Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Enzeze 5mg/0.5mg/actuation anaesthetic spray

(lidocaine hydrochloride and phenylephrine hydrochloride)

PL 28335/0001

MMEU Limited

LAY SUMMARY

Enzeze 5mg/0.5mg/actuation anaesthetic spray

(lidocaine hydrochloride and 0.5 mg of phenylephrine hydrochloride)

This is a summary of the Public Assessment Report (PAR) for Enzeze 5mg/0.5mg/actuation anaesthetic spray. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Enzeze anaesthetic spray in this lay summary for ease of reading.

For practical information about using Enzeze anaesthetic spray, patients should read the package leaflet or contact their doctor or pharmacist.

What is Enzeze anaesthetic spray and what is it used for?
This application is for a medicine that has a well-established use. This means that the use of the active substances in this medicine have been well-established in the European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Enzeze anaesthetic spray is used for the following:

- to numb the inside of the nose or throat before surgery
- to help numb the nose if a foreign body (such as a small bead or any other small object becomes wedged in the nose) needs removing
- to numb the inside of your nose or throat before having a fine telescope passed into your nose or throat to view (laryngoscopy and endoscopy).

How does Enzeze anaesthetic spray work?
Enzeze anaesthetic spray contains a combination of the active substances lidocaine hydrochloride and phenylephrine hydrochloride. Lidocaine hydrochloride belongs to a group of medicines called 'local anaesthetics'. Phenylephrine hydrochloride belongs to a group of medicines called 'sympathomimetics'. Lidocaine hydrochloride works by 'numbing' the area and phenylephrine hydrochloride works by causing the small blood vessels near the surface of the tissue to constrict.

How is Enzeze anaesthetic spray used?
The pharmaceutical form of this medicine is anaesthetic spray and the route of administration is nasal (by nose) or pharyngeal (by the throat).

Enzeze anaesthetic spray will always be given to the patient by a doctor or nurse.

Enzeze anaesthetic spray is for single use only and is to be discarded after first use.

Adults and children over 12 years of age:
The recommended dose is 5 sprays in each nostril or 5 sprays to the throat.
This dose is given once only. The doctor may decide to increase or decrease this dose depending on your condition.

This medicine is not for use in children under the age of 12 years.

For further information on how Enzeze anaesthetic spray is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Enzeze anaesthetic spray have been shown in studies?
As the active substances Enzeze anaesthetic spray have been in clinical use for over 10 years, data were provided in the form of literature references to show that Enzeze anaesthetic spray is a safe and efficacious treatment in the proposed indications (please see the above section 'What is Enzeze anaesthetic spray and what is it used for?')

What are the possible side effects of Enzeze anaesthetic spray?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects include:
Allergic Reactions
Signs of an allergic reaction include swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing, itchy rash, feeling faint and light headed, and collapse.

If the patient notices any of the above reactions they should tell your doctor or nurse immediately.

The most common side effect is a bitter taste in the mouth. This usually lasts for one to two minutes and then disappears. Other common side effects are nausea and vomiting

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

Why was Enzeze anaesthetic spray approved?
It was concluded that the data provided from literature references had shown that Enzeze anaesthetic spray is effective in the treatment of the proposed indications (please see the section 'What is Enzeze anaesthetic spray and what is it used for?' above). Furthermore, use of the active substance lidocaine and phenylephrine in the European Union has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Enzeze anaesthetic spray?
A Risk Management Plan (RMP) has been developed to ensure that Enzeze anaesthetic spray is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored and reviewed continuously.

Other information about Enzeze anaesthetic spray
A Marketing Authorisation for Enzeze anaesthetic spray was granted in the UK on 17 March 2020.

The full PAR for Enzeze anaesthetic spray follows this summary.

This summary was last updated in May 2020.

TABLE OF CONTENTS

Contents

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Enzeze 5mg/0.5mg/actuation anaesthetic spray (PL 28335/0001) could be approved.

The product is approved for the following indications:
- for the preparation of the nasal mucosa for surgery.
- to aid removal of foreign bodies from the nose.
- for topical anaesthesia of the pharynx prior to direct or indirect laryngoscopy.
- for topical anaesthesia and local vasoconstriction prior to endoscopy of the upper airways.

The active substances in Enzeze 5mg/0.5mg/actuation anaesthetic spray are lidocaine hydrochloride and phenylephrine hydrochloride. Lidocaine is a local anaesthetic of the amide type. It is one of the most widely used local anaesthetics and has been in clinical use for over 60 years. Like other anaesthetics lidocaine prevents generation and transmission of impulses along nerve fibres and at nerve endings by slowing depolarisation. This action occurs following blockade of the transient increase in cell membrane permeability to sodium ions that follows initial membrane depolarization and results from the action of lidocaine on the sodium channel. It is believed that lidocaine interacts primarily with voltage-gated sodium channels. Surface or topical anaesthetics block sensory nerve endings in the skin or mucous membranes and many local anaesthetics are effective surface anaesthetics. To be effective, surface anaesthetics need to penetrate the lipoprotein nerve sheath and high lipid solubility confers greater potency, duration of action and speed of onset. Lidocaine is highly lipid soluble and hence penetrates the nerve sheath.

Phenylephrine is a sympathomimetic vasoconstrictor that has been used as a nasal decongestant for many years. It is a relatively selective alpha-adrenergic agonist and the majority of its sympathomimetic action is due to direct stimulation of the adrenoceptors and relatively little is due to an indirect effect via release of noradrenaline. Its pressor effects are weaker but longer lasting than those of noradrenaline. When applied topically phenylephrine constricts blood vessels locally, which can reduce the systemic absorption if lidocaine (thereby increasing its duration of action) and may reduce bleeding. The nasal decongestant effects of phenylephrine can assist the passage of endoscopes.

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, as a well-established use application. Published literature cited in support of the claim for well-established use includes references to an Australian product, Co-phenylcaine Forte Spray (ENT Technologies Australia) and the UK product, which has been available in the UK since 1998, Lidocaine Hydrochloride 5% w/v and Phenylephrine Hydrochloride 0.5% w/v Topical Solution (PL 12064/0027; Aurum Pharmaceuticals UK),a sterile, preservative-free, single-use topical solution containing the same active substances, in the same fixed proportion as the proposed product. Extensive clinical experience with both products supports their efficacy and safety when used as recommended and suggests that the differences in their dosage regimens are unlikely to have serious clinical implications. The active ingredients are also present in other prescription and over-the-counter products and experience with both is extensive.

No new non-clinical or clinical studies were submitted, as the data submitted for this application is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Advice was sought from the Commission of Human Medicines (CHM) on 19 September 2014 and 06-07 December 2018 because major objections were raised with respect to quality (and quality in relation to safety) aspects of the dossier. The Committee provisionally concluded that further information on quality should be requested before the product could be approved. In response to the CHM advice, the applicant provided additional data, and detailed clarification of the points that had been raised. Following consideration of the applicant's responses and further data that were submitted, the approval of the Marketing Authorisation was recommended.

A national marketing authorisation was granted in the UK on 17 March 2020.

II QUALITY ASPECTS

II.1 Introduction

This product consists of 5 mg of lidocaine hydrochloride and 0.5 mg of phenylephrine hydrochloride delivered in each actuation (or spray).

In addition to lidocaine hydrochloride and of phenylephrine hydrochloride, this product also contain the excipients sodium phosphate monobasic, disodium edetate, benzalkonium chloride, sodium hydroxide and citric acid.

The finished product is packaged in 15 ml white high-density polyethylene bottles, each with a white screw on pump. A flexible polypropylene spray nozzle with atomiser is included in each pack. Each bottle contains 4.9 ml of solution.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

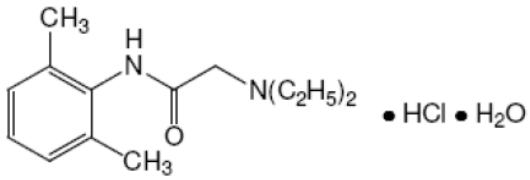
II.2 ACTIVE SUBSTANCES

rINN: Lidocaine hydrochloride

Chemical Name: 2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide, monohydrochloride, monohydrate 2-dithylamino-2',6'-acetoxylidide, monohydrochloride, monohydrate

Molecular Formula: $C_{14}H_{22}N_2O.HCl.H_2O$

Chemical Structure:



Molecular Weight: 288.8 g/mol

Appearance: Lidocaine is a white or almost white, crystalline powder.

Lidocaine is the subject of a European Pharmacopoeia monograph.

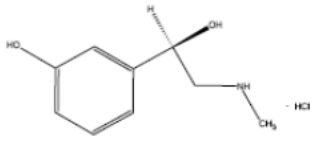
All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

rINN: Phenylephrine Hydrochloride

Chemical Name: (S)-1-(3-Hydroxyphenyl)-2-methylaminoethanol hydrochloride

Molecular Formula: $C_9H_{14}ClNO_2$

Chemical Structure:



Molecular Weight: 203.7 g/mol

Appearance: Phenylephrine is a white, crystalline powder, freely soluble in water and in alcohol.

Phenylephrine hydrochloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a EDQM Certificate of Suitability.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

The applicant has provided appropriate bridging data, including dissolution profile comparisons with suitable marketed products and comparative evaluation of formulations in terms of their excipients.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.
This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specifications is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions ‘Do not store above 30°C. Store in original container in order to protect from light. Do not refrigerate or freeze,’ is acceptable.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application was submitted under Article 10a of Directive 2001/83/EC, as amended, a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. In addition to information on the individual active substances, the non-clinical overview briefly addresses available literature describing the pharmacology, pharmacokinetics and toxicology of the combination.

The literature review provided is satisfactory.

III.2 Pharmacology

No new pharmacology data were submitted, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were submitted, and none were required for this application.

III.4 Toxicology
No new toxicology data were submitted, and none were required for this applications.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing active substances of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
Published literature references have been provided to demonstrate well-established use of the lidocaine/phenylephrine fixed combination for the proposed indications. The literature review provided is satisfactory. Based on quality data submitted by the applicant, the proposed product is considered comparable with the bibliography, hence no clinical bridging studies were submitted or required.

IV. 2 Pharmacokinetics
No new pharmacokinetic data have been submitted for this application, and none were required. The applicant has presented an overview of the pharmacokinetic characteristics of the two active substances, based on bibliographic data. A summary is provided below:

Lidocaine hydrochloride

Absorption

Lidocaine is readily absorbed from mucous membranes and through damaged skin. Absorption through intact skin is poor (2009). Lidocaine is rapidly absorbed from the upper airway, tracheobronchial tree and alveoli into the bloodstream (1981). It is also well-absorbed from the gastrointestinal tract, but oral bioavailability is only 35% due to extensive first-pass metabolism (1971). When injected into tissues, lidocaine is rapidly absorbed. The absorption rate is related to vascularity and the presence of tissue and fat capable of binding lidocaine of the particular tissues. Thus, the absorption rate from the site of injection decreases in the order intercostal > paracervical > lumbar epidural > brachial > spinal > subcutaneous (1979, 2006). Addition of a vasoconstrictor, e.g. epinephrine, to the solution reduces the rate of absorption by limiting the local blood flow, and therefore, the local anaesthetic effect is prolonged.

Distribution

When lidocaine is administered intravenously, it is rapidly distributed into highly perfused tissues, which achieve fast equilibration, followed by redistribution into skeletal muscle and adipose tissue, which reach equilibration slower. Thus, lidocaine plasma concentrations decline rapidly after an intravenous dose, with an initial half-life of less than 30 min. The elimination half-life (t½) is 1-2 h. The t½ may be prolonged if lidocaine is administered with an infusion lasting longer than 24 h, or if hepatic blood flow is reduced. Lidocaine has a steady-state volume of distribution (Vss) in the range of 50-160 litres (1978).

Elimination

Lidocaine is eliminated mainly metabolically, with less than 5% of the dose excreted unchanged in urine (1979). 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 drug with a medium to high extraction ratio (0.65), and therefore, its clearance is significantly dependent on liver blood flow (1978). Consequently, an inverse relationship exists between lidocaine levels and estimated hepatic blood flow (1971).

The metabolism of lidocaine has been thoroughly investigated since the drug entered the market more than half a century ago. However, 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-de-ethylation 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 (1972, 1979). Based on *in vitro* studies, this hydroxylation is formed mainly from MEGX, evidence has emerged that some 4-hydroxy-xylidine is formed via direct hydrolysis of lidocaine (1974). A minor metabolic pathway of lidocaine is hydroxylation of the aromatic ring to form 3-OH-lidocaine (1980). All hydroxylated metabolites are prone to subsequent phase II conjugation reactions (1999).

Earlier *in vitro* studies with human liver microsomes suggested that the formation of MEGX and 3-OH-lidocaine is catalysed mainly by CYP3A4 and CYP1A2, respectively (1989; 1990). Therefore, lidocaine was initially considered to be a probe for *in vivo* assessment of CYP3A4 activity (1994).

In a recent review article, lidocaine is still presented as a model substrate of CYP3A4 (2008b). Accordingly, the MEGX test, which measures the formation of MEGX following an intravenous bolus of lidocaine, has been used as a marker to evaluate the *in vivo* activity of hepatic CYP3A4 and as a dynamic test of liver function (1998; 2007). However, recent *in vitro* studies (1999a, 2000) confirm that both CYP3A4 and CYP1A2 are important in the metabolism of lidocaine, but their relative roles can differ at different lidocaine concentrations. There is also some evidence that CYP2C9 can catalyse the formation of MEGX, but its role seems to be negligible (2000, 2005). CYP1A2 appears to be the major enzyme catalysing the formation of both MEGX and 3-OH-lidocaine at therapeutically relevant plasma lidocaine concentrations. Some evidence has emerged of extrahepatic formation of MEGX. After lidocaine injection, formation of MEGX was demonstrated in a patient in unhepatic phase waiting for a liver transplant (1992).

Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage and conjugation. The pharmacological action of the metabolites are similar to but not less potent than those of lidocaine itself. About 90% of lidocaine is excreted in the form of metabolites and less than 10% excreted unchanged.

Plasma binding of lidocaine is dependent on the drug concentration, the fraction bound decreases with increasing concentration. At concentration of 1-4 micrograms free base/mL, 60 – 80% of the lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1- acid glycoprotein.

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

Absorption from wound surfaces and mucous membranes is relatively high, especially in the bronchi. Accordingly, application to these surfaces should be with caution in the event of mucosal wounds and infection. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 5 microgram free base/mL.

Bioavailability of lignocaine
Lignocaine has a rapid onset of action, usually 5-15 minutes after infiltration or 1-5 minutes after topical mucosal application. Its mucosal effects last about 15-30 minutes.
References for the bioavailability of lignocaine from nasal application are few in number. A published study (1989) included the following:

Six healthy males participated in a single-dose two-way crossover study of the bioavailability of intranasal vs intravenous administration of lignocaine (lidocaine) hydrochloride. Subjects received a single 100 mg dose of lignocaine HCl intranasally from a gel preparation on one occasion and intravenously by a 3 min infusion on another occasion. Multiple plasma samples drawn during 8 h following each dose were analysed for lignocaine by gas chromatography using nitrogen phosphorous detection. The mean (+/- s.e. mean) peak plasma concentration of lignocaine following intranasal administration was 144 +/- 48 ng ml-1, and the time to peak was 0.92 +/- 0.12 h. The mean AUC values for intranasal and intravenous routes were 421 +/- 121 vs 1616 +/- 30 ng ml-1 h, respectively, and the mean bioavailability of the intranasal formulation (AUC ratio) was 0.26 +/- 0.08. In all subjects, intranasal absorption was less than 50% complete, and bioavailability varied from 0.05 to 0.48 between individuals.

Lignocaine is variably and incompletely absorbed when administered by the intranasal route. The literature (2000,1990, and 1988) report on serum lignocaine levels below the critical 5micrograms/mL despite doses of lignocaine to the upper airways of 8.2mg/Kg, 7-8.5mg/Kg and 4mg/Kg respectively. One of the studies (2000) indicates the variability of absorption from mucous membranes depending on the degree of “moistness” of those tissues. It is noted that the doses recommended to be administered by the proposed drug product are significantly below those given in each of these clinical studies.

Phenylephrine Hydrochloride
Phenylephrine hydrochloride undergoes extensive pre-systemic metabolism, with a majority of the metabolism taking place within the enterocytes of the gastrointestinal tract. Phenylephrine hydrochloride 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. Investigators (1983) measured the metabolism of phenylephrine hydrochloride 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 phenylephrine hydrochloride 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 phenylephrine hydrochloride (47%)
(4) glucuronide conjugate of phenylephrine hydrochloride (12%).

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

In one study (1982), the pharmacokinetics of phenylephrine hydrochloride and its major metabolites were investigated. Approximately 1 mg of 3H-phenylephrine free base was administered as an intravenous (iv) infusion over 12.5 to 20 minutes (mean 0.84 mg ± standard deviation 0.17 mg) and as an oral solution (0.99 ± 0.15 mg) to a small number of

adult volunteers (N = 4 and 10, respectively). Upon intravenous administration, phenylephrine rapidly distributes into the peripheral tissue, which yields a very low plasma concentration. Its distribution volume during steady state (V_{SS}) ranged from 184 to 543 litres, indicating most of the drug was distributed in the peripheral tissue or organs. The calculated oral phenylephrine absolute bioavailability was reported as 38% relative to intravenous dosing but the validity of this value is questionable. The biphasic distribution showed that the drug partitioned into the peripheral tissue or organs upon administration, accounting for extremely low plasma concentration observed for parent phenylephrine relative to its major metabolites. The biphasic distribution of unchanged phenylephrine hydrochloride was confirmed by another study (1993).

Total 3H-activity was measured in the urine and serum. The serum was separated using chromatographic techniques to quantitate parent 3H-phenylephrine, conjugated 3H-phenylephrine and 3H-m-hydroxymandelic acid. The cumulative urinary excretion of 3H-activity, 3H-phenylephrine, conjugated 3H-phenylephrine and 3H-mhydroxymandelic acid after iv administration were reported as percent of dose: 86.3, 16.0, 8.3 and 56.9 respectively; and after oral administration – 79.5, 2.6, 45.7 and 24.2, respectively. The urinary recovery data showed that the administered dose of phenylephrine is well absorbed and approximately 80 percent of the dose was recovered.

An in-depth investigation of the pharmacokinetics of phenylephrine hydrochloride and its metabolites was reported (1993). The author reported that, after oral administration of Comhist tablets containing 10 mg or 20 mg of phenylephrine hydrochloride, the plasma concentrations of parent-phenylephrine hydrochloride were below the limit of quantitation (2 ng/ml) and the concentrations of m-hydroxymandelic acid were not detectable for the 10 mg dose. M-hydroxymandelic acid is not extensively conjugated, whereas m-hydroxyphenylglycol is extensively conjugated. The plasma concentrations of phenylephrine conjugates were the highest, followed by m-hydroxymandelic acid, m-hydroxyphenylglycol conjugates and m-hydroxyphenylglycol.

Bioavailability
Phenylephrine is completely absorbed following oral administration and undergoes extensive first-pass metabolism in the intestinal wall.

Bioavailability following oral administration is approximately 38% relative to intravenous administration, but because of extensive first-pass metabolism, considerable inter-individual and possibly intra-individual variation in oral bioavailability exists.

Peak serum concentrations occur at 0.75–2 hours following oral administration of 1mg - 7.8mg dose.

Onset of action
Intravenous administration: Pressor effect occurs almost immediately.
Intramuscular administration: Pressor effect occurs within 10–15 minutes.
Oral administration: Nasal decongestion may occur within 15 or 20 minutes.

Duration of action
Intravenous administration: Pressor effect persists for 15–20 minutes.
Intramuscular administration: Pressor effect persists for 30 minutes to 1–2 hours.
Oral administration: Nasal decongestion may persist for 2–4 hours.

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. It is not known whether

phenylephrine crosses the placenta. Phenylephrine does not appear to be distributed to any significant extent into breast milk.

Elimination
Phenylephrine undergoes extensive metabolism in the intestinal wall (first-pass) and in the liver.

Principal routes of metabolism involve sulfate 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 intravenous dose, respectively.

Half-life
The half-life of phenylephrine hydrochloride is 2–3 hours following oral or intravenous administration.

Clinical data regarding effects of renal or hepatic impairment on phenylephrine pharmacokinetics are limited.

Because of extensive first-pass metabolism in the intestinal wall, hepatic impairment is unlikely to result in major changes following oral administration; however, phenylephrine pharmacokinetics may be substantially altered following intravenous administration.

IV.3 Pharmacodynamics
A summary of the main conclusions from the pharmacodynamic literature review is provided below.

Lidocaine is a local anaesthetic of the amide type. It is one of the most widely used local anaesthetics and has been in clinical use for over 60 years. Like other anaesthetics lidocaine prevents generation and transmission of impulses along nerve fibres and at nerve endings by slowing depolarisation. This action occurs following blockade of the transient increase in cell membrane permeability to sodium ions that follows initial membrane depolarization and results from the action of lidocaine on the sodium channel. It is believed that lidocaine interacts primarily with voltage-gated sodium channels. Surface or topical anaesthetics block sensory nerve endings in the skin or mucous membranes and many local anaesthetics are effective surface anaesthetics. To be effective, surface anaesthetics need to penetrate the lipoprotein nerve sheath and high lipid solubility confers greater potency, duration of action and speed of onset. Lidocaine is highly lipid soluble and hence penetrates the nerve sheath; its high lipid solubility also means that it crosses the placenta and blood brain barrier and is distributed into breast milk. The intrinsic vasoactivity of local anaesthetics can influence the rate of removal of the drug from the site of action and hence influence the duration of action. Ester-type anaesthetics such as procaine are more likely to produce vasodilatation than amide-type agents such as lidocaine. The duration of activity of local anaesthetics may be increased by the addition of a vasoconstrictor such as adrenaline or phenylephrine to slow the rate of drug removal from its intended site of action.

Lidocaine has effects on the central nervous system and can produce restlessness, tremor, dizziness, tinnitus, blurred vision and convulsions. Central nervous system excitation may be transient and can be followed by depression with drowsiness, respiratory failure and coma. Lidocaine has cardiovascular effects causing myocardial depression and peripheral vasodilatation resulting in hypotension and bradycardia, arrhythmias and cardiac arrest may occur. Adherence to recommended doses is important to avoid systemic effects.

Phenylephrine is a sympathomimetic vasoconstrictor. It is a relatively selective alpha-adrenergic agonist and the majority of its sympathomimetic action is due to direct stimulation of the adrenoceptors and relatively little is due to an indirect effect via release of noradrenaline. Its pressor effects are weaker but longer lasting than those of noradrenaline.

At therapeutic doses it does not cause significant stimulation of the central nervous system or cardiovascular effects.

At higher doses phenylephrine can cause increased blood pressure accompanied by reflex bradycardia, an effect that can be antagonised by atropine. Cardiac output is slightly decreased but there is a marked fall in blood flow to the renal, cutaneous, splanchnic and skeletal vascular beds. However, coronary blood flow is increased, as is pulmonary arterial pressure. When applied topically phenylephrine constricts blood vessels locally, which can reduce the systemic absorption if lidocaine (thereby increasing its duration of action) and may reduce bleeding. The nasal decongestant effects of phenylephrine can assist the passage of endoscopes.

IV.4 Clinical efficacy

The applicant has presented an overview of the efficacy of lidocaine and phenylephrine:

The use of the combination of lidocaine/phenylephrine is well established for preparation of the nasal mucosa for surgery, endoscopy and laryngoscopy and the applicant has presented submitted adequate evidence from published literature to support these indications.

A summary of the data provided in the clinical overview is provided below:

Some of the studies discussed below allowed 10 minutes between drug administration and the procedure, some allowed less time and some did not record the time allowed. The doses of cophenylcaine used in the studies also varied. The licensed adult dose (in Australia) of Cophenylcaine Forte nasal spray is up to 5 sprays per nostril and for the Aurum product it is up to 4 sprays per nostril. Because of differences in the volume of solution per actuation, this corresponds to doses of 50mg lidocaine and 5mg phenylephrine for Cophenylcaine Forte nasal spray and 52mg lidocaine and 5.2mg phenylephrine for the Aurum product. In some of the studies only 40% of the manufacturers' recommended doses were given.

A study was conducted to determine the optimal timing of cophenylcaine administration before rigid nasendoscopy. The study showed that both the anaesthetic and decongestant effects of cophenylcaine are maximal 10 minutes after administration.

A study compared nasal cocaine with phenylephrine or with phenylephrine and lidocaine for minimising hypertension, tachycardia and epistaxis in patients undergoing blind nasotracheal intubation (1984). Ninety-nine patients participated in this randomised controlled double blind study. The aim was to determine the haemodynamic effects of successful blind nasotracheal intubation after the use of either 4% cocaine, a mixture of 3% lidocaine in 0.25% phenylephrine or 0.25% phenylephrine alone. If blind nasotracheal intubation was not accomplished within 30 seconds, laryngoscopy was used and the patients' haemodynamic data was excluded from the analysis. Successful blind nasal intubation was achieved in 75 of the 99 patients. There was no significant difference between the treatment groups regarding the number of patients requiring laryngoscopy, neither was there any significant difference in the incidence and severity of epistaxis. The results of the study indicate that increases in mean arterial pressure and heart rate during the 5 minutes after intubation are significantly less in patients receiving phenylephrine and lidocaine than they are in those receiving cocaine or phenylephrine alone. The authors suggest that the superiority of lidocaine with phenylephrine compared to phenylephrine alone was probably related to the lack of topical anaesthetic in the patients receiving phenylephrine alone. They consider that the superiority of the combination to cocaine may be related to the central and peripheral sympathomimetic properties of cocaine. Although the peak increases in mean arterial pressure were essentially the same for patients receiving cocaine and phenylephrine with lidocaine, the values remained elevated for a longer time in patients receiving cocaine, resulting in higher mean levels during the 5 minutes after intubation. The quantities of lidocaine and phenylephrine used in this study are lower than those found in cophenylcaine.

A small randomised, double-blind study compared the effect of cocaine and phenylephrine combined with lidocaine on nasal patency (1986). Twelve adult volunteers were studied. Each subject received 4% lidocaine plus 0.5% phenylephrine or 5% cocaine solution intranasally; they received the other solution 48 hours later. The sprays were administered to each nostril using a manual atomizer and patients received a total of 30 mg cocaine or 24 mg of lidocaine plus 3mg of phenylephrine. On each day baseline tests of nasal resistance and transnasal peak expiratory flow were conducted. The same tests were repeated 5 minutes after drug administration. Binasal resistance decreased significantly and transnasal peak expiratory flow rates increased significantly after both study solutions. The changes observed were of a similar magnitude for both solutions. The authors recommended that lidocaine/phenylephrine solution be used instead of cocaine as an aid to nasotracheal intubation. The doses of lidocaine and phenylephrine used in this study were lower than those obtained when using the maximum recommended dose of Cophenylcaine Forte nasal spray.

A randomised controlled trial compared cophenylcaine to placebo (2002). The aim of the study was to assess the need for topical nasal anaesthesia before flexible nasendoscopy. Ninety patients were randomised to one of three groups and received two sprays of cophenylcaine into each nostril, placebo spray or no nasal preparation. Ten minutes was allowed to let the test preparation take effect and then the nasendoscopy was performed using lubricating gel on the tip of the nasendoscope. After completion of the procedure the patient and doctor filled in a questionnaire. There was no significant difference between the groups regarding pain and overall discomfort. Also, there was no significant effect on the quality of view or ease of examination from the operator's point of view. There was a correlation between anxiety and the main outcomes measures with more anxious patients giving higher scores for pain and overall unpleasantness. There was also a correlation between higher pain and unpleasantness scores with poorer scores for ease of examination and quality of view. The authors of this study concluded that routine use of topical nasal preparations before flexible nasendoscopy could be discontinued, as it offers no significant advantage. The dose of cophenylcaine employed in this study was low.

In two other studies published in 2002, cophenylcaine was compared to cocaine prior to flexible and rigid nasendoscopy. One of the conducted studies was a two-part study. The investigators first assessed the decongestant and anaesthetic efficacy of cophenylcaine in 25 healthy volunteers and then they compared cophenylcaine to cocaine in 84 patients undergoing flexible transnasal fibrescopic endoscopy of the nasal cavity, pharynx and larynx. In the first part of the study a painful sensation was induced in the nostril by probing the mucosa overlying the inferior turbinate with a ring-ended Jobson-Horne probe. The discomfort produced was recorded by each subject on a visual analogue scale. Three sprays of cophenylcaine were then instilled into the nasal cavity and the pain sensation was retested 3, 6, 9 and 12 minutes after the spray had been used. The decongestant effects of cophenylcaine were assessed by comparing nasal inspiratory peak flow and acoustic rhinometry before and after using the spray. Pulse rate, systolic and diastolic blood pressure were measured before and 1, 2, 5, 10, 15 and 30 minutes after using the spray to monitor any potential cardiovascular effects. The pain scores confirmed a significant local anaesthetic effect that was maximal after 9 minutes. There was also a significant decongestant effect. There was no significant alteration in pulse rate or systolic pressure throughout the study, a slight reduction in systolic pressure was noted in the first 4 minutes. In the second part of the study, patients were randomly allocated to one of two groups and received 3 sprays of either cophenylcaine or 10% cocaine. Nasal inspiratory peak flow was measured at baseline and 5 minutes after administration of the spray. Upper respiratory tract transnasal endoscopy was then performed. Patients scored the discomfort of the procedure using a visual analogue scale as before. Subjects were asked to describe the taste of the spray. Pulse and blood pressure were recorded at baseline and again 1, 2, 5, 10, 15 and 20 minutes after the spray was administered. Both test solutions produced statistically significant increases in nasal inspiratory peak flow indicating that they are effective

decongestants. There was no significant difference between the treatments in terms of decongestion. Patients in both treatment groups rated discomfort associated with the procedure between 0 and 5 on the visual analogue scale and there was no significant difference between the groups. Despite the use of a higher strength of cocaine in this study the anaesthesia obtained was equivalent to cophenylcaine. The cocaine spray was considered less palatable than the cophenylcaine spray. As with the first part of the study there was a slight reduction in systolic blood pressure in both groups but no change in diastolic blood pressure. The reduction in systolic pressure was associated with a slight reduction in pulse rate in the cophenylcaine group but not in the cocaine treatment group. The authors concluded that cophenylcaine is a safe, effective and more palatable alternative to cocaine.

In the other study, cophenylcaine was compared to 10% cocaine in patients undergoing rigid nasendoscopy. It is recognised that rigid nasendoscopy is a more uncomfortable procedure than flexible nasendoscopy. Thirty-three patients were included in this study and as one nostril was treated with cophenylcaine and one with cocaine, each patient served as their own control. The endoscopist was unaware which nostril had been prepared with which agent. Ten minutes after drug administration the nasendoscopy was conducted and the view of the nasal passages was recorded. After the procedure, the patients were asked to record the pain they experienced using a visual analogue scale. There was no significant difference between the test solutions in terms of nasal analgesia or vasoconstriction despite only two sprays of cophenylcaine being compared to 10% cocaine.

In a further comparison between cocaine and cophenylcaine, a study investigated 25 healthy volunteers undergoing nasal intubation. The volunteers received either cocaine 5% or cophenylcaine on their first visit and then the other agent on their second visit two weeks later. Randomisation was double blind. Nasendoscopy was performed to assess the most favourable nostril for airway insertion. Pain ratings were recorded using visual analogue scores and verbal responses. Pain scores were higher for the larger nasotracheal tube sizes, but there was no significant difference between the 7 mm and 6.5mm tubes or between the two drugs, although there was a trend in favour of cophenylcaine. Interestingly neither drug provided reliable analgesia in this study with pain scores at the upper limit of acceptability. The authors state that higher doses of cophenylcaine might result in improved analgesia, however, the doses used in this study correspond to the maximum licensed dose and are the same as has been used in other studies where there was an adequate anaesthetic response. In this study the time between drug administration and intervention is not specified but only 5 minutes was allowed before nasal patency was assessed and it may be that insufficient time was allowed for the drug to be effective, in other studies it was found that it takes 10 minutes for the drug to be maximally effective.

In contrast to the above study comparing the efficacy of cocaine and cophenylcaine, a placebo-controlled study found that flexible nasendoscopy was associated with minimal pain and discomfort. The investigators found no significant difference between pain and overall discomfort in 98 patients who were randomised to receive cophenylcaine or placebo nasal spray before the procedure. The sensation of bad taste was significantly worse in the cophenylcaine group and the results led the authors to conclude that routine use of cophenylcaine prior to flexible nasendoscopy is not justified. It is noted that at a low dose of cophenylcaine was used in this study: two sprays per nostril were administered compared to the maximum licensed dose of 5 sprays.

A study comparing cophenylcaine and lidocaine sprays in 30 patients requiring rigid nasendoscopy found that either drug allowed the procedure to be performed with minimal discomfort but that only cophenylcaine increased the ease of passage of the endoscope and improved the quality of view obtained by the endoscopist.

Cophenylcaine has also been compared to xylometazoline in patients undergoing rigid nasendoscopy. A prospective, double-blind randomised trial was conducted in 73 patients.

Patients received the study medication, either two sprays of cophenylcaine or xylometazoline into each nostril 10 minutes prior to the endoscopy. After the procedure the patients and the endoscopist completed questionnaires relating to discomfort and ease of examination. Cophenylcaine was found to be marginally better than xylometazoline but the difference was not statistically significant. It is noted that the study employed a low dose of cophenylcaine and a higher than recommended dose of xylometazoline.

One study compared cophenylcaine spray to lidocaine and epinephrine nasal packing prior to flexible laryngoscopy. Eighty-one patients were included in the study and the surgeon decided if the patients would receive 5 sprays of cophenylcaine or lidocaine/epinephrine nasal packing, generally cophenylcaine was used during the first two months of the study and packing during the final two months. After at least 10 minutes the nasal packing was removed and the procedure performed. The patients recorded unpleasantness of the nasal preparation and the procedure and the surgeon reported degree of decongestion and ease of endoscope passage. Bad taste was significantly worse with cophenylcaine but there was no statistically significant difference between the treatments in terms of pain, anxiety, gagging or overall unpleasantness. There was also no significant difference between the treatments in terms of degree of decongestion or ease of endoscope passage. The authors acknowledge the inherent bias in this study, which was non-blinded and non-randomised. They concluded that lidocaine/epinephrine packing is preferable to cophenylcaine spray based on cost.

A systematic review and meta-analysis was conducted to assess the effectiveness of local anaesthetic, vasoconstrictive and lubricating agents in flexible fibreoptic nasolaryngoscopy (2008). Eight randomised controlled trials were included in the analysis. Five of the eight studies included involved the use of cophenylcaine. The authors concluded that there was no significant difference between cophenylcaine and cocaine. Based on the finding that cophenylcaine offered no advantage over saline or no treatment, the overall conclusion was that the benefit of cophenylcaine in flexible fibreoptic nasolaryngoscopy is minimal. However, flexible nasendoscopy may only be associated with minimal pain and discomfort and this could account for the apparent lack of efficacy of cophenylcaine in relieving pain in comparison with placebo. Furthermore, the doses of cophenylcaine tested in this indication were only 40% of the dose proposed in this application. It is of note that the two studies in this review that compared cophenylcaine to normal saline or no treatment were the studies discussed above used low doses of cophenylcaine.

A patient satisfaction survey involving 39 patients undergoing laser turbinectomy in an outpatient setting was conducted. Each nostril was sprayed with 1.5ml cophenylcaine solution 10 minutes before the turbinectomy was performed. Patients were observed for 30 minutes and then followed up by telephone after four days, two, four and six weeks and six months. During the procedure, 69% of patients reported mild or no pain, 26% reported moderate pain and 5% reported severe pain. The pain score was zero throughout the follow-up period. 83% of the patients felt that they would have the procedure again if necessary. The authors concluded that patient satisfaction for having the procedure under topical local anaesthesia with cophenylcaine was very high.

IV.5 Clinical safety

Cophenylcaine products were well tolerated in the studies reviewed above in Section IV.4, Clinical Efficacy and, in most cases, no side effects were reported. The most consistent comment regarding tolerability was that some patients report an unpleasant taste associated with the preparation. Some of the studies investigated the potential cardiovascular effects of cophenylcaine and found no significant effect on heart rate and systolic or diastolic blood pressure, there was one report of self-limiting bradycardia (<50 beats/minute) which occurred in one patient following nasal intubation with both cocaine and cophenylcaine.

One author reported a case of ventricular arrhythmias in an 8-year-old boy following administration of 5 drops of phenylephrine in a 10% ophthalmic solution (a concentration of

100mg/ml) for excessive bleeding. The patient was given intravenous atropine without effect but reverted to sinus rhythm following administration of intravenous lidocaine. The surgery resumed and the patient's recovery was uneventful. The author points out that the dose of phenylephrine given to this patient represented an overdose. The concentration of phenylephrine in this preparation is 20 times greater than in Cophenylcaine Forte nasal spray.

As with all sympathomimetic nasal decongestants, phenylephrine has the potential to cause hypertension and hypertensive crisis. However, such reports are rare and tend to involve inappropriate use. Studies in normal subjects have shown that oral doses of 50 mg of phenylephrine are required to elicit an increase in blood pressure and doses in excess of 120mg are required to elicit a significant effect on blood pressure. Following the use of Cophenylcaine Forte nasal spray at the maximum recommended dose of 5 sprays per nostril, patients would receive a dose of phenylephrine of 5 mg, significantly less than the doses required to elicit effects on blood pressure. The studies reviewed above confirm that the use of cophenylcaine nasal spray is not associated with increases in blood pressure in normal clinical use.

The most common toxicity associated with lidocaine is CNS toxicity and this can be seen following topical use. The recommended maximum adult dose of lidocaine for local anaesthesia in the UK is 200 mg but maximum doses of up to 400 mg have been suggested in some sources. It is recommended that certain precautions are taken to reduce the risk of rapid systemic absorption, these precautions include avoiding use in the presence of sepsis or severely traumatised mucosa in the area of application and avoiding delivery of the product to the lower respiratory tract where absorption is much more rapid than in the laryngotrachea. Topical administration in usual clinical practice results in plasma levels far below the toxic range and is therefore usually safe. The risk of adverse effects is further reduced by the inclusion of phenylephrine in the formulation as the resulting vasoconstriction slows the rate of systemic absorption.

There have been reports in the published literature of the ability of decongestants, including phenylephrine, to cause mydriasis. This is of particular relevance for ENT surgeons during sinus surgery. It is routine practice to examine the eye repeatedly during sinus surgery as a dilated pupil may signal intraorbital injury. Authors report a case report of unilateral pupillary dilatation in a patient undergoing nasal polypectomy under general anaesthesia, which may have been due to accidental spillage of lidocaine and phenylephrine solution into the patient's eye (2009). The patient's vision and pupil returned to normal after 4 hours and he was discharged home the following day without complications. There is also a published report of unilateral mydriasis in a 74-year old woman following the use of cophenylcaine spray for bronchoscopic tracheal intubation and induction of general anaesthesia (1994).

Safety profile of benzalkonium chloride
The inclusion of benzalkonium chloride as an excipient in the proposed product is discussed. Benzalkonium chloride is a preservative and for most multiuse aqueous nasal and ophthalmic products it is considered the preservative of choice. It has been in clinical use since 1935 and is contained in a variety of prescription and over-the-counter medicinal products.

Concerns have been raised over the years regarding the use of benzalkonium chloride and there have been reports in the literature of studies demonstrating toxicity to nasal cells *in vitro.* However, safety reviews and efficacy studies have demonstrated the superiority of benzalkonium chloride to other preservatives. There are no grounds for concern regarding the inclusion of benzalkonium chloride in this preparation.

IV.6 Risk Management Plan (RMP)

A suitable justification has been provided for non-submission of a RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. This bibliographic application is for

a well-established use product that has been marketed in Australia for many years and is similar to a product which has been available for many years in the UK. A safety concern requiring additional risk minimisation activities has not been identified with any of these products.

As this product does not fit into any of the categories requiring submission of a detailed description of risk management system. The applicant has provided an assurance to provide a RMP if a safety concern is identified with the medicinal product at any stage of its life. This is acceptable.

IV.7 Discussion on the clinical aspects

The published literature cited in the clinical overview involves investigations of many different topical formulations of lidocaine and phenylephrine, including (but not limited to) the UK product and the Cophenylcaine Forte nasal spray on which the proposed product is based. Assessment or comparison of the results is hampered by the wide variety of concentrations and doses of the active substances tested (or, in some cases, a lack of information about the formulation or doses used), poor study design, small-scale studies, inadequate intervals between dosing and efficacy assessments and the difficulty of evaluating efficacy from procedures associated with different levels of pain and discomfort. Nevertheless, the results do provide evidence of the anaesthetic and vasoconstrictive effects of a combination of lidocaine and phenylephrine at a variety of concentrations and doses, particularly those proposed in this application. The evidence from these studies (together with experience from clinical practice) supports the proposed dosage regimen and the assertion that small differences in the quantity of cophenylcaine delivered from the proposed product or reference product would not have a clinically significant effect on efficacy or safety.

The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to Co-phenylcaine Nasal Spray (MMEU Ltd)]. The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified from the literature. Extensive clinical experience with lidocaine hydrochloride and phenylephrine hydrochloride is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with Directive 2012/84/EU, the current approved UK version of the SmPC and PIL for this product are available on the MHRA website.

The following text is the currently approved label text. No label mock-ups have been provided for this product. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Label

1. NAME OF THE MEDICINAL PRODUCT

Enzeze 5mg/0.5mg/actuation anaesthetic spray
(lidocaine hydrochloride and phenylephrine hydrochloride)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each spray delivers lidocaine hydrochloride (5mg) and phenylephrine hydrochloride (0.5mg).

3. LIST OF EXCIPIENTS

Also contains: benzalkonium chloride, disodium edetate, sodium phosphate monobasic, sodium hydroxide, citric acid and water.

4. PHARMACEUTICAL FORM AND CONTENTS

ANAESTHETIC SPRAY
NON-STERILE
4.9ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

This product is for use by Healthcare Professionals (HCPs) in a clinical setting.
Route of administration: nasal or pharyngeal.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30˚C. Store in the original container in order to protect from light. Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MMEU Limited
2 Burns Drive
Rotherham
S65 2QH
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 28335/0001

13. BATCH NUMBER

Batch No:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Dosage:

Adults and children over 12 years:
5 sprays per nostril or 5 sprays to the throat depending on the site of activity required.

Each spray delivers 100 microliters.

A Flexi nozzle (short) is supplied in the carton.

16. INFORMATION IN BRAILLE

Not applicable – product only intended for use by healthcare professionals

17. UNIQUE IDENTIFIER – 2D BARCODE

N/A included on outer packaging

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

N/A included on outer packaging

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Enzeze 5mg/0.5mg/actuation anaesthetic spray
(lidocaine hydrochloride and phenylephrine hydrochloride)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each spray delivers lidocaine hydrochloride (5mg) and phenylephrine hydrochloride (0.5mg).

3. LIST OF EXCIPIENTS

Also contains: benzalkonium chloride, disodium edetate, sodium phosphate monobasic, sodium hydroxide, citric acid and water.

4. PHARMACEUTICAL FORM AND CONTENTS

ANAESTHETIC SPRAY
NON-STERILE
4.9ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

This product is for use by Healthcare Professionals (HCPs) in a clinical setting.
Route of administration: nasal or pharyngeal.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Expiry:

9. SPECIAL STORAGE CONDITIONS

Do not store above 30˚C. Store in the original container in order to protect from light. Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

MMEU Limited
2 Burns Drive
Rotherham
S65 2QH
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 28335/0001

13. BATCH NUMBER

Batch No:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Dosage:

Adults and children over 12 years:
5 sprays per nostril or 5 sprays to the throat depending on the site of activity required.

Each spray delivers 100 microliters.

A Flexi nozzle (short) is supplied in the carton.

16. INFORMATION IN BRAILLE

Not applicable – product only intended for use by healthcare professionals

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Human readable data included.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report
(non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**