IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0970/054/001
Case No: 2062869

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

AstraZeneca UK Limited

600 Capability Green, **Luton**, **LU1 3LU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Xylocaine 4%w/v Topical Mucosal Solution

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **01/04/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xylocaine 4% w/v Topical Mucosal Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each millilitre contains lidocaine hydrochloride corresponding to 40 mg lidocaine hydrochloride anhydrous.

Excipients: Each millilitre also contains 1mg methyl parahydroxybenzoate (E218).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Mucosal Solution
A clear, colourless, aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Anaesthesia of mucous membranes of the oropharyngeal, tracheal and bronchial areas e.g. in bronchoscopy, bronchography, laryngoscopy, oesophagoscopy and endotracheal intubation.

Biopsy in the mouth and throat, puncture of the maxillary sinus or polypectomy.
Tonsillectomy, resection of nasal turbinates.
In dentistry.

4.2 Posology and method of administration

As with any local anaesthetic, reactions and complications are best averted by employing the minimal effective dosage. Debilitated, elderly patients and children should be given a lower dosage commensurate with their age and physical condition.

The degree of absorption from mucous membranes is variable but especially high from the bronchial tree. Application only to areas below the vocal cords may result in excessive plasma concentrations because of less transfer to the intestine and less first-pass loss. When inhaled from a nebuliser, the resulting plasma concentrations are lower than following spray applications.

The Xylocaine 4% Topical solution may be applied from a swab, which should be discarded after use. Surface anaesthesia may also be achieved by instillation into a cavity or on to a surface. When spraying, the solution should be transferred from the original container to an atomiser.

The suggested dosage for adults is 1-7.5 ml Xylocaine 4% Topical (= 40-300 mg lidocaine HCl). During prolonged procedures (>5 min) up to 400 mg lidocaine may be administered. In addition, when combined with other lidocaine products, the total dose should not exceed 400 mg. With applications mainly to the larynx, trachea and bronchi, the dose should not exceed 5 ml (200 mg lidocaine hci). When inhaled from a nebuliser, 5-10 ml (200-400 mg lidocaine hci) may be used.

For children, smaller amounts and a lower concentration should be administered depending on their age and weight. In

children less than 12 years the dose should not exceed 3 mg/kg. Higher doses may result in plasma levels which have been associated with toxic manifestations. Concomitant use of lidocaine via other routes should be borne in mind - total dosage in any one session of use should not exceed 3 mg/kg or 200 mg lidocaine base when used without adrenaline.

Biopsy: 3 – 4 ml may be sprayed on the area or the solution may be applied for a few minutes with a swab. Adrenaline may be added to this solution in order to produce vasoconstriction (add 1 - 2 drops, 0.05 ml, 1:1,000, solution to 5 ml Xylocaine 4% Topical).

Puncture of maxillary sinus or polypectomy: A swab soaked in the solution may be applied for two to three minutes. The addition of adrenaline is advised in these procedures, made up as indicated above.

Tonsillectomy, resection of nasal turbinates: For surface anaesthesia, dosage is approximately 1 ml in all.

4.3 Contraindications

Hypersensitivity to local anaesthetics of the amide type, or to any of the excipients.

Hypersensitivity to methyl and/or propyl parahydroxybenzoate (methyl/-/propyl paraben), or to their metabolite para amino benzoic acid (PABA). Formulations of lidocaine containing parabens should be avoided in patients allergic to ester local anaesthetics or their metabolite PABA.

4.4 Special warnings and precautions for use

Absorption from wound surfaces and mucous membranes is relatively high, especially in the bronchial tree. Xylocaine 4% Topical should therefore be used with caution especially in patients with traumatised mucosa and/or inflammation in the region of the proposed application.

If the dose or site of administration is likely to result in high blood levels, lidocaine, in common with other local anaesthetics, should be used with caution in patients with epilepsy, impaired cardiac conduction, bradycardia, impaired hepatic function, severe liver dysfunction and in severe shock. Lidocaine should also be used with caution in the elderly and patients in poor general health.

The use of oral topical anaesthetic agents may interfere with swallowing and thus enhance the danger of aspiration. This is particularly important in children because of their frequency of eating.

Numbness of the tongue or buccal mucosa may increase the danger of biting trauma.

Patients treated with anti-arrhythmic drugs class III (e.g. amiodarone) should be kept under close surveillance and ECG monitoring considered, since cardiac effects may be additive (see also section 4.5).

The use of Xylocaine 4% Topical as a gargle is not indicated. The use of concentrated Xylocaine 4% Topical for gargling increases the risk of systemic toxicity due to overdosing and rapid uptake over the mucosa and/or ingestion.

Xylocaine 4% Topical is probably porphyrinogenic and should only be prescribed to patients with acute porphyria on strong or urgent indications. Appropriate precautions should be taken for all porphyric patients.

Xylocaine 4% Topical contains methyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

Lidocaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. antiarrhythmics such as mexiletine since the toxic effects are additive. Specific interaction studies with lidocaine and antiarrhythmic drugs class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4).

Drugs that reduce the clearance of lidocaine (e.g. cimetidine or beta-blockers) may cause potentially toxic plasma

concentrations when lidocaine is given in repeated high doses over a long time period. Such interactions should therefore be of no clinical importance following short term treatment with lidocaine (e.g. Xylocaine 4% Topical) at recommended doses.

If adrenaline is added to this preparation it should be administered with caution to patients taking certain anti-hypertensive drugs, tricyclic antidepressants, or monoamine oxidase inhibitors, or in thyrotoxicosis. If volatile anaesthetic agents are being administered simultaneously with a local anaesthetic/vasoconstrictor combination, suitable beta-blockers should be immediately available and both hypoxia and hypercapnia should be avoided.

4.6 Pregnancy and lactation

There is no or inadequate evidence of safety of the drug in human pregnancy but it has been in wide use for many years without apparent ill consequence, animal studies have shown no hazard. If drug therapy is needed in pregnancy, this drug can be used if there is no safer alternative.

Lidocaine enters breast milk but in such small quantities that there is generally no risk of affecting the child at therapeutic dose levels.

4.7 Effects on ability to drive and use machines

Depending on the dose, local anaesthetics may have a very mild effect on mental function and may temporarily impair locomotion and co-ordination.

4.8 Undesirable effects

In rare cases (<0.1%) amide-type local anaesthetic preparations have been associated with allergic reactions (in the most severe instances anaphylactic shock). Other constituents of the solution e.g. methyl parahydroxybenzoate, may also cause this type of reaction.

Systemic adverse reactions are rare and may result from high plasma levels due to excessive dosage, rapid absorption or may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system.

CNS reactions are excitatory and/or depressant and may be characterised by nervousness, dizziness, blurred vision and tremors followed by drowsiness, convulsions, unconsciousness and, possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

Cardiovascular reactions are depressant and may be characterised by hypotension, myocardial depression, bradycardia and, possibly, cardiac arrest.

4.9 Overdose

Acute systemic toxicity

Toxic reactions originate mainly in the central nervous system and the cardiovascular system.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis and tinnitus. Visual disturbance and muscular tremors are more serious and precede the onset of generalized convulsions. 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 the increased muscular activity, together with the interference with normal respiration. In severe cases apnoea may occur. Acidosis increases the toxic effects of local anaesthetics.

Cardiovascular effects are only seen in cases with high systemic concentrations. Severe hypotension, bradycardia,

arrhythmia and cardiovascular collapse may be the result in such cases.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as a benzodiazepine or barbiturate.

Recovery is due to redistribution and metabolism of the local anaesthetic drug from the central nervous system. Recovery may be rapid unless large amounts of the drug have been administered.

Treatment of acute toxicity
Should symptoms of systemic toxicity occur, the signs are anticipated to be similar in nature to those following the administration of local anaesthetics by other routes. Local anaesthetic toxicity is manifested by symptoms of nervous system excitation and, in severe cases, central nervous and cardiovascular depression.

Severe neurological symptoms (convulsions, CNS depression) must be treated symptomatically by respiratory support and the administration of anticonvulsive drugs.

If circulatory arrest should occur, immediate cardiopulmonary resuscitation should be instituted. Optimal oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: N01B B02.

The active ingredient in Xylocaine 4% Topical is lidocaine, which provides prompt and profound anaesthesia of mucous membranes. Absorption occurs most rapidly after intratracheal administration. Anaesthesia usually occurs rapidly (within 1-5 minutes depending on the area of application) and lasts for approximately 15-30 minutes. (see also Section 4.2).

Lidocaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

Local anaesthetic drugs may also have similar effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach the systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating from the central nervous and cardiovascular systems.

Central nervous system toxicity (see 'Overdosage') usually precedes the cardiovascular effects since it occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

5.2 Pharmacokinetic properties

Lidocaine is absorbed following topical administration to mucous membranes, its rate and extent of absorption being dependent upon the concentration and total dose administered, the specific site of application, and the duration of exposure. In general, the rate of absorption of local anaesthetic agents following topical applications is most rapid after intratracheal and bronchial administration. Lidocaine is also well-absorbed from the gastrointestinal tract, although little of the intact drug appears in the circulation because of biotransformation in the liver.

The plasma protein binding of lidocaine is dependent on the drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 micrograms of free base per ml, 60 to 80 per cent of lidocaine is protein-bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein.

Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion.

Lidocaine is metabolised rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide. The pharmacological/toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2 6-dimethylaniline.

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolised, any condition that affects liver function may alter lidocaine kinetics. The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites.

Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6 micrograms free base per ml.

5.3 Preclinical safety data

Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. A metabolite of lidocaine, 2,6-xylidine, showed weak evidence of activity in some genotoxicity tests. The metabolite 2,6-xylidine has been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure. Risk assessments comparing the calculated maximum human exposure from intermittent use of lidocaine, with the exposure used in preclinical studies, indicate a wide margin of safety for clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Sodium hydroxide (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Unopened: 3 years
Opened: Use within 3 months

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

Amber glass bottles with tamper-evident aluminium screw caps containing 30 ml of solution.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

AstraZeneca UK Ltd.
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8 MARKETING AUTHORISATION NUMBER

PA 970/54/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

April 2010