Applicant/PHRC: *Hetero Drugs South Africa (Pty) Ltd*

Product proprietary name: *DOBISIM*

Dosage form and strength: *Injection, Each 2 ml contains 20 mg lidocaine hydrochloride*

Each 5 ml contains 50 mg lidocaine hydrochloride

Each 30 ml contains 300 mg lidocaine hydrochloride

APPROVED PROFESSIONAL INFORMATION FOR DOBISIM

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

DOBISIM 2 ml solution for injection

DOBISIM 5 ml solution for injection

DOBISIM 30 ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mg/ 1ml (1 %)

Each 2 ml contains 20 mg lidocaine (lignocaine) hydrochloride

Each 5 ml contains 50 mg lidocaine (lignocaine) hydrochloride

Each 30 ml contains 300 mg lidocaine (lignocaine) hydrochloride

Excipient(s):

No excipient with known effect.

DOBISIM is preservative free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

DOBISIM is a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DOBISIM is used as a local anaesthetic in infiltration and field block anaesthesia. As a local anaesthetic it has an action of intermediate duration which can be increased by adding adrenaline (epinephrine).

4.2 Posology and method of administration

Posology

It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper.

The dosage will depend on the area to be anaesthetised:

1. Infiltration anaesthesia: 0,5 – 1,0 % solution is used.
2. Field block anaesthesia: As for infiltration anaesthesia.
3. Epidural anaesthesia: Determined by the segmental level of anaesthesia required. The volume of anaesthetic required is determined by which nerve fibres are to be blocked, what level of anaesthesia is required and whether epinephrine (adrenaline) is used. The addition of epinephrine (adrenaline) 1:200 000 is often used to increase the duration of anaesthesia.

The maximum 24hour dose is 300 mg of DOBISIM.

Method of administration

DOBISIM is administered subcutaneously (SC) or intramuscularly (IM).

4.3 Contraindications

Hypersensitivity to lidocaine (lignocaine), other local anaesthetics of the amide type, or any other component of DOBISIM (see section 6.1)

DOBISIM should not be given to patients with:

- Hypovolaemia

- Heart block or other conduction disturbances
- Bradycardia
- Cardiac decompensation
- Hypotension unrelated to treatable tachydysrhythmias
- Myasthenia gravis

4.4 Special warnings and precautions for use

DOBISIM should not be given intravenously. In such case, the rapid absorption is likely to cause systemic toxic symptoms, such as hypotension, pallor, dysrhythmias, sweating, nausea, vomiting and muscular twitching.

The local anaesthetic effect of DOBISIM may be reduced if the injection is administered into an inflamed area with a low tissue pH.

DOBISIM is considered to be unsafe in patients with porphyria.

DOBISIM should be used with caution in patients with:

- Epilepsy
- Congestive heart failure
- Severe shock
- Impaired respiratory function or impaired renal function with a creatinine clearance of less than 10 ml/minute.
- DOBISIM is metabolised in the liver and it should be used with caution in patients with impaired hepatic function.
- Hypokalaemia, hypoxia and disorders of acid-base balance should be corrected before treatment with DOBISIM begins.

- Facilities for resuscitation should be available when administering local anaesthetics.
- Intra-articular administration of DOBISIM may cause chondrotoxicity.
- Central nerve blocks may cause cardiovascular depression, especially in the presence of hypovolaemia, and therefore epidural anaesthesia should be used with caution in patients with impaired cardiovascular function.
- Epidural anaesthesia may lead to hypotension and bradycardia. This risk can be reduced by preloading the circulation with crystalloidal or colloidal solution. Hypotension should be treated promptly.
- Retrobulbar injections may reach the cranial subarachnoid space causing serious/ severe reactions, including cardiovascular collapse, apnoea, convulsions and temporary blindness.
- Retro- and peribulbar injections of local anaesthetics carry a low risk of persistent ocular motor dysfunction. The primary causes include trauma and/or local toxic effects on muscles and/ or nerves.
- The severity of such tissue reactions is related to the degree of trauma, the concentration of the local anaesthetic and the duration of exposure of the tissue to the local anaesthetic. For this reason, as with all local anaesthetics, the lowest effective concentration and dose of local anaesthetic should be used.
- Doses should be reduced in elderly and debilitated patients and in children.
- DOBISIM is not recommended for use in neonates.

DOBISIM contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of

interaction

<u>Effects of DOBISIM on other medicines</u>

- DOBISIM should be used with caution in patients receiving other local anaesthetics or medicines structurally related to amide-type local anaesthetics (e.g., anti-dysrhythmics, such as mexiletine), since the systemic toxic effects are additive.

- There may be an increased risk of enhanced and prolonged neuromuscular blockade in patients treated concurrently with other muscle elaxants (e.g., suxamethonium).

Effects of other medicines on DOBISIM

- The clearance of lidocaine (lignocaine) may be reduced by beta-adrenoceptor blocking medicines (e.g., propranolol) and by cimetidine, requiring a reduction in the dosage of DOBISIM.
- Increase in serum levels of lidocaine (lignocaine) may also occur with anti- viral medicines (e.g., amprenavir, atazanavir, darunavir, lopinavir).
- There may be an increased risk of ventricular dysrhythmia in patients treated concurrently with antipsychotics which prolong or may prolong the QT interval (e.g., pimozide, sertindole, olanzapine, quetiapine, zotepine), or 5HT3 antagonists (e.g., tropisetron, dolasetron).
- While epinephrine (adrenaline) when used in conjunction with DOBISIM might decrease vascular absorption, it greatly increases the danger of ventricular tachycardia and fibrillation if accidentally injected intravenously.
- Concomitant use of quinupristin or dalfopristin should be avoided.
- Hypokalaemia produced by acetazolamide, loop diuretics and thiazides may antagonize the effect of DOBISIM if administered concomitantly (see section 4.4).
- Inhibition of CYP1A2 by fluvoxamine considerably reduces elimination of DOBISIM and increases the risk of DOBISIM toxicity. Concomitant use of both fluvoxamine and a CYP3A4 inhibitor such as erythromycin can further increase lidocaine (lignocaine) concentrations. Because lidocaine (lignocaine) possesses a narrow therapeutic window, doses of DOBISIM may need to be adjusted accordingly.
- Phenytoin can also increase plasma concentrations of α_1-acid glycoprotein and thereby reduce the free fraction of lidocaine in plasma.
- Lidocaine (lignocaine) is markedly bound to 1- acid glycoprotein (AAG). AAG concentration may be reduced by oestrogens leading to a higher free fraction of lidocaine in women than in men and the free fraction is

further increased during pregnancy and in women taking oral contraceptives or HRT.

- Opioid-antiemetic combination sometimes used for sedation in children could reduce the convulsant threshold to lidocaine (lignocaine) and increase the CNS depressant effect.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

- Lidocaine (lignocaine) is markedly bound to 1- acid glycoprotein (AAG).
- AAG concentration may be reduced by oestrogens leading to a higher free fraction of lidocaine (lignocaine) in women than in men and the free fraction is further increased during pregnancy and in women taking oral contraceptives or HRT (see section 4.5)

Pregnancy

DOBISIM crosses the placenta and blood- brain barrier and should not be administered during early pregnancy.

DOBISIM given by epidural or paracervical block, especially in large doses, or by local perineal infiltration prior to delivery crosses rapidly into the foetal circulation. Elevated lidocaine (lignocaine) levels may persist in the newborn for at least 48 hours after delivery.

Foetal bradycardia or neonatal bradycardia, hypotonia or respiratory depression may occur.

Breastfeeding

Small amounts of DOBISIM are secreted into breast milk and possibility of an allergic reaction in the infant, albeit remote, should be bored in mind when using DOBISIM in nursing mothers.

4.7 Effects on ability to drive and use machines

When outpatient anaesthesia affects areas of the body involved in driving or operating machinery, patients should be advised to avoid these activities until normal function is fully restored.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions to DOBISIM are infrequent and are usually the result of raised plasma concentrations due to accidental intravascular injection, excessive dosage or rapid absorption from highly vascular areas, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Systemic toxicity mainly involves the central nervous system and/ or the cardiovascular system (see section 4.9).

Following regional blockade as when DOBISIM is injected intrathecally or extradurally, hypotension, hypoventilation, Homers Syndrome and hypoglycaemia may be seen. The degree of these effects will depend on the dose and the height of the block.

Urinary

Retention may occur following sacral or lumbar epidural block. It should not outlast the duration of the block. Apnoea and hemiparesis may occur following stellate ganglion block. The probable cause is a direct injection of DOBISIM into the vertebral or carotid arteries.

b. Tabulated list of adverse reactions

Blood and lymphatic system disorders	
Frequency not known	Methaemoglobinaemia.
Immune system disorders	
Frequency not known	Hypersensitivity reactions (allergic or anaphylactic reaction, anaphylactic shock)
Nervous system disorders	
Frequency not known	Stimulation of the central nervous system (CNS), (manifested by yawning, restlessness, excitement, nervousness, dizziness, light-headedness, tremor, circumoral paraesthesia, blurred vision, nausea, vomiting,

	muscle twitching and convulsions). Excitation of the central nervous system may be transient, followed by depression, with drowsiness, respiratory failure and coma. Seizures have also been reported after excessive doses administered subcutaneously. Numbness of the tongue and perioral region is an early sign of systemic toxicity. Amnesia
Eye disorders	
Frequency not known	Blurred vision, diplopia and transient amaurosis may be signs of lidocaine toxicity. Bilateral amaurosis may also be a consequence of accidental injection of the optic nerve sheath during ocular procedures. Orbital inflammation and diplopia have been reported following retro-or peribulbar anaesthesia (see section 4.4).
Ear and labyrinth disorders	
Frequency not known	Tinnitus, hyperacusis
Cardiac disorders	
Frequency not known	Depression of the cardiovascular system (characterised by pallor, sweating and hypotension, dysrhythmias, bradycardia or cardiac arrest).
Respiratory, thoracic and mediastinal disorders	
Frequency not known	Dyspnoea, bronchospasm, respiratory depression, respiratory arrest
Gastrointestinal disorders	
Frequency not known	Drowsiness, vomiting
Skin and subcutaneous tissue disorders	
Frequency not known	Rash, urticaria, oedema

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. Health care providers are asked to report any suspected adverse to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/publications/Index/8 or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.com.

4.9 Overdose

Symptoms of acute systemic toxicity

Central nervous system toxicity presents with symptoms of increasing severity. Patients may present initially with circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus.

Visual disturbance and muscular tremors or muscle twitching are more serious and precede the onset of generalised convulsions (see section 4.8). These signs must not be mistaken for neurotic behaviour. Unconsciousness and grand mal convulsions may follow, which may last from a few seconds to several minutes.

Hypoxia and hypercapnia occur rapidly following convulsions due to increased muscular activity, together with the interference with normal respiration and loss of the airway. In severe cases, apnoea may occur. Acidosis increases the toxic effects of local anaesthetics.

Effects on the cardiovascular system may be seen in severe cases. Hypotension, bradycardia, dysrhythmia and cardiac arrest may occur as a result of high systemic concentrations, with potentially fatal outcome.

Recovery occurs as a consequence of redistribution of the local anaesthetic medicine from the central nervous system, and metabolism and may be rapid unless large amounts of the medicine have been injected.

Treatment

Symptomatic and supportive

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 4 Local anaesthetics.

Pharmacotherapeutic group: Anaesthetics, local. Amides.

ATC code: N01BB02.

Lidocaine (lignocaine) has local anaesthetic action (it blocks conduction of nerve impulses by decreasing or preventing the large transient increase in permeability of the cell membrane to sodium ions) and antidysrhythmic properties, last mentioned, as a result of its direct influence on the depolarising of the cardiac membrane. It increases the electrical stimulation threshold of the ventricle during diastole.

5.2 Pharmacokinetic properties

Absorption

Lidocaine (lignocaine) is well absorbed from injection sites, including muscle, and its rate of absorption is determined by factors such as the site of administration and the tissue vascularity. Except for intravascular administration, the highest blood levels occur following intercostal nerve block and the lowest after subcutaneous administration.

Distribution

Lidocaine (lignocaine) is bound to plasma proteins, including alpha-1-acid-glycoprotein. Lidocaine (lignocaine) crosses the blood-brain and placental barriers.

Biotransformation

Lidocaine (lignocaine) is metabolised in the liver and about 90 % of a given dose undergoes N-dealkylation to form monoethylglycinexylidide and glycinexylidide, both of which may contribute to the therapeutic and toxic effects of lidocaine (lignocaine). Further metabolism occurs, and metabolites are excreted in the urine with less than 10 % of the lidocaine (lignocaine) unchanged.

Elimination

The elimination half-life of lidocaine (lignocaine) following an intravenous bolus injection is one to two hours, but this may be prolonged in patients with hepatic dysfunction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Sodium Chloride
- Sodium Hydroxide
- Hydrochloric acid
- Water for Injection

6.2 Incompatibilities

Lidocaine (lignocaine) caused precipitation of amphotericin, methohexitone sodium and sulfadiazine sodium in glucose injection. It is recommended that admixtures of lidocaine (lignocaine) and glyceryl trinitrate should be avoided.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

Store vial in original carton before and after use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

DOBISIM 2 ml: 2 ml, Type I, tubular glass vial with 13 mm grey bromobutyl rubber stopper and 13 mm dark blue flip-off aluminium seal.1 vial or 21 vials in an outer carton.

DOBISIM 5 ml:5 ml, Type I, tubular glass vial with 13 mm grey bromobutyl rubber stopper and 13 mm Raymond blue flip-off aluminium seal.1 vial in an outer carton.

DOBISIM 30 ml:30 ml, Type I, tubular glass vial with 20 mm grey bromobutyl rubber stopper and 20 mm Raymond blue flip-off aluminium seal. 1 vial in an outer carton.

6.6 Special precautions for disposal and other handling

Not applicable

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

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8 REGISTRATION NUMBER(S)

DOBISIM 2 ml: 53/4/0164

DOBISIM 5 ml: 53/4/0165

DOBISIM 30 ml: 53/4/0166

Applicant/PHRC: *Hetero Drugs South Africa (Pty) Ltd*

Product proprietary name: *DOBISIM*

Dosage form and strength: *Injection, Each 2 ml contains 20 mg lidocaine hydrochloride*

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Each 30 ml contains 300 mg lidocaine hydrochloride

9 DATE OF FIRST AUTHORISATION

17 October 2023

10 DATE OF REVISION OF THE TEXT