Part VI: Summary of the risk management plan for Atomoxetine MEDICE 10 mg film-coated tablets

Summary of risk management plan for Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets

This is a summary of the risk management plan (RMP) for Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets. The RMP details important risks of Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets's risks and uncertainties (missing information).

Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets should be used.

I. The medicine and what it is used for

Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets is authorised for Attention-Deficit/Hyperactivity Disorder (ADHD) in children of 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme (see SmPC for the full indication). It contains Atomoxetine hydrochloride as the active substance and it is given by tablets orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Atomoxetine MEDICE 10 mg film-coated tablet’s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets. Potential risks are concerns for which an association with the use of this

medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

List of important risks and missing information	
Important identified risks	• Suicidal ideation (thoughts or an unusual preoccupation with killing oneself), • Hepatic injury (liver problems), • Increased blood pressure and increased heart rate, • Peripheral vascular instability (Raynaud's phenomenon (poor blood circulation which makes toes and fingers numb and pale))
Important potential risks	• Cardiovascular and cerebrovascular outcomes: o Myocardial ischaemia (condition of insufficient blood flow to the heart muscle via the coronary arteries, often resulting in chest pain), o Tachyarrhythmia (very fast heartbeat), o Cerebrovascular accident (stroke) • QTc prolongation (heart rhythm disorder that can potentially cause fast, chaotic heartbeats) • Aggression/hostility (feeling aggressive, unfriendly and angry) • Seizures
Missing information	None

II.B Summary of important risks

Important identified risk Suicidal ideation (thoughts or an unusual preoccupation with killing oneself)	
Evidence for linking the risk to the medicine	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.

Risk factors and risk groups	ADHD as such is a risk for suicidal ideation as well as the treating population. It seems that early adolescents have a greater risk than later adolescents.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 SmPC section 4.8 PL section 2 and 4 Prescription only medicine Use should be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist Additional risk minimisation measures None

Important identified risk Hepatic injury (liver problems)	
Evidence for linking the risk to the medicine	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, has been reported.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 SmPC section 4.8 PL section 2 and 4 Prescription only medicine Use should be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist Additional risk minimisation measures None

Important identified risk Increased blood pressure and increased heart rate	
Evidence for linking the risk to the medicine	Some ADHD studies 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 studies 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. Salbutamol when taken concomitantly with atomoxetine, by mouth or injected may interact with atomoxetine and increase the heart rate.
Risk factors and risk groups	Cardiovascular diseases or cerebrovascular diseases. Interaction with other medications, e.g. Salbutamol.

Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2 SmPC section 4.4 SmPC section 4.5 SmPC section 4.8 PL section 2 and 4 Prescription only medicine Use should be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist Additional risk minimisation measures Prescriber Pack includes: - Physician's Guide including additional tools: o Checklist for actions to take before prescribing / dispensing or administering atomoxetine o Checklist for monitoring to manage cardiovascular risks with atomoxetine treatment o Measurements recording chart

Important identified risk Peripheral vascular instability (Raynaud's phenomenon (poor blood circulation which makes toes and fingers numb and pale))	
Evidence for linking the risk to the medicine	In clinical studies and during post-marketing, poor blood circulation which makes toes and fingers numb and pale was rarely reported in children, adolescents, and adults.
Risk factors and risk groups	Unknown
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.8 PL section 4 Prescription only medicine Use should be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist Additional risk minimisation measures None

Important potential risk Cardiovascular and cerebrovascular outcomes	
Evidence for linking the risk to the medicine	In clinical studies events on cardiovascular and cerebrovascular outcomes have been reported.
Risk factors and risk groups	History of heart and vascular disease and concomitant medications that increase blood pressure.

Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2 SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 PL section 2 Prescription only medicine Use should be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist Additional risk minimisation measures None

Important potential risk QTc prolongation	
Evidence for linking the risk to the medicine	In clinical studies events of QTc prolongations have been reported.
Risk factors and risk groups	History of heart and vascular disease and concomitant medications that increase blood pressure.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.2 SmPC section 4.3 SmPC section 4.4 SmPC section 4.8 PL section 2 Prescription only medicine Use should be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist Additional risk minimisation measures None

Important potential risk Aggression / hostility (feeling aggressive, unfriendly and angry)	
Evidence for linking the risk to the medicine	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. Emotional lability was more frequently observed in studies among children treated with atomoxetine compared to those treated with placebo.
Risk factors and risk groups	ADHD, various psychosocial problems including alcohol and drug abuse, depression, suicide attempts, violent crimes, and neglectful and abusive parenting.

Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 SmPC section 4.8 PL section 2 and 4 Prescription only medicine Use should be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist Additional risk minimisation measures None

Important potential risk Seizures	
Evidence for linking the risk to the medicine	In clinical studies, literature and post-marketing source, seizures have been reported. In clinical studies /registries no statistically significant association between seizure and atomoxetine treatment could be observed. In the spontaneous reporting databases based on an estimated 2.233 million patients exposed to atomoxetine during a 2-year period, the reporting rate was 8 to 100,000 patients. Patients who experienced spontaneously reported seizures had clear or possible confounding/contributing factors, e.g. prior history of seizure or concomitant medications.
Risk factors and risk groups	ADHD as such and prior history of seizures.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 SmPC section 4.5 SmPC section 4.8 PL section 2 and 4 Prescription only medicine Use should be initiated by a specialist in the treatment of ADHD, such as a paediatrician, child/adolescent psychiatrist, or psychiatrist Additional risk minimisation measures None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Atomoxetine MEDICE 10 / 18 / 25 / 40 / 60 / 80 / 100 mg film-coated tablets.