Part VI: Summary of the risk management plan

Summary of risk management plan for <Lidocaine hydrochloride 10 mg / mL Solution for injection > and <Lidocaine hydrochloride 20 mg / mL Solution for injection>

This is a summary of the risk management plan (RMP) for <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 mg / mL Solution for injection>. The RMP details important risks of <Lidocaine hydrochloride 10 mg / mL Solution for injection > and <Lidocaine hydrochloride 20 mg / mL Solution for injection>, how these risks can be minimised, and how more information will be obtained about <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 mg / mL Solution for injection>'s risks and uncertainties (missing information).

<Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 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 <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 mg / mL Solution for injection> should be used.

I. The medicine and what it is used for

<Lidocaine hydrochloride 10 mg / mL Solution for injection> is authorised for local and regional anaesthesia (to numb a defined body area before a surgical operation) in adults, adolescents and children over 2 years of age.

<Lidocaine hydrochloride 20 mg / mL Solution for injection> is authorised for local and regional anaesthesia (to numb a defined body area before a surgical operation) in adults, adolescents and children over 2 years of age and to control a severe fast or abnormal heart beat (ventricular tachycardia or tachyarrhythmia) but only if the doctor has assessed the condition as life threatening in adults, adolescents and children over 2 years of age.

It contains lidocaine hydrochloride as the active substance and it is administered as an injection into either a vein, the skin, muscle, bone, spine or nerve area. These routes of administration concern local and regional anaesthesia. When <Lidocaine hydrochloride 20 mg / mL Solution for injection> is used as an antiarrhythmic therapy it is injected into the vein (intravenously).

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

Important risks of <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 mg / mL Solution for injection>, together with measures to minimise such risks and

the proposed studies for learning more about <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 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 <Lidocaine hydrochloride 10 mg / mL Solution for injection > and <Lidocaine hydrochloride 20 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 <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 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 administered. 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 <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 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	Central nervous system toxicity Cardiac toxicity
Important potential risks	None
Missing information	Use in children under 2 years of age

II.B Summary of important risks

Important identified risk: Central nervous system toxicity	
Evidence for linking the risk to the medicine	<u>Evidence source(s) and strength of evidence:</u> Lidocaine, when present in the systemic circulation, produces well-known concentration-dependent CNS toxicity whose manifestation initially reflects inhibitory symptoms such as sedation, drowsiness, and alterations in sensorium, before progressing to excitatory phenomena including

	generalized seizures, and, in the most severe cases, coma and death. That lidocaine affects the CNS is not surprising, because it readily passes the blood–brain barrier *(Putrenko et al 2016)*.
Risk factors and risk groups	*Effect of age* Patients at the extremes of age have consistently been shown to be at the greatest risk of systemic toxicity. Neonates and infants have reduced plasma concentrations of the binding protein α1-acid glycoprotein and immature hepatic enzyme systems that may increase the free fraction of LA in the plasma. Elderly patients have reduced clearance of LA due to reduced metabolic organ perfusion and pharmacodynamic function, thereby increasing the potential of drug accumulation with repeated boluses of LA or continuous infusions. Elderly patients may also have multiple comorbidities, and degenerative changes might render the elderly more susceptible to the systemic effects of LA, despite relatively unchanged levels of protein binding. As the skeletal muscle may act as a reservoir for LA, reduced skeletal muscle mass has also been implicated in increasing the risk of systemic toxicity *(El-Boghdadly et al 2018)*. *Pregnant women* Parturients have reduced plasma concentrations of α1-acid glycoprotein and an increased cardiac output. Together, these lead to accelerated perfusion of injection sites, rapid LA absorption, and higher peak free LA concentrations *(El-Boghdadly et al 2018)*. *Cardiac disease* Patients with cardiac disease are at an increased risk of local anaesthetic systemic toxicity. Patients with severe cardiac dysfunction are particularly susceptible to LA-induced myocardial depression and arrhythmias due to reduced hepatic and renal perfusion leading to reduced metabolism and elimination, respectively *(El-Boghdadly et al 2018)*. *Hepatic dysfunction* Liver disease increases the potential for toxicity. Hepatic dysfunction decreases metabolism, therefore increasing the potential for toxicity *(Cox et al 2003)*. *Other factors*

	Toxicity is also increased in the presence of acidosis, which decreases plasma protein binding *(Cox et al 2003)*.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections: 4.2., 4.3., 4.4., 4.5, 4.8., 4.9 and 5.2 PL sections: 2, 3 and 4

Important identified risk: Cardiac toxicity	
Evidence for linking the risk to the medicine	Systemic toxicity of lidocaine can be life-threatening *(Hasan et al 2017).* Toxic responses in the cardiovascular system (CVS) occur when the anaesthetics are at higher levels in the blood compared with the levels that cause toxic responses in the CNS. Cardiac toxicity with lidocaine is possible, but uncommon at clinically used doses *(Cox et al 2003)*. CV toxicity generally begins after signs of CNS toxicity have occurred. It is important to distinguish the CV changes related to toxic concentrations of LAs and those secondary to the regional anaesthetic procedure itself *(Naguib et al 1998).* One-third of the reported cases of local anaesthetic systemic toxicity begin with CNS features that progress to involve CVS signs, and one-fifth of local anaesthetic systemic toxicity episodes present with isolated CVS disturbances *(Gitman and Barrington 2018)*. Again, protean features of CVS toxicity are apparent, but dysrhythmias, conduction deficits, hypotension, and eventually cardiac arrest – most commonly of an asystolic nature – may be seen *(di Gregorio et al 2010)*. Local anaesthetic systemic toxicity events most frequently occur immediately following injection of LA *(Mulroy 2002)*, and recent data demonstrate that delayed presentation may occur at various time points up to several days following commencement of an infusion *(El-Boghdadly et al 2018)*.
Risk factors and risk groups	<u>Risk factors and risk groups:</u> *Effect of age* Patients at the extremes of age have consistently been shown to be at the greatest risk of local anaesthetic systemic toxicity. Neonates and infants have reduced plasma concentrations of the binding protein α1-acid glycoprotein and immature hepatic enzyme systems that may increase the free fraction of LA in the plasma.

	Elderly patients have reduced clearance of LA due to reduced metabolic organ perfusion and pharmacodynamic function, thereby increasing the potential of drug accumulation with repeated boluses of LA or continuous infusions. Elderly patients may also have multiple comorbidities, and degenerative changes might render the elderly more susceptible to the systemic effects of LA, despite relatively unchanged levels of protein binding. As the skeletal muscle may act as a reservoir for LA, reduced skeletal muscle mass has also been implicated in increasing the risk of systemic toxicity *(El-Boghdadly et al 2018)*. *Pregnant women* Parturients have reduced plasma concentrations of α1-acid glycoprotein and an increased cardiac output. Together, these lead to accelerated perfusion of injection sites, rapid LA absorption, and higher peak free LA concentrations *(El-Boghdadly et al 2018)*. *Cardiac disease* Patients with cardiac disease are at an increased risk of local anesthetic systemic toxicity. Those with pre-existing conduction disorders may be predisposed to cardiovascular toxicity. Patients with severe cardiac dysfunction are particularly susceptible to LA-induced myocardial depression and arrhythmias due to reduced hepatic and renal perfusion leading to reduced metabolism and elimination, respectively *(El-Boghdadly et al 2018)*. *Hepatic dysfunction* Liver disease increases the potential for toxicity. Hepatic dysfunction decreases metabolism, therefore increasing the potential for toxicity *(Cox et al 2003)*. *Other factors* Toxicity is also increased in the presence of acidosis, which decreases plasma protein binding *(Cox et al 2003)*.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections: 4.2., 4.3., 4.4., 4.5, 4.8., 4.9 and 5.2 PL sections: 2, 3 and 4

Missing information: Use in children under 2 years of age	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.1, 4.2. PL sections 1, 3

List of literature references

Cox B, Durieux ME, Marcus MA (2003): Toxicity of local anaesthetics; *Best Pract Res Clin Anaesthesiol, 17, 111-136.*

di Gregorio G, Neal J, Rosenquist R et al (2010): Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009; *Reg Anesth Pain Med, 35, 181–187.*

El-Boghdadly K, Pawa A, Chin K (2018): Local anesthetic systemic toxicity: current perspectives; *Local Reg Anesth, 11, 35-44.*

Gitman M, Barrington MJ (2018): Local Anesthetic Systemic Toxicity: A Review of Recent Case Reports and Registries; *Reg Anesth Pain Med, 43, 124–130.*

Hasan B, Asif T, Hasan M (2017): Lidocaine-Induced Systemic Toxicity: A Case Report and Review of Literature; *Cureus, 9, e1275.*

Mulroy MF (2002): Systemic toxicity and cardiotoxicity from local anesthetics: incidence and preventive measures; *Reg Anesth Pain Med, 27, 556–561.*

Naguib M, Magboul MM, Samarkandi AH et al (1998): Adverse effects and drug interactions associated with local and regional anaesthesia; *Drug Saf, 18, 221-250.*

Putrenko I, Ghavanini, Meyer Schoniger K (2016): Central Nervous System-Toxic Lidocaine Concentrations Unmask L-Type Ca^{2+} Current-Mediated Action Potentials in Rat Thalamocortical Neurons: An In Vitro Mechanism of Action Study; *Anesth Analg, 122, 1360-1369.*

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 <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 mg / mL Solution for injection>.

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

There are no studies required for <Lidocaine hydrochloride 10 mg / mL Solution for injection> and <Lidocaine hydrochloride 20 mg / mL Solution for injection>.