VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the common disorders of childhood affecting the brain. It is usually first diagnosed in childhood and often lasts into adulthood. Children with ADHD may have trouble paying attention, controlling impulsive behaviours (may act without thinking about what the result will be), or be overly active. A worldwide prevalence of 7.2% has been found from research studies in children aged 18 and under leading to a rough estimate of 129 million children who suffer from ADHD worldwide. ADHD affects 5% of school-aged children in the UK and the male to female ratio in diagnosed ADHD prevalence is at least 4 to 1.5 i.e. higher occurrence amongst boys/men. Whilst ADHD is perceived to be largely a childhood disorder, research suggests that up to 2 out of 3 children diagnosed with ADHD (65%) continue to experience symptoms into adulthood. Results show occurrence rates of ADHD medication use for the German child and adolescent population are considerably lower than published occurrence rates from the USA, but comparable with those of western European and Scandinavian countries.

VI.2.2 Summary of treatment benefits

Atomoxetine increases the amount of noradrenaline in the brain. This is a chemical that is produced naturally, and increases attention and decreases impulsiveness and hyperactivity in patients with ADHD. This medicine has been prescribed to help control the symptoms of ADHD.

The effectiveness of atomoxetine in the treatment of ADHD was initially established in six clinical studies of six to nine weeks duration. Additionally, the effectiveness of atomoxetine in maintaining long-term symptom response was demonstrated in a 1 year study with over 400 children and adolescents, primarily conducted in Europe.

The efficacy of atomoxetine in the treatment of adults was established in six randomised, double-blind, placebo-controlled trials of ten to sixteen weeks duration.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of atomoxetine in children under 6 years of age have not been established. Also the use of atomoxetine in patients over 65 years of age has not been systematically evaluated. Clinical data on exposed pregnancies are limited on atomoxetine. Such data are insufficient to indicate either an association or a lack of association between atomoxetine and adverse pregnancy and/or lactation outcomes. It is not known if atomoxetine is excreted in human milk.

VI.2.4 Summary of safety concerns

Table 11: Important Identified Risk(s)

Risk(s)	What is known	Preventability
Thinking about killing oneself (Suicidal Ideation)	This risk may affect up to 1 in 100 people. Patients who are being treated for ADHD should be carefully monitored for the appearance or worsening of suicide related behaviour	Both adult and children should be aware of this risk when they are taking atomoxetine. Patients and their care takers should tell their doctors and pharmacists if they have the feeling or the thoughts of killing oneself.
Damage to liver (Hepatic Injury)	This risk may occur rarely affecting up to 1 in 1,000 people. Symptoms of liver injury may include dark urine, yellow skin or yellow eyes, stomach pain which is sore on pressing (tenderness) on the right side just below the	Atomoxetine should be stopped in case there is evidence of damage to liver. Patients should inform the doctor immediately if they see any of these symptoms.

Risk(s)	What is known	Preventability
	ribs, feeling of sickness (nausea) that is unexplained, tiredness and itching Atomoxetine should be discontinued in patients with laboratory evidence of liver injury, and should not be restarted.	
Increased blood pressure and increased heart rate	This is a very common risk which may affect more than 1 in 10 people. Medicines that increase blood pressure can also cause an increase in the patients' blood pressure if taken along with atomoxetine.	Prior to prescribing atomoxetine, it is necessary to take an appropriate medical history and conduct a baseline evaluation of a patient's heart status, including blood pressure and heart rate and other medicines' details. Also patients should be regularly monitored with blood pressure and pulse recorded after each adjustment of dose and then at least every 6 months by the doctors.
Paleness, burning, prickling, or pain of the fingers and/or toes (Peripheral Vascular Instability [Raynaud's phenomenon])	This is a rare risk which may affect up to 1 in 1,000 people. Atomoxetine may cause poor blood circulation resulting in numbness and paleness of toes and fingers.	Patients should inform the doctor and pharmacist if they experience burning, prickling or numbness of fingers and toes while taking atomoxetine.

Table 12: Important Potential Risk(s)

Risk(s)	What is known
Heart and neurological problems i.e. heart attack, irregular/fast heart beat and stroke (brain damage due to interruption of its blood supply) (Cardiovascular and cerebrovascular outcomes: myocardial ischaemia, tachyarrhythmia, cerebrovascular accident)	Atomoxetine should not be used in patients with severe heart and neurological problems. Patients with additional risk factors for heart and neurological conditions (such as a history of heart disease) should be assessed at every visit for signs and symptoms related to heart and brain function after initiating treatment with atomoxetine.
Abnormal heart rhythm (QTc prolongation)	It is an uncommon risk that may affect up to 1 in 100 people. Atomoxetine should be used with caution in patients with abnormal heart rhythm or who have a family history of the same.
Unfriendly and Angry Feelings (Aggression/Hostility)	It is an uncommon risk which may affect up to 1 in 100 people. Patients should be closely monitored for the appearance or worsening of aggressive behaviour, hostility or emotional disturbance.
Fits (Seizure)	It is an uncommon risk which may affect up to 1 in 100 children. Adults have a reduced risk which may affect up to 1 in 1,000 people. Atomoxetine may lead to increase in seizure frequency or may lead to increased risk of seizures if taken with medicines that are known to cause this risk. Patients should inform the doctor immediately if they experience seizures.

Table 13: Missing Information

Risk(s)	What is known
Use in pregnant and breast-feeding women **(Use in pregnancy and lactation)**	It is not known if atomoxetine can affect an unborn baby or pass into breast milk. It should not be used during pregnancy, unless the doctor has advised to do so. Patients should either avoid taking this medicine if breastfeeding or discontinue breastfeeding.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics 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 (PL). 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). Full details on these conditions and the key elements of any educational material would be made available to doctors. Their implementation 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:

Increased Heart Rate and Increased Blood Pressure

Risk minimisation measure(s)
Objective
1. To provide the doctor with information to choose the right patients for an atomoxetine prescription. 2. To help make sure that patients are watched for heart and circulation problems during treatment. 3. To provide the doctor with information to take a medical history and evaluate other diseases before prescribing atomoxetine. 4. To help make sure that people who should not take atomoxetine do not take it. 5. To support patient monitoring (making sure that good records of patient's health information are kept).
Rationale To give doctors this information is a good way to help them prescribe atomoxetine for the right patients. This will point out important information about safety. They are intended to assist doctors with monitoring patients and keeping records of patient's health information.
Main Additional Risk Minimisation Measure: A doctor's guide and related tools to be made available to doctors who prescribe atomoxetine. These tools include: - A doctor's guide to help check for the risk of heart problems in patients taking atomoxetine. - A checklist for things to do before prescribing atomoxetine to someone. - A checklist for things to do during atomoxetine treatment, to reduce a patient's risk of heart problems. - A measurement chart to help keep records of blood pressure and heart rate during atomoxetine treatment.

VI.2.6 Planned post authorisation development plan

Not applicable.

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

Changes to the Risk Management Plan over time is provided in the table below.

Version	Date	Safety Concerns	Comments
1.0	22-May-2017	Important identified risks • Suicidal Ideation • Hepatic injury • Increased blood pressure and increased heart rate • Peripheral vascular instability (Raynaud's phenomenon) Important potential risks • Cardiovascular and cerebrovascular outcomes - Myocardial ischemia - Tachyarrhythmia - Cerebrovascular accident • QTc prolongation • Aggression/ hostility • Seizure Missing information • Use in pregnancy and lactation	First version of the RMP.
1.1	17-Jan-2018	No change in the list of safety concerns.	RMP updated to incorporate Day 70 comments from RMS. No changes in safety concerns.
1.2	07-Aug-2018	No change in the list of safety concerns.	Information on additional risk minimisation measures updated to align with the originator (Strattera – Eli Lilly and company limited).