SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

ADCO ROPIVACAINE 200 mg/100 ml (Infusion solution)

COMPOSITION

ADCO ROPIVACAINE 200 mg/100 ml: Each 100 ml of solution contains ropivacaine hydrochloride monohydrate equivalent to ropivacaine hydrochloride 200,00 mg

Sugar free.

The inactive ingredients are: sodium chloride, sodium hydroxide,

hydrochloric acid and water for injections.

CATEGORY AND CLASS

A. 4 Local anaesthetics·

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Ropivacaine is an amide-type local anaesthetic.

Ropivacaine causes reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the cell membrane of the nerve fibres**.**

Ropivacaine has both anaesthetic and analgesic effects. At high doses ropivacaine produces surgical anaesthesia, whereas at lower doses it produces sensory block (analgesia) with limited and non-progressive motor block.

It has a differential blocking effect on nerve fibres and at the lowest concentrations used there is differentiation between sensory and motor block.

The duration and intensity of ropivacaine block are not improved by the addition of epinephrine (adrenalin). Local anaesthetics may have similar effects on other excitable membranes, e.g. in the brain and myocardium. If excessive amounts of the medicine reach the systemic circulation rapidly, symptoms

and signs of toxicity may appear, emanating from the central nervous and cardiovascular systems. Hypotension and bradycardia are uncommon after caudal epidural block in children.

Pharmacokinetic properties

The plasma concentration depends on the dose, the route of administration and the vascularity of the injection site. Ropivacaine follows linear pharmacokinetics and the maximum plasma concentration is proportional to the dose. It shows complete and biphasic absorption from the epidural space with the half-lives of the two phases in the order of 14 minutes and 4 hours.

Slow absorption is the rate–limiting factor in the elimination of ropivacaine, which explains the longer apparent elimination half-life following epidural rather than intravenous administration.

Ropivacaine has a total plasma clearance in the order of 440 ml/minute, an unbound plasma clearance of 8 litres/minute, a volume of distribution at steady state of 47 litres and a terminal half-life of 1,8 hours. Ropivacaine has an intermediate hepatic extraction ratio of about 0,4. It is mainly bound to alpha-1-acid glycoprotein in plasma with an unbound fraction of about 6 %.

An increase in total plasma concentrations during continuous epidural infusion has been observed, related to a post-operative increase of alpha-1 acid glycoprotein. Variations in unbound, i.e. pharmacologically active, concentration have been much less than in total plasma concentration.

Ropivacaine pharmacokinetics after regional anaesthesia in children aged between 1 and 12 years, have been shown to be unrelated to age. In this group ropivacaine has a total plasma clearance in the order of 7,5 ml/min/kg, an unbound plasma clearance of 0,15 litre/min/kg, a volume of distribution at steady state of 2,4 litre/kg, an unbound fraction of 5 % and a terminal half-life of 3 hours. Ropivacaine shows a biphasic absorption from the caudal space. The clearance related to body weight in this age group is similar to that in adults.

Ropivacaine readily crosses the placenta. Ropivacaine is extensively metabolised, predominantly by aromatic hydroxylation. In total 86 % of the dose is excreted in the urine. The major metabolite is 3-hydroxy-ropivacaine, about 37 % of which is excreted in the urine, mainly conjugated. Urinary excretion of the 4-hydroxy-ropivacaine, the N-dealkylated metabolite and the 4-hydroxy-dealkylated metabolite accounts for 1-3 %. Conjugated plus unconjugated 3-hydroxy-ropivacaine shows only detectable concentration in plasma. 3-hydroxy and 4-hyroxy-ropivacaine have a local anaesthetic activity although less than that of ropivacaine.

A similar pattern of metabolites has been found on children above 1 year.

INDICATIONS

ADCO ROPIVACAINE 200 mg/100 ml is indicated for:

- Epidural infusion or intermittent bolus administration for post-operative or labour pain
- Minor nerve block and infiltration analgesia for acute pain management
- Acute pain management in paediatrics (caudal epidural block)

CONTRAINDICATIONS

ADCO ROPIVACAINE 200 mg/100 ml is contraindicated in:

- Children under the age of 1 year
- Patients with known hypersensitivity to any amide–type local anaesthetic.
- Intravenous regional anaesthesia (Bier's block)
- Obstetric paracervical anaesthesia
- Epidural and spinal anaesthesia in patients with uncorrected hypotension
- Instances when there is inflammation and /or sepsis in the region of the proposed injection and/or in the presence of septicaemia

General contraindications related to epidural anaesthesia, regardless of the local anaesthetic used should be taken into account.

WARNINGS and SPECIAL PRECAUTIONS

The safety of **ADCO ROPIVACAINE 200 mg/100 ml** in pregnancy and lactation, except when used in labour, has not been established **(**See **"HUMAN REPRODUCTION")**. Foetal bradycardia may follow the use of **ADCO ROPIVACAINE 200 mg/100 ml** in paracervical block and may be associated with foetal acidosis. Added risk appears to be present in prematurity, toxaemia of pregnancy and foetal distress.

ADCO ROPIVACAINE 200 mg/100 ml should not be used for the production of obstetrical paracervical block anaesthesia, retrobulbar block or spinal anaesthesia, (subarachnoid block) due to insufficient data to support such use. Intravenous regional anaesthesia (Bier`s block)

should not be performed due to lack of clinical experience and the risk of attaining toxic blood levels.

Unintended intravenous injection of ADCO ROPIVACAINE 200 mg/100 ml may result in cardiac arrest when performing blocks. ADCO ROPIVACAINE 200 mg/100 ml should be administered in incremental doses and not injected rapidly in large doses.
It is therefore not recommended for emergency situations where a fast onset of surgical anaesthesia is necessary.

ADCO ROPIVACAINE 200 mg/100 ml should be used only by clinicians trained in the diagnosis and management of dose related local anaesthetic toxicity, and other acute emergencies which may arise from the block to be employed. Equipment, personnel and medicines for resuscitation as well as suction and supplemental oxygen should be immediately available for the management of related emergencies. Delay in proper management of dose related toxicity, under ventilation from any cause and/or altered sensitivity may lead to the development of acidosis, cardiac arrest and possibly death

When using **ADCO ROPIVACAINE 200 mg/100 ml** in or near the spinal canal, aspiration to check for blood or cerebrospinal fluid (CSF) should be done prior to injection of **ADCO ROPIVACAINE 200 mg/100 ml** for both the original and all subsequent doses**.** However, failure to obtain blood or CSF on aspiration does not guarantee that intravascular or subarachnoid injection will not occur. A well-known risk of epidural anaesthesia may be an unintentional subarachnoid injection of local anaesthetic.

ADCO ROPIVACAINE 200 mg/100 ml should be used with caution in patients receiving local anaesthetics and medicines structurally related to amide-type local anaesthetics, since the toxic effects of these medicines are additive.

Resuscitative equipment and medicines, including oxygen, should always be immediately available when any local anaesthetic agent is used, to manage possible adverse reactions involving the cardiovascular, respiratory or central nervous system. An IV cannula should

always be inserted before the anaesthetic is injected, to accommodate for the possibility of hypotension and bradycardia following major blocks. Injections should be made slowly with frequent aspirations to avoid inadvertent intravascular injection, which can produce toxic effects.

The safety and efficacy of **ADCO ROPIVACAINE 200 mg/100 ml** depends on proper dosage, correct technique and adequate precautions. The lowest dosage that results in efficacious anaesthesia should be used (see "**DOSAGE AND DIRECTIONS FOR USE**").

Elderly, young and debilitated patients, including those with partial or complete heart conduction block, advanced liver disease or severe renal dysfunction should be given reduced doses commensurate with their age and physical condition.

There is a risk of cardiac arrest during the use of **ADCO ROPIVACAINE 200 mg/100 ml** for epidural anaesthesia or peripheral nerve blockade, especially after unintentional accidental intravascular administration in elderly patients and in patients with concomitant heart disease. Resuscitation may be difficult and prolonged resuscitative efforts may be required.
Use with caution in patients with partial or complete heart block.

There may be no need to modify the dose in patients with impaired renal function when used for single dose or short term treatment; however acidosis and reduced plasma protein concentrations, frequently seen in patients with chronic renal dysfunction may increase the risk of systemic toxicity. The risk should be considered in patients suffering from malnutrition or patients with hypovolaemia.

Certain procedures such as injection in the head and neck region, retrobulbar, dental and stellate ganglion blocks may be associated with a higher frequency of serious adverse reactions, regardless of the local anaesthetic used. The side effects may be similar to the systemic toxicity seen with unintentional intravascular injections.

Patients should be closely monitored after each injection of **ADCO ROPIVACAINE 200 mg/100 ml** for cardiovascular, respiratory vital signs and the patient's state of consciousness. Signs of restlessness, anxiety, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Local anaesthetics should be used with great caution (if at all) in patients with pre-existing abnormal neurological pathology e.g. myasthenia gravis. Use with extreme caution in epidural, caudal and spinal anaesthesia when there is serious disease of the of central nervous system or of the spinal cord, e.g. meningitis, spinal fluid block, cranial or spinal haemorrhage, tumours, poliomyelitis, syphilis, tuberculosis or metastatic lesions of the spinal cord.

ADCO ROPIVACAINE 200 mg/100 ml is metabolised in the liver and should therefore be used with caution in patients with severe liver disease and repeated doses may need to be reduced due to delayed elimination.
Epidural anaesthesia may lead to hypotension and bradycardia. The risk of such effects can be reduced by preloading the circulation. Hypotension should be treated promptly with suitable vasopressor intravenously, repeated as necessary.

EFFECTS ON ABILITY TO DRIVE OR USE MACHINES

Local anaesthetics may have an effect on mental function and co-ordination and may temporarily impair locomotion and alertness. Caution is advised when driving or operating machinery.

INTERACTIONS

Administration of **ADCO ROPIVACAINE 200 mg/100 ml** with general anaesthetics, opioid analgesics, or medicines structurally related to amide-type local anaesthetics may result in potentiation of adverse effects, e.g. certain anti-dysrhythmias.
Low molecular weight heparins and heparinoids – When neuraxial anaesthesia (epidural/spinal anaesthesia) is employed, patients anti-coagulated or scheduled to be anti-coagulated with low molecular weight heparins or heparinoids are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters. Traumatic or repeated epidural/spinal puncture and the concomitant use of medicines affecting haemostasis such as NSAIDs, platelet inhibitors or other anti-coagulants. Patients should be frequently monitored for signs and symptoms of neurological impairment.

Patients treated with anti-dysrhythmic medicines class III (e.g. amiodarone) should be under close surveillance and ECG monitoring considered, since cardiac effects may be additive.

When **ADCO ROPIVACAINE 200 mg/100 ml** is used in combination with cytochrome P450 1A inhibitors e.g. verapamil and fluvoxamine, toxic blood concentrations of **ADCO ROPIVACAINE 200 mg/100 ml** may occur.

HUMAN REPRODUCTION

The safe use of **ADCO ROPIVACAINE 200 mg/100 ml** in lactating and pregnant women, other than those in labour, has not been established. Until further clinical experience in pregnancy is gained, the use of **ADCO ROPIVACAINE 200 mg/100 ml** is not recommended. **(**See **"WARNINGS** and **SPECIAL PRECAUTIONS")**.

Foetal bradycardia may follow the use of **ADCO ROPIVACAINE 200 mg/100 ml** in paracervical block and may be associated with foetal acidosis. Added risk appears to be present in prematurity, toxaemia of pregnancy and foetal distress

DOSAGE AND DIRECTIONS FOR USE

ADCO ROPIVACAINE 200 mg/100 ml should be used only by clinicians trained in the diagnosis and management of dose related local anaesthetic toxicity, air way management and other acute emergencies which may arise from the block to be employed. Equipment and medicines for resuscitation as well as suction and supplemental oxygen should be immediately available.

Adults and children above 12 years of age:

The recommended doses are intended as a guide for use in the more commonly used blocks. The actual dose must be individualized based on the physical status of the patient and the expected rate of systemic absorption from the injection site. The lowest dose (volume and concentration) that produces the desired result should be used.

ADCO ROPIVACAINE 200 mg/100 ml causes dose-dependent motor block. Use of the lowest concentration and dose necessary for analgesia (e.g. epidural administration for acute pain management) is recommended; while surgical anaesthesia requires the use of higher concentrations and doses.

Aspiration to check for blood or cerebrospinal fluid (CSF) should be done prior to and during injection of **ADCO ROPIVACAINE 200 mg/100 ml**, however, failure to obtain blood or CSF on aspiration does not guarantee that intravascular or subarachnoid injection will not occur.

When a large dose is to be injected, e.g. in epidural block, a test dose of 3-4 ml 2 % lidocaine with adrenaline is recommended. Lidocaine hydrochloride solution containing adrenaline 1 in 200 000 is used for infiltration anaesthesia and nerve blocks including epidural block. When given with adrenaline, the suggested general maximum dose of lidocaine hydrochloride is 500 mg; without adrenaline the recommended maximum single dose in the UK is 200 mg and in the USA, 300 mg.

When an epidural dose is to be injected, a standard test technique is advised.

An inadvertent intravascular injection may be recognised in a temporary increase in heart rate and an accidental intrathecal injection by signs of spinal block. Aspiration should be repeated prior to and during administration of main dose, which should be injected slowly or in incremental doses at a rate of 25 – 50 mg/minute while closely observing the patient's vital function and maintaining verbal contact. If toxic symptoms occur the injection should be stopped immediately

There is an increased risk of accumulation **of ADCO ROPIVACAINE 200 mg/100 ml**, with resultant systemic toxicity or local neuronal injury, when it is used for prolonged blocks either through continuous infusion or through repeated bolus administration.

A cumulative dose of about 800 mg **ADCO ROPIVACAINE 200 mg/100 ml** administered over 24 hours is well tolerated in adults as were postoperative continuous epidural infusions at rates up to 28 mg/hour for 72 hours.

Postoperative pain management: the following can be recommended – unless preoperatively instituted, an epidural block with 7,5 mg/ml is induced via an epidural catheter (preoperatively placed). Analgesia is maintained with 2 mg/ml infusion. An infusion rate of 6-14 ml (12-28 mg) per hour provide

adequate analgesia with only slight and non-progressive motor block in most cases of moderate to severe postoperative pain.

ADCO ROPIVACAINE 200 mg/100 ml is not recommended for children under the age of 1 year and in patients under 60 kg for major nerve block anaesthesia.

Dosage recommendations for **ADCO ROPIVACAINE 200 mg/100 ml** in adults:

	Conc. mg/ml	**Volume (ml)**	**Dose (mg)**	**Onset minutes**	**Duration hours**
ACUTE PAIN MANAGEMENT					
Lumbar epidural administration: Bolus	2,0	10 – 20	20 – 40	10 – 15	0,5 – 1,5
Intermittent injections (top up) (e.g. labour pain management)	2,0	10 – 15 (min interval 30 mins)	20 - 30		
Lumbar epidural administration: Continuous infusion e.g. Labour pain	2,0	6 – 10 ml/h	12 – 20 mg/h	n/a	n/a
Postoperative pain management	2,0	6 – 14 ml/h	12 - 28 mg/h	n/a	n/a
Thoracic epidural administration: Continuous infusion (e.g. postoperative pain management)	2,0	6 – 14 ml/h	12 – 28 mg/h	n/a	n/a
Minor nerve block and	2,0	1 - 100	2 - 200	1 - 5	2 - 6

infiltration analgesia: (e.g. minor nerve blocks and infiltration)					

* Depending on level of injection

For single use only, any unused solution should be discarded.

Paediatrics:

Dosage recommendations for paediatric patients 1 to 12 years of age:

	Conc. **mg/ml**	**Volume** **(ml)**	**Dose** **(mg)**
ACUTE PAIN MANAGEMENT (pre- and postoperative)			
Caudal epidural administration: Blocks below T12, in children with a body weight up to 25 kg	2,0	1	2

The doses in the table should be regarded as guidelines for use in paediatrics. Individual variations occur. In children with a high body mass a gradual reduction of the dosage is often necessary and should be based on the ideal body mass.

In order to prevent intravascular injection, aspiration to check for blood or cerebrospinal fluid (CSF) should be done prior to and during injection of **ADCO ROPIVACAINE 200 mg/100 ml**. The patient's vital functions should be observed closely during the injection. If toxic symptoms occur, the injection should be stopped immediately.

A single caudal epidural injection of **ADCO ROPIVACAINE 200 mg/100 ml** produces adequate postoperative analgesia below T12 in the majority of patients when a dose of 2 mg/kg is used in a volume of 1 ml/kg. Doses up to 3 mg/kg have been used safely. The volume of the caudal epidural injection may be adjusted to achieve a different distribution of sensory block.

Fractionation of the calculated local anaesthetic dose is recommended, whatever the route of administration.

SIDE-EFFECTS

Immune System Disorders:

Less Frequent: Allergic reactions (anaphylactic reactions, angioedema and urticaria)

Psychiatric disorders:

Less frequent: Anxiety

Nervous system disorders:

Frequent: Headache; dizziness; paraesthesia

Less frequent: Hypoaesthesia; symptoms of CNS toxicity including convulsions, grand mal convulsions, seizures, light headedness, sedation, circumoral paraesthesia, numbness of the tongue, hyperacusis, tinnitus, visual disturbances, dysarthria, muscular twitching and tremor. These symptoms may indicate inadvertent intravascular injection, overdose or rapid absorption.

Cardiac disorders:

Frequent: Bradycardia; tachycardia

Less frequent: Cardiac arrest; cardiac dysrhythmias

Vascular disorders:

Frequent: Hypotension - hypertension

Less frequent: Syncope

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea

Gastrointestinal disorders:

Frequent: Nausea; vomiting

Less frequent: Metallic taste

Skin and subcutaneous tissue disorders:

Rare: Pruritus (itching)

Renal and urinary disorders:

Frequent: Urinary retention

General disorders and administration site conditions:

Frequent: Temperature elevation; rigor; back pain

Less frequent: Hypothermia; spinal haematoma; post-dural puncture headache; meningitis and epidural abscess.

KNOWN SYMPTOMS OF OVER DOSAGE AND PARTICULARS OF ITS TREATMENT

Immediate toxic effects may be seen after accidental intravascular injections, while in the event of overdose, signs of toxicity may be delayed. Thus the patient should be monitored for a few hours. Systemic toxic reactions may involve the central nervous system and the cardiovascular system. Central nervous system toxicity is a graded response with signs and symptoms of escalating severity. Initial symptoms include visual or hearing disturbances, perioral numbness, dizziness, light-headedness, tingling and paraesthesia. Symptoms such as dysarthria, muscular rigidity and muscular twitching may occur and must not be mistaken for neurotic behaviour. These symptoms may precede the onset of generalized convulsions. Unconsciousness and grand mal convulsions may follow which may last from a few seconds to several minutes. Hypoxia and hypercarbia occur rapidly during convulsions and in severe cases apnoea may occur.

Cardiovascular toxic effects are serious and include hypotension, bradycardia, dysrhythmia and cardiac arrest may occur. Recovery may be prolonged.

Treatment of acute toxicity:

ADCO ROPIVACAINE 200 mg/100 ml should be discontinued immediately.

Treatment of convulsions:

Protect the patient, administer oxygen immediately and assist ventilation. If seizures do not stop within 15-20 seconds, administration of an intravenous anticonvulsant is recommended.

Treatment of cardiovascular depression:

Immediate cardiopulmonary resuscitation is required should cardiac arrest occur. Repeated dose of epinephrine (adrenaline) may be needed. It is important to ensure optimal oxygenation, ventilation and circulatory support.

Systemic toxic effects of local anaesthetics are related to blood concentrations and, as absorption varies considerably according to the site of injection, it has been suggested that recommendation of a single maximum dose without regard to the site of procedure is meaningless. If a plasma-lidocaine concentration of 5 micrograms/mL were required for toxicity then this would be achieved by injection of 300 mg in the intercostal area, 500 mg epidurally, 600 mg in the region of the brachial plexus, or 1 g subcutaneously.

IDENTIFICATION

A sterile isotonic clear and colourless solution.

PRESENTATION

100 ml or 200 ml plastic infusion bag (PVC), enclosed in a high density polyethylene overpouch.

Five (5) individual units are packed in an outer carton.

STORAGE INSTRUCTIONS

Store at or below 25 ˚C. Do not freeze. Discard remaining contents after use.

Store all medicines out of reach of children.

REGISTRATION NUMBER

43/4/0525

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