PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S4**

1 NAME OF THE MEDICINE

LEVOBUPIVACAINE 2,5 mg/mL FRESENIUS Solution for injection/infusion

LEVOBUPIVACAINE 5,0 mg/mL FRESENIUS Solution for injection/infusion

LEVOBUPIVACAINE 7,5 mg/mL FRESENIUS Solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of solution for injection contains 2,5 mg, 5 mg or 7,5 mg levobupivacaine as levobupivacaine hydrochloride.

Each 10 mL ampoule contains 25 mg, 50 mg or 75 mg levobupivacaine as levobupivacaine hydrochloride.

Excipients with known effect:

LEVOBUPIVACAINE FRESENIUS contains 3,6 mg sodium per mL (36 mg/10 mL ampoule), equivalent to 0,18 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Sugar free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear colourless solution without any visible particulate matter.

pH 4,0 - 6,0

Osmolarity: 271 - 372 mOsmol/L

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LEVOBUPIVACAINE FRESENIUS 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 epidural administration for post-operative, labour or chronic pain.

For continuous epidural analgesia, LEVOBUPIVACAINE FRESENIUS may be administered in combination with epidural fentanyl, morphine or clonidine.

Paediatric population

LEVOBUPIVACAINE FRESENIUS is indicated in children for infiltration analgesia. No data are available in paediatric population < 6 months of age.

4.2 Posology and method of administration

LEVOBUPIVACAINE FRESENIUS should be administered only by doctors who are well versed in the diagnosis and management of medicine related toxicity and other acute emergencies, which might arise from the block being administered. The immediate availability of oxygen, other resuscitative medicines, cardiopulmonary resuscitative equipment, and the personnel resources needed for proper management of toxic reactions and related emergencies should be ensured (see sections 4.8 and 4.4).

Posology

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 anaesthetised, 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.

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 years	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 [a, b] 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)] 0,25	10 - 15 mL/h 5 - 7,5 mL/h	12,5 - 18,75 mg/h 12,5 - 18,75 mg/h	Minimal to moderate
a In pain management LEVOBUPIVACAINE FRESENIUS can be used epidurally with fentanyl, morphine or clonidine.				
b In cases where LEVOBUPIVACAINE FRESENIUS is combined with other medicines e.g. opioids in pain management, the LEVOBUPIVACAINE FRESENIUS dose should be reduced as use of a lower concentration (e.g. 1,25 mg/mL) is preferable.				
c Dilutions of LEVOBUPIVACAINE FRESENIUS 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.

Method of administration

LEVOBUPIVACAINE FRESENIUS is indicated for epidural use, intrathecal use, perineural use (peripheral nerve blocks) and for infiltration (see table of doses above).

The rapid injection of a large volume of LEVOBUPIVACAINE FRESENIUS solution should be avoided and fractional (incremental) doses should always be used.

For epidural technique it is advisable to use an adequate test dose (3 - 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.

Disinfecting substances 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.

For information on incompatibilities, see section 6.2 and for information on dilution before administration, see section 6.6.

4.3 Contraindications

LEVOBUPIVACAINE FRESENIUS solutions are contraindicated:

- in patients with a known hypersensitivity to levobupivacaine, other local anaesthetics of the amide-type or any of the excipients listed in section 6.1 (see section 4.8);
- for intravenous regional anaesthesia (Bier's block);
- for the production of obstetrical paracervical block anaesthesia. There are no data to support such use and there is an additional risk of foetal bradycardia and death (see section 4.6);

  The 7,5 mg/mL LEVOBUPIVACAINE FRESENIUS solution is not recommended for obstetric use due to an enhanced risk for cardiotoxic events based on experience with bupivacaine (see sections 4.4 and 4.6).
- severe renal and/or hepatic impairment;
- for concomitant use with known CYP3A4 inducers (e.g. phenytoin, phenobarbital, rifampicin);
- for concomitant use with known CYP3A4 inhibitors (azole antimycotics, e.g. ketoconazole);
- in patients with severe hypotension such as cardiogenic or hypovolaemic shock.

General contraindications related to regional anaesthesia, regardless of the local anaesthetic used, should be considered.

4.4 Special warnings and precautions for use

For Caesarean section, LEVOBUPIVACAINE 5 mg/mL FRESENIUS (0,5 % *m/v*) solution, in doses up to 150 mg is recommended. LEVOBUPIVACAINE 7,5 mg/mL FRESENIUS (0,75 % *m/v*) is not recommended for use in obstetrics. See sections 4.3 and 4.2.

All forms of local and regional anaesthesia with LEVOBUPIVACAINE FRESENIUS 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 FRESENIUS can cause acute allergic reactions, cardiovascular effects and neurological damage (see section 4.8).

LEVOBUPIVACAINE FRESENIUS should be used with caution for regional anaesthesia in patients with impaired cardiovascular function e.g. serious cardiac dysrhythmias. These patients may be less able to compensate for functional changes associated with prolonged A-V conduction caused by these medicines.

There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. Most reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for levobupivacaine.

The introduction of local anaesthetics via either intrathecal or epidural administration into the central nervous system in patients with pre-existing central nervous system (CNS) diseases may potentially exacerbate some of these disease states. Therefore, clinical judgement should be exercised when contemplating epidural or intrathecal anaesthesia in such patients.

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 LEVOBUPIVACAINE FRESENIUS. 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 (see section 4.2).

Injection of repeated doses of local anaesthetics (including LEVOBUPIVACAINE FRESENIUS) may cause significant increases in plasma levels with each repeated dose due to slow accumulation of the medicine or its metabolites or to slow metabolic degradation. Tolerance to elevated blood levels varies with the physical condition of the patient. LEVOBUPIVACAINE FRESENIUS 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, light-headedness, 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.

Epidural anaesthesia

During epidural administration of levobupivacaine, concentrated solutions (0,5 - 0,75 %) should be administered in incremental doses of 3 - 5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Cases of severe bradycardia, hypotension and respiratory compromise with cardiac arrest (some of them fatal) have been reported in conjunction with local anaesthetics, including levobupivacaine. When a large dose is to be injected, e.g. in epidural block, a test dose of 3 - 5 mL lidocaine with epinephrine (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 should have intravenous access established. The availability of appropriate fluids, vasopressors, anaesthetics with anticonvulsant properties, myorelaxants, atropine, resuscitation equipment and expertise should be ensured (see section 4.9).

Epidural analgesia

There has been post-marketing reports of cauda equina syndrome and events indicative of neurotoxicity (see section 4.8) temporally associated with the use of levobupivacaine for 24 hours or more for epidural analgesia. These events were more severe and, in some cases, led to permanent sequelae when levobupivacaine was administered for more than 24 hours. Therefore, infusion of levobupivacaine for a period exceeding 24 hours should be considered carefully and only be used when benefit to the patient outweighs the risk.

It is essential that aspiration for blood or cerebrospinal fluid (where applicable) be done prior to injecting any local anaesthetic, 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. LEVOBUPIVACAINE FRESENIUS should be used with caution in patients receiving other local anaesthetics or substances structurally related to amide-type local anaesthetics, since the toxic effects of these medicines are additive.

Major regional nerve blocks

The patient should have IV 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.

LEVOBUPIVACAINE FRESENIUS is therefore not recommended in emergency situations, where fast onset of surgical anaesthesia is necessary.

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. 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. 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. Dosage recommendations should not be exceeded.

Use in ophthalmic surgery

Medical practitioners 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, medicines, 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.

Labour and delivery

Local anaesthetics, including LEVOBUPIVACAINE FRESENIUS, 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 medicine used, and the technique of medicine 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 LEVOBUPIVACAINE FRESENIUS for obstetrical pain relief. LEVOBUPIVACAINE FRESENIUS 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.

Special populations

Debilitated, elderly or acutely ill patients:

LEVOBUPIVACAINE FRESENIUS should be used with caution in debilitated, elderly or acutely ill patients (see section 4.2).

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 cirrhotic patients (see section 5.2). Severe hepatic disease is a contraindication to its use.

Excipients with known effect

LEVOBUPIVACAINE FRESENIUS contains 1,57 mmol (or 36 mg) sodium per ampoule of 10 mL solution. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

LEVOBUPIVACAINE FRESENIUS should be used with caution in patients receiving other local anaesthetics or medicines structurally related to amide-type local anaesthetics, since the toxic effects of these medicines may 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, medicines likely to be concomitantly administered with LEVOBUPIVACAINE FRESENIUS that are metabolised by this isoenzyme family may potentially interact with LEVOBUPIVACAINE FRESENIUS. 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, rifampicin), 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 LEVOBUPIVACAINE FRESENIUS is concurrently administered with CYP3A4 inhibitors and CYP1A2 inhibitors, as systemic levobupivacaine levels may rise resulting in toxicity.

LEVOBUPIVACAINE FRESENIUS should be used with caution in patients receiving anti-dysrhythmic medicines with local anaesthetic activity, e.g. mexiletine, or class III anti-dysrhythmic medicines, since their effects may be additive.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

LEVOBUPIVACAINE FRESENIUS 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).

LEVOBUPIVACAINE FRESENIUS 7,5 mg/mL is not recommended for obstetric use due to an enhanced risk of cardiotoxic events (see sections 4.3 and 4.4).

Local anaesthetics, including LEVOBUPIVACAINE FRESENIUS, rapidly cross the placenta, and when used for epidural block, can cause varying degrees of maternal, foetal, and neonatal toxicity. See section 4.4 “Labour and delivery”.

The safety of LEVOBUPIVACAINE FRESENIUS in pregnancy has not been established.

Breastfeeding

The safety of LEVOBUPIVACAINE FRESENIUS in breastfeeding has not been established.
It is unknown whether levobupivacaine and its metabolites are excreted in human breast milk.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

LEVOBUPIVACAINE FRESENIUS 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

Summary of safety profile

The adverse medicine reactions for levobupivacaine are consistent with those known for its respective class of medicines. The most commonly reported adverse medicine reactions are hypotension, nausea, anaemia, vomiting, dizziness, headache, pyrexia, procedural pain, back pain and foetal distress syndrome in obstetric use (see table below).

Tabulated summary of adverse reactions

Adverse reactions reported either spontaneously or observed in clinical trials are depicted in the following table.

System Organ Class/	
Frequency	**Adverse Reaction**
Blood and lymphatic system disorders	
Frequent	Anaemia
Immune system disorders	
Not known	Allergic reactions (in serious cases anaphylactic shock), hypersensitivity, angioedema
Nervous system disorders	
Frequent	Dizziness, headache, post-operative pain
Not known	Convulsion, loss of consciousness, somnolence, syncope,

	paraesthesia, paraplegia, paralysis[1], numbness of the tongue, lightheadedness
Eye disorders	
Not known	Vision blurred, ptosis[2], miosis[2], enophthalmos[2]
Cardiac disorders	
Not known	Atrioventricular block, cardiac arrest, ventricular tachydysrhythmia, tachycardia, bradycardia
Vascular disorders	
Frequent	Hypotension
Not known	Flushing[2]
Respiratory, thoracic and mediastinal disorders	
Not known	Respiratory arrest, laryngeal oedema, apnoea, sneezing
Gastrointestinal disorders	
Frequent	Nausea, vomiting
Not known	Oral hypoaesthesia, loss of sphincter control[1]
Skin and subcutaneous tissue disorders	
Not known	Urticaria, pruritus, hyperhidrosis, anhidrosis[2], erythema
Musculoskeletal and connective tissue disorders	
Frequent	Back pain
Not known	Muscle twitching, muscular weakness
Renal and urinary disorders	
Not known	Bladder dysfunction[1]
Pregnancy, puerperium and perinatal conditions	
Frequent	Foetal distress syndrome
Reproductive system and breast disorders	
Not known	Priapism[1]
General disorders and administration site conditions	

Frequent	Pyrexia
Investigations	
Not known	Cardiac output decreased, electrocardiogram change
Injury, poisoning and procedural complications	
Frequent	Procedural pain
Less frequent	Neurological damage (see below)

[1] This may be a sign or symptom of cauda equina syndrome (see additional section 4.8 text below).

[2] This may be a sign or symptom of transient Horner's syndrome (see additional section 4.8 text below).

Description of selected adverse reactions

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.

Cross-sensitivity among members of the amide-type local anaesthetic group has been reported (see section 4.3).

Accidental intrathecal injection of local anaesthetics can lead to very high spinal anaesthesia.

Cardiovascular effects are related to depression of the conduction system of the heart and a reduction in myocardial excitability and contractility. Usually these will be preceded by major CNS toxicity, i.e. convulsions, but in rare cases, cardiac arrest may occur without prodromal CNS effects.

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. Rarely, these may be permanent.

There have been reports of prolonged weakness or sensory disturbance, some of which may have been permanent, in association with levobupivacaine therapy. It is difficult to determine whether the long-term effects were the result of medicine toxicity or unrecognised trauma during surgery or other mechanical factors, such as catheter insertion and manipulation.

Reports have been received of cauda equina syndrome or signs and symptoms of potential injury to the base of the spinal cord or spinal nerve roots (including lower extremity paraesthesia, weakness or paralysis, loss of bowel control and/or bladder control and priapism) associated with levobupivacaine administration. These events were more severe and, in some cases, did not resolve when levobupivacaine was administered for more than 24 hours (see section 4.4).

However, it cannot be determined whether these events are due to an effect of levobupivacaine, mechanical trauma to the spinal cord or spinal nerve roots, or blood collection at the base of the spine.

There have also been reports of transient Horner's syndrome (ptosis, miosis, enophthalmos, unilateral sweating and/or flushing) in association with use of regional anaesthetics, including levobupivacaine. This event resolves with discontinuation of therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med

Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

Acute emergencies from levobupivacaine 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 LEVOBUPIVACAINE FRESENIUS (see sections 4.8 and 4.4).

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.

<u>CNS effects</u>

Convulsions should be treated immediately with a suitable intravenous medicine, such as thiopentone or diazepam titrated as necessary. Thiopentone and diazepam 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 medical practitioner 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 dysrhythmias, ventricular fibrillation or cardiac arrest.

Cardiovascular effects

Hypotension should be treated symptomatically.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 4 – Local anaesthetics

Pharmacotherapeutic group: Local anaesthetics, amide

ATC Code: N01B B10

LEVOBUPIVACAINE FRESENIUS 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 effect on the medulla and on higher centres. The depressed stage may occur without a prior excited stage.

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

In human studies, the distribution kinetics of levobupivacaine following intravenous (IV) administration are essentially the same as bupivacaine.

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.

The volume of distribution after intravenous administration was 67 litres.

Biotransformation

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.

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

Elimination

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.

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

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 ± 0,2 µg/mL and AUC 70 ± 27 µg•min/mL.

Linearity

The mean C_{max} and AUC (0-24 h) 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.

Hepatic and renal impairment

There are no data in patients with hepatic impairment (see section 4.4).

There are no data in patients with renal impairment.

Levobupivacaine is extensively metabolised and unchanged. Levobupivacaine is not excreted in urine or faeces.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injection

6.2 Incompatibilities

LEVOBUPIVACAINE FRESENIUS is not compatible with alkaline solutions having a pH greater than 8,5.

Levobupivacaine may precipitate if diluted with alkaline solutions and should not be diluted or co-administered with sodium bicarbonate injections. This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Shelf life as packaged for sale: 24 months, stored at or below 30 °C.

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

Shelf life after dilution in sodium chloride solution 0,9 %:

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 and would normally not be longer than 24 hours at 2 to 8 °C, unless the dilution and admix have taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for Levobupivacaine diluted with sodium chloride 9 mg/mL (0,9 %) to a final concentration of 0,625 mg/mL and 1,25 mg/mL, respectively, for 30 days either at 2 - 8 °C or 20 - 25 °C.

Chemical and physical in-use stability has been demonstrated for Levobupivacaine diluted with sodium chloride 9 mg/mL (0,9 %) to a final concentration of 0,625 mg/mL and 1,25 mg/mL, respectively:

- With 8,4 µg/mL clonidine hydrochloride, 50 µg/mL morphine sulphate and 2 - 4 µg/mL fentanyl citrate for 30 days at either 2 - 8 °C or 20 - 25 °C.
- With sufentanil added in the concentration of 0,4 µg/mL for 30 days at 2 - 8 °C or 7 days at 20 - 25 °C.

6.4 Special precautions for storage

LEVOBUPIVACAINE FRESENIUS does not require any special storage conditions.

For storage conditions of the diluted medicine, see section 6.3.

6.5 Nature and contents of container

10 mL polypropylene ampoules (Ovalia), in sterile blister packs. It is supplied in packs of 5, 10 & 20 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only. Discard any unused solution.

Do not use if the container is damaged.

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, fentanyl 2 - 4 µg/mL and sufentanil 0,4 µg/mL have been shown to be compatible with levobupivacaine in sodium chloride 9 mg/mL (0,9 %) solution for injection.
For the shelf life of the diluted product, see section 6.3.
Compatibility studies with other parenteral products have not been studied.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

FRESENIUS KABI SOUTH AFRICA (PTY) LTD

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8 REGISTRATION NUMBER(S)

LEVOBUPIVACAINE 2,5 mg/mL FRESENIUS: 50/4/0737

LEVOBUPIVACAINE 5 mg/mL FRESENIUS: 50/4/0738

LEVOBUPIVACAINE 7,5 mg/mL FRESENIUS: 50/4/0739

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 February 2022

10 DATE OF REVISION OF THE TEXT

08 February 2022