Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levobupivacaine 0.625 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 0.625 mg of levobupivacaine as levobupivacaine hydrochloride.
Each bag of 100 ml contains 62.5 mg of levobupivacaine as levobupivacaine hydrochloride.
Each bag of 200 ml contains 125 mg of levobupivacaine as levobupivacaine hydrochloride.

Excipients with known effect:
This medicinal product contains 3.6 mg sodium per ml, equivalent to 0.18% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
Clear colourless solution
pH 4.0-6.0
Osmolarity: 271 – 332 mOsmol/l

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Adults

Pain management
Continuous epidural infusion, for the management of post operative pain and labour analgesia.

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.

Posology

Type of Block	Concentration mg/ml	Infusion Rate Per Hour	
		ml	mg
Continuous Infusion:			
Post operative pain management	0.625	20-30	12.5-18.75
Lumbar epidural (analgesia in labour)	0.625	8-20	5–12.5

There is limited safety experience with levobupivacaine therapy for periods exceeding 24 hours. In order to minimise the risk for severe neurological complications, the patient and the duration of administration of levbupivacaine should be closely monitored (see Section 4.4).

Maximum dose
The maximum dosage must be determined by evaluating the size and physical status of the patient. 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, however the accumulated dose for a 24 hour period should not exceed 400 mg. For labour analgesia by epidural infusion, the dose should not exceed 12.5 mg/ hour.

Paediatric population
The safety and efficacy of levobupivacaine in children for pain management has 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 and 5.2).

Method of administration
Levobupivacaine 0.625 mg/ml is for epidural use only. It must not be used for intravenous administration.

Careful aspiration before infusion is recommended to prevent intravascular injection. If toxic symptoms occur, the injection should be stopped immediately.

4.3 Contraindications

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

Levobupivacaine solutions are contraindicated in patients with a known hypersensitivity to levobupivacaine, local anaesthetics of the amide type or any of the excipients listed in section 6.1 (see section 4.8).

Levobupivacaine solutions are contraindicated for intravenous regional anaesthesia (Bier's block).

Levobupivacaine solutions are contraindicated in patients with severe hypotension such as cardiogenic or hypovolaemic shock.

Levobupivacaine solutions are contraindicated for use in paracervical block in obstetrics (see section 4.6).

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 can cause acute allergic reactions, cardiovascular effects and neurological damage (see section 4.8).

The introduction of local anesthetics via 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 anesthesia in such patients.

Epidural Anaesthesia
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. Cases of severe bradycardia, hypotension and respiratory compromise with cardiac arrest (some of them fatal), have been reported in conjunction with local anesthetics, including levobupivacaine. 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 anesthesia, 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).

Epidural Analgesia
There have been postmarketing 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 anesthetic, 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 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.

Chondrolysis
There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. The majority of 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.

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).

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).

4.5 Interaction with other medicinal products and other forms of interactions

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 eg: ketoconazole, and CYP1A2 inhibitors eg: 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 Fertility, 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).

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). 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.

Breast-feeding
Thus breastfeeding is possible after local anaesthesia.

Fertility
There are no or only limited data available for Levobupivacaine to assess its impact on fertility.

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

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

Adverse reactions reported either spontaneously or observed in clinical trials are depicted in the following table. Within each system organ class, the adverse drug reactions are ranked under headings of frequency, using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reaction
Blood and lymphatic system disorders	Very Common	Anaemia
Immune system disorders	Not known	Allergic reactions (in serious cases anaphylactic shock)
	Not known	Hypersensitivity
Nervous system disorders	Common	Dizziness
	Common	Headache
	Not known	Convulsion
	Not known	Loss of consciousness
	Not known	Somnolence
	Not known	Syncope
	Not known	Paraesthesia
	Not known	Paraplegia
	Not known	Paralysis[1]
Eye disorders	Not known	Vision blurred
	Not known	Ptosis[2]
	Not known	Miosis[2]
	Not known	Enophthalmos[2]
Cardiac disorders	Not known	Atrioventricular block
	Not known	Cardiac arrest
	Not known	Ventricular tachyarrhythmia
	Not known	Tachycardia
	Not known	Bradycardia
Vascular disorders	Very common	Hypotension
	Not known	Flushing[2]
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory arrest
	Not known	Laryngeal oedema
	Not known	Apnoea
	Not known	Sneezing
Gastrointestinal disorders	Very Common	Nausea
	Common	Vomiting
	Not known	Hypoaesthesia oral
	Not known	Loss of sphincter control[1]
Skin and subcutaneous tissue disorders	Not known	Angioedema

	Not known Not known Not known Not known Not known	Urticaria Pruritus Hyperhidrosis Anhidrosis[2] Erythema
Musculoskeletal and connective tissue disorders	Common Not known Not known	Back pain Muscle twitching Muscular weakness
Renal and urinary disorders	Not known	Bladder dysfunction[1]
Pregnancy, puerperium and perinatal conditions	Common	Foetal distress syndrome
Reproductive system and breast disorder	Not known	Priapism[1]
General disorders and administration site conditions	Common	Pyrexia
Investigations	Not known Not known	Cardiac output decreased Electrocardiogram change
Injury, poisoning and procedural complications	Common	Procedural pain

[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).

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 anesthetic group have 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 where the result of medication toxicity or unrecognized 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the HPRA Pharmacovigilance, Website: www.hpra.ie.

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 ofmaintaining 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.

There is limited safety experience with levobupivacaine therapy for periods exceeding 24 hours.

5.2 Pharmacokinetic properties

Absorption
In human studies, the distribution kinetics of levobupivacaine following i.v. administration are 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.

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 micogram/ml and AUC 70 $\pm$ 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·h/ml respectively.

Distribution
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.

The volume of distribution after intravenous administration was 67 litres.

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

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

The mean total plasma clearance and terminal half-life of levobupivacaine after intravenous infusion were 39 litres/hour and 1.3 hours, respectively.

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.

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 (for pH adjustment)
Hydrochloric acid (for pH adjustment)
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 6.6.

6.3 Shelf life

2 years.

After first opening : The product should be used immediately.

Shelf-life after dilution:
Chemical and physical in-use stability has been demonstrated for levobupivacaine solution for infusion
- With 8.4 micrograms/ml clonidine hydrochloride, 50 micrograms/ml morphine sulfate and 2-4 micrograms/ml fentanyl citrate for 30 days at either 2-8°C or 20°C–25°C.
- With sufentanil added in the concentration of 0.4 micrograms/ml for 30 days at 2-8 °C or 7 days at 20 °C-25 °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 and would normally not be longer than 24 hours at 2 to 8ºC, unless the admix has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Levobupivacaine is available in two presentations;

- 100 ml solution in polyolefin bag with a transparent foil overpouch.
- 200 ml solution in polyolefin bag with a transparent foil overpouch.

Each polyolefin bag contains an administration port (infusion port) and addition port (injection port) consisting of a polypropylene housing.

Pack sizes: 5, 24 or 60 bags of 100 ml solution.
5, 12 or 32 bags of 200 ml solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single epidural use only. Discard any unused solution.
Do not use unless the container is undamaged.

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

Clonidine 8.4 micrograms/ml, morphine 0.05 micrograms/ml, fentanyl 2-4 g/ml and sufentanil 0.4 micrograms/ml have been shown to be compatible with levobupivacaine in sodium chloride 9 micrograms/ml (0.9%) solution for injection.

For the shelf-life of the diluted product see section 6.3.

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

7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kroener Strasse 1
Bad Homburg v.d.H 61352
Germany

8 MARKETING AUTHORISATION NUMBER

PA2059/009/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th October 2014

Date of last renewal: 21st April 2019

10 DATE OF REVISION OF THE TEXT

May 2021