# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Atomoxetine Azure 40 mg hard capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains atomoxetine hydrochloride equivalent to 40 mg atomoxetine.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Hard capsule

Hard capsule (15.80 mm in length) with a blue cap imprinted in black with "ATO 4" and blue body imprinted in black with "40 mg".

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Atomoxetine Azure is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme. Treatment must be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist. Diagnosis should be made according to current DSM criteria or the guidelines in ICD.

In adults, the presence of symptoms of ADHD that were pre-existing in childhood should be confirmed. Third-party corroboration is desirable and Atomoxetine should not be initiated when the verification of childhood ADHD symptoms is uncertain. Diagnosis cannot be made solely on the presence of one or more symptoms of ADHD. Based on clinical judgment, patients should have ADHD of at least moderate severity as indicated by at least moderate functional impairment in 2 or more settings (for example, social, academic, and/or occupational functioning), affecting several aspects of an individual's life.

**Additional information for the safe use of this product:**
A comprehensive treatment programme typically includes psychological, educational and social measures and is aimed at stabilising patients with a behavioural syndrome characterised by symptoms which may include chronic history of short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.

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

### 4.2 Posology and method of administration

**Posology**
Atomoxetine Azure can be administered as a single daily dose in the morning. Patients who do not achieve a satisfactory clinical response (tolerability [e.g. nausea or somnolence] or efficacy) when taking Atomoxetine Azure as a single daily dose might benefit from taking it as twice daily evenly divided doses in the morning and late afternoon or early evening.

*Paediatric population:*

**Dosing of paediatric population up to 70 kg Body Weight:**
Atomoxetine Azure should be initiated at a total daily dose of approximately 0.5 mg/kg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is approximately 1.2 mg/kg/day (depending on the patient's weight and available dosage strengths of atomoxetine). No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day. The safety of single doses

over 1.8 mg/kg/day and total daily doses above 1.8 mg/kg have not been systematically evaluated. In some cases it might be appropriate to continue treatment into adulthood.

**Dosing of paediatric population over 70 kg Body Weight:**
Atomoxetine Azure should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance dose is 80 mg. No additional benefit has been demonstrated for doses higher than 80 mg. The maximum recommended total daily dose is 100 mg. The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

*Adults:*
Atomoxetine Azure should be initiated at a total daily dose of 40 mg. The initial dose should be maintained for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability. The recommended maintenance daily dose is 80 mg to 100 mg. The maximum recommended total daily dose is 100 mg. The safety of single doses over 120 mg and total daily doses above 150 mg have not been systematically evaluated.

**Additional information for the safe use of this product:**

*Pre-treatment screening:*
Prior to prescribing it is necessary to take an appropriate medical history and conduct a baseline evaluation of a patient's cardiovascular status, including blood pressure and heart rate (see sections 4.3 and 4.4).

*Ongoing monitoring:*
Cardiovascular status should be regularly monitored with blood pressure and pulse recorded after each adjustment of dose and then at least every 6 months. For paediatric patients the use of a centile chart is recommended. For adults, current reference guidelines for hypertension should be followed. (see section 4.4).

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

Treatment with Atomoxetine Azure need not be indefinite. Re-evaluation of the need for continued therapy beyond 1 year should be performed, particularly when the patient has reached a stable and satisfactory response.

**Special Populations**

*Hepatic Insufficiency*: for patients with moderate hepatic insufficiency (Child-Pugh Class B), initial and target doses should be reduced to 50% of the usual dose. For patients with severe hepatic insufficiency (Child-Pugh Class C), initial dose and target doses should be reduced to 25% of usual dose (see section 5.2).

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

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

*Elderly population:* the use of atomoxetine in patients over 65 years of age has not been systematically evaluated.

*Paediatric population under six years of age*: the safety and efficacy of Atomoxetine in children under 6 years of age have not been established. Therefore Atomoxetine Azure should not be used in children under 6 years of age (see section 4.4).

**Method of administration**
For oral use. Atomoxetine can be administered with or without food.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Atomoxetine should not be used in combination with monoamine oxidase inhibitors (MAOI). Atomoxetine should not be used within a minimum of 2 weeks after discontinuing therapy with MAOI. Treatment with MAOI should not be initiated within 2 weeks after discontinuing atomoxetine.
- Atomoxetine should not be used in patients with narrow angle glaucoma, as in clinical trials the use of atomoxetine was associated with an increased incidence of mydriasis.
- Atomoxetine should not be used in patients with severe cardiovascular or cerebrovascular disorders (see section 4.4 Special Warnings and Special Precautions for Use – Cardiovascular Effects)]. Severe cardiovascular disorders may include severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels). Severe cerebrovascular disorders may include cerebral aneurysm or stroke.
- Atomoxetine should not be used in patients with pheochromocytoma or a history of pheochromocytoma (see section 4.4 Special Warnings and Special Precautions for Use – Cardiovascular Effects).

**4.4 Special warnings and precautions for use**

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

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

**Cardiovascular effects**
Atomoxetine can affect heart rate and blood pressure.

Most patients taking atomoxetine experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg) (see section 4.8).

However, combined data from controlled and uncontrolled ADHD clinical trials show that approximately 8-12% of children and adolescents, and 6-10% adults experience more pronounced changes in heart rate (20 beats per minute or greater) and blood pressure (15-20 mmHg or greater). Analysis of these clinical trial data showed that approximately 15-26% of children and adolescents, and 27-32% of adults experiencing such changes in blood pressure and heart rate during atomoxetine treatment had sustained or progressive increases. Long-term sustained changes in blood pressure may potentially contribute to clinical consequences such as myocardial hypertrophy.

As a result of these findings, patients who are being considered for treatment with atomoxetine should have a careful history and physical exam to assess for the presence of cardiac disease, and should receive further specialist cardiac evaluation if initial findings suggest such history or disease.

It is recommended that heart rate and blood pressure be measured and recorded before treatment is started and, during treatment, after each adjustment of dose and then at least every 6 months to detect possible clinically important increases. For paediatric patients the use of a centile chart is recommended. For adults, current reference guidelines for hypertension should be followed.
Atomoxetine should not be used in patients with severe cardiovascular or cerebrovascular disorders (see section 4.3 Contraindications – Severe Cardiovascular and Cerebrovascular Disorders).

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

Patients who develop symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during atomoxetine treatment should undergo a prompt specialist cardiac evaluation.

In addition, atomoxetine should be used with caution in patients with congenital or acquired long QT or a family history of QT prolongation (see sections 4.5 and 4.8).

As orthostatic hypotension has also been reported, atomoxetine should be used with caution in any condition that may predispose patients to hypotension or conditions associated with abrupt heart rate or blood pressure changes.

**Cerebrovascular effects**
Patients with additional risk factors for cerebrovascular conditions (such as a history of cardiovascular disease, concomitant medications that elevate blood pressure) should be assessed at every visit for neurological signs and symptoms after initiating treatment with atomoxetine.

**Hepatic effects**
Very rarely, spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported. Also very rarely, severe liver injury, including acute liver failure, have been reported. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.

**Psychotic or manic symptoms**
Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, mania or agitation in patients without a prior history of psychotic illness or mania can be caused by atomoxetine at usual doses. If such symptoms occur, consideration should be given to a possible causal role of atomoxetine, and discontinuation of treatment should be considered. The possibility that Atomoxetine will cause the exacerbation of pre-existing psychotic or manic symptoms cannot be excluded.

**Aggressive behaviour, hostility or emotional lability**
Hostility (predominantly aggression, oppositional behaviour and anger) was more frequently observed in clinical trials among children, adolescents and adults treated with atomoxetine compared to those treated with placebo. Emotional lability was more frequently observed in clinical trials among children treated with atomoxetine compared to those treated with placebo. In general, patients should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional lability.
Severe cases have been reported concerning paediatric patients, including reports of physical assault, or threatening behaviour and thoughts of harming others. Families and caregivers of paediatric patients treated with atomoxetine should be counselled to alert a healthcare professional immediately if significant changes in mood or patterns of behaviour are noted, particularly after starting treatment or changing the dose. Physicians should evaluate the need for dose adjustment or treatment discontinuation in patients experiencing behavioural changes.

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

**Seizures**
Seizures are a potential risk with atomoxetine. Atomoxetine should be introduced with caution in patients with a history of seizure. Discontinuation of atomoxetine should be considered in any patient developing a seizure or if there is an increase in seizure frequency where no other cause is identified.

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

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

**New-onset or worsening of Comorbid Depression, Anxiety and Tics**
In a controlled study of paediatric patients with ADHD and co morbid chronic motor tics or Tourette's Disorder, atomoxetine-treated patients did not experience worsening of tics compared to placebo-treated patients. In a controlled study of adolescent patients with ADHD and co morbid Major Depressive Disorder, atomoxetine-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 co-morbid anxiety disorders, atomoxetine-treated patients did not experience worsening of anxiety compared to placebo-treated patients.

There have been rare postmarketing reports of anxiety and depression or depressed mood and very rare reports of tics in patients taking atomoxetine (see section 4.8).

Patients who are being treated for ADHD with atomoxetine should be monitored for the appearance or worsening of anxiety symptoms, depressed mood and depression or tics.

**Serotonin syndrome:**
Serotonin syndrome has been reported following concomitant use of atomoxetine with other serotonergic medicinal products (e.g. serotonin-norepinephrine reuptake inhibitors [SNRIs], selective serotonin reuptake inhibitors [SSRIs], other SNRIs, triptans, opioids, and tricyclic and tetracyclic antidepressants). If concomitant use of atomoxetine with a serotonergic medicinal product is warranted, prompt recognition of the symptoms of serotonin syndrome is important. These symptoms may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

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

**Other therapeutic use**
Atomoxetine is not indicated for the treatment of major depressive episodes and/or anxiety as the results of clinical trials in adults in these conditions, where ADHD is not present, did not show an effect compared to placebo (see section 5.1).

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

Effects of other drugs on atomoxetine

*MAOIs*
Atomoxetine should not be used with MAOIs (see section 4.3).

*CYP2D6 inhibitors (SSRIs (e.g. fluoxetine, paroxetine), quinidine, terbinafine)*
In patients receiving these drugs, atomoxetine exposure may be 6-to 8-fold increased and Css max 3 to 4 times higher, because it is metabolised by the CYP2D6 pathway. Slower titration and final lower dosage of atomoxetine may be necessary in patients who are already taking CYP2D6 inhibitor drugs. If a CYP2D6 inhibitor is prescribed or discontinued after titration to the appropriate atomoxetine dose has occurred, the clinical response and tolerability should be re-evaluated for that patient to determine if dose adjustment is needed.

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

*Salbutamol (or other beta$_2$ agonists)*
Atomoxetine should be administered with caution to patients treated with high dose nebulised or systemically administered salbutamol (or other beta2 agonists) because cardiovascular effects can be potentiated.

Contradictory findings regarding this interaction were found. Systemically administered salbutamol (600 µ g i.v. over 2 hrs) in combination with atomoxetine (60 mg twice daily for 5 days) induced increases in heart rate and blood pressure. This effect was most marked after the initial coadministration of salbutamol and atomoxetine but returned towards baseline at the end of 8 hours. However, in a separate study the effects on blood pressure and heart rate of a standard inhaled dose of salbutamol (200 µ g) were not increased by the short term coadministration of atomoxetine (80 mg once daily for 5 days) in a study of healthy Asian adults who were extensive atomoxetine metabolisers. Similarly heart rate after multiple inhalations of salbutamol (800 µ g) did not differ in the presence or absence of atomoxetine. Attention should be paid to monitoring heart rate and blood pressure, and dose adjustments may be justified for either atomoxetine or salbutamol (or other beta2 agonists) in the event of significant increases in heart rate and blood pressure during coadministration of these drugs.

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

Seizures are a potential risk with atomoxetine. Caution is advised with concomitant use of medicinal drugs which are known to lower the seizure threshold (such as tricyclic antidepressants or SSRIs, neuroleptics, phenothiazines or butyrophenone, mefloquine, chloroquine, bupropion or tramadol). (see section 4.4). In addition, caution is advised when stopping concomitant treatment with benzodiazepines due to potential withdrawal seizures.

*Anti-hypertensive drugs*
Atomoxetine should be used cautiously with antihypertensive drugs. Because of a possible increase in blood pressure, atomoxetine may decrease the effectiveness of antihypertensive drugs / drugs used to treat hypertension. Attention should be paid to monitoring of blood pressure and review of treatment of atomoxetine or antihypertensive drugs may be justified in the case of significant changes of blood pressure.

*Pressor agents or drugs that increase blood pressure*
Because of possible increase in effects on blood pressure, atomoxetine should be used cautiously with pressor agents or medications that may increase blood pressure (such as salbutamol). Attention should be paid to monitoring of blood pressure, and review of treatment for either atomoxetine or pressor agents may be justified in the case of significant change in blood pressure.

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

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

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

*Serotoninergic medications*
Atomoxetine should be used with caution in combination with serotonergic medicinal products, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs), opioids as tramadol, and tetracyclic or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**
Animal studies in general do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). For atomoxetine clinical data on exposed pregnancies are limited. Such data are insufficient to indicate either an association or a lack of association between atomoxetine and adverse pregnancy and/or lactation outcomes. Atomoxetine should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

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

**4.7 Effects on ability to drive and use machines**

Data on the effects on the ability to drive and use machines are limited. Atomoxetine has a minor influence on the ability to drive and use machines. Atomoxetine has been associated with increased rates of fatigue, somnolence, and dizziness relative to

placebo in paediatric and adult patients. Patients should be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

**4.8 Undesirable effects**

**Paediatric population**:

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

Associated with decreased appetite, some patients experienced growth retardation early in therapy in terms of both weight and height gain. On average, after an initial decrease in weight and height gain, patients treated with atomoxetine recovered to mean weight and height as predicted by group baseline data over the long-term treatment.

Nausea, vomiting and somnolence[2] can occur in about 10% to 11% of patients particularly during the first month of therapy. However, these episodes were usually mild to moderate in severity and transient, and did not result in a significant number of discontinuation from therapy (discontinuation rates ≤ 0.5%).

In both paediatric and adult placebo-controlled trials, patients taking atomoxetine experienced increases in heart rate, systolic and diastolic blood pressure (see section 4.4).

Because of its effect on noradrenergic tone, orthostatic hypotension (0.2%) and syncope (0.8%) have been reported in patients taking atomoxetine. Atomoxetine should be used with caution in any condition that may predispose patients to hypotension.

The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials and post marketing spontaneous reports in children and adolescents:

***Tabulated list of adverse reactions***
Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

| **System Organ Class** | **Very common** ≥1/10 | **Common** ≥1/100 to <1/10 | **Uncommon** ≥1/1,000 to <1/100 | **Rare** ≥1/10,000 to <1/1,000 | **Unknown** |
|---|---|---|---|---|---|
| **Metabolism and nutrition disorders** | Appetite decreased. | Anorexia (loss of appetite). | | | |
| **Psychiatric disorders** | | Irritability, mood swings, insomnia[3], agitation *, anxiety, depression and depressed mood *, tics *. | Suicide-related events, aggression, hostility, emotional lability*, Psychosis (including hallucinations) *. | | Bruxism. |
| **Nervous system disorders** | Headache, somnolence[2]. | Dizziness. | Syncope, tremor, migraine, paraesthesia*, hypoaesthesia*, Seizure**. | | |
| **Eye disorders** | | Mydriasis. | Vision blurred. | | |
| **Cardiac disorders** | | | Palpitations, | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | sinus tachycardia. QT interval prolongation **. | | |
| **Vascular disorders** | | | | Raynaud's phenomenon. | |
| **Respiratory, thoracic and mediastinal disorders** | | | Dyspnoea (See section 4.4) | | |
| **Gastrointestinal disorders** | Abdominal pain[1], vomiting, nausea. | Constipation, dyspepsia. | | | |
| **Hepatobiliary disorders** | | | Blood bilirubin increased*. | Abnormal/ increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure*. | |
| **Skin and subcutaneous tissue disorders** | | Dermatitis, pruritus, rash. | Hyperhidrosis, allergic reactions. | | |
| **Renal and urinary disorders** | | | | Urinary hesitation, urinary retention. | |
| **Reproductive system and breast disorders** | | | | Priapism, male genital pain. | |
| **General disorders and administration site conditions** | | Fatigue, lethargy. Chest pain (see section 4.4). | Asthenia. | | |
| **Investigations** | Blood pressure increased[4], heart rate increased[4]. | Weight decreased. | | | |

[1]Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort.
[2] Also includes sedation
[3] Includes initial, middle and terminal (early morning wakening) insomnia
[4] Heart rate and blood pressure findings are based on measured vital signs
* See section 4.4
** See section 4.4 and section 4.5

**CYP2D6 poor metabolisers (PM)**
The following adverse events occurred in at least 2% of CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: appetite decreased (24.1% of PMs, 17.0% of EMs); insomnia combined (including insomnia, middle insomnia and initial insomnia, 14.9% of PMs, 9.7% of EMs); depression combined (including depression, major depression, depressive symptom, depressed mood and dysphoria, 6.5% of PMs and 4.1% of EMs), weight decreased (7.3% of PMs, 4.4% of EMs), constipation 6.8% of PMs, 4.3% of EMs); tremor (4.5% of PMs, 0.9% of EMs); sedation (3.9% of PMs, 2.1% of EMs); excoriation (3.9% of PMs, 1.7% of EMs); enuresis (3.0% of PMs, 1.2% of EMs); conjunctivitis (2.5% of PMs, 1.2% of EMs); syncope (2.5% of PMs, 0.7% of EMs); early morning awakening (2.3% of PMs, 0.8% of EMs); mydriasis (2.0% of PMs, 0.6% of EMs). The following event did not meet the above

criteria but is noteworthy: generalised anxiety disorder (0.8% of PMs and 0.1% of EMs). In addition, in trials lasting up to 10 weeks, weight loss was more pronounced in PM patients (mean of 0.6 kg in EM and 1.1kg in PM).

**Adults:**

***Summary of the safety profile***
In adult ADHD clinical trials, the following system organ classes had the highest frequency of adverse events during treatment with atomoxetine: gastrointestinal, nervous system and psychiatric disorders. The most common adverse events (≥ 5%) reported were appetite decreased (14.9%), insomnia (11.3%) headache (16.3%), dry mouth (18.4%) and nausea (26.7%). The majority of these events were mild or moderate in severity and the events most frequently reported as severe were nausea, insomnia, fatigue and headache. A complaint of urinary retention or urinary hesitancy in adults should be considered potentially related to atomoxetine.

The following table of undesirable effects is based on adverse event reporting and laboratory investigations from clinical trials and post marketing spontaneous reports in adults.

***Tabulated list of adverse reactions***
Frequency estimate: Very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

| **System Organ Class** | **Very common** ≥1/10 | **Common** ≥1/100 to <1/10 | **Uncommon** ≥1/1,000 to <1/100 | **Rare** ≥1/10,000 to <1/1,000 | **Not known** |
|---|---|---|---|---|---|
| **Metabolism and nutrition disorders** | Appetite decreased. | | | | |
| **Psychiatric disorders** | Insomnia[2]. | Agitation*, libido decreased, sleep disorder, depression and depressed mood*, anxiety, | Suicide-related events*, aggression, hostility and emotional lability*, restlessness, tics*. | Psychosis (including hallucinations) *. | Bruxism. |
| **Nervous system disorders** | Headache. | Dizziness, dysgeusia, paraesthesia, somnolence (including sedation), tremor. | Syncope, migraine. hypoaesthesia *. | Seizure**. | |
| **Eye Disorders** | | | Vision blurred. | | |
| **Cardiac disorders** | | Palpitations, tachycardia. | QT interval prolongation** | | |
| **Vascular disorders** | | Flushing, hot flush. | Peripheral coldness. | Raynaud's phenomenon. | |
| **Respiratory, thoracic and mediastinal disorders** | | | Dyspnoea (see section 4.4). | | |
| **Gastrointestinal disorders** | Dry mouth, nausea. | Abdominal pain[1], constipation, dyspepsia, flatulence, vomiting. | | | |
| **Hepatobiliary disorders** | | | | Abnormal/increased liver function tests, jaundice, hepatitis, liver injury, acute hepatic failure, blood bilirubin increased*. | |

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|---|---|---|---|---|---|
| **Skin and subcutaneous tissue disorders** | | Dermatitis, hyperhydrosis, rash. | Allergic reactions[4], pruritis, urticaria. | | |
| **Musculoskeletal and connective** | | | Muscle spasms. | | |
| **Renal and urinary disorders** | | Dysuria, pollakuria, urinary hesitation, urinaryretention. | Micturation urgency. | | |
| **Reproductive system and breast disorders** | | Dysmenorrhoea, ejaculation disorder, erectile dysfunction, prostatitis, male genital pain. | Ejaculation failure, menstruation irregular, orgasm abnormal. | Priapism. | |
| **General disorders and administration site conditions** | | Asthenia, fatigue, lethargy, chills feeling jittery, irritability, thirst. | Feeling cold. Chest pain (see section 4.4) | | |
| **Investigations** | Blood pressure increased[3], heart rate increased[3]. | Weight decreased. | | | |

[1]Also includes abdominal pain upper, stomach discomfort, abdominal discomfort and epigastric discomfort.
[2] Also includes initial insomnia, middle insomnia and terminal (early morning wakening) insomnia.
[3] Heart rate and blood pressure findings are based on measured vital signs.
[4] Includes anaphylactic reactions and angioneurotic oedema.
* See section 4.4
** See section 4.4 and section 4.5

**CYP2D6 poor metabolisers (PM)**
The following adverse events occurred in at least 2% of CYP2D6 poor metaboliser (PM) patients and were statistically significantly more frequent in PM patients compared with CYP2D6 extensive metaboliser (EM) patients: 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% 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% of PMs, 0.5% of EMs).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

**4.9 Overdose**

**Signs and symptoms**
During postmarketing, there have been reports of non-fatal acute and chronic overdoses of atomoxetine alone. The most commonly reported symptoms accompanying acute and chronic overdoses were 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 and reports of pruritus and rash have been received. Most events were mild to moderate. In some cases of overdose involving atomoxetine, seizures, and very rarely QT prolongation and serotonin syndrome have been reported. There have also been reports of fatal, acute overdoses involving a mixed ingestion of atomoxetine and at least one other drug.

There is limited clinical trial experience with atomoxetine overdose.

**Management**
An airway should be established. Activated charcoal may be useful in limiting absorption if the patient presents within 1 hour of ingestion. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. The patient should be observed for a minimum of 6 hours. Because atomoxetine is highly protein-bound, dialysis is not likely to be useful in the treatment of overdose.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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

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

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

**Clinical efficacy and safety**

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

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

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

*Active Comparator Studies*
In a randomised, double-blind, parallel group, 6 week paediatric study to test the non-inferiority of atomoxetine to a standard extended-release methylphenidate comparator, the comparator was shown to be associated with superior response rates compared to atomoxetine. The percentage of patients classified as responders was 23.5% (placebo), 44.6% (atomoxetine) and

56.4% (methylphenidate). Both atomoxetine and the comparator were statistically superior to placebo and methylphenidate was statistically superior to atomoxetine (p=0.016). However, this study excluded patients who were stimulant nonresponders.

**Adult population**
Atomoxetine has been studied in trials in over 4800 adults who met DSM-IV diagnostic criteria for ADHD. The acute efficacy of Atomoxetine in the treatment of adults was established in six randomised, double-blind, placebo-controlled trials of ten to sixteen weeks' duration. Signs and symptoms of ADHD were evaluated by a comparison of mean change from baseline to endpoint for atomoxetine treated and placebo treated patients. In each of the six trials, atomoxetine was statistically significantly superior to placebo in reducing ADHD signs and symptoms (Table X). Atomoxetine-treated patients had statistically significantly greater improvements in clinical global impression of severity (CGI-S) at endpoint compared to placebo-treated patients in all of the 6 acute studies, and statistically significantly greater improvements in ADHD-related functioning in all 3 of the acute studies in which this was assessed (Table X). Long-term efficacy was confirmed in 2 six-month placebo controlled studies, but not demonstrated in a third (Table X).

**Table X: Mean Changes in Efficacy Measures for Placebo-Controlled Studies**

| | | Changes from Baseline in Patients with at Least One Postbaseline Value (LOCF) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | CAARS-Inv:SV or AISRS[a] | | CGI-S | | AAQoL | |
| Study | Treatment | N | Mean Change | p-value | Mean Change | p-value | Mean Change | p-value |
| **Acute Studies** | | | | | | | | |
| LYAA | ATX<br>PBO | 133<br>134 | -9.5<br>-6.0 | 0.006 | -0.8<br>-0.4 | 0.011 | - | - |
| LYAO | ATX<br>PBO | 124<br>124 | -10.5<br>-6.7 | 0.002 | -0.9<br>-0.5 | 0.002 | - | - |
| LYBY | ATX<br>PBO | 72<br>75 | -13.6<br>-8.3 | 0.007 | -1.0<br>-0.7 | 0.048 | - | - |
| LYDQ | ATX<br>PBO | 171<br>158 | -8.7<br>-5.6 | <0.001 | -0.8<br>-0.6 | 0.022 | 14.9<br>11.1 | 0.030 |
| LYDZ | ATX<br>PBO | 192<br>198 | -10.7<br>-7.2 | <0.001 | -1.1<br>-0.7 | <0.001 | 15.8<br>11.0 | 0.005 |
| LYEE | ATX<br>PBO | 191<br>195 | -14.3<br>-8.8 | <0.001 | -1.3<br>-0.8 | <0.001 | 12.83<br>8.20 | <0.001 |
| **Long-Term Studies** | | | | | | | | |
| LYBV | ATX<br>PBO | 185<br>109 | -11.6<br>-11.5 | 0.412 | -1.0<br>-0.9 | 0.173 | 13.90<br>11.18 | 0.045 |
| LYCU | ATX<br>PBO | 214<br>216 | -13.2<br>-10.2 | 0.005 | -1.2<br>-0.9 | 0.001 | 13.14<br>8.62 | 0.004 |
| LYCW | ATX<br>PBO | 113<br>120 | -14.3<br>-8.3 | <0.001 | -1.2<br>-0.7 | <0.001 | - | - |

Abbreviations: AAQoL = Adult ADHD Quality of Life Total Score; AISRS = Adult ADHD Investigator Symptom Rating Scale Total Score; ATX = atomoxetine; CAARS-Inv:SV = Conners Adult ADHD Rating Scale, Investigator Rated, screening version Total ADHD Symptom Score; CGI-S = Clinical Global Impression of Severity; LOCF = last observation carried forward; PBO = placebo.
[a] ADHD symptom scales; results shown for Study LYBY are for AISRS; results for all others are for CAARS-Inv:SV.
In sensitivity analyses using a baseline-observation-carried-forward method for patients with no postbaseline measure (i.e. all patients treated), results were consistent with results shown in Table X.
In analyses of clinically meaningful response in all 6 acute and both successful long-term studies, using a variety of a priori and post hoc definitions, atomoxetine-treated patients consistently had statistically significantly higher rates of response than placebo-treated patients (Table Y).

**Table Y Number (n) and Percent of Patients Meeting Criteria for Response in Pooled Placebo-Controlled Studies**

| Group Treatment | Response Defined by Improvement of at least 1 point on CGI-S | | | Response Defined by 40% Improvement on CAARS-Inv:SVat Endpoint | | |
|---|---|---|---|---|---|---|
| | N | n (%) | p-value | N | n (%) | p-value |
| **Pooled Acute Studies[a]** | | | | | | |
| ATX | 640 | 401 (62.7%) | <0.001 | 841 | 347 (41.3%) | <0.001 |
| PBO | 652 | 283 (43.4%) | | 851 | 215 (25.3%) | |
| **Pooled Long-Term Studies[a]** | | | | | | |
| ATX | 758 | 482 (63.6%) | <0.001 | 663 | 292 (44.0%) | <0.001 |
| PBO | 611 | 301 (49.3%) | | 557 | 175 (31.4%) | |

[a] Includes all studies in Table X except: Acute CGI-S response analysis excludes 2 studies in patients with comorbid disorders (LYBY, LYDQ); Acute CAARS response analysis excludes 1 study in which the CAARS was not administered (LYBY).

In two of the acute studies, patients with ADHD and comorbid alcoholism or social anxiety disorder were studied and in both studies ADHD symptoms were improved. In the study with comorbid alcohol abuse, there were no differences between atomoxetine and placebo with respect to alcohol use behaviours. In the study with co-morbid anxiety, the comorbid condition of anxiety did not deteriorate with atomoxetine treatment.

The efficacy of atomoxetine in maintaining symptom response was demonstrated in a study where after an initial active treatment period of 24 weeks, patients who met criteria for clinically meaningful response (as defined by improvement on both CAARS-Inv:SV and CGI-S scores) were randomized to receive atomoxetine or placebo for an additional 6 months of double-blind treatment. Higher proportions of atomoxetine-treated patients than placebo-treated patients met criteria for maintaining clinically meaningful response at the end of 6 months (64.3 % vs. 50.0 %; p=0.001). Atomoxetine-treated patients demonstrated statistically significantly better maintenance of functioning than placebo-treated patients as shown by lesser mean change on the Adult ADHD Quality of Life (AAQoL) total score at the 3-month interval (p=0.003) and at the 6-month interval (p=0.002).

*QT/QTc study*
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 a slight increase in QTc interval with increased atomoxetine concentration.

**5.2 Pharmacokinetic properties**

The pharmacokinetics of atomoxetine in children and adolescents are similar to those in adults. The pharmacokinetics of atomoxetine have not been evaluated in children under 6 years of age.

Pharmacokinetic studies have shown that atomoxetine capsules and oral solution are bioequivalent.

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

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

**Biotransformation**
Atomoxetine undergoes biotransformation primarily through the cytochrome P450 2D6 (CYP2D6) enzymatic pathway. Individuals with reduced activity of this pathway (poor metabolisers) represent about 7% of the Caucasian population and, have higher plasma concentrations of atomoxetine compared with people with normal activity (extensive metabolisers). For poor metabolisers, AUC of atomoxetine is approximately 10-fold greater and Css, max is about 5- fold greater than extensive

metabolisers. The major oxidative metabolite formed is 4-hydroxyatomoxetine that is rapidly glucuronidated. 4-Hydroxyatomoxetine is equipotent to atomoxetine but circulates in plasma at much lower concentrations. Although 4-hydroxyatomoxetine is primarily formed by CYP2D6, in individuals that lack CYP2D6 activity, 4-hydroxyatomoxetine can be formed by several other cytochrome P450 enzymes, but at a slower rate. Atomoxetine does not inhibit or induce CYP2D6 at therapeutic doses.

*Cytochrome P450 Enzymes*: Atomoxetine did not cause clinically significant inhibition or induction of cytochrome P450 enzymes, including CYP1A2, CYP3A, CYP2D6, and CYP2C9.

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

Linearity/non-linearity: pharmacokinetics of atomoxetine are linear over the range of doses studied in both extensive and poor metabolisers.

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

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

**5.3 Preclinical safety data**

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, or reproduction and development. Due to the dose limitation imposed by the clinical (or exaggerated pharmacological) response of the animals to the drug combined with metabolic differences among species, maximum tolerated doses in animals used in nonclinical studies produced atomoxetine exposures similar to or slightly above those that are achieved in CYP2D6 poor metabolizing patients at the maximum recommended daily dose.

A study was conducted in young rats to evaluate the effects of atomoxetine on growth and neurobehavioral and sexual development. Slight delays in onset of vaginal patency (all doses) and preputial separation (≥ 10 mg/kg/day) and slight decreases in epididymal weight and sperm number (≥ 10 mg/kg/day) were seen; however, there were no effects on fertility or reproductive performance. The significance of these findings to humans is unknown.

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

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Pregelatinised maize starch
Dimeticone

Capsule shell:
Gelatin
Indigo carmine (E 132)
Titanium dioxide (E 171)

Printing ink:
Shellac (E 904)
Black iron oxide (E 172)
Potassium hydroxide
Propylene glycol (E1520

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Do not store above 25 °C.

**6.5 Nature and contents of container**

PVdC/PVC/PE/PVdC//Alu blister.

Pack size(s):
28 hard capsules.

Not all pack sizes may be marketed

**6.6 Special precautions for disposal and other handling**

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

**7 MARKETING AUTHORISATION HOLDER**

Azure Pharmaceuticals Ltd.
12 Hamilton Drive
The Rock Road
Blackrock
Co. Louth
A91 T997
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA22871/034/004

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

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**10 DATE OF REVISION OF THE TEXT**