VI.2. Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Attention deficit/hyperactivity disorder (ADHD) is a condition in which patients, especially children, have trouble paying attention, getting organised, and staying focused, and tend to be too active or fidgety. They may not think about what the results of their actions might be. ADHD can cause problems at home, at school, at work, and with other people. ADHD usually begins in childhood and can continue into adulthood. More boys/men than girls/women have ADHD. Often, ADHD occurs with other conditions such as mood-related disorders, conduct-related disorders, learning disabilities, or drug and/or alcohol abuse that could cause patients to have a difficult personality; to feel sad, nervous, or angry; or to make it hard to learn.

Percentage of Patients with ADHD

In European countries, approximately 1.9% to 7.0% of children and approximately 1% to 7% of adults have ADHD.

In non-European countries approximately 5% to 12.3% children and approximately 1% to 7% of adults have ADHD.

VI.2.2. Summary of Treatment Benefits

Since the first approval of atomoxetine in 2002, it has been used by more than 13 million patients world-wide. Attention deficit/hyperactivity disorder can be treated with behaviour therapy (help or support that does not involve the use of medicine) and/or the use of medicine. In patients with ADHD, atomoxetine should be used as part of a comprehensive treatment program, which includes psychological, educational, and social measures. There are different kinds of medicine to treat patients with ADHD. These medicines can help with symptoms of ADHD, such as trouble paying attention, activity levels that are too high, and acting without thinking about the results.

Atomoxetine has been studied in over 8,600 children and teenagers and in over 4,800 adults with ADHD in clinical studies. In these studies, atomoxetine helped to treat symptoms of ADHD and functioning (such as increasing attention and focus and decreasing too-high activity levels and acting without thinking about what would happen). Atomoxetine also helped to improve how the patient felt physically, moods, behaviour, and social interactions with other people. These improvements helped patients feel more satisfied with their lives in terms of how they felt and what they were able to do day-to-day. Atomoxetine was also given to children and teenagers for up to 18 months and to adults for up to 12 months. In these studies, patients that had an initial response to atomoxetine continued to have improvement over 1 year of treatment. Treatment with atomoxetine may not be needed forever and patients should be assessed by a doctor after 1 year of treatment for the need for further atomoxetine, especially if the patient is having a good response to atomoxetine. Taking atomoxetine does not cause addiction.

VI.2.3. Unknowns Relating to Treatment Benefits

There is not much information about atomoxetine use in children who are younger than 6 years old, in the elderly, or in pregnant or breastfeeding women. However, the safety of atomoxetine in these groups seems to be similar to that in other people based on safety reviews of events that have happened in these groups. Women and their doctors should think carefully about whether atomoxetine is needed during pregnancy and breastfeeding because the risk of taking atomoxetine while pregnant or breastfeeding may not be worth the help it provides. There is not much information about the efficacy of atomoxetine beyond 18 months of treatment in children and adolescents; 231 children and adolescents have been exposed to atomoxetine for 18 months or longer in clinical trials: hence the decision for treatment beyond 1 year should be made with a doctor.

VI.2.4. Summary of Safety Concerns

Table VI.4. Important Identified Risks

Risk	What is Known	Preventability
Thinking About Killing Oneself (Suicidal Ideation)	Thinking about killing oneself affects about 1 to 10 patients in 1,000 who take atomoxetine. Thoughts of killing oneself can vary widely in the number of times they happen and how serious they are. Stopping atomoxetine treatment has been shown to stop thoughts about killing oneself.	The instructions your doctor receives suggest that he or she watch you or ask you questions about thoughts of killing yourself, worsening of ADHD, or unusual changes in behaviour. Patients and those who care for them should also watch for suicidal thoughts or behaviours. If these are seen, notify the doctor immediately.
Damage to the Liver (Hepatic Injury)	Damage to the liver affects less than 1 patient in 10,000 who takes atomoxetine. Liver injury can range from mild to severe. Mild cases of liver injury will most likely have no symptoms. Symptoms of liver injury include tiredness, dark urine, upset stomach, itching, stomach pain, and yellowing of the skin or eyes.	The instructions your doctor receives about prescribing atomoxetine recommend that atomoxetine be stopped in patients with yellowing of the skin or eyes or laboratory tests showing liver damage, and should not be restarted. Patients and those who care for them should also watch for signs of liver damage. If these are seen, notify the doctor immediately.
Increased Blood Pressure and Increased Heart Rate	Increased blood pressure and heart rate affect about 1 patient in 10 who takes atomoxetine. Higher and important increases may occur in more than 1 out of 10 atomoxetine users. Although it is possible that such increases can cause heart rhythms that are not regular or damage to organs, these events do not seem to be associated with atomoxetine use.	The instructions your doctor receives about prescribing atomoxetine recommend that he or she examine you or ask you questions about early symptoms. It is recommended that your blood pressure and heart rate be taken by your doctor before starting atomoxetine, and during treatment after each change in dose for 6 months to see if there are any clinically important increases. Patients and those who care for them should also watch for signs of extremely high blood pressure, such as severe headache, severe anxiety, shortness of breath, nosebleeds, or fast heartbeat. If these are seen, notify the doctor immediately.

Important Identified Risks (Concluded)

Risk	What is Known	Preventability

Paleness, burning, prickling, or pain of the fingers and/or toes (Peripheral Vascular Instability [Raynaud's phenomenon])	Paleness, burning, prickling, or pain of the fingers and/or toes affects about 1 to 10 patients in 1,000 who take atomoxetine. If this is severe, it could affect blood circulation to the fingers and/or toes causing damage to them.	Your doctor is informed of the possible occurrence of this condition and he/she may examine you or ask you questions about early symptoms. If you have experienced these symptoms in the past, tell your doctor about them. Patients and those who care for them should also be examined for signs of paleness, burning, prickling, or pain in the fingers and toes. If these are seen, notify the doctor immediately.

Table VI.5. Important Potential Risks

Risk	What is known (including Reason Why it is Considered a Potential Risk)
Heart Problems (Cardiovascular Outcomes)	Heart problems affect less than 1 in 10,000 patients who take atomoxetine. The risk of heart problems is considered potential as they may be the result of increased heart rate and/or increased blood pressure. However, large studies have not actually shown that heart problems occur more frequently in patients taking medicines for ADHD, including atomoxetine.
Aggression/Hostility or Unfriendly and Angry Feelings	Aggression and hostility affect about 1 to 10 patients in 1,000 who take atomoxetine. People with aggression or hostility can have temper tantrums or attack people, lie, or destroy property. Aggression and hostility are considered a potential risk because aggressive, unfriendly, and angry feelings occur frequently in patients with ADHD and other psychiatric diseases, regardless of treatment. Studies have not confirmed that taking atomoxetine will make patients be aggressive or hostile. Also, it is not understood how atomoxetine would affect a person's body to lead to aggression or hostility.
Seizure/Convulsion	Convulsions affect less than 1 in 10,000 patients who take atomoxetine. In general, patients with ADHD have convulsions more often than people without ADHD, regardless of treatment. However, large studies have not shown that convulsions occur more frequently in patients taking atomoxetine. Also, there is no understood way that atomoxetine would affect a person's body to lead to convulsions.

Table VI.6. Missing Information

There is no missing information for atomoxetine.

Risk	What is Known
None.	

VI.2.5. Summary of Additional Risk Minimisation Measures by Safety Concern

Table VI.7. Increased Heart Rate and Increased Blood Pressure

Risk Minimisation Measure(s)
Objectives and Rationale: • To provide the doctor with tools to choose the right patients for an atomoxetine prescription. • To help make sure that patients are watched for heart and circulation problems during treatment. • To support advice to doctors to take a medical history and evaluate other diseases before prescribing atomoxetine. • To help make sure that people who should not take atomoxetine do not. • To support patient monitoring (making sure that good records of patient's health information are kept). Rationale: Giving doctors these tools is a good way to help them prescribe atomoxetine for the right patients. These tools 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 will continue to be made available to doctors who prescribe atomoxetine, either through a website or by phone. These tools include: • A doctor's guide to help check for the risk of heart problems in person 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. The English language versions of these tools are provided in Annex 7.

VI.2.6. Planned Postauthorisation Development Plan

Table VI.8. List of Studies in Postauthorisation Development Plan

Study/Activity (including Study Number)	Objectives	Safety Concerns /Efficacy Issue Addressed	Status	Planned Date for Submission of Interim and Final Results
Study to determine how atomoxetine is used, how many patients are treated, and how many remain on treatment in the UK, Germany, and the Netherlands (Drug utilisation study: Strattera patient exposures and adherence in the UK, Germany, and the Netherlands)	To see over the last 24 months: • The number of patients who have taken atomoxetine, broken down by age groups (children, teenagers, adults, elderly) • The length of time that patients took atomoxetine • The percentage of time that a patient has access to atomoxetine • The dose of atomoxetine that they took • The number of patients who stopped taking atomoxetine • The number of patients who started taking atomoxetine again • The length of time that patients waited before starting atomoxetine again • The length of time that patients used atomoxetine when they started taking it again.	To see if atomoxetine is used correctly in the general population in European countries	This activity was planned as a series of assessments, the following of which have been completed: • B4Z-MC-B019 • B4Z-MC-B022	The following reports have been submitted: B4Z-MC-B019 B4Z-MC-B022. The following reports are planned: B4Z-MC-B025 in 2016 and B4Z-MC-B026 in 2018.

Studies which are a Condition of the Marketing Authorisation

None of the above studies are a condition of the marketing authorisation.

VI.2.7. Summary of Changes to the Risk Management Plan over Time

Table VI.9. Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comments
Revision 1 (rv1)	August 2005	Removed some identified and potential risks (sweating, trouble going to the bathroom, damage to the main nerve in the eye [glaucoma]) to meet new guidance.	None
Revision 2 (rv2)	September 2005	Added new safety findings about thinking about killing one's self in children.	None
Revision 3 (rv3)	October 2005	Added paleness, burning, prickling, or pain of the fingers and/or toes (peripheral vascular instability including Raynaud's phenomenon) as an identified risk. Added further information about thinking about committing suicide as an identified risk. Added heart problems as a potential risk.	None
Revision 4 (rv4)	July 2006	Added seizures and aggression/hostility as potential risks. Additional types of heart problems were added to the list of heart problems that are looked for in people taking atomoxetine.	None
Revision 5 (rv5)	November 2006	More types of heart problems were added to the list of heart problems that are looked for in people taking atomoxetine.	None
Revision 8 (rv8)	July 2009	Added and updated information on the risk of thinking about killing oneself, seizures, and heart problems. Added information on the risk of thinking of or trying to kill oneself and aggression/hostility in studies with children. Added language about how to better prevent these events in children.	None
Revision 10 (rv10) and 10.1	August 2011	Added a summary of findings for a recent blood pressure and heart rate analysis and based on this analysis, the known risks of increased blood pressure and increased heart rate were moved up to important identified risks.	None
Revision 11 (rv11)	February 2012	Included additional pharmacovigilance and risk minimisation activities for heart problems. Added a description of the risk minimisation tools and a proposal to evaluate the risk minimisation activities.	None
Revision 15 (rv 15)	January 2015	Included results from the risk minimisation effectiveness survey conducted in prescribers treating adult patients with ADHD.	None