**APPROVED PACKAGE INSERT (MCC APPROVAL 7.7.2006)**

## SCHEDULING STATUS: S4

## PROPRIETARY NAME (AND DOSAGE FORM)

**CHIROCANE 2,5 mg/ml** Solution for Injection
**CHIROCANE 5,0 mg/ml** Solution for Injection
**CHIROCANE 7,5 mg/ml** Solution for Injection

## COMPOSITION

**CHIROCANE 2,5 mg/ml**: each one ml contains 2,5 mg levobupivacaine as levobupivacaine hydrochloride.
**CHIROCANE 5,0 mg/ml**: each one ml contains 5,0 mg levobupivacaine as levobupivacaine hydrochloride.
**CHIROCANE 7,5 mg/ml**: each one ml contains 7,5 mg levobupivacaine as levobupivacaine hydrochloride.

## PHARMACOLOGICAL CLASSIFICATION

A.4 - Local anaesthetics

## PHARMACOLOGICAL ACTION

**CHIROCANE®** injection contains a single enantiomer of bupivacaine hydrochloride which is chemically described as (S)-1-butyl-2-piperidylformo-2,6'-xylidide hydrochloride.

Levobupivacaine is a member of the amino amide class of local anaesthetics. It blocks the generation and the conduction of nerve impulses by increasing the threshold for electrical excitation in the nerve, by slowing propagation of the nerve impulse, and by reducing the rate of rise of the action potential. The progression of anaesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibres. Clinically, the order of loss of nerve function is as follows: 1) pain, 2) temperature, 3) touch, 4) proprioception, and 5) skeletal muscle tone.

Systemic absorption can produce effects on the cardiovascular system, i.e. changes in cardiac conduction, excitability, refractoriness, contractility and peripheral vascular resistance. Myocardial contractility is depressed and peripheral vasodilatation occurs, leading to decreased cardiac output and arterial blood pressure.

Following systemic absorption, levobupivacaine can produce central nervous system stimulation, depression, or both. Apparent central nervous system stimulation is usually manifested as restlessness, tremors, and shivering, progressing to convulsions. Ultimately central nervous system depression may progress to coma and cardio-respiratory arrest. However, levobupivacaine has a primary depressant affect on the medulla and on higher centres. The depressed stage may occur without a prior excited stage.

### *Pharmacokinetics*

In human studies, the distribution kinetics of levobupivacaine following i.v. administration are similar to that of bupivacaine. The plasma concentration of levobupivacaine following therapeutic administration depends on dose and, as absorption from the site of administration is affected by

the vascularity of the tissue, on route of administration.

There are no data in patients with renal impairment or hepatic impairment. Levobupivacaine is extensively metabolised and unchanged levobupivacaine is not excreted in urine or faeces.

Plasma protein binding of levobupivacaine in man was evaluated *in vitro* and was found to be > 97 % at concentrations between 0,1 and 1,0 microgram/ml.

In a clinical pharmacology study where 40 mg levobupivacaine was given by intravenous administration, the mean half-life was approximately 80 ± 22 minutes, $C_{max}$ 1,4 ± 0,5 microgram/ml and AUC 70 ± 27 microgram. min/ml.

The mean $C_{max}$ and AUC (0 - 24h) of levobupivacaine were approximately dose-proportional following epidural administration of 75 mg (0,5 %) and 112,5 mg (0,75 %) and following doses of 1 mg/kg (0,25 %) and 2 mg/kg (0,5 %) used for brachial plexus block. Following epidural administration of 112,5 mg (0,75 %), the mean $C_{max}$ and AUC values were 0,58 microgram/ml and 3,56 microgram.hr/ml respectively.

The mean total plasma clearance and terminal half-life of levobupivacaine after intravenous infusion were 39 litres/hour and 1,3 hours, respectively. The volume of distribution after intravenous administration was 67 litres.

3-Hydroxylevobupivacaine, a major metabolite of levobupivacaine, is excreted in the urine as glucuronic acid and sulphate ester conjugates. *In vitro* studies showed that CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to desbutyl-levobupivacaine and 3-hydroxylevobupivacaine respectively. These studies indicate that the metabolism of levobupivacaine and bupivacaine are similar.

Following intravenous administration, recovery of levobupivacaine was quantitative with a mean total of about 95 % being recovered in urine (71 %) and faeces (24 %) in 48 hours.

There is no evidence of *in vitro* racemisation of levobupivacaine.

## INDICATIONS

### *Adults*

**CHIROCANE®** is indicated in adults for:

### Surgical Anaesthesia

Major: Epidural (including for caesarean section), intrathecal, peripheral nerve block.
Minor: Local infiltration, peribulbar block in ophthalmic surgery.

### Pain Management

Continuous epidural infusion, single or multiple bolus administration for post-operative, labour or chronic pain.

For continuous epidural analgesia, **CHIROCANE®** may be administered in combination with epidural fentanyl, morphine or clonidine.

***Children***

**CHIROCANE®** is indicated in children for infiltration analgesia.

## CONTRA-INDICATIONS

**CHIROCANE®** is contra-indicated in patients with a known hypersensitivity to levobupivacaine or to any local anaesthetic agent of the amide type.

**CHIROCANE®** is contra-indicated for intravenous regional anaesthesia (Bier's Block), severe renal and or hepatic impairment.

Solutions of levobupivacaine should not be used for the production of obstetrical paracervical block anaesthesia. There are no data to support such use and there is additional risk of foetal bradycardia and death.

**CHIROCANE®** is contra-indicated for concomitant use with known CYP3A4 inducers (eg. phenytoin, phenobarbital, rifampin).

**CHIROCANE®** is contra-indicated for concomitant use with known CYP3A4 inhibitors (azole antimycotics, eg. ketoconazole).

## WARNINGS

The epidural use of **CHIROCANE®** is contra-indicated in severe hypotension such as cardiogenic or hypovolaemic shock. In performing levobupivacaine blocks, unintended intravenous injection is possible and may result in cardiac arrest. Despite rapid detection and appropriate treatment, prolonged resuscitation may be required. **CHIROCANE®** should be administered in incremental doses. Since levobupivacaine should not be injected rapidly in large doses, it is not recommended for emergency situations, where fast onset of surgical anaesthesia is necessary.

For caesarean section, the 5 mg/ml (0,5 %) levobupivacaine solution in doses up to 150 mg is recommended. The 0,75 % concentration is not recommended for use in obstetrics.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting **CHIROCANE®**, both before the original dose and all subsequent doses, to avoid intravascular or intrathecal injection. However, a negative aspiration does not ensure against intravascular or intrathecal injection. **CHIROCANE®** should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, since the toxic effects of these drugs are additive.

When contemplating a peripheral nerve block, where large volumes of local anaesthetic are needed, caution should be exercised when using the higher mg/ml concentrations of **CHIROCANE®**. Animal studies demonstrate CNS and cardiac toxicity that is dose related, thus, equal volumes of higher concentration will be more likely to produce cardiac toxicity. Maximum single dose should not exceed 2 mg/kg and repeated dose should not exceed 6 mg/kg in 24 hours.

## INTERACTIONS

### Drug-Drug Interactions

**CHIROCANE®** should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics since the toxic effects of these drugs could be

additive. *In vitro* studies indicate CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively. Thus, agents likely to be concomitantly administered with **CHIROCANE®** that are metabolised by this isoenzyme family may potentially interact with **CHIROCANE®**. Although no clinical studies have been conducted, it is likely that the metabolism of levobupivacaine may be affected by the known CYP3A4 inducers (such as phenytoin, phenobarbital, rifampin), CYP3A4 inhibitors (azole antimycotics, e.g. ketoconazole, certain protease inhibitors, e.g. ritonavir, macrolide antibiotics, e.g. erythromycin, and calcium channel antagonists, e.g. verapamil), CYP1A2 inducers (omeprazole) and CYP1A2 inhibitors (furafylline and clarithromycin). Dosage adjustments may be warranted when **CHIROCANE®** is concurrently administered with CYP3A4 inhibitors and CYP1A2 inhibitors, as systemic levobupivacaine levels may rise resulting in toxicity.

**CHIROCANE®** should be used with caution in patients receiving anti-arrhythmic agents with local anaesthetic activity, e.g. mexilitine, or class III anti-arrhythmic agents since their effect may be additive.

## PREGNANCY AND LACTATION

The safety of **CHIROCANE®** in pregnancy and breast-feeding has not been established.

## DOSAGE AND DIRECTIONS FOR USE

**CHIROCANE®** should be administered only by doctors who are well versed in the diagnosis and management of drug-related toxicity and other acute emergencies, which might arise from the block being administered. The immediate availability of oxygen, other resuscitative drugs, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper management of toxic reactions and related emergencies must be ensured (see also **SIDE-EFFECTS AND SPECIAL PRECAUTIONS**).

The rapid injection of a large volume of **CHIROCANE®** solution should be avoided and fractional (incremental) doses should always be used. The smallest dose and concentration required to produce the desired result should be administered. The dose differs with the anaesthetic procedure, the area to be anesthetised, the vascularity of the tissues, the number of neuronal segments to be blocked, the intensity of the block, the degree of muscle relaxation required, the duration of the anaesthesia desired, individual tolerance, and the physical condition of the patient. Patients in poor general condition due to aging or other compromising factors, such as impaired cardiovascular function, advanced liver disease, or severe renal dysfunction, require special attention.

For epidural technique it is advisable to use an adequate test dose (3 to 5 ml) of a short acting local anaesthetic solution containing epinephrine prior to induction of complete nerve block. This test dose should be repeated if the patient is moved in such a fashion as to have displaced the epidural catheter. It is recommended that adequate time be allowed for the onset of anaesthesia following administration of each test dose.

**CHIROCANE®** is not compatible with alkaline solutions having a pH greater than 8,5. Studies have shown that levobupivacaine is compatible with 0,9 % Sodium Chloride Injection USP and with saline solutions containing morphine, fentanyl and clonidine. Compatibility studies with other parenteral products have not been studied.

Disinfecting agents containing heavy metals, which cause release of ions (mercury, zinc, copper, etc.) should not be used for skin or mucous membrane disinfection since they have been related to incidents of swelling and oedema.

When chemical disinfection of the container surface is desired, either isopropyl alcohol (91 %) or

ethyl alcohol (70 %) is recommended. It is recommended that chemical disinfection be accomplished by wiping the vial stopper thoroughly with cotton or gauze that has been moistened with the recommended alcohol prior to use.

These products are intended for single use and do not contain preservatives; any solution remaining from an open container should be discarded.

| **Dosage Recommendations** | | | | |
|---|---|---|---|---|
| | **Concentration %** | **Dose (ml)** | **Dose (mg)** | **Motor Block** |
| **Surgical Anaesthesia** | | | | |
| Epidural for Surgery | 0,5 - 0,75 | 10 - 20 | 50 - 150 | Moderate to Complete |
| Epidural for Caesarean Section | 0,5 | 15 - 30 | 75 - 150 | Moderate to Complete |
| Peripheral nerve | 0,25 - 0,5 | 1 - 40 | Maximum 150 | Moderate to Complete |
| Intrathecal | 0,5 | 3 | 15 | Moderate to Complete |
| Ophthalmic | 0,75 | 5 - 15 | 37,5 - 112,5 | Moderate to Complete |
| Local Infiltration - Adults | 0,25 | 1 - 60 | Maximum 150 | Not applicable |
| Local Infiltration Children < 12 yrs | 0,25 - 0,5 | 0,25 - 0,50 ml/kg | 1,25 - 2,5 mg/kg | Not applicable |
| Dental | 0,5 - 0,75 | 5 - 10 | 25 - 75 | Not applicable |
| **Pain (*ab) Management** | | | | |
| Labour Analgesia (epidural bolus) | 0,25 | 10 -20 | 25 - 50 | Minimal to Moderate |
| Labour Analgesia (epidural infusion) | 0,125 **(c)** | 4 - 10 ml/h | 5 - 12,5 mg/h | Minimal to Moderate |
| Post-Operative Pain (epidural infusion) | 0,125 **(c)**<br><br>0,25 | 10 - 15 ml/h<br><br>5 - 7,5 ml/h | 12,5 - 18,75 mg/h<br>12,5 - 18,75 mg/h | Minimal to Moderate |
| **a** In pain management **CHIROCANE®** can be used epidurally with fentanyl, morphine or clonidine | | | | |
| **b** In cases where **CHIROCANE®** is combined with other agents e.g. opioids in pain management, the **CHIROCANE®** dose should be reduced as use of a lower concentration (e.g. 1,25 mg/ml) is preferable. | | | | |
| **c** Dilutions of **CHIROCANE®** standard solutions should be made with preservative free 0,9 % saline according to standard hospital procedures for sterility. | | | | |
| The doses in the table are those considered to be necessary to produce a successful block and should be regarded as guidelines for use. Individual variations in onset and duration occur. | | | | |

The maximum single dose recommended is 2 mg/kg (150 mg).

The maximum dose in 24 hours for intra-operative block and post-operative pain management is 6 mg/kg (400 mg).

In children, the maximum recommended dose for infiltration analgesia (ilioinguinal-iliohypogastric block) is 1,25 mg/kg/side.

## SIDE EFFECTS AND SPECIAL PRECAUTIONS

### *Side Effects*

Reactions to **CHIROCANE®** are characteristic of those associated with amide-type anaesthetics. A major cause of the adverse reactions is excessive plasma levels, which may be due to overdose, unintentional intravascular injection, or slow metabolic degradation.

Less frequent reports of convulsions have occurred following accidental intravenous administration.

Accidental intrathecal injection of local anaesthetics can lead to high spinal anaesthesia with apnoea, severe hypotension and loss of consciousness. High epidural anaesthesia may produce a similar effect.

Central nervous system effects: numbness of the tongue, light headedness, dizziness, blurred vision and muscle twitch followed by drowsiness, convulsions, unconsciousness and possible respiratory arrest.

Cardiovascular effects are related to depression of the conduction system of the heart and a reduction in myocardial excitability and contractility. This results in decreased cardiac output, hypotension and ECG changes indicative of either heart block, bradycardia or ventricular tachyarrythmias that may lead to cardiac arrest. These may be preceded by CNS toxicity, i.e. convulsions, but cardiac arrest may occur without prodromal CNS effects.

The most frequent adverse events reported in clinical trials irrespective of causality include hypotension (22 %), nausea (13 %), anaemia (11 %), post-operative pain (8 %), vomiting (8 %), back pain (7 %), fever (6 %), dizziness (6 %), foetal distress (6 %) and headache (5 %).

Neurological damage is a less frequent but well recognised consequence of regional and particularly epidural and spinal anaesthesia. It may be due to direct injury to the spinal cord or spinal nerves, anterior spinal artery syndrome, injection of an irritant substance or an injection of a non-sterile solution. These may result in localised areas of paraesthesia or anaesthesia, motor weakness, loss of sphincter control and paraplegia. Less frequently, these may be permanent.

Allergic-type reactions may occur as a result of sensitivity to **CHIROCANE®**. These reactions are characterised by signs such as urticaria, pruritus, erythema, angioneurotic oedema (including laryngeal oedema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and, possibly, anaphylactoid-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anaesthetic group have been reported.

### *Special Precautions*

Systemic adverse reactions following overdose or accidental intravascular injection reported with long acting local anaesthetic agents involve both CNS and cardiovascular effects.

Injection of repeated doses of local anaesthetics may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the drug or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. **CHIROCANE®** should be used with caution in patients with hypotension, hypovolaemia, or impaired cardiovascular function, especially heart block.

Careful and constant monitoring of cardiovascular and respiratory vital signs (adequacy of ventilation) and the patient's state of consciousness should be performed after each local anaesthetic injection. The clinician must be aware that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be early signs of central nervous system toxicity.

As **CHIROCANE®** is metabolised by the liver, it should be used cautiously in patients with any hepatic disease. Severe hepatic disease is a contra-indication to its use. **CHIROCANE®** should also be used with caution in patients with impaired cardiovascular function as they may be less able to compensate for functional changes associated with prolonged A-V conduction caused by these drugs.

**Epidural Anaesthesia**

During epidural anaesthesia, **CHIROCANE®** should be administered in incremental volumes of three to five millilitres (3 to 5 ml), with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Syringe aspirations should also be performed before and during each supplemental injection in continuous catheter techniques. An intravascular injection is still possible even if aspirations are negative. During the administration of epidural anaesthesia, it is recommended that a test dose is administered initially and the effects monitored before the full dose is given. A test dose of a short-acting amide anaesthetic, such as three millilitres (3 ml) of lidocaine, is recommended to detect unintentional intrathecal administration. This will be manifested within a few minutes by signs of a subarachnoid block (e.g. decreased sensation of the buttocks, paresis of the legs or, in the sedated patient, absent knee jerk). Unintentional intrathecal injection of local anaesthetics can lead to high spinal anaesthesia, possibly apnoea, severe hypotension and loss of consciousness. An intravascular or intrathecal injection is still possible, even if the results of the test dose are negative. The test dose itself may produce a systemic toxic reaction, extensive subarachnoid block or cardiovascular effects.

**Use in Head and Neck Area**

Small doses of **CHIROCANE®** injected into the head and neck area may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anaesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their respirations and circulation monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded (see **DOSAGE AND DIRECTIONS FOR USE**).

**Labour and Delivery**

Local anaesthetics, including **CHIROCANE®**, rapidly cross the placenta, and when used for epidural block, can cause varying degrees of maternal, foetal, and neonatal toxicity. The incidence and degree of toxicity depend upon the procedure performed, the type and amount of drug used, and the technique of drug administration. Adverse reactions in the parturient, foetus, and neonate involve alterations of the central nervous system, peripheral vascular tone, and cardiac function. Maternal hypotension, foetal bradycardia and foetal decelerations have resulted from regional anaesthesia with **CHIROCANE®** for obstetrical pain relief. **CHIROCANE®** produces vasodilatation by blocking sympathetic nerves. Administration of intravenous fluids, elevation of the patient's legs and left uterine displacement will help prevent decreases in blood pressure. The foetal heart rate should also be monitored continuously and electronic foetal monitoring is highly advisable.

The 7,5 mg/ml solution is not recommended for obstetric use due to an enhanced risk of cardiotoxic events.

**Effects on ability to drive or operate machinery**

Patients should be warned not to drive or operate machinery until all the effects of the anaesthesia and the immediate effects of surgery are passed.

## KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Acute emergencies from **CHIROCANE®** are generally related to high plasma levels or high dermatomal levels encountered during therapeutic use of local anaesthetics or to unintended intrathecal or intravascular injection of **CHIROCANE®** (see **SIDE EFFECTS**, **WARNINGS** and **SPECIAL PRECAUTIONS**).

**Management of Toxic Reactions**

At the first sign of change of vital signs or the patient's state of consciousness after injection or during continuous infusion, oxygen should be administered.

Systemic adverse reactions following overdose or accidental intravascular injection involve both CNS and cardiovascular effects.

**CNS Effects**

Convulsions should be treated immediately with a suitable intravenous agent, e.g. thiopentone or diazepam titrated as necessary. These agents will depress the central nervous system, respiratory and cardiac function. Therefore their use may result in apnoea. Neuro-muscular blockers may be used only if the clinician is confident of maintaining a patent airway and managing a fully paralysed patient.

If not treated promptly, convulsions with subsequent hypoxia and hypercarbia plus myocardial depression from the effects of the local anaesthetic on the heart, may result in cardiac arrhythmias, ventricular fibrillation or cardiac arrest.

**Cardiovascular Effects**

Hypotension must be treated symptomatically.

Cardiac arrhythmia should be treated as required and ventricular fibrillation should be treated by cardioversion.

## IDENTIFICATION

**CHIROCANE 2,5 mg/ml**
**CHIROCANE 5,0 mg/ml**
**CHIROCANE 7,5 mg/ml**

A clear, colourless solution for injection, free of visible particles.

## PRESENTATION

**CHIROCANE** is available in two presentations:

**Cartons containing:**
10 ml polypropylene ampoules in packs of 10.
10ml polypropylene ampoules in over-wrapped, sterile blister packs of 10.

## STORAGE INSTRUCTIONS

Store at or below 30 °C in a cool place. Keep out of reach of children.

Shelf-life (after first opening of container):
When used as a solution for injection: for immediate use.
Discard any unused portion after opening the container.

Shelf-life (after dilution):
When used as a concentrate for infusion where dilution is required and it is carried out under aseptic conditions, the diluted product may be stored for a maximum period of 24 hours at 2 - 8 ºC.

## REGISTRATION NUMBER

**CHIROCANE®** 2,5 mg/ml – 35/4/0192
**CHIROCANE®** 5,0 mg/ml – 35/4/0193
**CHIROCANE®** 7,5 mg/ml – 35/4/0194

## NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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