Part VI: Summary of the risk management plan

Summary of risk management plan for <Atropine> 1.0 mg/ml solution for injection

This is a summary of the risk management plan (RMP) for <Atropine> 1.0 mg/ml solution for injection. The RMP details important risks of <Atropine> 1.0 mg/ml solution for injection, how these risks can be minimised, and how more information will be obtained about <Atropine> 1.0 mg/ml solution for injection's risks and uncertainties (missing information).

<Atropine>1.0 mg/ml solution for injection's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how <Atropine>1.0 mg/ml solution for injection should be used.

I. The medicine and what it is used for

<Atropine>1.0 mg/ml solution for injection is authorised for children of all ages and adults for the treatment of:

- Bradycardia, induced by anesthetics, or by other drugs.

- To diminish the muscarinic effects of neostigmine, when it is administered after surgery to neutralize non-depolarizing muscle relaxants.

- Intoxication by organophosphate pesticides and other anticholinesterase agents.

<Atropine> may also be used as pre-anesthetic prior to the induction of the general anesthesia (decreases the risk of vagal inhibition and reduces salivary and bronchial secretions).

It contains atropine sulfate as the active substance and it is given by an injection into either a vein (intravenously), the skin (subcutaneously) or, muscle (intramuscularly).

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

Important risks of <Atropine> 1.0 mg/ml solution for injection, together with measures to minimise such risks and the proposed studies for learning more about <Atropine>1.0 mg/ml solution for injection'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.

If important information that may affect the safe use of <Atropine> 1.0 mg/ml solution for injection is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of <Atropine>1.0 mg/ml solution for injection 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 <Atropine> 1.0 mg/ml solution for injection. 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	Increase in intraocular pressure (elevated pressure in the eye) Urinary retention (urinary difficulties) Aggravation (worsening) of symptoms of myasthenia gravis Oesophagus and intestinal disease Arrhythmia (abnormal heartbeats)
Important potential risks	Medication error
Missing information	Use during pregnancy Use in patients with renal or hepatic impairment

II.B Summary of important risks

Important identified risk 1: Increase in intraocular pressure (elevated pressure in the eye)	
Evidence for linking the risk to the medicine	Glaucoma is considered a common undesirable effect associated with the use of atropine. Clinical trials with atropine however, have not, in general, been designed to identify and document this adverse event. Thus, no solid data are available from clinical trials. There have been a few post-marketing reports describing the development of acute angle closure glaucoma in patients not formerly known to have glaucoma. However, this has not been documented in small case series of patients with *(Schwartz et al 1957, Tammisto et al 1964)* or without *(Tammisto et al 1964, Cozanitis et al 1979)* glaucoma.
Risk factors and risk groups	Patients predisposed to glaucoma are at high risk for atropine-induced increase in intraocular pressure, ultimately resulting in acute glaucoma attack. In general, muscarinic receptor antagonists including atropine administered systemically have little effect on intraocular pressure in healthy subjects except in patients predisposed to angle-closure glaucoma, in whom the pressure may

	occasionally rise dangerously. The rise in pressure occurs when the anterior chamber is narrow, and the iris obstructs outflow of aqueous humor into the trabeculae. Muscarinic antagonists may precipitate a first attack in unrecognized cases of this relatively rare condition *(Goodman and Gillman's 2011).* Within this notion, the development of drug-induced acute angle-closure glaucoma by atropine has been widely reported, with authors pointing out that it will not contribute to acute angle-closure glaucoma unless there are predisposing factors such as a shallow anterior chamber *(Greenstein et al 1984, Lachkar and Bouassida 2007, Lee et al 2016).* A higher risk is considered for patients already suffering from glaucoma. Concomitant treatment of glucocorticoids with atropine will result in further increase in intraocular pressure and thus, carries a higher risk of inducing an attack of acute angle closure glaucoma in susceptible patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3., 4.4., 4.5., 4.8. and 5.1. PL sections 2 and 4 A contraindication for using atropine in patients with angle-closure or narrow-angle glaucoma between the iris and the cornea is included in SmPC section 4.3. Moreover, monitoring intraocular pressure is recommended in SmPC section 4.4. and a warning that concomitant administration with glucocorticoids may result in an increased intraocular pressure is also included in SmPC section 4.5. Glaucoma has been listed in the SPC as an undesirable effect under Section 4.8. The effect of atropine in the eye is described in SmPC section 5.1. In the PL section 2, patients are instructed not to take atropine in angle-closure or narrow-angle glaucoma between the iris and the cornea, as it may increase intraocular pressure. Moreover, a warning stating that anti-muscarinic may increase intraocular is included, thus, patients are instructed to talk to their doctor, pharmacist or nurse before taking atropine and depending on their condition, to monitor this parameter. Additionally, patients are instructed to inform their doctor or pharmacist before

	taking the drug, if they are taking, have recently taken or might take glucocorticoids or corticotropin (ACTH) as concomitant long-term anti-muscarinic therapy may result in an increased intraocular pressure. The PL under Possible Side Effects (Section 4) includes "glaucoma".
Important identified risk 2: Urinary retention (urinary difficulties)	
Evidence for linking the risk to the medicine	Urinary retention is recognized as a possible side-effect of anticholinergic drugs, including atropine *(Orko and Rosenberg 1984, Verhamme et al 2008).* The normal human bladder's excitatory innervation is almost exclusively muscarinic cholinergic. Voiding can be halted with atropine *(Faure Walker et al 2015)*. In the post-operative setting, approximately 10% of urinary retention episodes might be attributable to the type of drugs used during surgery *(Verhamme et al 2008).* For instance, anticholinergics and alpha-adrenergic agonists may block detrusor contractions *(Tammela et al 1986, Petros et al 1991, Baldini et al 2009, Stegall et al 2013).* Atropine can potentially relax the detrusor musculature and contract the bladder neck and thereby inhibit the patient's ability to urinate. This effect is well-known. Among anticholinergic agents, all drugs with anti-muscarinic effects are thought to cause or exacerbate urinary retention, as a result of failure of bladder contraction, especially where there is pre-existing bladder outflow obstruction possibly secondary to the disease *(Drake et al 1998).*
Risk factors and risk groups	Men with benign prostatic hypertrophy represent an important risk group with respect to atropine-driven urinary retention *(Martin-Merino et al 2009).* Of note, growing age in male patients is also a predisposing factor, as elderly men are at higher risk for developing drug-induced urinary retention, due to existing co-morbidities including benign prostatic hyperplasia as well as the use of other concomitant medication that could reinforce the impairing effect on micturition *(Verhamme et al 2008).* In the postoperative period, treatment of pain with opiates or opioid analogues decreases the sensation of bladder fullness by partially inhibiting the parasympathetic nerves that innervate the bladder. In addition, they have been shown to increase the tonus of the neurotransmitters involved in the central control sphincter of the urinary bladder via sympathetic overstimulation, which leads to

	increased resistance in the outflow tract of the bladder *(Verhamme et al 2008).* This, in combination with the use of concomitant therapy with atropine, increases the risk of severe constipation, and may ultimately result in acute urinary retention.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3., 4.5., 4.8. and 5.1. PL sections 2 and 4 A contraindication for using atropine in patients with prostatic hypertrophy and warnings for concomitant administration with opiate analgesics are included in the SmPC sections 4.3. and 4.5. Dysuria and urinary retention have been listed in the SPC as an undesirable effect under Section 4.8. The effect of atropine on the urinary system is described in SmPC section 5.1. In the PL section 2, patients are instructed not to take the drug if they have prostatic hypertrophy, since it may stimulate urinary retention. Moreover, they are instructed to inform their doctor or pharmacist before taking atropine, if they are taking, have recently taken or might take opiate analgesics. The PL under Possible Side Effects (Section 4) includes "urinary retention".
Important identified risk 3: Aggravation (worsening) of symptoms of myasthenia gravis	
Evidence for linking the risk to the medicine	Myasthenia gravis is an autoimmune disease *(Wittbrodt 1997).* It is postulated that in myasthenia gravis patients, atropine competes with the small amount of acetylcholine that has the potential to act on the body, leading to worsening of the symptoms of the disease. Worsening of the disease may lead to myasthenic crisis which is defined as a severe and acute exacerbation of myasthenic weakness often precipitated by systemic medications. It is a life-threatening form of myasthenia gravis where the muscles used for breathing become weak. If untreated, this can lead to breathing difficulties and ultimately lung failure *(Hetherington and Losek 2005, Gold et al 2008).*
Risk factors and risk groups	In patients with a known history of myasthenia gravis, the use of anticholinergic medications including atropine may exacerbate the risk of myasthenic crisis.

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3. PL section 2 A contraindication for use of atropine in patients with myasthenia gravis is included in SmPC section 4.3. In the PL section 2, patients are instructed not to take the drug, if they have myasthenia gravis, unless administered with the purpose of reducing adverse muscarinic effects caused by anticholinesterase agents.
Important identified risk 4: Oesophagus and intestinal disease	
Evidence for linking the risk to the medicine	Therapeutic doses of atropine cause a reduction in motility and tone of stomach *(Eger 1962)*, duodenum, jejunum *(Elsom et al 1939),* ileum *(Elsom et al 1939, Adler et al 1942)* and colon *(Elsom et al 1939, Adler et al 1942, Atkinson et al 1943).* Atropine may induce difficulty in swallowing *(Goodman and Gillman's 2011)*. Atropine-like compounds do not usually give rise to ileus, except in overdose or in combination with other drugs predisposing to bowel immobility, such as opiates *(George 1980)*. Furthermore, obstruction of the bowel is a painful condition which requires treatment and frequently surgery *(Sinicrope 2003, Reddy and Cappell 2017)*.
Risk factors and risk groups	In patients with underlying conditions resulting in decreased gastrointestinal motility, administration of atropine has the potential to deteriorate their condition. Gastrointestinal disorders which may be adversely affected by atropine include paralytic ileus, intestinal atony. Atropine may also have an adverse impact on conditions such as obstruction of the gastrointestinal tract, ulcerative colitis, gastric ulcers since decreased motility might result in ileus and gastric stasis. Concomitant administration with opiates which predispose to bowel immobility increase the risk of constipation and ileus *(George 1980)*. Moreover, patients taking potassium chloride preparations are prone to increased severity of the gastrointestinal disorders caused by potassium chloride *(McMahon et al 1982)*. Similarly, in patients with esophageal reflux disorders, decreased gastric motility and pressure exerted by the lower esophageal sphincter may result in increased frequency of esophageal reflux.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3., 4.4., 4.5., 4.8.

	PL sections 2 and 4 A contraindication for use of atropine in patients with obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony, ulcerative colitis is included in SmPC section 4.3. Warnings for use in patients with gastric ulcers, esophageal reflux problems, those with hiatal hernia associated with gastroesophageal reflux or those who take opiate analgesics are included in SmPC sections 4.4. and 4.5. Tonicity and motility decrease of the gastrointestinal tract, constipation, vomiting, ileus paralytic, dysphagia, taste change have been listed in the SmPC as undesirable effects under Section 4.8. The effect of atropine on the gastrointestinal tract is described in SmPC section 5.1. In the PL section 2, patients are instructed not to take the drug, if they have obstruction of the gastrointestinal tract, paralytic ileus, intestinal atony or ulcerative colitis. Moreover, a warning stating that atropine may delay gastric emptying, leading to stasis in patients with gastric ulcers is included and thus, patients with gastric ulcers, esophageal reflux problems, hiatal hernia associated with gastroesophageal reflux are instructed to talk to their doctor, pharmacist or nurse before using atropine and to take precautionary measures. Additionally, patients are instructed to inform their doctor or pharmacist before taking the drug, if they are taking, have recently taken or might take opiate analgesics. The PL under Possible Side Effects (Section 4) includes "Tonicity and motility decrease of the gastrointestinal tract, constipation, vomiting, ileus paralytic, dysphagia, taste change".
Important identified risk 5: Arrhythmia (abnormal heartbeats)	
Evidence for linking the risk to the medicine	Atropine often produces cardiac arrhythmias, but without significant cardiovascular symptoms *(Shutt and Bowes 1979)*. Administration of small doses may lead to paroxysmal bradycardia. Maximum slowing has been seen with doses of 0.2-0.3 mg IV *(Morton and Thomas 1958, Lonnerholm and Widerlov 1975)*. With higher doses, however, atropine causes an increase rate, especially in young healthy adults where vagal tone is at its peak. The removal of vagal influence on the heart may also cause conduction changes with decreased AV conduction time and

	subsequent decrease in PR interval on ECG *(Thurlow 1972, , Lonnerholm and Widerlov 1975, Fassi and Rosenberg 1979)*. Toxic doses can cause a variety of arrhythmias including AV block, nodal rhythm, ventricular extrasystoles and even ventricular fibrillation *(Averill and Lamb 1959)*.
Risk factors and risk groups	Because atropine can alter the heart rate (producing tachycardia), patients with cardiac dysrhythmias, congestive heart failure, coronary artery disease, angina, or other cardiac instability are in increased risk of arrhythmias given that an increase in heart rate could be detrimental. Atropine should be used with caution during AMI because the drug can potentiate dysrhythmias. In addition, the increase in heart rate caused by atropine increases the oxygen demand on the heart and can exacerbate myocardial ischemia. The incidence of ventricular arrhythmias is also increased when atropine is given with cyclopropane *(Eger 1962)*. Patients suffering from thyrotoxicosis present symptoms of tachycardia, hypertension, atrial arrhythmia and high output cardiac failure *(Gilbert 2017)*. Thus, they consist a population with increased risk for atropine-induced arrhythmias.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.3., 4.4., 4.5., 4.8. PL sections 2 and 4 A contraindication for use in patients with heart failure, heart surgery, tachycardia or thyrotoxicosis is included in SmPC section 4.3. Warnings regarding paroxysmal bradycardia and concomitant administration with cyclopropane are included in SmPC sections 4.4. and 4.5. Bradycardia (after the administration of low doses), tachycardia (following the administration of high doses), palpitations and cardiac arrhythmia have been listed in the SPC as an undesirable effect under Section 4.8. In the PL section 2, patients are instructed not to take the drug, if they have heart failure, heart surgery, tachycardia, or thyrotoxicosis. Moreover, a warning stating that administration of small doses of atropine may lead to paroxysmal bradycardia is included and thus, patients are instructed to talk to their doctor or nurse before taking the drug. Additionally, patients are instructed to inform their doctor or pharmacist, if they are taking, have recently taken or might take cyclopropane. The PL under Possible Side Effects (Section 4) includes

	"Bradycardia (after the administration of low doses), tachycardia (following the administration of high doses), palpitations and cardiac arrhythmia".
Important Potential Risk 1: Medication error	
Evidence for linking the risk to the medicine	Atropine should be carefully administered at a different dosage depending on the indication. The differences on the posology among the various indications for atropine are small. As such, medication errors may occur. Moreover, the volume of atropine solution used is small predisposing to medication errors a risk commonly observed for small injectable medicinal products *(Muffly et al 2017)*.
Risk factors and risk groups	Young adults seem to be more susceptible to cardiac arrhythmias. Moreover, pharmacokinetic studies have shown that neonates, younger children (<2 yr) and the elderly (70 years and older) have a longer half-life, making both the younger and older patient more sensitive to a given dose *(Smith et al 1979, Adams et al 1982, Virtanen et al 1982, Hinderling et al 1985, Ali-Melkkila et al 1993, Blanc 1995)*. Additionally, patients with Down's syndrome may exhibit abnormally greater cardioaccelerator response to intravenously administered atropine *(Harris and Goodman 1968)*. Therefore, children, elderly people and patients with Down's syndrome are considered to be at increased risk of experiencing adverse events in case of a medication error.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2., 4.4.,4.9. and 5.1. Posology is clearly defined according to indication and age in SmPC section 4.2. Special warnings are included in SmPC section 4.4. regarding the use of atropine in children, elderly patients and patients with Down's syndrome. In section 5.1. it is mentioned that young healthy adults appear to be more susceptible to cardiac effects. Instructions for the handling of atropine intoxication are included in SmPC section 4.9. PL sections 2 and 3 In PL section 2, there is a warning regarding the use of atropine in children, elderly people and people with Down's syndrome. PL section 3 provides information and instructions on atropine intoxication.

Missing information 1: Use in pregnancy	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.6. PL section 2 In SmPC section 4.6., it is mentioned that atropine should only be administered during pregnancy when the potential benefits justify the possible risks to the fetus. In the PL section 2, patients are instructed to ask their doctor for advice before taking this medicine, if they are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby. Moreover, it is recommended that atropine should only be administered during pregnancy when the potential benefits justify the possible risks to the foetus.
Missing information 2: Use in patients with renal or hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2. and 4.4. PL section 2SmPC sections 4.2. and 4.4. advise caution in use of atropine in patients with renal or hepatic impairment. The same applies for PL section 2.

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 <Atropine> 1.0 mg/ml solution for injection.

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

There are no studies required for <Atropine> 1.0 mg/ml solution for injection.