PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets:

This is a summary of the risk management plan (RMP) for Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets. The RMP details important risks of Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets' risks and uncertainties (missing information).

Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets' summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets should be used.

Important new concerns or changes to the current ones will be included in updates of Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets are authorised for treatment of depression in adults (major depressive episodes); neuropathic pain (pain response from stimuli which do not normally provoke pain) in adults; chronic tension type headache prophylaxis in adults; migraine (recurrent throbbing headache that typically affects one side of head) prophylaxis in adults; and bed-wetting at night in children aged 6 years and above, only when causes such as spina bifida and related disorders have been excluded and no response has been achieved to all other non-drug and drug treatments, including muscle relaxants and desmopressin. This medicine should only be prescribed by doctors with expertise in treating patients with persistent bed-wetting.

Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets contain amitriptyline hydrochloride as the active substance and it is given by oral route.

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

Important risks of Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets' 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 PL 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 addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets and is not yet available, it has been listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Amitriptylin Abcur 10 mg, 25 mg and 50 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 Amitriptylin Abcur 10 mg, 25 mg and 50 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. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Heart problems (Cardiac disorders) • Thoughts and behaviour to harm/kill oneself (Suicidality)
Important potential risks	• Intake of more than the medically recommended dose (Overdose) • Use in pregnant women (Use during pregnancy) • Use in breast-feeding women (Use during lactation) • Drug interaction – due to shared metabolic pathway – Other
Missing information	• Long-term use in children and adolescents (growth, maturation and cognitive and behavioural development)

II.B Summary of important risks

Important identified risks

Heart problems (Cardiac disorders)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, irregular heartbeats and severely decreased blood pressure are likely to occur with high dosage. They may also occur in patients with pre-existing heart disease taking normal dosage. Cases of QT interval prolongation (abnormal, serious ECG finding) and irregular heartbeats have been reported during the post-marketing period. Electrolyte disturbances (low/high blood potassium level, low blood magnesium level) are

	known to be conditions increasing the risk to develop irregular heartbeats. Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of irregular heartbeats and decreased blood pressure. Great care is necessary if amitriptyline is administered in patients with overactive thyroid gland or to those receiving thyroid medication, since irregular heartbeats may develop. Amitriptyline may potentiate the cardiovascular effects of sympathomimetic agents like adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in cough or cold medicine, and in some anaesthetics). Drugs which prolong the QT-interval including medicines used to treat irregular heartbeats such as quinidine, the medicines used to treat allergies such as astemizole and terfenadine, some medicines used to treat some mental illnesses (notably pimozide and sertindole), cisapride, halofantrine, and sotalol, may increase the likelihood of irregular heartbeats when taken with tricyclic antidepressants. Simultaneous use of amitriptyline and methadone (medicine used to treat pain) has a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Simultaneous use of amitriptyline and diuretics (water tablets) induces low blood potassium level (e.g. furosemide). Simultaneous use of amitriptyline and thioridazine (medicine used to treat mental illness called schizophrenia) should be avoided due to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects. Medicines to treat fungal infections such as fluconazole and terbinafine increase serum concentrations of tricyclics and accompanying toxicity. Fainting and life threatening irregular heartbeat have occurred. Heart muscle disease and hypersensitivity inflammation of heart muscle are side effects of amitriptyline.
Risk factors and risk groups	• Pre-existing heart disease • Simultaneous administration of QT-prolonging drugs, anaesthetics, sympathomimetic agents, diuretics, methadone, thioridazine • High dosage of drug • Electrolyte disturbances (low/high blood potassium level, low blood magnesium level) • Use in patients with overactive thyroid gland or to those receiving thyroid medication • Elderly patients

Risk minimisation measures	**Routine risk minimisation measures:** The safety information in the proposed product information is aligned to the reference medicinal product "*Saroten 10 mg, 25 mg film-coated tablets*". **Additional risk minimisation measures:** No risk minimisation measures

Thoughts and behaviour to harm/kill oneself (Suicidality)	
Evidence for linking the risk to the medicine	Published literature and SmPC mention that, depression is associated with an increased risk of thoughts and behaviour to harm/kill oneself (suicide-related events). This risk persists until significant remission occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Suicidal thoughts and behaviours may also develop during early treatment with antidepressants for disorders other than depression. Clinical trials of antidepressant drugs in adult patients with mental disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old. Case reports of suicidal thoughts or behaviour were reported during the treatment with or just after conclusion of the treatment with amitriptyline.
Risk factors and risk groups	• Depression/Concomitant use with antidepressant drugs • Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal ideation (self-harm).
Risk minimisation measures	**Routine risk minimisation measures:** The safety information in the proposed product information is aligned to the reference medicinal product "*Saroten 10 mg, 25 mg film-coated tablets*". **Additional risk minimisation measures:** No risk minimisation measures

Important potential risks

Intake of more than the medically recommended dose (Overdose)	
Evidence for linking the risk to the medicine	Published literature and SmPC mentions that, TCAs are identified as one of the most frequently ingested substances in self poisoning along with paracetamol, benzodiazepines and alcohol. They are

	second only to analgesics as the commonest drug taken in fatal drug overdose. SmPC mentions that, anticholinergic symptoms of overdose are dilated pupil, rapid heart rate, urinary retention, dry mucous membranes, reduced intestinal motility, fits, fever, sudden occurrence of CNS depression, lowered consciousness progressing into coma, respiratory depression. Cardiac symptoms of overdose are arrhythmias (rapid or irregular heartbeats, abnormal heart rhythm). The ECG characteristically show prolonged PR interval, widening of the QRS-complex, QT prolongation, T-wave flattening or inversion, ST segment depression, and varying degrees of heart block progressing to cardiac standstill. Widening of the QRS-complex usually correlates well with the severity of the toxicity following acute overdoses. Heart failure, low blood pressure, cardiogenic shock. Metabolic acidosis, low blood potassium level. There is considerably individual variability in response to overdose. Children are especially susceptible to heart related toxicity and fits. During awakening possibly again confusion, agitation and hallucinations and ataxia. Deaths by deliberate or accidental overdosage have occurred with this class of medicament.
Risk factors and risk groups	• Ingestion of 750 mg or more by an adult • Simultaneous ingestion of alcohol and other drugs to treat mental disorders • Poor metabolisers of CYP2D6 or CYP2C19
Risk minimisation measures	**Routine risk minimisation measures:** The safety information in the proposed product information is aligned to the reference medicinal product "*Saroten 10 mg, 25 mg film-coated tablets*". **Additional risk minimisation measures:** No risk minimisation measures

Use in pregnant women (Use during pregnancy)	
Evidence for linking the risk to the medicine	Published literature states that antidepressants with effects on serotonin reuptake during embryogenesis (formation and development of an embryo) increased the risk of some organ-specific defects in a cohort of pregnant women with depression. Studies revealed that there is an increased risk of defects with first trimester exposure of amitriptyline. SmPC states that for amitriptyline only limited clinical data are available regarding exposed pregnancies. Animal studies have shown reproductive toxicity.

	In reproductive studies, harmful effects on development of the embryo or fetus were not observed in mice, rats, or rabbits when amitriptyline was given orally at doses of 2-40 mg/kg/day (up to 13 times the maximum recommended human amitriptyline dose of 150 mg/day or 3 mg/kg/day for a 50-kg patient). However, literature data suggested a risk for malformations and delays in ossification (the process of creating bone, i.e. of transforming cartilage or fibrous tissue into bone) of mice, hamsters, rats and rabbits at 9 33 times the maximum recommended dose.
Risk factors and risk groups	• Pregnant women
Risk minimisation measures	**Routine risk minimisation measures:** The safety information in the proposed product information is aligned to the reference medicinal product "*Saroten 10 mg, 25 mg film-coated tablets*". **Additional risk minimisation measures:** No risk minimisation measures

Use in breast feeding women (Use during lactation)	
Evidence for linking the risk to the medicine	SmPC states that amitriptyline and its metabolites are excreted into breast milk (corresponding to 0.6 % - 1 % of the maternal dose). A risk to the suckling child cannot be excluded.
Risk factors and risk groups	• Breast-feeding women
Risk minimisation measures	**Routine risk minimisation measures:** The safety information in the proposed product information is aligned to the reference medicinal product "*Saroten 10 mg, 25 mg film-coated tablets*". **Additional risk minimisation measures:** No risk minimisation measures

Drug interactions (due to shared metabolic pathway and other)	
Evidence for linking the risk to the medicine	SmPC mentions that, simultaneous administration of amitriptyline and MAOIs (non-selective as well as selective A (moclobemide) and B (selegiline)) may cause serotonin syndrome (a combination of symptoms, possibly including agitation, confusion, tremor, myoclonus and hyperthermia). Anaesthetics given during tri/tetracyclic antidepressant therapy may increase the risk of irregular heartbeats and low blood pressure.

	Hyperpyrexia has been reported with TCAs when administered with anticholinergic or with neuroleptic medications, especially in hot weather. Amitriptyline may potentiate the cardiovascular effects of adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine (e.g. as contained in local and general anaesthetics and nasal decongestants). TCAs may counteract the antihypertensive effects of centrally acting antihypertensives such as guanethidine, betanidine, reserpine, clonidine and methyldopa. TCAs may potentiate the effects of anticholinergic agents on the eye, central nervous system, bowel and bladder. Drugs which prolong the QT-interval including antiarrhythmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, and sotalol, may increase the likelihood of irregular heartbeats when taken with TCAs. Co-administration of amitriptyline and methadone has a potential for additive effects on the QT interval and increased risk of serious cardiovascular effects. Co-administration of amitriptyline and diuretics may induce hypokalaemia (e.g. furosemide). Co-administration of amitriptyline and thioridazine (CYP2D6 substrate) leads to inhibition of thioridazine metabolism and consequently increased risk of cardiac side effects. Concomitant use of tramadol (a CYP2D6 substrate) and TCAs, such as amitriptyline increases the risk for fits and life threatening reaction (including high fever, agitation, increased reflexes, fits, sweating, dilated pupils, and diarrhea). Additionally, this combination can inhibit the metabolism of tramadol to the active metabolite and thereby increasing tramadol concentrations potentially causing opioid toxicity. The CYP2D6 isozyme can be inhibited by a variety of drugs, e.g. neuroleptics, serotonin reuptake inhibitors, beta blockers, and antiarrhythmics. Examples of strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine and quinidine. These drugs may produce substantial decreases in TCA metabolism and marked increases in plasma concentrations. Other Cytochrome P450 inhibitors like cimetidine, methylphenidate and calcium-channel blockers (e.g. diltiazem and verapamil) may increase plasma levels of TCAs and accompanying toxicity. Antifungals such as fluconazole (CYP2C9 inhibitor) and terbinafine (CYP2D6 inhibitor) have been observed to increase serum levels of amitriptyline and nortriptyline accompanying toxicity. Fainting and life-threatening irregular heartbeat have occurred. The CYP3A4 and CYP1A2 isozymes metabolise amitriptyline to a lesser extent. However, fluvoxamine (strong CYP1A2 inhibitor) was shown to increase amitriptyline plasma concentrations.

	Clinically relevant interactions may be expected with concomitant use of amitriptyline and strong CYP3A4 inhibitors such as ketoconazole, itraconazole and ritonavir. Patients who are known poor metabolisers of CYP2D6 or CYP2C19 may have higher plasma concentrations of amitriptyline and its active metabolite nortriptyline. Amitriptyline may enhance the sedative effects of alcohol, barbiturates and other CNS depressants.
Risk factors and risk groups	• Patients who are known poor metabolisers of CYP2D6 or CYP2C19 • Simultaneous use of cytochrome P450 inhibitors • Concomitant treatment with MAOIs, anaesthetics, alcohol, barbiturates and other CNS depressants • Concomitant treatment of amitriptyline with sympathomimetic agents (adrenaline, ephedrine, isoprenaline, noradrenaline, phenylephrine, and phenylpropanolamine), adrenergic neurone blockers (guanethidine, betanidine, reserpine, clonidine and methyldopa), anticholinergic agents and drugs which prolong the QT-interval (e.g. antiarrhythmics such as quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide and sertindole), cisapride, halofantrine, sotalol) methadone and diuretics (e.g. furosemide)
Risk minimisation measures	**Routine risk minimisation measures:** The safety information in the proposed product information is aligned to the reference medicinal product "*Saroten 10 mg, 25 mg film-coated tablets*". **Additional risk minimisation measures:** No risk minimisation measures

Missing information

Long-term use in children and adolescents (growth, maturation and cognitive and behavioural development)	
Risk minimisation measures	**Routine risk minimisation measures:** The safety information in the proposed product information is aligned to the reference medicinal product "*Saroten 10 mg, 25 mg film-coated tablets*". **Additional risk minimisation measures:** No risk minimisation measures

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 Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets.

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

There are no studies required for Amitriptylin Abcur 10 mg, 25 mg and 50 mg film-coated tablets.