Levobupivacaine - SLS
Levobupivacaine HCl 1.25 mg/ml
solution for epidural infusion

1 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains 1.25 mg levobupivacaine (as hydrochloride).

Each 100ml-bag contains 125 mg levobupivacaine (as hydrochloride).

Excipients with known effect: 3.5 mg/ml of sodium per bag.
For the full list of excipients, see section 6.1.

2 PHARMACEUTICAL FORM

Solution for infusion. Clear colourless solution.pH : 4.0 – 6.5
Osmolality: 260 – 310 mOsmol/Kg

3 CLINICAL PARTICULARS

3.1 Therapeutic indications

Adults

Pain management

- Continuous epidural infusion for the management of postoperative pain and labour analgesia.

3.2 Posology and method of administration

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

Posology

"invented name". 1.25 mg/ml solution for infusion is for epidural use only. It mustnot be used for intravenous administration

Type of block	Concentration mg/ml	Infusion Rate Per Hour	
		ml	mg
Continuous Infusion:Post operative pain management	1.25	10-15	12.5 -18.75

Dr.Mona

Lumbar Epidural (analgesia in labour)	1.25	4-10	5-12.5

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

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 levobupivacaineshould be closely monitored (see section 4.4).

Maximum dose

The maximum dosage must be determined by evaluating the size and physical statusof 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. Forlabour 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 notbeen established.

Special populations

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

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

There are no relevant data in patients with hepatic impairment (see sections 4.4 and5.2).

Contraindications

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

Levobupivacaine solutions are contraindicated in patients with a known hypersensitivity to the active substance, local anaesthetics of the amide type or any ofthe 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

inobstetrics (see section 4.6).

3.3 Special warnings and precautions for use

All forms of local and regional anaesthesia with levobupivacaine intravenous regional anaesthesia(Bier's block).

Levobupivacaine solutions are contraindicated in patients with severe hypotension such as cardiogenic 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 anyunwanted adverse effects that may occur.

Levobupivacaine can cause acute allergic reactions, cardiovascular effects andneurological damage (see section 4.8).

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 mechanismof action, causality has not been established. Intra-articular continuous infusion is notan approved indication for levobupivacaine.

The introduction of local anaesthetics via epidural administration into the central nervous system in patients with preexisting CNS diseases may potentially exacerbatesome of these disease states. Therefore, clinical judgment should be exercised when contemplating epidural anaesthesia 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 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 adrenaline isrecommended. An inadvertent intravascular injection may then be recognized 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 dosebe 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 ofappropriate fluids, vasopressors, anaesthetics with anticonvulsant properties, myorelaxants, and atropine, resuscitation equipment and expertise must be ensured (see section 4.9).

Epidural Analgesia

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General Administration of pharmaceutical References and leaflets
leaflets Administration According to: MHRA

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 at least for 24 hours for epidural analgesia. These events were moresevere 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 negativeaspiration 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 thetoxic effects of these drugs are additive.

Special populations

Debilitated, elderly or acutely ill patients: levobupivacaine should be used withcaution in debilitated, elderly or acutely ill patients (see section 4.2).

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

This medicinal product contains 15mmol (3.5 mg/ml) sodium in the 100 ml-bag to be taken into consideration by patients on a controlled sodium diet.

3.4 Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that the CYP3A4 isoform and CYP1A2 isoform mediate themetabolism 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-arrhythmicagents 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 combinationwith adrenaline.

3.5 Fertility, pregnancy and lactation

Pregnancy

evobupivacaine solutions are contraindicated for use in paracervical block in obstetrics. Based on experience with bupivacaine foetal bradycardia may occurfollowing paracervical block

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 (atthe term of pregnancy or for delivery) is extensive and has not shown foetotoxic effects.

Lactation

It is unknown whether levobupivacaine or its metabolites are excreted in humanbreast milk.

As for bupivacaine, levobupivacaine is likely to be poorly transmitted in the breastmilk. Thus, breastfeeding is possible after local anaesthesia.

Fertility

No data or limited data is available on the use of levobupivacaine and its relation withfertility.

3.6 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 theanaesthesia and the immediate effects of surgery are passed

3.7 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 drugreactions 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 organ or system, the adverse drug reactions are decreasingly ranked under headings of frequency, using the followingconvention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000,
<1/100), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reaction
Blood and lymphatic system	Very Common	Anaemia
Immune system disorders	Not known	Allergic reactions (in serious cases anaphylactic shock) Hypersensitivity
Nervous system disorders	Common	Dizziness
	Common	Headache
	Not known	Convulsion
	Not known	Loss of consciousness
	Not known	Somnolence
	Not known	Syncope
	Not known	
	Not known	
Eye disorders	Not known	Vision blurred
	Not known	Ptosis[2]
	Not known	Enophthalmos[2]
Cardiac disorders	Not known	Atrioventricular block

Investigations	Not known	Cardiac output decreased
	Not known	Electrocardiogram change
Injury, poisoning and proceduralcomplications	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 additionalsection 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 beserious.

Cross-sensitivity among members of the amide-type local anaesthetic group havebeen reported

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

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 mayoccur 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 irritantsubstance 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 ascatheter 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 eventswere 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 bloodcollection 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 regionalanaesthetics, including levobupivacaine. This event resolves with discontinuation of therapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 Egyptian Pharmaceutical Vigilance Center directly on hotline 15301 or by sending an e-mail to: pv.followup@edaegypt.gov.eg

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. Systemicadverse 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 diazepamtitrated 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 plusmyocardial 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/orthe 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 restorethe heart rate to an acceptable level.

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

4 PHARMACOLOGICAL PROPERTIES

4.1 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

psodium channels on the cell membrane, but also potassium and calcium channels areblocked. 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 tobupivacaine. 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, levobupivacainewas equipotent with bupivacaine.

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

4.2 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 i.v. administration are essentially the same as bupivacaine.

Plasma protein binding of levobupivacaine in man was evaluated in vitro and wasfound 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 levobupivacainedetected in urine or faeces.

3-hydroxylevobupivacaine, a major metabolite of levobupivacaine, is excreted in theurine as glucuronic acid and sulphate ester conjugates. In vitro studies showed that CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaineto 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%) in48 hours.

In a clinical pharmacology study where 40 mg levobupivacaine was given by intravenous administration, the mean half-life was approximately 80 + 22 minutes,Cmax 1.4 + 0.2 µg/ml and AUC 70 + 27 µg•min/ml.

Linearity

The mean Cmax 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%) themean Cmax and AUC values were 0.58 µg/ml and 3.56µg•h/ml respectively.

Hepatic and renal impairment

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

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

5 PHARMACEUTICAL PARTICULARS

5.1 List of excipients

5.2 Incompatibilities

Levobupivacaine may precipitate if diluted with alkaline solutions and should not be diluted or co-administered with sodium bicarbonate injections.

5.3 Shelf life

See outer Pack

5.4 Special precautions for storage

Store at a temperature not exceeding 30°C,

use after opening immediately – Protect from Light

Sodium Chlorid, Sodium Hydroxide, Hydrochloric acid Water for Injections

5.5 Nature and contents of container

Levobupivacaine is available in
Carton box contains single use Transparent Plastic Polypropylene bag with 2 SFC systems(Single function container) (2 SFC port and 2 SFC cap assembled with rubber disc type I) of 100 ml solution containing Levobupivacaine hydrochloride 1.25 mg / ml with outer label.

Manufacturer: El-Nasr for Pharmaceutical Chemicals for Human, veterinary and medical device

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