Part VI: Summary of the risk management plan by product

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Acute, post-operative pain:

The relief of pain has been one of the primary reasons for development of health care. Pain has been introduced as the fifth vital sign by Joint commission on health care organization (JCAHO). Pain is omnipresent, is an intolerable sensation and makes the patient vulnerable. Pain inadequately relieved is deleterious and can lead to a number of complications in the period after surgery. Therefore the pain of surgery must be relieved totally. [1] As the population ages, research into the assessment of postoperative pain in older patients is urgently needed. An elevated number of patients experience pain in the first 24 hours after the surgery. The incidence of pain was higher in patients undergoing general surgery. [2]

VI.2.2 Summary of treatment benefits

A study was conducted to compare the effect of ropivacaine with dummy drug (placebo) for management of pain after operation in patients undergoing operation of removal of gall bladder (cholecystectomy). All patients were given standard general anaesthesia with propofol (2 - 2.5 mg/kg), fentanyl 2 μg/kg, and succinylcholine (2 mg/kg) to facilitate placement of a flexible plastic tube into the windpipe (tracheal intubation). Group A: Patients received 20 ml of 0.9% normal saline as dummy drug (n = 25). Group B: Patients received 20 ml of 0.5% ropivacaine (n = 25). In both groups, the treatment related adverse events were mostly symptoms of vomiting and shoulder pain with the highest being in Group A. The authors conclude that administration of local anaesthetic is an easy, cheap, and non-invasive method which provides good pain management in the immediate postoperative period after operation. [3]

VI.2.3 Unknowns relating to treatment benefits

There are no adequate data on the use of ropivacaine in human pregnancy, passing of ropivacaine in breast milk, use in premature babies and effects on driving and using machines.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergy (Hypersensitivity) to Ropivacain or other ingredients of the medicinal product or to other local anaesthetics of the amide type	Hypersensitivity to Ropivacaine or other ingredients of the medicinal product or to other local anaesthetics of the amide type have been reported rarely ($\geq$ 1/10,000 to < 1/1,000).	Ropivacaine should not be given to the patients with known allergy to ropivacaine or other local anaesthetics belonging to amide class of drugs. Ropivacaine should only be used by, or under the supervision of, clinicians experienced in regional anaesthesia.
Regional anaesthesia resulting from the injection of a local anaesthetic on each side of the cervix; used during labour and childbirth (Obstretic paracervical anaesthesia)	Ropivacaine is contraindicated in patients with obstetric paracervical anaesthesia. Ropivacaine should not be used as regional anaesthesia resulting from the injection of a local anaesthetic on each side of the cervix; used during labour and childbirth.	Ropivacaine should only be used by, or under the supervision of, clinicians experienced in regional anaesthesia.
Intravascular injection, intrathecal use, intracerebral use, intra-articular use	The use of ropivacaine is contraindicated as intravascular injection, intrathecal use, intracerebral use, intra-articular use. There are rare reports of cardiac arrest during the use of ropivacaine, especially after unintentional accidental intravascular administration in elderly patients and	Ropivacaine should only be used by, or under the supervision of, clinicians experienced in regional anaesthesia.

Risk	What is known	Preventability
	in patients with concomitant heart disease.	
Intravenous regional anaesthesia	The use of ropivacaine is contraindicated as intravenous regional anaesthesia.	Ropivacaine should only be used by, or under the supervision of, clinicians experienced in regional anaesthesia.
Acute systemic toxicity (due to accidental intravascular injection or overdose)	Acute systemic toxicity, including CNS and CVS, may occur due to accidental exposure to high blood concentration of a local anaesthetic, through intravascular injection or overdose.	If there is any symptom of acute systemic toxicity, the patient is recommended to contact the physician.
Harmful effects on nervous system (CNS toxicity)	CNS toxicity may occur due to high blood concentration of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularized areas. Effects on central nervous systems included: Paraesthesia, dizziness, headache: Common (> 1/100 to < 1/10) Symptoms of CNS toxicity (Convulsions, Grand mal convulsions, Seizures, light-headedness, circumoral paraesthesia, Numbness of the tongue, hyperacusis, tinnitus, visual disturbances, dysarthria, muscular twitching, tremor), hypoaesthesia: Uncommon (>1/1,000 to < 1/100).	If there is any symptom of CNS toxicity, the patient is recommended to contact the physician.

Risk	What is known	Preventability
	Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. Initially symptoms such as visual or hearing disturbances, perioral numbness, dizziness, light-headedness, tingling and paraesthesia are seen. Dysarthria, muscular rigidity and muscular twitching are more serious and may precede the onset of generalised convulsions. These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly during convulsions due to the increased muscular activity, together with the interference with respiration. In severe cases even apnoea may occur. The respiratory and metabolic acidosis increases and extends the toxic effects of local anaesthetics.	
Harmful effect on cardiovascular system (Cardiovascular system toxicity)	Symptoms of CVS toxicity usually occur because of inadvertent intravascular injection, overdose or rapid absorption. CVS toxicity reactions are caused by high blood concentration of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or	If there is any symptom of CVS toxicity, the patient is recommended to contact the physician.

Risk	What is known	Preventability
	exceptionally rapid absorption from highly vascularized areas CVS toxicity has been reported with rare (>1/10,000 to < 1/1,000) frequency.	
Difficulties of nervous system (Neurological complications)	Neurological complications like neuropathy and spinal cord dysfunction (e.g. anterior spinal artery syndrome, arachnoiditis, cauda equina), which may result in rare cases of permanent sequelae, have been associated with regional anaesthesia, regardless of the local anaesthetic used.	If there is any symptom of neurological complication, the patient is recommended to contact the physician.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
Major peripheral nerve block	Major peripheral nerve blocks may imply the administration of a large volume of local anaesthetic in highly vascularized areas, often close to large vessels where there is an increased risk of intravascular injection and/or rapid systemic absorption, which can lead to high plasma concentrations. There have been rare reports of cardiac arrest during the use of ropivacaine for peripheral nerve blockade.
Head and necks blocks	Certain local anaesthetic procedures, such as injections in the head and neck regions, may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used.
Severe liver and kidney disorders (Severe hepatic and renal impairment)	Ropivacaine is a long-acting drug. It is metabolised by liver. It is highly lipid-soluble. All metabolites have a local anaesthetic effect but of considerably lower potency and shorter duration than that of ropivacaine. In patients with hepatic or renal impairment, accumulation or delayed elimination may occur with repeated doses of ropivacaine. Normally there is no need to modify the dose in patients with impaired renal function when used for single dose or short-term treatment. Acidosis and reduced plasma protein concentration, frequently seen in patients with chronic renal failure, may increase the risk of systemic toxicity.
Acute porphyria	Ropivacaine is possibly porphyrinogenic and should only be prescribed to patients with acute porphyria when no safer alternative is available. Appropriate precautions should be taken in the case of vulnerable patients, according to standard textbooks and/or in consultation with disease area experts.
Interactions with other medicinal products such as concomitant use of	Cytochrome P450 (CYP) 1A2 is involved in the formation of 3-hydroxy-ropivacaine, the major metabolite. *In vivo*, the plasma clearance of ropivacaine was reduced by up to 77 % during co-

Risk	**What is known (Including reason why it is considered a potential risk)**
other amide type drugs and strong inhibitors CYP1A2	administration of fluvoxamine, a selective and potent CYP1A2 inhibitor. Thus, strong inhibitors of CYP1A2, such as fluvoxamine and enoxacin given concomitantly during prolonged administration of ropivacaine, can interact with ropivacaine.
Heart stops pumping the blood (cardiac arrest)	Symptoms of CVS toxicity including cardiac arrest usually occur because of inadvertent intravascular injection, overdose or rapid absorption. CVS toxicity reactions are caused by high blood concentration of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularized areas. Cardiac arrest has been reported with rare (>1/10,000 to < 1/1,000) frequency.
Chondrolysis	There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics, including ropivacaine. The majority of reported cases of chondrolysis have involved the shoulder joint. Intra-articular continuous infusion is not an approved indication for ropivacaine. Intra-articular continuous infusion with ropivacaine should be avoided, as the efficacy and safety has not been established.
Error while administering or using ropivacaine (medication error)	Ropivacaine needs to be administered using a dispenser device *OneDose Readyfusor* and it should be administered as per the instructions mentioned in the SmPC. Hence it carries potential for medication errors. Ropivacaine should only be used by, or under the supervision of, clinicians experienced in regional anaesthesia.

Missing Information

Risk	What is known (Including reason why it is considered a potential risk)
Use during pregnancy and breastfeeding	Apart from epidural administration for obstetrical use, there are no adequate data on the use of ropivacaine in human pregnancy. Experimental animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. There are no data available concerning the excretion of ropivacaine into human milk. As a precautionary measure, ropivacaine should be avoided during pregnancy. Also the patient should temporarily discontinue breastfeeding while being treated with ropivacaine.
Fertility	There are no data available concerning the administration of ropivacaine on fertility.
Paediatric population and premature neonates	Ropivacaine is not indicated in children and adolescents.
Effects on the ability to drive and use machines	There is no data available on effects of ropivacaine on ability to drive and use machines. Depending on the dose, local anaesthetics may have a minor influence on mental function and co-ordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

VI.2.5 Summary of risk minimisation measures by safety concern

Ropivacaine has a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for ropivacaine can be found in Annex 2.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
01	Initial submission of MAA.	-	-
02	08/2016	-	Update according to comments in the DCP
03	10/2017	-	Update according to comments in the DCP, update of annex 2

1 Acute Post Operative Pain. *Indian J Anaesth* 2006; 50(5): 340-344

2 Prevalence and influence of gender, age, and type of surgery on postoperative pain. *Rev. Bras. Anestesiol* vol.59 no.3 Campinas May/June 2009

3 The Effect of Intraperitoneal Ropivacaine for Post-Operative Pain Management in Patients Undergoing Laparoscopic Cholecystectomy: A Prospective Double-Blind Randomized Control Study. *Open Journal of Anesthesiology* 2013, 3; 193-198.