Core Safety Profile

Active substance: Ropivacaine (intrathecal)
Pharmaceutical form(s)/strength: Solution for injection 5 mg/ml
P RMS: NL/H/PSUR/0040/001
Date of FAR: 20.04.2011
4.3 Contra-indications

- Hypersensitivity to ropivacaine or to other local anaesthetics of the amide type.

- General contra-indications related to regional anaesthesia, regardless of the local anaesthetic used, should be taken into account.

- Intravenous regional anaesthesia.

- Obstetric paracervical anaesthesia

- Major nerve blocks are contraindicated in hypovolaemic patients

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and medicinal products necessary for monitoring and emergency resuscitation should be immediately available.

Patients receiving major blocks should be in optimal condition and have an intravenous line inserted before the blocking procedure.

The clinician responsible should take the necessary precautions to avoid intravascular injection and be appropriately trained and familiar with diagnosis and treatment of undesirable effects, systemic toxicity and other complications. After intrathecal administration, systemic toxicity is not expected to occur, due to the low dose administered. An excessive dose administered into the subarachnoid space may give rise to a total spinal block (see 4.9 Overdose).

**Cardiovascular**

Patients treated with anti-arrhythmic drugs class III (eg, amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

**Hypersensitivity**

A possible cross – hypersensitivity with other amide – type local anaesthetics should be taken into account, see section 4.3 Contra-indications.

**Hypovolaemia**

Patients with hypovolaemia due to any cause can develop sudden and severe hypotension
during intrathecal anaesthesia, regardless of the local anaesthetic used.

Patients in poor general health

Patients in poor general condition due to ageing or other compromising factors such as partial or complete heart conduction block, advanced liver disease or severe renal dysfunction require special attention, however regional anaesthesia is frequently indicated in these patients.

Patients with hepatic and renal impairment

Ropivacaine is metabolised in the liver and should therefore be used with caution in patients with severe liver disease. Repeated doses may need to be reduced due to delayed elimination. 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 solution for injection 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.

Excipients with recognised action/effect

This medicinal product contains maximum 3.5 mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

Prolonged administration

Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, such as fluvoxamine and enoxacin, (see 4.5 Interactions with other medicinal products and other forms of interaction).

Paediatric patients

Intrathecal administration for use in infants, toddlers or children has not been documented.
4.5 Interactions with other medicinal products and other forms of interaction

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, eg, certain antiarrhythmics, such as lidocaine and mexiletine, since the systemic toxic effects are additive. Simultaneous use of ropivacaine with general anaesthetics or opioids may potentiate each other's (adverse) effects. Specific interaction studies with ropivacaine and anti-arrhythmic drugs class III (eg, amiodarone) have not been performed, but caution is advised (see also section 4.4 Special warnings and precautions for use).

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-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. Prolonged administration of ropivacaine should be avoided in patients concomitantly treated with strong CYP1A2 inhibitors, (see 4.4 Special warnings and precautions for use).

In vivo the plasma clearance of ropivacaine was reduced by 15% during co-administration of ketoconazole, a selective and potent inhibitor of CYP3A4. However the inhibition of this isozyme is not likely to have clinical relevance.

In vitro ropivacaine is a competitive inhibitor of CYP2D6 but does not seem to inhibit this isozyme at clinically attained plasma concentrations.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 (see 5.3 Preclinical safety data).

Lactation

There is no data available concerning the excretion of ropivacaine into human milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Depending on the dose, local anaesthetics may have a minor influence on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.
4.8 Undesirable effects

General

The adverse reaction profile for ropivacaine is similar to those for other long acting local anaesthetics of the amide type. Adverse reactions should be distinguished from the physiological effects of the nerve block itself eg, hypotension and bradycardia during intrathecal anaesthesia, and events caused by needle puncture (eg, spinal hematoma, postdural puncture headache, meningitis and epidural abscess). Many of the most frequently reported adverse reactions, such as nausea, vomiting and hypotension, are very frequent during anaesthesia and surgery in general and it is not possible to distinguish those caused by the clinical situation from those caused by the medicinal product or the block.

Total spinal block may occur with all local anaesthetics if an epidural dose is inadvertently administered intrathecally, or if a too large intrathecal dose is administered. Systemic and localised adverse reactions of ropivacaine usually occur because of excessive dosage, rapid absorption, or inadvertent intravascular injection. However, due to the low doses used for intrathecal anaesthesia, systemic toxic reactions are not expected.

Table of adverse reactions

The frequencies used in the table in Section 4.8 are: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous System disorders</td>
<td>Very common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Paraesthesia, Dizziness, Hypoaesthesia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very common</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Very common</td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Syncope</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
<td>Common</td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Very common</td>
<td>Nausea, Vomiting</td>
</tr>
<tr>
<td>Renal and Urinary disorders</td>
<td>Very common</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>General disorder and Administration site</td>
<td>Common</td>
<td>Back pain, Hypothermia, Rigors</td>
</tr>
<tr>
<td>conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>Allergic reactions (anaphylactic reactions, angioneurotic oedema and urticaria)</td>
</tr>
</tbody>
</table>
Class-related adverse reactions

Neurological complications

Neuropathy and spinal cord dysfunction (eg, 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.

Total spinal block

Total spinal block may occur if too large an intrathecal dose is administered.

Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS). Such 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. CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively.

Central nervous system toxicity

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.

Recovery follows the redistribution of the active substance from the central nervous system and subsequent metabolism and excretion. Recovery may be rapid unless large amounts of the medicinal product have been injected.

Cardiovascular system toxicity

Cardiovascular toxicity indicates a more severe situation. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics. In volunteers the intravenous infusion of ropivacaine resulted in signs of depression of conductivity and contractility.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with medicinal products such as benzodiazepines or barbiturates.
Treatment of acute systemic toxicity

See section 4.9 Overdose.

4.9 Overdose

Symptoms

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, peak plasma concentrations may not be reached for one to two hours, depending on the site of the injection, and signs of toxicity may thus be delayed. (See section 4.8 Acute systemic toxicity, Central nervous system toxicity and Cardiovascular system toxicity).

After intrathecal administration, systemic toxicity is not expected to occur, due to the low dose administered. An excessive dose administered into the subarachnoid space may give rise to a total spinal block.

Treatment

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately and CNS symptoms (convulsions, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, and or inotropic agents should be considered.

Should cardiac arrest occur, a successful outcome may require prolonged resuscitative efforts.