabolisers and 21 hours in poor metabolisers. 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 0.35L/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 atomoxetine dose is excreted as unchanged atomoxetine (less than 3% of the dose), indicating extensive biotransformation.

Special Populations

Hepatic Impairment: Single doses of atomoxetine 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 poor metabolisers. Dosage adjustment is recommended for patients with moderate or severe hepatic impairment (see **DOSAGE AND ADMINISTRATION, Hepatic Impairment**).

Renal Impairment: Single doses of atomoxetine 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 poor metabolisers. atomoxetine may exacerbate hypertension in patients with end stage renal disease. For those

ADHD patients who have end stage renal disease, cautious titration of atomoxetine 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 atomoxetine 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 atomoxetine 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 atomoxetine 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).

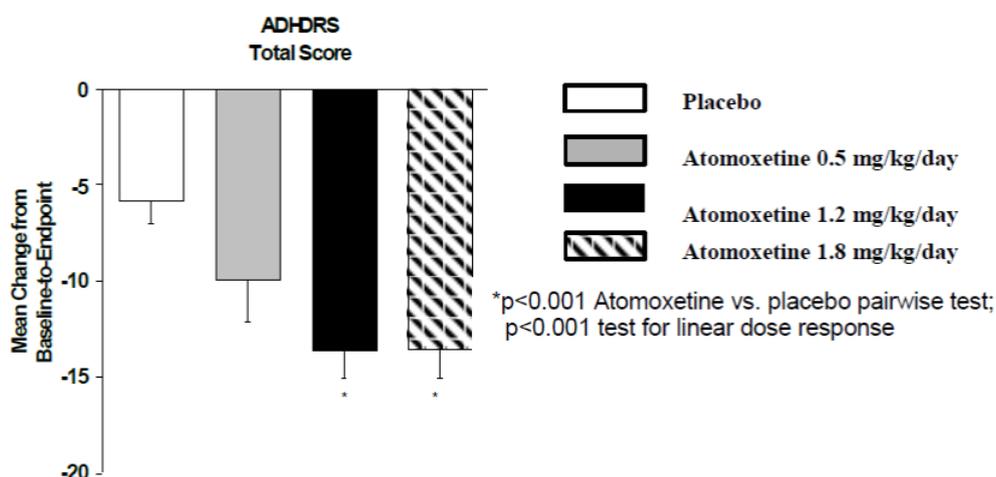
Approximately one third of the patients met DSM-IV criteria for inattentive subtype and two thirds met criteria for both inattentive and hyperactive/impulsive subtypes.

Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for atomoxetine-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 atomoxetine (0.5 mg/kg/day, 1.2 mg/kg/day or 1.8 mg/kg/day) or placebo. Atomoxetine was administered as a divided dose in the early morning and late afternoon / early evening. Treatment with atomoxetine showed an overall improvement in the reductions from baseline

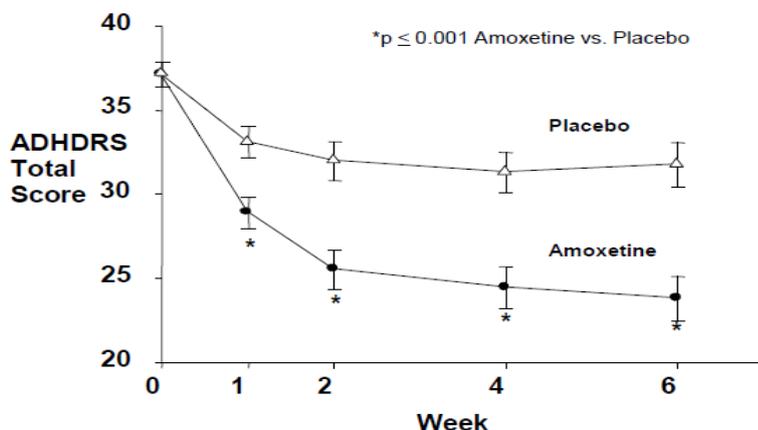
in mean ADHDRS total score. The average score decreased by 25% on 0.5mg/kg/day, 35% on 1.2 mg/kg/day and 34% on 1.8 mg/kg/day atomoxetine, compared to 15% with placebo. At the two higher doses, improvements in ADHD symptoms were superior and statistically significant ($p < 0.001$ vs placebo) in atomoxetine-treated 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 – Atomoxetine 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 atomoxetine or placebo. Atomoxetine was administered as a single dose in the early morning and titrated on a weight-adjusted basis according to clinical response. The maximum atomoxetine dose was 1.5 mg/kg/day. The mean final dose of atomoxetine was approximately 1.3mg/kg/day. Treatment with atomoxetine showed an overall improvement in the reductions from baseline in mean ADHDRS total score. The average score decreased by 34% on atomoxetine, compared to 13% with placebo ($p < 0.001$ vs placebo). Improvements in ADHD symptoms were superior and statistically significant in atomoxetine-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 atomoxetine is effective when administered once daily in the morning. The results of Study LYAT are summarized in Figure 2.

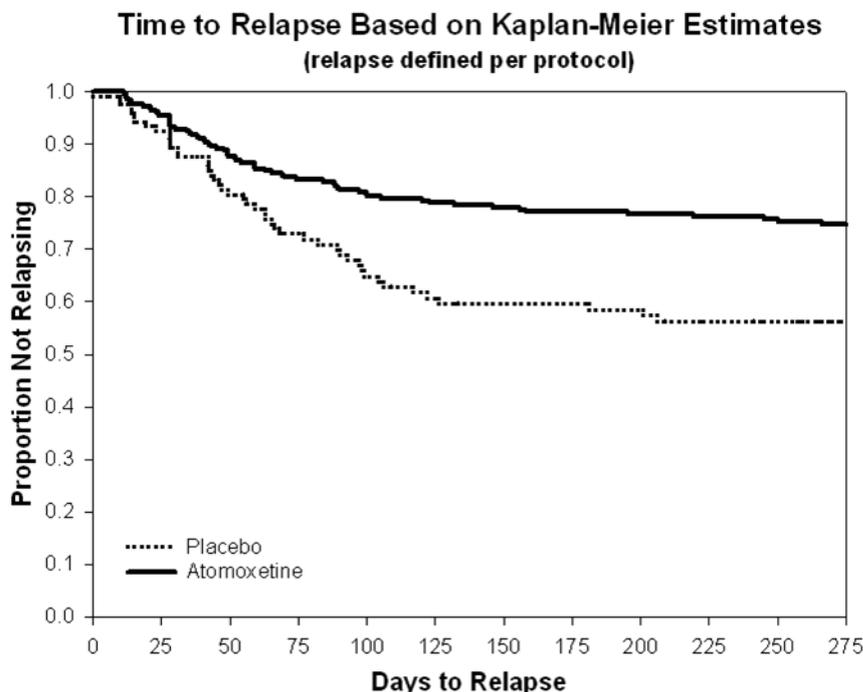
Figure 2. Study LYAT – Once-Daily Administration of Amoxetine.



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), atomoxetine or methylphenidate was compared with placebo. Methylphenidate was only used to show that the study design was valid (ie. by its separation from placebo). These studies were not statistically powered to provide a comparative analysis between atomoxetine and methylphenidate (patient numbers per treatment, Study HFBD, atomoxetine N=65, methylphenidate N=20, placebo N=62; Study HFBK, atomoxetine N=64, methylphenidate N=18, placebo N=62). The primary comparison of interest in both studies was atomoxetine versus placebo. Atomoxetine 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 atomoxetine dose was 2.0 mg/kg/day. The mean final dose of atomoxetine for both studies was approximately 1.6 mg/kg/day. Treatment with atomoxetine showed an overall improvement from baseline in mean ADHDRS total score. The average score decreased by 38% on atomoxetine, compared to 13% with placebo ($p < 0.0001$ vs placebo) in study HFBD and 38% on atomoxetine, compared to 16% with placebo ($p < 0.0003$ vs placebo) in study HFBK.

Study LYAF: was 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 atomoxetine and responders were randomised to a further 40 weeks of treatment discontinuation phase (N=292 atomoxetine, N=124 placebo). At endpoint (1 year), atomoxetine was superior to placebo in maintaining clinical response (refer to Kaplan-Meier plot provided as Figure 2). The relapse rate was 18.7% on atomoxetine versus 31.4% on placebo ($p = 0.021$ all qualified patients).

Figure 3. Study LYAF – Relapse Prevention Study of atomoxetine



Study LYAB: was 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 atomoxetine (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 atomoxetine-treated patients decreased by 48.5% as measured by the ADHD rating scale total score for study periods II and III. Atomoxetine was well tolerated in this long-term safety study and adverse events did not increase over time. The adverse event profile for poor metaboliser patients was similar to that for extensive metaboliser 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.

Study LYBP: a randomised, double-blind, placebo controlled study to assess the efficacy of atomoxetine compared with placebo in children and adolescents with ADHD and comorbid anxiety. Patients enrolled in the trial met the DSM-IV criteria for ADHD and also had at least one of the following anxiety disorders: separation anxiety disorder, generalised anxiety disorder, or social phobia. The study confirmed the efficacy of atomoxetine in treating the core symptoms of ADHD as evidenced by the statistically significant improvement in the pre-specified co-primary measure for ADHD (ADHDRS). See **PRECAUTIONS, Effects on Comorbid Anxiety**

Study LYAS: a randomised, double-blind, placebo controlled study of atomoxetine in children and adolescents with ADHD and comorbid Tourette's Disorder or chronic motor tics. Patients were aged 7 to 17 years 6 months and met the DSM-IV criteria for ADHD with comorbid Tourette's Disorder or chronic motor tics. Consistent with other studies, atomoxetine produced

a significant improvement in ADHD symptoms as measured by the ADHDRS and CGI-ADHD-S. See **PRECAUTIONS, Effects on Comorbid Chronic Tics or Tourette's Disorder**

Adults:

The efficacy of atomoxetine 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 atomoxetine or placebo. Atomoxetine was administered as a divided dose in the early morning and late afternoon/early evening and titrated according to clinical response. The maximum atomoxetine dose was 120 mg/day. The mean final dose of atomoxetine for both studies was approximately 95 mg/day. Treatment with atomoxetine showed an overall improvement from baseline in mean CAARS total score. The average score decreased by 28% on atomoxetine, compared to 18% with placebo ($p<0.001$ vs placebo) in study LYAA and 30% on atomoxetine, 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 atomoxetine-treated patients compared with placebo-treated patients as measured on the CAARS scale.

Study LYAR: was an open-label, multi-centre investigation of the long-term safety and tolerability of atomoxetine 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.

Study LYDQ: was a randomized, double-blind, placebo-controlled study of atomoxetine in adults (18 – 65 years) with ADHD and comorbid social anxiety disorder. Patients enrolled in the trial met the DSM-IV criteria for ADHD and social anxiety disorder. Patients showed statistically significant mean-change improvements over placebo-treated patients from baseline to endpoint on the CAARS investigator rated scale (see **PRECAUTIONS, Effects on Comorbid Anxiety**).

Cardiac Electrophysiology: The effect of atomoxetine on QTc prolongation was evaluated in a randomized, double-blinded, positive-(moxifloxacin 400 mg) and placebo-controlled, cross-over study in healthy male CYP2D6 poor metabolizers. A total of 120 healthy subjects were administered atomoxetine (20 mg and 60 mg) 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** and **INTERACTIONS WITH OTHER MEDICINES**).

INDICATIONS

Treatment of Attention Deficit Hyperactivity Disorder (ADHD) as defined by DSM-IV criteria in children 6 years of age and older, adolescents and adults.

CONTRAINDICATIONS

Atomoxetine is contraindicated in patients with:

- **Known hypersensitivity** to atomoxetine or any excipients in this product.
- **Symptomatic cardiovascular disease** - moderate to severe hypertension, atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation, or ventricular flutter, advanced arteriosclerosis (also see **PRECAUTIONS**)
- **Severe Cardiovascular Disorders** - atomoxetine should not be used in patients with severe cardiovascular disorders whose condition would be expected to deteriorate if they experienced increases in blood pressure or in heart rate (for example, 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate) (see **PRECAUTIONS - Cardiovascular Effects**).
- **Uncontrolled hyperthyroidism**
- **Phaeochromocytoma** - atomoxetine should not be used in patients with pheochromocytoma or a history of pheochromocytoma (see **PRECAUTIONS - Cardiovascular Effects**).
- **Monoamine Oxidase Inhibitors** - atomoxetine should not be taken with monoamine oxidase inhibitors (MAOI) or within 2 weeks after discontinuing MAOI. Treatment with MAOI should not be initiated within 2 weeks after discontinuing atomoxetine.

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 atomoxetine 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 atomoxetine in children and adolescents showed a greater risk of suicidal ideation during treatment in those receiving atomoxetine. 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 atomoxetine was 0.4% (5/1357) compared with 0% (0/851) in patients treated with placebo.

There was 1 suicide attempt in patients treated with atomoxetine and none in patients treated with placebo. No suicides occurred in these trials. All events of suicidal ideation and behaviour associated with atomoxetine 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 atomoxetine. A similar meta-analysis in adult patients treated with atomoxetine 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 atomoxetine.

All children being treated with atomoxetine 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 atomoxetine: 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 atomoxetine, 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 atomoxetine 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 wouldn't 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.

Emergence of New Psychotic or Manic Symptoms:

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by atomoxetine at usual doses. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine, and discontinuation of treatment should be considered. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.2% (4 patients with reactions out of 1939 exposed to atomoxetine for several weeks at usual doses) of atomoxetine-treated patients compared to 0 out of 1056 placebo-treated patients.

Screening Patients for Bipolar Disorder:

In general, particular care should be taken in treating ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with atomoxetine, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Possible Allergic Events:

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

Seizures:

The pre-clinical and clinical trial data for atomoxetine do not suggest that atomoxetine is proconvulsive. However, seizures have been very rarely reported in post-marketing spontaneous reports. Atomoxetine should be used with caution in patients with a history of seizures. Discontinuation of atomoxetine 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 during the course of treatment.

Atomoxetine can affect heart rate and blood pressure. It is recommended that heart rate and blood pressure should be measured at baseline, following atomoxetine dose increases, and periodically while on therapy to detect possible clinically important increases.

Most patients taking atomoxetine experience a modest increase in heart rate (mean <10bpm) and/or increase in blood pressure (<5mm Hg) that are not clinically important. In children and adolescents, pulse increased an average of 6-8 bpm in EMs (90-95% of patients) or 10-14 bpm in PMs (5-10% of patients) and systolic or diastolic blood pressure increased an average of 2mmHg in EMs (90-95% of patients) or 4mmHg in PMs (5-10% of patients). Adult patients experienced a mean pulse increase of 5 bpm and/or mean increases in systolic (3mmHg) or diastolic (1mmHg) blood pressures (see **ADVERSE EFFECTS**). However, data from ADHD clinical trials show that some patients do experience clinically important changes in heart rate or blood pressure.

Paediatric use:

Additional data from ADHD clinical trials (controlled and uncontrolled) has shown that approximately 39% of paediatric patients experienced clinically relevant changes (≥ 20 beats per min) in heart rate during the study, and paediatric patients experiencing clinically relevant changes in heart rate at study endpoint were 12%; 33% of paediatric patients experienced clinically relevant changes (≥ 15 mm Hg) in diastolic and 23% in systolic (≥ 20 mm Hg) blood pressure during the study and paediatric patients experiencing clinically relevant changes in diastolic and systolic blood pressure (≥ 15 and ≥ 20 mm Hg) at study endpoint were 11% and 8%, respectively.

Adult:

Additional data from ADHD clinical trials (controlled and uncontrolled) has shown that approximately 26% of adult patients experienced clinically relevant changes (≥ 20 beats per min) in heart rate during the study and adult patients experiencing clinically relevant changes in heart rate at study endpoint were approximately 10%; 16% of adult patients experienced clinically relevant changes (≥ 15 mm Hg) in diastolic and 14% in systolic (≥ 20 mm Hg) blood pressure during the study and adult patients experiencing clinically relevant changes in diastolic and systolic blood pressure (≥ 15 and ≥ 20 mm Hg) at study endpoint were 7% and 6%, respectively.

Atomoxetine 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.

Atomoxetine 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, atomoxetine 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 with a family history of QT prolongation.

A thorough QT/QTc study, conducted in healthy adult CYP2D6 poor metabolizer (PM) subjects dosed up to 60 mg of atomoxetine BID, demonstrated that at maximum expected concentrations the effect of atomoxetine on QTc interval was not significantly different from placebo. There was an increase in QTc interval with increased atomoxetine concentration (see **Pharmacodynamics, CLINICAL TRIALS – Cardiac Electrophysiology, PRECAUTIONS, INTERACTIONS WITH OTHER MEDICINES**).

As orthostatic hypotension has also been reported, atomoxetine 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**)

Atomoxetine should be used with caution in patients with a history of hyperthyroidism.

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: *a*) are involved in strenuous exercise or activities, *b*) use stimulants, or *c*) have a family history of sudden/cardiac death. Atomoxetine 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, atomoxetine 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 atomoxetine subjects compared with placebo subjects (0%, 0/263). A complaint of urinary retention or urinary hesitancy should be considered potentially related to atomoxetine. Use with caution in patients with enlarged prostates or other conditions predisposing to urinary retention.

Effects on Growth (Height and Weight)

Data from longer-term trials (≥ 2 years) suggest that any effect of atomoxetine 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 10.7 kg), 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 0.9 kg. At 24 months, there was also marked absolute mean height gain (approximately 13.1 cm), 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 0.5 cm.

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 versus 0.76 for placebo group) and normative weights (-3.93 percentiles for atomoxetine group versus 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 atomoxetine. The potential effect of treatment with atomoxetine on final adult stature is unknown. Periodic monitoring of height and weight is recommended for patients requiring long-term therapy.

Effects on Comorbid Chronic Tics or Tourette's Disorder

A randomized, double-blind study of atomoxetine and placebo in paediatric outpatients with ADHD and comorbid tic disorders, showed that atomoxetine did not worsen tics in patients with ADHD and comorbid chronic motor tics or Tourette's disorder (see **CLINICAL TRIALS**).

There have been very rare post-marketing reports of tics with atomoxetine treatment (see **Adverse Events Based On Post Marketing Reports**).

Effects on Comorbid Anxiety

Two randomised, double-blind, placebo-controlled studies of atomoxetine, one in children and adolescents with ADHD and comorbid anxiety and one in adults with comorbid social anxiety disorder, showed that atomoxetine did not worsen anxiety in patients with ADHD and comorbid anxiety (see **CLINICAL TRIALS**).

There have been rare postmarketing reports of anxiety with atomoxetine treatment (see **Adverse Events Based On Post Marketing Reports**).

Hepatic Effects

Post-marketing reports indicate that atomoxetine can cause severe liver injury in rare cases, including acute liver failure. Very rarely, spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported. More than 2 million patients have received atomoxetine during the first two years of global post-marketing experience. During such time, there have been two reported cases of markedly elevated hepatic enzymes and bilirubin, in the absence of other obvious explanatory factors. In one of these cases, liver injury recurred upon rechallenge, and was followed by recovery upon drug discontinuation. The patients described above recovered from their liver injury. Such reactions may occur several months after therapy is started, but laboratory abnormalities may continue to worsen for several weeks after drug is stopped.

As with other medications which can cause severe drug-related liver injury, it is possible that a small percentage of patients may progress to acute liver failure resulting in death or the need for a liver transplant.

Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted. Laboratory testing to determine liver enzyme levels should be conducted on the first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms).

Hepatic Impairment (see **PHARMACOLOGY, Pharmacokinetics, Special Populations and DOSAGE and ADMINISTRATION**)

Renal Impairment (see **PHARMACOLOGY, Pharmacokinetics, Special Populations and DOSAGE and ADMINISTRATION**)

Male and female sexual dysfunction

Atomoxetine appears to inhibit sexual function in some patients. Changes in sexual desire, sexual performance, and sexual satisfaction are not well assessed in most clinical trials because they need special attention and because patients and physicians may be reluctant to discuss them.

Carcinogenicity

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/m² basis. Systemic exposure (plasma AUC) to active moiety (atomoxetine + 4-hydroxyatomoxetine) in rats was estimated to be less than that in extensive or poor metabolisers receiving the maximum dose, and exposure in mice was estimated to be 1 to 3 times that in extensive metabolisers but less than that in poor metabolisers.

Genotoxicity

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.

Effects on 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/m² 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/m² 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 fetuses 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/m² basis; exposure (plasma AUC) to active moiety (atomoxetine + 4-hydroxyatomoxetine) at this dose is estimated to be less than that in extensive metabolisers or poor metabolisers 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/m² 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 foetal and pup body weight and foetal skeletal anomalies were seen at 41-98 mg/kg/day (3-7 times the maximum tolerated human adult dose on a mg/m² 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/m² basis) and reduced pup survival at 23-39 mg/kg/day (2-3 times the maximum adult dose on a mg/m² basis) along with maternal toxicity. No adverse foetal effects were seen when pregnant rats were treated with up to 150 mg/kg/day (11 times the maximum human dose on a mg/m² basis) by gavage during the period of organogenesis only.

No adequate and well-controlled studies have been conducted in pregnant women.

Atomoxetine 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 atomoxetine 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 atomoxetine is administered to a nursing woman.

Paediatric Use

The safety and efficacy of atomoxetine in paediatric patients less than 6 years of age have not been established. The safety and efficacy of atomoxetine has been established in acute studies (up to 9 weeks) and long-term studies (up to 2 years). When considering treatment with atomoxetine 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/m² basis) by gavage from the early postnatal 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.

Use in the elderly

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

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 atomoxetine.

INTERACTIONS WITH OTHER MEDICINES

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-desmethyatomoxetine 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 extensive metabolisers, inhibitors of CYP2D6 increase atomoxetine steady-state plasma concentrations to exposures similar to those observed in CYP2D6 poor metabolisers. In extensive metabolisers, selective inhibitors of

CYP2D6 increased atomoxetine steady-state plasma concentrations to exposures less than or similar to those observed in poor metaboliser subjects. This pharmacokinetic interaction did not result in an increased sensitivity to atomoxetine.

In vitro studies suggest that several CYP isoforms are involved in the formation of 4-hydroxyatomoxetine in CYP2D6 poor metabolisers (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 atomoxetine 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.

A thorough QT/QTc study, conducted in healthy adult CYP2D6 poor metabolizer (PM) subjects dosed up to 60 mg of atomoxetine BID, demonstrated that at maximum expected concentrations the effect of atomoxetine on QTc interval was not significantly different from placebo. There was an increase in QTc interval with increased atomoxetine concentration (see **Pharmacodynamics, CLINICAL TRIALS – Cardiac Electrophysiology, PRECAUTIONS - Cardiovascular Effects**).

In post marketing reports, QT prolongation has been very rarely reported amongst patients taking atomoxetine in overdose, and in conjunction with CYP2D6 inhibitors such as fluoxetine, paroxetine or quinidine. Concomitant administration of atomoxetine with drugs that prolong QT interval, drugs that cause electrolyte disturbance and drugs that inhibit CYP2D6 is cautioned. Dosage adjustment of atomoxetine 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 atomoxetine did not increase cardiovascular effects beyond those seen with methylphenidate administration alone.

Midazolam: Co-administration of atomoxetine 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: Due to possible effects on blood pressure, atomoxetine 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 α 1 agonists or those that inhibit the reuptake of noradrenaline should be used cautiously when co-administered with atomoxetine because of the potential for additive or synergistic pharmacological effects.

Beta-Adrenergic Receptor Agonists: atomoxetine should be administered with caution to patients being treated with systemically-administered (oral or intravenous) salbutamol (or other beta₂ agonists) because the action of salbutamol on the cardiovascular system can be potentiated.

Tricyclic Antidepressants: atomoxetine 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 ($\geq 300\mu\text{g/mL}$) caused up to a 3- fold increase in the unbound fraction of atomoxetine.

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

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

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 atomoxetine 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 atomoxetine. There was no evidence of symptom rebound or adverse events suggesting a drug-discontinuation or withdrawal syndrome.

Study LYBO – a randomised, double-blind, placebo- and comparator-controlled study compared the subjective, euphoriant effects of atomoxetine at doses of 45 mg, 90 mg and 180 mg with placebo, methylphenidate (90 mg), phentermine (60 mg free base), and desipramine (100, 200 mg) in 40 drug abusing adults with the extensive metaboliser (EM) genotype for cytochrome P450 2D6 (CYP2D6) substrates. This patient group did not report euphoriant effects from use of atomoxetine.

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/m² basis) and rats (at 5-50 mg/kg, 0.4-3.8 times the maximum adult dose on a mg/m² basis). The main 4-hydroxyatomoxetine metabolite has moderate affinity (K_i 95-422 nM) for opioid receptors.

ADVERSE EFFECTS

Adverse Events Identified From Clinical Trials

Atomoxetine was administered to over 3000 children or adolescent patients with ADHD and over 470 adults with ADHD in clinical studies. During the ADHD clinical trials, 1236 children or adolescent patients and 173 adult patients were treated for longer than 1 year, 1704 children or adolescent patients and 236 adult patients were treated for over 6 months.

Associated with Discontinuation of Treatment

In acute child and adolescent placebo-controlled trials, 3.5% (15/427) of atomoxetine subjects and 1.4% (4/294) placebo subjects discontinued for adverse events. For all studies, (including open-label and long-term studies), 5% of extensive metaboliser (EM) patients and 7% of poor metaboliser (PM) patients discontinued because of an adverse event. Among atomoxetine-treated patients, aggression (0.5%, N=2); irritability (0.5%, N=2); somnolence (0.5%, N=2); and vomiting (0.5%, N=2) were the reasons for discontinuation reported by more than 1 patient.

In the acute adult placebo-controlled trials, 8.5% (23/270) atomoxetine subjects and 3.4% (9/266) placebo subjects discontinued for adverse events. Among atomoxetine -treated patients, insomnia (1.1%, N=3); chest pain (0.7%, N=2); palpitations (0.7%, N=2); and urinary retention (0.7%, N=2) were the reasons for discontinuation reported by more than 1 patient.

Child and Adolescent Clinical Trials

The most commonly observed adverse events associated with the use of atomoxetine (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (atomoxetine incidence at least twice placebo) are listed in Table 1.

Table 1. Treatment-emergent adverse events reported by at least 2% of patients treated with atomoxetine and at least twice the placebo incidence in acute (up to 9 weeks) child and adolescent trials

Adverse Event	Percentage of Patients Reporting Event	
	Atomoxetine (n=425)	Placebo (n=292)
System Organ Class/Adverse Event		
Gastrointestinal Disorders		
Constipation	2	1
Dyspepsia	4	1
Infections and Infestations		
Influenza	2	1

Metabolism and Nutritional Disorders		
Appetite decreased	14	6
Nervous System Disorders		
Dizziness	6	2
Psychiatric Disorders		
Mood swings	2	1
Skin and Subcutaneous Tissue Disorders		
Dermatitis	4	2

The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: **very common (>10%)**: abdominal pain (includes abdominal pain upper, stomach discomfort, abdominal discomfort, and epigastric discomfort), vomiting, nausea, blood pressure increased, heart rate increased (heart rate and blood pressure are based on measured vital signs from clinical trials), somnolence (including sedation) and **common (> 1% and <10%)**: anorexia, insomnia (also includes initial insomnia, middle insomnia, and terminal insomnia), irritability, mydriasis, pruritus, rash, weight decreased, depression (also includes major depression, depressive symptoms, depressed mood, and dysphoria) and **uncommon (>0.1% and <1%)**: flushing, palpitations, sinus tachycardia, conjunctivitis, syncope (also includes syncope vasovagal), tremor.

In a post-hoc meta-analysis of the placebo-controlled paediatric clinical trial database, suicidal ideation (suicidal thoughts) was statistically more frequently observed among children and adolescents treated with atomoxetine (5/1357; [0.4%]) compared to those treated with placebo (0/851; [0%]). There was one report of suicidal behaviour in a patient in this age group treated with atomoxetine compared with no reports in patients treated with placebo (see **PRECAUTIONS – Suicidal Ideation and Behaviour**).

Adverse events that occurred after acute treatment were assessed in study LYAF. Table 2 presents new or worsened adverse events in patients who after an initial 3 month period continued on atomoxetine for 9 months or who were switched to placebo.

Table 2. Treatment-emergent adverse events reported by at least 2% of patients treated with atomoxetine and at least twice the placebo incidence reported during long-term treatment (Study LYAF)

Adverse Event	Percentage of Patients Reporting Event	
	Atomoxetine (n=291)	Placebo (n=123)
System Organ Class/Adverse Event		
Gastrointestinal Disorders		
Gastroenteritis	8	2
Vomiting	8	3
Diarrhoea	4	2
Abdominal pain	4	1

Abdominal pain upper	4	0
Infections and Infestations		
Upper respiratory tract infection	5	2
Investigations		
Weight decreased	2	0
Metabolism and Nutritional Disorders		
Anorexia	5	0
Appetite decreased	4	2
Respiratory, thoracic and mediastinal Disorders		
Pharyngitis	6	2

The following events did not meet this criterion but were reported by more atomoxetine-treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: **very common (>10%)**: headache, nausea **common (> 1% and <10%)**: constipation, fatigue, pyrexia, irritability, rash **uncommon (>0.1% and <1%)**: palpitations, sinus tachycardia, tachycardia, asthenia, pruritus.

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

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

Adult Clinical Trials

The most commonly observed adverse events associated with the use of atomoxetine (incidence of 2% or greater) and not observed at an equivalent incidence among placebo-treated patients (atomoxetine incidence at least twice placebo) are listed in Table 3.

Table 3. Treatment-emergent adverse events reported by at least 2% of patients treated with atomoxetine and at least twice the placebo incidence in acute (up to 10 weeks) adult trials

Adverse Event	Percentage of Patients Reporting Event	
	Atomoxetine (n=269)	Placebo (n=263)
System Organ Class/Adverse Event		
Cardiac Disorders		
Palpitations	4	1
Gastrointestinal Disorders		
Dry mouth	21	6

Nausea	12	5
Constipation	10	4
Flatulence	2	1
General Disorders and Administration Site Conditions		
Rigors	3	1
Investigations		
Weight decreased	2	1
Metabolism and Nutritional Disorders		
Appetite decreased	10	3
Nervous System Disorders		
Dizziness	6	2
Headache	3	1
Psychiatric Disorders		
Insomnia	13	6
Middle insomnia	4	1
Libido decreased	6	2
Sleep disorder	4	2
Renal and Urinary Disorders		
Urinary hesitation	3	0
Urinary retention	3	0
Dysuria	2	0
Reproductive System and Breast Disorders		
Erectile dysfunction ¹	7	1
Dysmenorrhoea ²	7	3
Impotence ¹		0
Prostatitis ¹	3	0
Orgasm abnormal	2	1
Menstruation irregular ²	2	0
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	4	1
Vascular Disorders		
Hot flush	3	1

¹Based on total number of males (atomoxetine, n=174; placebo, n=172).

²Based on total number of females (atomoxetine, n=95; placebo, n=91).

The following events did not meet this criterion but were reported by more atomoxetine- treated patients than placebo-treated patients and are possibly related to atomoxetine treatment: **very common (>10%)**: blood pressure increased, heart rate increased (heart rate and blood pressure are based on measured vital signs from clinical trials) and **common (> 1% and <10%)**: abdominal pain (includes abdominal pain upper, stomach discomfort, abdominal discomfort, and epigastric discomfort), rash, dyspepsia, terminal insomnia, ejaculation disorder, ejaculation failure, fatigue, lethargy, tachycardia, paraesthesia, chills, vomiting, asthenia, feeling jittery, irritability, thirst, dysgeusia, somnolence (including sedation), tremor, agitation, pollakiuria, testicular pain¹, flushing, urine flow decreased and **uncommon (>0.1% and <1%)**: peripheral

coldness, feeling cold, muscle spasms, restlessness, micturition urgency, pruritus, urticaria, blurred vision.

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

Adverse Events Based On Post Marketing Reports

The following list of undesirable effects (adverse drug effects) is based on post-marketing spontaneous reports, and corresponding reporting rates have been provided.

General Disorders and Administration Site Conditions: – Very rare (<0.01%): lethargy.

Psychiatric: Rare (>0.01% to <0.1%): completed suicide, suicide attempt, suicidal ideation, aggression/hostility, psychosis/mania, anxiety, depression and depressed mood. Very rare (<0.01%): sensory disturbances including hallucinations.

As of October 2005, the reporting rate of suicidal and self-injurious behaviours was 0.0126% (or about 1/8000) from a cumulative exposure of approximately 3.4 million patients.

Vascular Disorders: Very rare (<0.01%): peripheral vascular instability and/or Raynaud's phenomenon, potential to exacerbate pre-existing Raynaud's phenomenon.

Urogenital System: Very rare (<0.01%): painful or prolonged erection, male genital pain, urinary hesitation in children and adolescents, urinary retention in children and adolescents.

Cardiovascular System: Very rare (<0.01%): QT prolongation, syncope. Rare (>0.01% to <0.1%): Blood pressure increased.

Nervous System: Very rare (<0.01%): seizures, paraesthesia in children and adolescents, hypoaesthesia, tics.

Skin and Subcutaneous Tissue Disorders: Very Rare (<0.01%): Hyperhidrosis

DOSAGE AND ADMINISTRATION

Instructions for Use/Handling

Atomoxetine capsules are not intended to be opened. Atomoxetine is an ocular irritant. In the event of capsule content coming in contact with the eye, the affected eye should be flushed

immediately with water, and medical advice obtained. Hands and any potentially contaminated surfaces should be washed as soon as possible.

Initial Treatment

Dosing of Children and Adolescents up to 70kg Body Weight: Atomoxetine 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 100 mg, whichever is less.

Dosing of Children and Adolescents over 70 kg Body Weight and Adults: Atomoxetine should be initiated at a total daily dose of 40 mg and increased after a minimum of 3 days to a target total daily dose of approximately 80 mg 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 100 mg 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 70 kg and adults is 100 mg.

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 atomoxetine. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. Nevertheless, the physician who elects to use atomoxetine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

General Dosing Information

Atomoxetine may be taken with or without food.

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

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

Atomoxetine 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 70 kg body weight administered strong CYP2D6 inhibitors, e.g. paroxetine, fluoxetine and quinidine, Atomoxetine 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 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g. paroxetine, fluoxetine and quinidine, Atomoxetine 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

Contact the Poisons Information Centre on telephone 13 11 26 for advice on management of overdose.

During post-marketing overseas, there have been no fatalities involving overdose with atomoxetine alone, including intentional overdoses at amounts up to or exceeding 1500 mg. 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 atomoxetine, seizures and QT prolongation have been reported. There have also been reports of fatal, acute overdoses involving 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.

No specific information is available on the treatment of overdose with atomoxetine. Patients who overdose with atomoxetine should be monitored carefully and receive supportive care. Activated charcoal may be useful in limiting absorption. Dialysis is not likely to be useful in the treatment of overdose because atomoxetine is highly protein-bound.

PRESENTATION AND STORAGE CONDITIONS

ATOMOXETINE SANDOZ capsules containing 10 mg, 18 mg, 25 mg, 40 mg, 60 mg, 80 mg and 100 mg atomoxetine (as hydrochloride) in PVC/PVdC/PVC/aluminium blister packs of 7 and 28.

The capsule colours and markings are as follows:

- 10 mg capsules : White opaque cap and body and marked with “A910” on cap and body in black ink
- 18 mg capsules : Gold opaque cap and white opaque body and marked with “A918” on cap and body in black ink
- 25 mg capsules : Blue opaque cap and white opaque body and marked with “A925” on cap and body in black ink
- 40 mg capsules : Blue opaque cap and body and marked with “A940” on cap and body in black ink
- 60 mg capsules : Blue opaque cap and gold opaque body and marked with “A960” on cap and body in black ink
- 80 mg capsules : Brown opaque cap and white opaque body and marked with “A980” on cap and body in black ink
- 100 mg capsules : Brown opaque cap and body and marked with “A900” on cap and body in black ink

Not all presentations may be marketed in Australia.

Store below 30°C in the original packaging.

NAME AND ADDRESS OF THE SPONSOR

Medis Pharma Pty Ltd
1002/53 Walker Street
North Sydney, NSW 2060
Australia

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 10 November 2015

DATE OF MOST RECENT AMENDMENT: 07/11/2016