VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Attention-Deficit/Hyperactivity Disorder (ADHD)

ADHD occurs in 3-7%, of children many of whom may also have the disorder as adults. The existing data suggest that ADHD occurs in approximately 4 % of the adult population. ADHD often occurs with other important conditions such as mood or conduct-related disorders, learning disabilities or drug and/or alcohol abuse. ADHD is more frequently diagnosed in boys than in girls. ADHD can be well managed if the patient has no other major disorders/diseases and the medication is correctly adapted to the patient's situation. Other important factors influencing the outcome are an appropriate education about ADHD for patients and caregivers and proper treatment of any learning difficulties and emotional problems. Atomoxetine is used only as a part of the total treatment of the disorder which also requires, non-medical treatment such as counselling and behavioural therapy.

VI.2.2 Summary of treatment benefits

Paediatric population

Atomoxetine has been studied in trials in over 5000 children and adolescents with ADHD. The short term effectiveness of atomoxetine in the treatment of ADHD was initially established in six studies of six to nine weeks duration. Signs and symptoms of ADHD were evaluated by a comparison of atomoxetine-treated and placebo-treated (a substance having no

pharmacological effect) patients. In each of the six trials, atomoxetine was significantly superior to placebo in reducing ADHD signs and symptoms.

Additionally, the effectiveness 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 treatment). After 1 year of atomoxetine treatment, patients who continued atomoxetine for 6 additional months were less likely to experience partial symptom return compared with patients who discontinued active treatment and switched to placebo (2% versus 12%, respectively).

Adult population

Atomoxetine has been studied in trials in over 4800 adults who met diagnostic criteria for ADHD. The acute efficacy of atomoxetine in the treatment of adults was established in six studies of ten to sixteen weeks' duration. Signs and symptoms of ADHD were evaluated by a comparison of atomoxetine-treated and placebo-treated patients. In each of the six studies, atomoxetine was statistically significantly superior to placebo in reducing ADHD signs and symptoms.

These studies were conducted for Strattera by Eli Lilly and Company (Ireland) Limited and not by Mylan.

VI.2.3 Unknowns relating to treatment benefits

Little information is available on the use of atomoxetine in children under 6 years of age, in the elderly or in pregnant or breastfeeding women. However the data suggest that safety of atomoxetine treatment of these patients is no different from other patients. In addition, as long-term data are limited, patients needing long-term therapy should be carefully monitored and the need for continued therapy re-evaluated.

VI.2.4 Summary of safety concerns

Table 22 Part VI - Summary table of safety concerns

Important identified risks

Risk	What is known	Preventability
Thoughts on or preoccupation with killing oneself (Suicidal Ideation)	Thoughts or an unusual preoccupation with killing oneself has been reported in patients treated with atomoxetine. In studies, unusual preoccupation with killing oneself were uncommon but more frequently observed among children and adolescents treated with atomoxetine compared to those treated with placebo (a substance having no pharmacological effect), where there were no events, while in adults there was no difference.	Patients who are being treated for ADHD should be carefully monitored for unusual preoccupation of killing oneself that may first appear or worsen.
Liver problems (Hepatic injury)	Liver damage can occur on rare occasions and may range from mild to severe. Symptoms include tiredness, dark urine, upset stomach, itching and stomach pain. Liver damage can be detected by laboratory testing.	Yes, by monitoring for early symptoms. Atomoxetine should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted.

Risk	What is known	Preventability
Increased blood pressure and increased heart rate.	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). Long-term sustained changes in blood pressure may potentially contribute to complications like thickening of the heart muscle (myocardial hypertrophy).	Prior to prescribing it is necessary to take an appropriate medical history and physical exam and evaluate patient's heart status, including blood pressure and heart rate. Ongoing monitoring is also recommended for 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 high blood pressure should be followed. Atomoxetine should not be used in patients with severe disease affecting the heart and/or blood vessels (cardiovascular disease) or stroke. 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

Risk	What is known	Preventability
		increased blood pressure, increased heartbeat, cardiovascular disease or past medical history of stroke.
Poor blood circulation which makes toes and fingers numb and pale (Peripheral vascular instability (Raynaud's phenomenon))	In studies and post-marketing, poor blood circulation which makes toes and fingers numb and pale (Raynaud's phenomenon) was rarely reported in children, adolescents and adults.	Yes, by monitoring for early symptoms.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Heart, vessels and brain effects • condition of insufficient blood flow to the heart muscle via the coronary arteries, often resulting in chest pain (Myocardial ischaemia) • Very fast heartbeat (Tachyarrhythmia)	There are underlying medical conditions that could be worsened by increases in blood pressure and heart rate, such as in patients with previously diagnosed high blood pressure or faster heart beat, diseases related to blood vessels or brain diseases. Patients who develop symptoms such as palpitations (sensation of rapid, irregular, or forceful heartbeats), chest pain, unexplained fainting, shortness of breath or other symptoms suggestive of heart disease during atomoxetine treatment should undergo a prompt specialist heart evaluation. Patients with additional risk factors for brain and

Risk	**What is known (Including reason why it is considered a potential risk)**
• Stroke (Cerebrovascular accident)	blood vessels conditions (such as a history of heart and vascular disease, concomitant medications that increase blood pressure) should be assessed at every visit for signs and symptoms of nervous systems after initiating treatment with atomoxetine. In addition, if the patient has serious problems with the blood vessels in the brain - such as a stroke, swelling and weakening of part of a blood vessel (aneurysm) or narrow or blocked blood vessels or have a tumour of adrenal gland (phaeochromocytoma) cannot use atomoxetine.
Heart rhythm disorder that can potentially cause fast, chaotic heartbeats (QTc prolongation)	Atomoxetine should be used with caution in patients with inherited or acquired long QT or a family history of QT prolongation. Patients, who have serious problems with the heart which may be affected by an increase in heart rate and/or blood pressure, cannot take atomoxetine.
Feeling aggressive, unfriendly and angry (Aggression/hostility)	Feeling aggressive, unfriendly and angry were more frequently observed in studies among children, adolescents and adults treated with atomoxetine compared to those treated with placebo (substance having no pharmacological effect). Emotional lability was more frequently observed in studies among children treated with atomoxetine compared to those treated with placebo. Patients should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional lability.

Risk	What is known (Including reason why it is considered a potential risk)
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. Caution is advised with concomitant use of medicinal drugs which are known to increase the risk of seizures.

Missing information

Risk	What is known
NA	NA

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). How they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Risk minimisation measure(s)
Increased blood pressure and increased heart rate Objective and rationale:

Risk minimisation measure(s)
• To provide the prescriber with tools to choose the right patients for an atomoxetine prescription and to ensure that unsuitable patients do not take atomoxetine. • To ensure that patients are monitored for heart rate and blood pressure before and during treatment. • To advise prescribers to take a medical history and carefully evaluate for other diseases before prescribing atomoxetine. • To ensure prescribers are fully aware of the appropriate manner of prescribing atomoxetine. <u>Proposed action:</u> Distribution of Educational materials to all atomoxetine prescribers (e.g. psychiatrists), consisting of • Physician's Guide • Checklist for actions to take before prescribing / dispensing or administering atomoxetine • Checklist for monitoring to manage cardiovascular risks with atomoxetine treatment • Measurements recording chart

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the Risk Management Plan over time

The RMP was updated from version 3 to version 4 (this document) to include changes recommended by day 70 and 100 comments and TFU questionnaires.