Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Chirocaine 5 mg/ml solution for injection/concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 5 mg levobupivacaine as levobupivacaine hydrochloride.
Each ampoule contains 50 mg in 10 ml. For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/concentrate for solution for infusion.
Clear colourless solution, practically free of particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

Surgical anaesthesia

- Major, e.g. epidural (including for caesarean section), intrathecal, peripheral nerve block.
- Minor, e.g. local infiltration, peribulbar block in ophthalmic surgery.

Pain management

- Continuous epidural infusion, single or multiple bolus epidural administration for the management of pain especially post-operative pain or labour analgesia.

Children

Analgesia (ilioinguinal/iliohypogastric blocks).

4.2 Posology and method of administration

Levobupivacaine should be administered only by, or under the supervision of, a clinician having the necessary training and experience.

The table below is a guide to dosage for the more commonly used blocks. For analgesia (e.g. epidural administration for pain management), the lower concentrations and doses are recommended. Where profound or prolonged anaesthesia is required with dense motor block (e.g. epidural or peribulbar block), the higher concentrations may be used. Careful aspiration before and during injection is recommended to prevent intravascular injection.

Aspiration should be repeated before and during administration of a bolus dose, which should be injected slowly and in incremental doses, at a rate of 7.5–30 mg/min, while closely observing the patient's vital functions and maintaining verbal contact.

If toxic symptoms occur, the injection should be stopped immediately.

Maximum dose

The maximum dosage must be determined by evaluating the size and physical status of the patient, together with the concentration of the agent and the area and route of administration. Individual variation in onset and duration of block does occur. Experience from clinical studies shows onset of sensory block adequate for surgery in 10-15 minutes following epidural administration, with a time to regression in the range of 6-9 hours.

The recommended maximum single dose is 150 mg. Where sustained motor and sensory block are required for a prolonged procedure, additional doses may be required. The maximum recommended dose during a 24 hour period is 400 mg. For post-operative pain management, the dose should not exceed 18.75 mg/hour.

Obstetrics

For caesarean section, higher concentrations than the 5.0 mg/ml solution should not be used (See section 4.3, Contraindications). The maximum recommended dose is 150 mg.

For labour analgesia by epidural infusion, the dose should not exceed 12.5 mg/hour.

Children

In children, the maximum recommended dose for analgesia (ilioinguinal/iliohypogastric blocks) is 1.25 mg/kg/side.

The safety and efficacy of levobupivacaine in children for other indications have not been established.

Special populations

Debilitated, elderly or acutely ill patients should be given reduced doses of levobupivacaine commensurate with their physical status.

In the management of post-operative pain, the dose given during surgery must be taken into account.

There are no relevant data in patients with hepatic impairment (see sections 4.4, Special warnings and precautions for use and 5.2, Pharmacokinetic properties).

Table of Doses

	Concentration (mg/ml)[1]	Dose	Motor Block
Surgical Anaesthesia			
Epidural (slow) bolus[2] for surgery - Adults	5.0-7.5	10-20 ml (50-150 mg)	Moderate to complete
Epidural slow injection[3] for Caesarean Section	5.0	15-30 ml (75-150 mg)	Moderate to complete
Intrathecal	5.0	3 ml (15 mg)	Moderate to complete
Peripheral Nerve	2.5-5.0	1-40 ml (2.5-150 mg max.)	Moderate to complete
Ilioinguinal/ Iliohypogastric blocks in children <12 years	2.5-5.0	0.25-0.5 ml/kg (0.625-2.5 mg/kg)	Not applicable

Ophthalmic (peribulbar block)	7.5	5–15 ml (37.5-112.5 mg)	Moderate to complete
Local Infiltration - Adults	2.5	1-60 ml (2.5-150 mg max.)	Not applicable
Pain Management[4] Labour Analgesia (epidural bolus[5])	2.5	6-10 ml (15-25 mg)	Minimal to moderate
Labour Analgesia (epidural infusion)	1.25[6]	4-10 ml/h (5-12.5 mg/h)	Minimal to moderate
Post-operative pain	1.25[6] 2.5	10-15ml/h (12.5-18.75mg/h) 5-7.5ml/h (12.5 – 18.75mg/h)	Minimal to moderate

[1] Levobupivacaine solution for injection/concentration for solution for infusion is available in 2.5, 5.0 and 7.5 mg/ml solutions.

[2] Spread over 5 minutes (see also text).

[3] Given over 15-20 minutes.

[4] In cases where levobupivacaine is combined with other agents e.g. opioids in pain management, the levobupivacaine dose should be reduced and use of a lower concentration (e.g. 1.25 mg/ml) is preferable.

[5] The minimum recommended interval between intermittent injections is 15 minutes.

[6] For information on dilution, see section 6.6, Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.

4.3 Contraindications

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

Levobupivacaine solutions are contra-indicated in patients with a known hypersensitivity to levobupivacaine, local anaesthetics of the amide type or any of the excipients. (see section 4.8, Undesirable effects).

Levobupivacaine solutions are contra-indicated for intravenous regional anaesthesia (Bier's block).

Levobupivacaine solutions are contra-indicated in patients with severe hypotension such as cardiogenic or hypovolaemic shock.

Levobupivacaine solutions are contra-indicated for use in paracervical block in obstetrics (see section 4.6, Pregnancy and lactation).

4.4 Special warnings and precautions for use

All forms of local and regional anaesthesia with levobupivacaine should be performed in well-equipped facilities and administered by staff trained and experienced in the required anaesthetic techniques and able to diagnose and treat any unwanted adverse effects that may occur.

Levobupivacaine should be used with caution for regional anaesthesia in patients with impaired cardiovascular function e.g. serious cardiac arrhythmias.

The introduction of local anesthetics via either intrathecal or epidural administration into the central nervous system in patients with preexisting CNS diseases may potentially exacerbate some of these disease states. Therefore, clinical judgment should be exercised when contemplating epidural or intrathecal anesthesia in such patients.

Epidural Anesthesia

During epidural administration of levobupivacaine, concentrated solutions (0.5-0.75%) should be administered in incremental doses of 3 to 5 ml with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. When a large dose is to be injected, e.g. in epidural block, a test dose of 3-5 ml lidocaine with adrenaline is recommended. An inadvertent intravascular injection may then be recognised by a temporary increase in heart rate and accidental intrathecal injection by signs of a spinal block.
Syringe aspirations should also be performed before and during each supplemental injection in continuous (intermittent) catheter techniques. An intravascular injection is still possible even if aspirations for blood are negative. During the administration of epidural anaesthesia, it is recommended that a test dose be administered initially and the effects monitored before the full dose is given.

Epidural anaesthesia with any local anaesthetic may cause hypotension and bradycardia. All patients must have intravenous access established. The availability of appropriate fluids, vasopressors, anaesthetics with anticonvulsant properties, myorelaxants, and atropine, resuscitation equipment and expertise must be ensured (see section 4.9, Overdose).

Major regional nerve blocks

The patient should have I.V. fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anaesthetic that results in effective anaesthesia should be used to avoid high plasma levels and serious adverse effects. The rapid injection of a large volume of local anaesthetic solution should be avoided and fractional (incremental) doses should be used when feasible.

Use in Head and Neck Area

Small doses of local anaesthetics injected into the head and neck area, including retrobulbar, dental and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Reactions may be due to intra-arterial injection of the local anaesthetic with retrograde flow to the cerebral circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anaesthetic along the subdural space to the midbrain. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available.

Use in Ophthalmic Surgery

Clinicians who perform retrobulbar blocks should be aware that there have been reports of respiratory arrest following local anaesthetic injection. Prior to retrobulbar block, as with all other regional procedures, the immediate availability of equipment, drugs, and personnel to manage respiratory arrest or depression, convulsions, and cardiac stimulation or depression should be assured. As with other anaesthetic procedures, patients should be constantly monitored following ophthalmic blocks for signs of these adverse reactions.

Special populations

Debilitated, elderly or acutely ill patients: levobupivacaine should be used with caution in debilitated, elderly or acutely ill patients (see section 4.2, Posology and method of administration).

Hepatic impairment: since levobupivacaine is metabolised in the liver, it should be used cautiously in patients with liver disease or with reduced liver blood flow e.g. alcoholics or cirrhotics (see section 5.2, Pharmacokinetic properties).

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that the CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine. Although no clinical studies have been conducted, metabolism of levobupivacaine may be affected by CYP3A4 inhibitors e.g.: ketoconazole, and CYP1A2 inhibitors e.g.: methylxanthines.

Levobupivacaine should be used with caution in patients receiving anti-arrhythmic agents with local anaesthetic activity, e.g., mexiletine, or class III anti-arrhythmic agents since their toxic effects may be additive.

No clinical studies have been completed to assess levobupivacaine in combination with adrenaline.

4.6 Pregnancy and lactation

Pregnancy

Levobupivacaine solutions are contraindicated for use in paracervical block in obstetrics. Based on experience with bupivacaine foetal bradycardia may occur following paracervical block (see section 4.3, Contraindications).

For levobupivacaine, there are no clinical data on first trimester-exposed pregnancies. Animal studies do not indicate teratogenic effects but have shown embryo-foetal toxicity at systemic exposure levels in the same range as those obtained in clinical use (see section 5.3, Preclinical safety data). The potential risk for human is unknown. Levobupivacaine should therefore not be given during early pregnancy unless clearly necessary.

Nevertheless, to date, the clinical experience of bupivacaine for obstetrical surgery (at the term of pregnancy or for delivery) is extensive and has not shown a foetotoxic effect.

Lactation

Levobupivacaine excretion in breast milk is unknown. However, levobupivacaine is likely to be poorly transmitted in the breast milk, as for bupivacaine. Thus breast feeding is possible after local anaesthesia.

4.7 Effects on ability to drive and use machines

Levobupivacaine can have a major influence on the ability to drive or use machines. 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.

4.8 Undesirable effects

Adverse reactions with local anaesthetics of the amide type are rare, but they may occur as a result of overdosage or unintentional intravascular injection and may be serious.

Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. 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, anaphylactic-like symptomatology (including severe hypotension). Cross sensitivity among members of the amide-type local anaesthetic group have been reported (see section 4.3, Contraindications).

Accidental intrathecal injection of local anaesthetics can lead to very high spinal anaesthesia possibly with apnoea, severe hypotension and loss of consciousness.

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. Usually these will be preceded by major CNS toxicity, i.e. convulsions, but in rare cases, cardiac arrest may occur without prodromal CNS effects.

SOC	FREQUENCY	ADVERSE EVENT
Blood and the lymphatic system disorders	Very Common	Anaemia
Nervous system disorders	Common	Dizziness Headache
Cardiac disorders	Very Common	Hypotension
Gastrointestinal disorders	Very Common Common	Nausea Vomiting
Pregnancy, puerperium and perinatal conditions	Common	Foetal distress
General disorders and administration site conditions	Common Common Common	Back pain Fever Post-operative pain

The most frequent adverse events reported in clinical trials irrespective of causality are listed in the table above.

Neurological damage is a rare 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. Rarely, these may be permanent.

Postmarketing reports

Anaphylaxis has been reported. Very rare reports of convulsions have occurred following accidental intravenous administration.

4.9 Overdose

Accidental intravascular injection of local anaesthetics may cause immediate toxic reactions. In the event of overdose, peak plasma concentrations may not be reached until 2 hours after administration depending upon the injection site and, therefore, signs of toxicity may be delayed. The effects of the drug may be prolonged.

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

CNS Effects

Convulsions should be treated immediately with intravenous thiopentone or diazepam titrated as necessary. Thiopentone and diazepam also depress 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 may be prevented or attenuated by pre-treatment with a fluid load and/or the use of vasopressors. If hypotension occurs it should be treated with intravenous crystalloids or colloids and/or incremental doses of a vasopressor such as ephedrine 5-10 mg. Any coexisting causes of hypotension should be rapidly treated.

If severe bradycardia occurs, treatment with atropine 0.3-1.0 mg will normally restore the heart rate to an acceptable level.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Local anaesthetics, amide
ATC Code N01B B10

Levobupivacaine is a long acting local anaesthetic and analgesic. It blocks nerve conduction in sensory and motor nerves largely by interacting with voltage sensitive sodium channels on the cell membrane, but also potassium and calcium channels are blocked. In addition, levobupivacaine interferes with impulse transmission and conduction in other tissues where effects on the cardiovascular and central nervous systems are most important for the occurrence of clinical adverse reactions.

The dose of levobupivacaine is expressed as base, whereas, in the racemate bupivacaine the dose is expressed as hydrochloride salt. This gives rise to approximately 13% more active substance in levobupivacaine solutions compared to bupivacaine. In clinical studies at the same nominal concentrations levobupivacaine showed similar clinical effect to bupivacaine.

In a clinical pharmacology study using the ulnar nerve block model**,** levobupivacaine was equipotent with bupivacaine.

5.2 Pharmacokinetic properties

In human studies, the distribution kinetics of levobupivacaine following i.v. administration is essentially the same as 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 relevant data in patients with hepatic impairment (see section 4.4, Special warning and precautions for use).
There are no data in patients with renal impairment. Levobupivacaine is extensively metabolised and unchanged levobupivacaine is not excreted in urine.

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 μg/ml.

In a clinical pharmacology study where 40 mg levobupivacaine was given by intravenous administration, the mean half-life was approximately 80 $\pm$ 22 minutes, C_{max} 1.4 $\pm$ 0.2 μg/ml and AUC 70 $\pm$ 27 μg 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 μg/ml and 3.56 μg h/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.

Levobupivacaine is extensively metabolised with no unchanged levobupivacaine detected in urine or faeces. 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 vivo* racemisation of levobupivacaine.

5.3 Preclinical safety data

In an embryo-foetal toxicity study in rats, an increased incidence of dilated renal pelvis, dilated ureters, olfactory ventricle dilatation and extra thoraco-lumbar ribs was observed at systemic exposure levels in the same range as those obtained at clinical use. There were no treatment-related malformations.

Levobupivacaine was not genotoxic in a standard battery of assays for mutagenicity and clastogenicity. No carcinogenicity testing has been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Sodium Hydroxide
Hydrochloric acid
Water for Injections

6.2 Incompatibilities

Levobupivacaine may precipitate if diluted with alkaline solutions and should not be diluted or co-administered with sodium bicarbonate injections. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.3, Shelf life.

6.3 Shelf Life

Shelf life as packaged for sale: 3 years

Shelf life after first opening: The product should be used immediately.

Shelf life after dilution in sodium chloride solution 0.9%: Chemical and physical in-use stability has been demonstrated for 7 days at 20-22°C. Chemical and physical in-use stability with clonidine, morphine or fentanyl has been demonstrated for 40 hours at 20-22°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Glass ampoules: store in the original package in order to protect from light.
Polypropylene ampoules: polypropylene ampoules do not require any special storage conditions.

6.5 Nature and contents of container

Chirocaine is available in two presentations;

10 ml polypropylene ampoule in packs of 5, 10 & 20
10 ml polypropylene ampoule, in sterile blister packs of 5, 10 & 20

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused solution.

The solution/dilution should be inspected visually prior to use. Only clear solutions without visible particles should be used.

A sterile blister container should be chosen when a sterile ampoule surface is required. Ampoule surface is not sterile if sterile blister is pierced.

Dilutions of levobupivacaine standard solutions should be made with sodium chloride 9 mg/ml (0.9%) solution for injection using aseptic techniques.

Clonidine 8.4 µg/ml, morphine 0.05 mg/ml and fentanyl 4 µg/ml have been shown to be compatible with levobupivacaine in sodium chloride 9 mg/ml (0.9%) solution for injection.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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