SCHEDULING STATUS

S1

1. NAME OF THE MEDICINE

Entop Spray (Nasal and Pharyngeal spray)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each actuation (or spray) delivers 5 mg of lidocaine (lignocaine) hydrochloride 5 % *w/v* and 0,5 mg of phenylephrine hydrochloride 0,5 % *w/v*.

Excipient with known effect:

Entop Spray contains benzalkonium chloride solution 0,01 % *w/v*.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nasal and Pharyngeal spray solution.

Entop Spray is a clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Preparation of nasal mucosa for surgery (e.g. Cautery to Little's area) or endoscopy
- Aid the treatment of acute nose bleeds and removal of foreign bodies from the nose
- Topical anaesthesia of the pharynx prior to direct or indirect laryngoscopy
- Topical anaesthesia and local vasoconstriction prior to endoscopy of the upper airways

4.2 Posology and method of administration

Posology

- Do not exceed the recommended dosage regimes
- Do not administer to children under 12 years of age
- Doses are to be administered once only

Adults and children over 12 years:

5 sprays per nostril, or 5 sprays to the throat.

Each spray measures 100 microlitres.

A new spray nozzle must be used for each patient.

Method of administration

Nasal or pharyngeal.

4.3 Contraindications

- Known hypersensitivity to lidocaine hydrochloride, local anaesthetics of the amide type or phenylephrine hydrochloride or to any of the excipients listed in section 6.1
- Hypersensitivity to other local anaesthetics of the amide type and to other sympathomimetic medicines
- Pregnancy and breastfeeding
- Hypovolaemia, hypertension, acute ischaemic heart disease and complete heart block
- Thyrotoxicosis
- Glaucoma
- Urinary retention
- Children under 12 years of age

4.4 Special warnings and precautions for use

- Elderly and debilitated patients should be given reduced dosages.
- Eating and drinking: the use of topical anaesthetic medicines in the oral cavity and upper airway tissues may interfere with swallowing and thus enhance the danger of aspiration of food or drink. For this reason, food or drink should not be ingested within 2 hours of using local anaesthetics in the mouth area. Numbness of the tongue or buccal mucosa may increase the risk of trauma from hot drinks or biting.
- Patients with cardiovascular diseases. Entop Spray should be given with caution to patients with cardiovascular disease, especially those suffering from hypertension, severe bradycardia, conduction disturbances or severe digoxin intoxication.

  There is a small but transient increase in pulse rate (up to 12 beats per minute) and blood pressure (average 8,2 mmHg systolic and 7,5 mmHg diastolic) lasting for 10 minutes after the administration of this medication to healthy individuals. This must be taken into account if this medication is given to hypertensive patients.
- Entop Spray should be administered with caution to taking β-adrenoceptor blocking medicines (see section 4.5) and those with cardiovascular disease, diabetes mellitus, hypertension or hyperthyroidism, hypoxia, hypercapnia and porphyria.
- Patients with impaired kidney or liver function. Lidoocaine is metabolised in the liver and must be given with caution to patients with hepatic insufficiency. Metabolites of lidocaine may accumulate in patients with renal impairment.
- **Asthmatic patients:** This preparation contains Sodium metabisulfite. A sulphite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulphite sensitivity in the general population is unknown and probably low. Sulphite sensitivity is seen more frequently in asthmatic than non-asthmatic people.
- **General precautions:** genetic predisposition to malignant hyperthermia and pre-existing abnormal neurological conditions.
- Entop Spray should be used with caution in patients with traumatised mucosa and/or sepsis in the region of the proposed application.
- Entop Spray should also be used with caution in patients with epilepsy, impaired cardiac conduction, bradycardia, impaired hepatic function and in severe shock.

- The medical practitioner or pharmacist should check that sympathomimetic containing preparations are not simultaneously administered by several routes i.e. orally and topically (nasal, aural and eye preparations).
- Sympathomimetic-containing products should be used with great care in patients suffering from angina pectoris.
- Mydriasis (prolonged dilation of the pupils of the eye) has been reported with phenylephrine. Patients should be advised to notify their medical practitioner if they have a history of glaucoma or a history of increased intraocular pressure.

Entop Spray contains benzalkonium chloride. Long-term use may cause oedema of the nasal mucosa. Benzalkonium chloride may cause wheezing and breathing difficulties (bronchospasm), especially in asthmatic patients. Benzalkonium chloride may cause local irritation.

4.5 Interaction with other medicines and other forms of interaction

Monoamine Oxidase Inhibitors (MAOIs)

Phenylephrine is metabolised by MAOs in the gut. Irreversible MAOIs may therefore increase the effect of oral phenylephrine resulting in a dangerous hypertensive crisis. This effect has not been reported with MAOIs and phenylephrine given by nasal spray. In view of this risk however this product should not be used on patients taking irreversible MAOIs or within three weeks of their discontinuation.

Antihypertensive medicines, anti-dysrythmics and cardiac glycosides (digoxin)

Anti-hypertensive medicines such as β-adrenoceptor blocking medicines may have their effects reversed by the co-administration of phenylephrine, with possible fatal reactions.

Hypertensive reactions have been reported in a patient stabilised on debrisoquine when given phenylephrine by mouth, in patients receiving reserpine or guanethidine when given phenylephrine eye drops, and a fatal reaction occurred in a patient receiving propranolol and hydrochlorothiazide also after the instillation of phenylephrine eye drops.

Products that contain phenylephrine should be used with caution in patients receiving guanethedine, reserpine, digoxin and methyldopa.

Lidocaine may cause an increased risk of myocardial depression: increased risk of lidocaine toxicity with propranolol.

Lidocaine should be used with caution in patients receiving anti-dysrhythmic medicines, such as tocainide, since the toxic effects are additive.

Diuretics

Effects of lidocaine may be antagonised by hypokalaemia with acetazolamide, loop diuretics and thiazide diuretics.

Antidepressants

Sympathomimetic-containing products should be used with great care in patients receiving phenothiazines or tricyclic antidepressants.

Cimetidine

Cimetidine may reduce the clearance of lidocaine (lignocaine) so that patients given these medicines together may show signs of lidocaine toxicity. They should be observed closely.

Muscle relaxants

Lidocaine (lignocaine) prolongs the action of suxamethonium.

Phenylephrine may cause hypertension when used concomitantly with doxapram or oxytocin.

There is an increased risk of ergotism when phenylephrine and ergot alkaloids are taken concomitantly.

Phenytoin

Lidocaine (lignocaine) and phenytoin have additive cardiac depressant effects.

Halogenated anaesthetic medicines

Concurrent use with halogenated anaesthetic medicines such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular dysrhythmias.

4.6 Fertility, pregnancy and lactation

Pregnancy

Entop Spray should not be used during pregnancy (see section 4.3).

Breastfeeding

Entop Spray should not be used by breastfeeding mothers.

4.7 Effects on ability to drive and use machines

Entop Spray has no or neglibible influence on the ability to drive and use machines.

4.8 Undesirable effects

a) Summary of safety profile

The most frequently occurring adverse reaction is a transient bitter taste in the mouth.

Tabulated list of adverse reactions due to the Entop Spray administration

Cardiac disorders	
Less frequent	Palpitations.
Nervous system disorders	
Less frequent	Tremor, nervousness, dizziness, numbness or disorientation.

Vascular disorder	
Frequency unknown	Hypertension.
Gastrointestinal disorders	
Frequent	Transient bitter taste in the mouth lasting one to two minutes and then disappearing.
Less frequent	Nausea, vomiting.
Eye disorders	
Frequency unknown	Mydriasis.
Ear and labyrinth disorders	
Less frequent	Tinnitus.

Local anaesthetics (e.g. lidocaine) and sympathomimetics (e.g. phenylephrine) may produce systemic adverse effects as a result of the raised plasma concentrations which ensue when the rate of absorption into the circulation exceeds the rate of breakdown, for example, by absorption of large amounts through mucous membranes or damaged skin or from highly vascular areas.

Possible systemic side effects due to Lidocaine

The systemic toxicity of local anaesthetics mainly involves the central nervous system and the cardiovascular system. Excitation of the CNS may be manifested by restlessness, excitement, nervousness, dizziness, tinnitus, blurred vision, nausea and vomiting, muscle twitching and tremors and convulsions. Numbness of the tongue and perioral region may appear as an early sign of systemic toxicity. Excitation may be transient and followed by depression with drowsiness, respiratory failure and coma. There may be simultaneous effects on the cardiovascular system with myocardial depression and peripheral vasodilation resulting in hypotension and bradycardia: dysrhythmias and cardiac arrest may occur.

Some local anaesthetics cause methaemoglobinaemia.

Possible systemic side effects due to Phenylephrine

Sympathomimetics may produce a wide range of adverse effects, most of which mimic the results of excessive stimulation of the sympathetic nervous system. These effects are mediated via the various types of adrenergic receptor and the adverse effects of an individual drug depend to some extent upon its relative agonist activity on these different types of receptor at a given dose.

Central effects of sympathomimetic medicines include fear, anxiety, nervousness, restlessness, tremors, insomnia, confusion, irritability, psychotic states and epileptiform convulsions. Appetite may be reduced and nausea and vomiting may occur.

Effects on the cardiovascular system are complex. Stimulation of alpha-adrenergic receptors produced vasoconstriction with resultant hypertension. This vasoconstriction is sometimes sufficiently severe to produce gangrene when sympathomimetics are infiltrated into the digits. The rise of blood pressure may produce cerebral haemorrhage and pulmonary oedema. There may also be a reflex bradycardia but stimulation of β1-adrenergic receptors of the heart may produce tachycardia and cardiac dysrhythmias, angina pectoris, palpitations and cardiac arrest: hypotension with dizziness and fainting and flushing may occur. An increased incidence of sudden death, sometimes attributed to the induction of ventricular dysrhythmias has been associated with the excessive use of sympathomimetic medicines in aerosol form; although the association has been questioned by some authorities, it is important to avoid excessive doses.

Other effects that may occur with sympathomimetic medicines include difficulty in micturition, particularly in the case of prostatic hypertrophy, and urinary retention, dyspnoea, weakness, altered metabolism, sweating, hyperpyrexia and hypersalivation. Headache is also common.

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 asked to report any suspected

adverse reactions to SAHPRA via the "**6.04**

Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/wp-content/uploads/2020/01/6.04 ARF1 v5.1 27Jan2020.pdf

4.9 Overdose

Symptoms of overdosage:

Systemic toxicity is manifested by central nervous system excitation such as restlessness, excitement, blurred vision, nausea and vomiting, muscle twitching and in more severe cases convulsions. Toxicity due to alpha adrenergic over stimulation may result in tachycardia and dysrhythmia.

Treatment:

Consists of insuring adequate ventilation and arresting convulsions with intravenous diazepam if required. Cardiac resuscitation may be required to reverse pathologic dysrhythmias. Injection of a rapidly acting vasodilator.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Lidocaine: Anaesthetics for topical use, ATC code: D04AB01

Phenylephrine: Sympathomimetics excluding antiglaucoma preparations, ATC code: SO1FBO1

Mechanism of action

Phenylephrine hydrochloride

This is a postsynaptic alpha-adrenoceptor stimulant that causes local vasoconstriction. The phenylepherine in Entop Spray constricts the blood vessels locally, which can decrease the systemic absorption of lignocaine and restrict bleeding. It also decreases the onset of action and increases the duration of action of lignocaine. Its nasal decongestant action can assist in easier passage of endoscopes.

Lidocaine (lignocaine) hydrochloride

Lidocaine is a local anaesthetic. It stabilises the neuronal membrane and blocks the initiation and transmission of nerve impulses in sensory nerves by slowing sodium permeability (depolarisation), reducing height and rate of rise of the action potential, increasing excitation threshold, and slowing conduction velocity.

5.2 Pharmacokinetic properties

Lidocaine:

Onset of action is rapid and may last for 1 hour. It does not produce irritation to mucous membranes due to its non-ester structure and it is not detoxified by circulating plasma esterases. The liver is the main site of biotransformation of lidocaine and both free and conjugated forms of the drug are excreted in the urine.

Absorption

Lidocaine is readily absorbed from mucous membranes and through damaged skin.

Absorption through intact skin is poor.

Lidocaine is rapidly absorbed from the upper airway, tracheobronchial tree and alveoli into the bloodstream. It is also well-absorbed from the gastrointestinal tract, but oral bioavailability is only 35 % due to extensive first-pass metabolism. Addition of a vasoconstrictor, e.g. phenylephrine hydrochloride, to the solution reduces the rate of absorption by limiting the local blood flow, and therefore, the local anaesthetic effect is prolonged.

Distribution

Lidocaine has a steady-state volume of distribution (Vss) in the range of 50 - 160 litres.
Systemic bioavailability is only about 40 % following administration, peak plasma concentrations are achieved in 1 - 2 hours. The mean plasma half-life is in the range 2 - 3 hours. Penetration into the brain appears to be minimal.

Biotransformation

The metabolism has been shown to be complex, and different results have been obtained from in vitro and *in vivo* studies. The principal metabolic pathway of lidocaine is oxidative N-deethylation to MEGX, which is further de-ethylated to 2,6-xylidine and glycinexylidide (GX). 2,6-xylidine is hydrolysed to 4-hydroxy-xylidine, which is the major metabolite found in urine. Based on in vitro studies, this hydroxylation is catalysed by CYP2A6. Although 4-hydroxy-xylidine appears to be formed mainly from MEGX, evidence has emerged that some 4-hydroxy-xylidine is formed via direct hydrolysis of lidocaine. A minor metabolic pathway of lidocaine is hydroxylation of the aromatic ring to form 3-OH-lidocaine. All hydroxylated metabolites are prone to subsequent phase II conjugation reactions.

Lidocaine crosses the blood-brain barrier as well as the placental barrier.

Distribution

The volume of distribution is between 200 and 500 L.

Elimination

Lidocaine is eliminated mainly metabolically, with less than 5 % of the dose excreted unchanged in urine. Like the volume of distribution, the clearance of lidocaine varies markedly in healthy volunteers; estimates for plasma clearance range from 0,54 to 1,44 l/min.

Lidocaine is a medicine with a medium to high extraction ratio (0,65), and therefore, its clearance is significantly dependent on liver blood flow. Consequently, an inverse relationship exists between lidocaine levels and estimated hepatic blood flow.

Elimination half-life is usually 1,5 – 2 hours. This can be prolonged significantly in patients with liver disease. Renal dysfunction does not affect lidocaine kinetics but can increase the accumulation of metabolites.

Phenylephrine:

Following topical application phenylephrine is absorbed through the mucosa and topical use can therefore give rise to systemic effects. Phenylephrine is extensively metabolised in the gut wall and the liver. The principal routes of metabolism are sulphonation and glucuronidation, sulphate conjugates are formed from the metabolites. Excretion is via the kidneys.

Distribution

Phenylephrine undergoes rapid distribution into peripheral tissues; it may be stored in certain organ compartments. Pharmacologic effects are terminated at least partially by uptake into tissues.

Penetration into the brain appears to be minimal.

Not known if phenylephrine crosses the placenta.

Does not appear to be distributed to any great extent into breastmilk.

Biotransformation

Phenylephrine undergoes extensive pre-systemic metabolism, with the majority of the metabolism taking place within the enterocytes of the gastrointestinal tract. Phenylephrine is metabolised by Phase I and Phase II enzyme systems, mainly monoamine oxidase and sulfotransferase, respectively. The ratios of the metabolites differ depending on the route of administration.

The metabolism of Phenylephrine after oral and inhalation administration using a gas chromatographic/mass spectrometric ion monitoring method with deuterated internal standards. After oral administration of a dose equivalent to approximately 24 mg of PE to 3 healthy human volunteers, four main metabolites were excreted in urine, reported as percent of dose:

(1) unconjugated m-hydroxymandelic acid (30%)

(2) sulfate conjugate of m-hydroxyphenylglycol,

(3) sulfate conjugate of PE (47%)

(4) glucuronide conjugate of PE (12%).

The amounts of the same metabolites after inhalation of PE were 24, 6, 56 and 5 %, respectively.

Elimination

Undergoes extensive metabolism in the intestinal wall (first-pass) and in the liver.

Principal routes of metabolism involve sulphate conjugation (principally in the intestinal wall) and oxidative deamination (by the enzyme MAO); glucuronidation also occurs to a lesser extent.

It is excreted in urine (80–86 %) mainly as metabolites; unchanged drug accounts for 2,6 or 16 % of an oral or IV dose, respectively.

Half-life

2–3 hours following oral or IV administration. Clinical data regarding effects of renal or hepatic impairment on phenylephrine pharmacokinetics are limited.

5.3 Preclinical safety data

There are no pre-clinical safety data of relevance to the prescriber which are additional to that already included in other sections of the Professional Information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Disodium edetate

Sodium metabisulfite

Sodium phosphate – monobasic (pH adjustment)

Sodium hydroxide (pH adjustment)

Citric acid (pH adjustment)

Water purified

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

Entop Spray is supplied in white 50 ml HDPE bottles with screw on pump, packaged in outer carton made of cardboard.

The Flexi Nozzle for the application is available separately.

The following pack size is proposed:

Bottle: 50 ml white, HDPE bottle

Pump: White screw on pump with dip tube

6.6 Special precautions for disposal and other handling

No special precautions.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Medfour Healthcare CC

31 Burger Street

Baillie Park

Potchefstroom

2531

8. REGISTRATION NUMBER(S)

55/16.3/0512

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 November 2022

10. DATE OF REVISION OF THE TEXT

22 November 2022