PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

[Pr]XYLOCAINE® Ointment 5%

lidocaine ointment

Ointment, 50 mg/g, Topical

USP

Topical anesthetic

Aspen Pharmacare Canada Inc.
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Oakville, ON
L6H 0H2

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RECENT MAJOR LABEL CHANGES
N/A

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

XYLOCAINE Ointment 5% (lidocaine) is indicated for:

- Temporary relief of pain associated with minor burns and abrasions of the skin, e.g. sunburn, herpes zoster and labialis, pruritus, sore nipples, insect bites;
- Anesthesia of mucous membranes, e.g. various anal conditions such as hemorrhoids and fissures;
- The alleviation of pain during examination and instrumentation, e.g. proctoscopy, sigmoidoscopy, cystoscopy, endotracheal intubation.

1.1 Pediatrics

Pediatrics (2-18 years of age): Children should be given reduced doses commensurate with their age; weight and physical condition (see 4.2.1 DOSAGE AND ADMINISTRATION, Special Populations).

Pediatrics (<2 years of age): Lidocaine should be used with caution in children younger than two years of age as there are insufficient data to support the safety and efficacy of this product in this patient population at this time. (see 7.1.3 WARNINGS AND PRECAUTIONS, Special Populations).

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. Elderly patients should be given reduced doses commensurate with their age and physical condition as they may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses and may require dose reductions. (see 4.2.1 DOSAGE AND ADMINISTRATION, Special Populations and 7.1.4 WARNINGS AND PRECAUTIONS, Special Populations).

2 CONTRAINDICATIONS

- Lidocaine is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anesthetics of the amide type or to other components of the ointment (see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Lidocaine is contraindicated in patients with congenital or idiopathic methemoglobinemia.
- Lidocaine is contraindicated in infants who require treatment with methemoglobin-inducing agents, e.g., sulfonamides and are 12 months of age or younger (see 9 DRUG INTERACTIONS).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

When XYLOCAINE Ointment 5% (lidocaine) is used concomitantly with other products containing

lidocaine, the total dose contributed by all formulations must be kept in mind.

4.2 Recommended Dose and Dosage Adjustment

Maximum Dosage

Adults
No more than 2 g (100 mg lidocaine base) in a single dose for endotracheal intubation.
No more than 10 g (500 mg lidocaine base) in a single dose for other indications.

After a maximum endotracheal dose or application to mucous membranes the next dose should not be applied until 4 hours later. After a maximal dose given rectally or to burns the minimum dosing interval should be 8 hours.

The total maximum dose administered in a 24-hour period to healthy adults should not exceed 20 g (1000 mg lidocaine base).

Children

XYLOCAINE Ointment 5% should be used with caution in children under the age of 2 as there is insufficient data to support the safety and efficacy of this product in this patient population at this time.

Children should be closely observed during and after use of topical anesthetics, as they are at greater risk than adults for serious adverse events (e.g., methemoglobinemia).

- **2-11 Years**

It is difficult to recommend a maximum dose of any drug for children since this varies as a function of age and weight. Hence, for safety reasons, in children less than 12 years of age 100% bioavailability should be assumed following application to mucous membranes and broken skin, and the maximum amount of XYLOCAINE Ointment 5% administered to children should not exceed 0.1 g ointment/kg body weight (corresponding to 5 mg lidocaine/kg of body weight). The minimum dosing interval in children should be 8 hours.

- **12-18 Years**

For children over 12 years of age doses should be commensurate with weight and physical condition.

Dosage Adjustment

4.2.1 Special Populations

Debilitated, elderly patients, acutely ill patients, patients with sepsis, and children should be given reduced doses commensurate with their age, weight and physical condition because they may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses.

4.4 Administration

The ointment should be applied in a thin layer for adequate control of symptoms. A sterile gauze pad is recommended for application to broken and burned tissue.

For sore nipples, apply on a small piece of gauze; the ointment must be washed away before the next feeding.

For endotracheal intubation, apply 1-2 g of ointment to the tube prior to intubation.

5 OVERDOSAGE

Acute systemic toxicity from local anesthetics is generally related to high plasma levels encountered during therapeutic use of local anesthetics and originates mainly in the central nervous and the cardiovascular systems (see 8 ADVERSE REACTIONS and 7 WARNINGS AND PRECAUTIONS). It should be kept in mind that clinically relevant pharmacodynamic drug interactions (i.e., toxic effects) may occur with lidocaine and other local anesthetics or structurally related drugs, and Class I and Class III antiarrhythmic drugs due to additive effects (see 9 DRUG INTERACTIONS).

Symptoms
Central nervous system toxicity is a graded response, with symptoms and signs of escalating severity. The first symptoms are circumoral paresthesia, numbness of the tongue, lightheadedness, 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 hypercarbia occur rapidly following convulsions due to the increased muscular activity, together with the interference with normal respiration. In severe cases apnea may occur. Acidosis increases the toxic effects of local anesthetics.
Recovery is due to redistribution and metabolism of the local anesthetic drug. Recovery may be rapid unless large amounts of the drug have been administered.

Cardiovascular effects may be 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 anesthetic or is heavily sedated with drugs such as a benzodiazepine or barbiturate.

Methemoglobinemia
Rare cases of methemoglobinemia have been reported.
Mild methemoglobinemia is characterized by tissue cyanosis, a bluish-grey or brownish discoloration of the skin, especially around the lips and nail beds, which is not reversed by breathing 100% oxygen. Clinical signs may also include pallor and marbleization.

Severe methemoglobinemia (MetHb concentrations above approximately 25%) is associated with signs of hypoxemia, ie. dyspnea, tachycardia and depression of consciousness.

Drug-induced methemoglobinemia may occur with the use of drugs including but not limited to amino-amide, sulfonamides, acetanilid, aniline dyes, benzocaine, lidocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-

aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine.

Acetaminophen has been shown to induce methemoglobin formation in vitro and in animals. In humans, methemoglobin formation is very rare at therapeutic doses and overdoses of acetaminophen.

It should be kept in mind that XYLOCAINE Ointment 5% is contraindicated for patients with congenital or idiopathic methemoglobinemia and for infants 12 months of age or younger who require treatment with methemoglobin-inducing drugs. Patients with glucose-6-phosphate dehydrogenase deficiency are more susceptible to drug-induced methemoglobinemia (see also 2 CONTRAINDICATIONS and 7 WARNINGS AND PRECAUTIONS).

Treatment
The first consideration is prevention, best accomplished by careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic administration. At the first sign of change, oxygen should be administered.

The first step in the management of systemic toxic reactions consists of immediate attention to the maintenance of a patent airway and assisted or controlled ventilation with oxygen and a delivery system capable of permitting immediate positive airway pressure by mask. This may prevent convulsions if they have not already occurred.

If convulsions occur, the objective of the treatment is to maintain ventilation and oxygenation and support circulation. Oxygen must be given and ventilation assisted if necessary (mask and bag or tracheal intubation). Should convulsions not stop spontaneously after 15-20 seconds, an anticonvulsant should be given iv to facilitate adequate ventilation and oxygenation. Thiopental sodium 1-3 mg/kg iv is the first choice. Alternatively diazepam 0.1 mg/kg bw iv may be used, although its action will be slow. Prolonged convulsions may jeopardise the patient's ventilation and oxygenation. If so, injection of a muscle relaxant (e.g. succinylcholine 1 mg/kg bw) will facilitate ventilation, and oxygenation can be controlled. Early endotracheal intubation is required when succinylcholine is used to control motor seizure activity.

If cardiovascular depression is evident (hypotension, bradycardia), ephedrine 5-10 mg i.v. should be given and may be repeated, if necessary, after 2-3 minutes.

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. Continual oxygenation and ventilation and circulatory support as well as treatment of acidosis are of vital importance, since hypoxia and acidosis will increase the systemic toxicity of local anesthetics. Epinephrine (0.1-0.2 mg as intravenous or intracardial injections) should be given as soon as possible and repeated, if necessary.

Children should be given doses of epinephrine commensurate with their age and weight.

In neonates, methemoglobin concentrations of up to 5 - 6% are not considered to be of clinical significance, with treatment of symptomatic methemoglobinemia not typically necessary unless methemoglobin concentrations are above 25 - 30%. However, the severity of clinical symptoms should be the primary consideration in the decision to initiate treatment, rather than the level of methemoglobin. Most patients recovered spontaneously after removal of the jelly.

Methemoglobinemia may be treated with a slow intravenous injection of methylene blue. It has been reported in published literature that methylene blue should be used cautiously as a treatment for methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency because it may not be effective for these patients and may cause hemolytic anemia.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Topical	Ointment 5% (50 mg/g)	polyethylene glycol, propylene glycol purified water

Dosage Forms
XYLOCAINE Ointment 5% (lidocaine) is a white to greyish-white ointment.
Packaging
XYLOCAINE Ointment 5% is available in 35 g aluminum tubes.

7 WARNINGS AND PRECAUTIONS

General

Excessive dosage, or short intervals between doses, can result in high plasma levels of lidocaine or its metabolites and serious as well as life-threatening adverse effects, including methemoglobinemia. Absorption from wound surfaces and the mucous membranes is variable but is especially high from the bronchial tree. Such applications may therefore result in rapidly rising or excessive plasma concentrations, with an increased risk for toxic symptoms, such as convulsions and methemoglobinemia. Patients should be instructed to strictly adhere to the recommended dosage. This is especially important in children where doses vary with weight. The management of serious adverse reactions may require the use of resuscitative equipment, oxygen and other resuscitative drugs (see 5 OVERDOSAGE).

The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Tolerance to elevated blood levels varies with the status of the patient.

Lidocaine should be used with caution in patients with sepsis and/or traumatized mucosa at the area of application, since under such conditions there is the potential for rapid systemic absorption.

When using XYLOCAINE Ointment 5% in younger children, especially infants under the age of 3 months, care must be taken to ensure that the caregiver understands the need to limit the dose and area of application and to prevent accidental ingestion (see 4 DOSAGE AND ADMINISTRATION). Children should be closely observed during and after use of lidocaine, as they are at greater risk than adults for serious adverse events (e.g., methemoglobinemia).

In patients under general anesthesia who are paralyzed, higher plasma concentrations may occur than

in spontaneously breathing patients. Unparalyzed patients are more likely to swallow a large proportion of the dose, which then undergoes considerable first-pass hepatic metabolism following absorption from the gut.

Avoid contact with eyes.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It has been shown that the use of amide local anesthetics in malignant hyperthermia patients is safe. However, there is no guarantee that neural blockade will prevent the development of malignant hyperthermia during surgery. It is also difficult to predict the need for supplemental general anesthesia. Therefore, a standard protocol for the management of malignant hyperthermia should be available.

When topical anesthetics are used in the mouth, the patient should be aware that the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. Numbness of the tongue or buccal mucosa may enhance the danger of unintentional biting trauma. Food or chewing gum should not be taken while the mouth or throat area is anesthetized. See also the Patient Medication Information Section.

XYLOCAINE Ointment 5% is ineffective when applied to intact skin.

Carcinogenesis and Mutagenesis
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. A chronic oral toxicity study of the metabolite 2,6-xylidine (0, 14, 45, 135 mg/kg) administered in feed to rats showed that there was a significantly greater incidence of nasal cavity tumors in male and female animals that had daily oral exposure to the highest dose of 2,6-xylidine for 2 years. The lowest tumor-inducing dose tested in animals (135 mg/kg) corresponds to approximately 40 times the amount of 2,6-xylidine to which a 50 kg subject would be exposed following the application of 8 g of lidocaine ointment 5% for 24 hours on the mucosa, assuming the highest theoretical extent of absorption of 100% and 80% conversion to 2,6-xylidine. Based on a yearly exposure (once daily dosing with 2,6-xylidine in animals and 5 treatment sessions with 8 g lidocaine ointment 5% in humans), the safety margins would be approximately 3000 times when comparing the exposure in animals to man.

Cardiovascular
Lidocaine should be used with caution in patients with bradycardia or impaired cardiovascular function since they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by amide-type local anesthetics.

Lidocaine should be used with caution in patients in severe shock.

Driving and Operating Machinery
Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

With the recommended doses, XYLOCAINE Ointment 5% has no effect on the ability to drive and use machines. However, in case of overdosage it will not be the case. It is suggested that the patient should know how he/she feels and be aware that due caution should be exercised when driving or

operating a vehicle or potentially dangerous machinery.

Hepatic
Because amide-type local anesthetics such as lidocaine are metabolized by the liver, these drugs, especially repeated doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease, because of their inability to metabolize local anesthetics normally, are at greater risk of developing toxic plasma concentrations.

Neurologic

Epilepsy: The risk of central nervous system side effects when using lidocaine in patients with epilepsy is very low, provided that the dose recommendations are followed (See 4 DOSAGE AND ADMINISTRATION).

Locomotion and Coordination: Topical lidocaine formulations generally result in low plasma concentrations because of a low degree of systemic absorption. However, depending on the dose, local anesthetics may have a very mild effect on mental function and coordination even in the absence of overt CNS toxicity and may temporarily impair locomotion and alertness.

Renal
Lidocaine is metabolized primarily by the liver to monoethylglycinexylidine (MEGX, which has some CNS activity), and then further to metabolites glycinexylidine (GX) and 2,6-xylidine (see 10 CLINICAL PHARMACOLOGY). Only a small fraction (2%) of lidocaine is excreted unchanged in the urine. The pharmacokinetics of lidocaine and its main metabolite were not altered significantly in haemodialysis patients (n=4) who received an intravenous dose of lidocaine. Therefore, renal impairment is not expected to significantly affect the pharmacokinetics of lidocaine when XYLOCAINE Ointment 5% is used for short treatment durations, according to dosage instructions (see 4 DOSAGE AND ADMINISTRATION). Caution is recommended when lidocaine is used in patients with severely impaired renal function because lidocaine metabolites may accumulate during long term treatment (see 4 DOSAGE AND ADMINISTRATION).

Sensitivity
Lidocaine should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivates (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine.

7.1 Special Populations

Debilitated patients, acutely ill patients, and patients with sepsis should be given reduced doses commensurate with their age, weight and physical condition because they may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses.

XYLOCAINE Ointment 5% is contraindicated for patients with congenital or idiopathic methemoglobinemia and patients with glucose-6-phosphate dehydrogenase deficiency which are more susceptible to drug-induced methemoglobinemia (see also 2 CONTRAINDICATIONS).

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women on the effect of lidocaine on the developing fetus.

It is reasonable to assume that a large number of pregnant women and women of child-bearing age have been given lidocaine. No specific disturbances to the reproductive process have so far been reported, e.g. no increased incidence of malformations. However, care should be given during early pregnancy when maximum organogenesis takes place.

Labour and Delivery: Should XYLOCAINE Ointment 5% be used concomitantly with other products containing lidocaine during labour and delivery, the total dose contributed by all formulations must be kept in mind.

7.1.2 Breast-feeding

Lidocaine and its metabolites are excreted in the breast milk. At therapeutic doses the quantities of lidocaine and its metabolites in breast milk are small and generally are not expected to be a risk for the infant.

7.1.3 Pediatrics

Children should be closely observed during and after use of topical anesthetics, as they are at greater risk than adults for serious adverse events (e.g., methemoglobinemia).

When using XYLOCAINE Ointment 5% in younger children, care must be taken to ensure that the caregiver understands the need to limit the dose and area of application and to prevent accidental ingestion (see 4 DOSAGE AND ADMINISTRATION).

Parents should be reminded of the importance of emotional and psychological support of younger children undergoing medical or surgical procedures.

Pediatrics (2-18 years of age): Children should be given reduced doses commensurate with their age, weight and physical condition because they may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses (see 4 DOSAGE AND ADMINISTRATION).

Pediatrics (< 2 years of age): XYLOCAINE Ointment 5% should be used with caution in children under the age of 2 as there is insufficient data to support the safety and efficacy of this product in this patient population at this time.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Elderly patients may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses and may require dose reductions.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse experiences following the administration of lidocaine are similar in nature to those observed with other amide local anesthetic agents. These adverse experiences are, in general, dose-related and may result from high plasma levels caused by overdosage or rapid absorption, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.
Serious adverse experiences are generally systemic in nature.

8.5 Post-Market Adverse Reactions

The following adverse reactions are those most commonly reported:

Central Nervous System: CNS manifestations are excitatory and/or depressant and may be characterized by the following signs and symptoms of escalating severity: circumoral paresthesia, light-headedness, nervousness, apprehension, euphoria, confusion, dizziness, drowsiness, hyperacusis, tinnitus, blurred vision, vomiting, sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, respiratory depression and arrest. The excitatory manifestations (e.g., twitching, tremors, convulsions) may be very brief or may not occur at all, in which case the first manifestation of toxicity may be drowsiness merging into unconsciousness and respiratory arrest.

Drowsiness following the administration of lidocaine is usually an early sign of a high lidocaine plasma level and may occur as a consequence of rapid absorption.

Cardiovascular System: Cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, arrhythmia and cardiovascular collapse, which may lead to cardiac arrest.

Allergic: Allergic reactions are characterized by cutaneous lesions, urticaria, edema or, in the most severe instances, anaphylactic shock. Allergic reactions of the amide type are rare (<0.1%) and may occur as a result of sensitivity either to the local anesthetic agent or to other components in the formulation (See 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

Skin Irritation: Topical products that contain propylene glycol may cause skin irritation.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Lidocaine is mainly metabolized in the liver by CYP1A2 and CYP3A4 to its two major metabolites, monoethylglycinexylidine (MEGX) and glycinexylidine (GX), both of which are pharmacologically active. Lidocaine has a high hepatic extraction ratio. Only a small fraction (2%) of lidocaine is excreted unchanged in the urine. The hepatic clearance of lidocaine is expected to depend largely on blood flow.

Strong inhibitors of CYP1A2, such as fluvoxamine, given concomitantly with lidocaine, can cause a metabolic interaction leading to an increased lidocaine plasma concentration. Therefore, prolonged administration of lidocaine should be avoided in patients treated with strong inhibitors of CYP1A2, such as fluvoxamine. When co-administered with intravenous lidocaine, two strong inhibitors of CYP3A4, erythromycin and itraconazole, have each been shown to have a modest effect on the pharmacokinetics of intravenous lidocaine. Other drugs such as propranolol and cimetidine have been

reported to reduce intravenous lidocaine clearance, probably through effects on hepatic blood flow and/or metabolism.

When lidocaine is used topically, plasma concentrations are of importance for safety reasons (see 0 WARNINGS AND PRECAUTIONS, General and 8 ADVERSE REACTIONS). However, with the low systemic exposure and short duration of topical application, the abovementioned metabolic drug-drug interactions are not expected to be of clinical significance when XYLOCAINE Ointment 5% is used according to dosage recommendations.

Clinically relevant pharmacodynamic drug interactions may occur with lidocaine and other local anesthetics or structurally related drugs, and Class I and Class III antiarrhythmic drugs due to additive effects.

Co-administration of XYLOCAINE Ointment 5% and other methemoglobin-inducing agents to patients 12 months of age or younger may result in clinical signs of methemoglobinemia (see 2 CONTRAINDICATIONS; 7 WARNINGS AND PRECAUTIONS; 9 DRUG INTERACTIONS; and 8 ADVERSE REACTIONS)

9.3 Drug-Behavioural Interactions

Interactions of lidocaine with lifestyle have not been established.

9.4 Drug-Drug Interactions

Local anesthetics and agents structurally related to amide-type local anesthetics
Lidocaine should be used with caution in patients receiving other local anesthetics or agents structurally related to amide-type local anesthetics (e.g. antiarrhythmics such as mexiletine), since the toxic effects are additive.

Antiarrhythmic Drugs
Class I Antiarrhythmic drugs
Class I antiarrhythmic drugs (such as mexiletine) should be used with caution since toxic effects are additive and potentially synergistic.

Class III Antiarrhythmic drugs
Caution is advised when using Class III antiarrhythmic drugs concomitantly with lidocaine due to potential pharmacodynamic or pharmacokinetic interactions with lidocaine, or both. A drug interaction study has shown that the plasma concentration of lidocaine may be increased following administration of a therapeutic dose of intravenous lidocaine to patients treated with amiodarone (n=6). Case reports have described toxicity in patients treated concomitantly with lidocaine and amiodarone. Patients treated with Class III antiarrhythmic drugs (e.g. amiodarone) should be kept under close surveillance and ECG monitoring should be considered, since cardiac effects of these drugs and lidocaine may be additive.

Strong Inhibitors of CYP1A2 and CYP3A4

Cytochrome CYP1A2 and CYP3A4 are involved in the formation of the pharmacologically active lidocaine metabolite MEGX.

Fluvoxamine: Strong inhibitors of CYP1A2, such as fluvoxamine, given during prolonged administration of lidocaine to areas with a high extent of systemic absorption (e.g., mucous membranes) can cause a metabolic interaction leading to an increased lidocaine plasma concentration. The plasma clearance of a single intravenous dose of lidocaine was reduced by 41 to 60% during co-administration of fluvoxamine, a selective and potent CYP1A2 inhibitor, to healthy volunteers.

Erythromycin and Itraconazole: Erythromycin and itraconazole, which are strong inhibitors of CYP3A4, have been shown to reduce clearance of lidocaine by 9 to 18%, following a single intravenous dose of lidocaine to healthy volunteers.

During combined co-administration with fluvoxamine and erythromycin the plasma clearance of lidocaine was reduced by 53%.

β-blockers and cimetidine

Following a single intravenous dose of lidocaine, administered to healthy volunteers, the clearance of lidocaine has been reported to be reduced up to 47% when co-administered with propanolol and up to 30% when co-administered with cimetidine. Reduced clearance of lidocaine when co-administered with these drugs is probably due to reduced liver blood flow and/or inhibition of microsomal liver enzymes. The potential for clinically significant interactions with these drugs should be considered during long-term treatment with high doses of lidocaine.

Methemoglobinemia

In patients treated concomitantly with XYLOCAINE Ointment 5% and other methemoglobin-inducing agents including but not limited to sulfonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine and quinine, XYLOCAINE Ointment 5% may induce the formation of methemoglobin and result in overt clinical signs of methemoglobinemia (see 2 CONTRAINDICATIONS and 5 OVERDOSAGE).

Acetaminophen has been shown to induce methemoglobin formation in vitro and in animals. In humans, methemoglobin formation is very rare at therapeutic doses and overdoses of acetaminophen.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and

conduction of impulses, thereby effecting local anesthetic action. Local anesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

10.2 Pharmacodynamics

Onset of Action
Anesthesia usually occurs within 3-5 minutes when applied to mucous membrane. The duration of analgesia for burn wound pain is about 4 hours. The application of gauze over the cream may prolong duration of analgesia in burn wounds. XYLOCAINE Ointment 5% (lidocaine) is ineffective when applied to intact skin.

Hemodynamics
Lidocaine, like other local anesthetics, may also have effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach systemic circulation rapidly, symptoms and signs of toxicity will appear, emanating from the central nervous and cardiovascular systems.
Central nervous system toxicity (see 5 OVERDOSAGE) usually precedes the cardiovascular effects since it occurs at lower plasma concentrations. Direct effects of local anesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

10.3 Pharmacokinetics

Absorption
The rate and extent of absorption depends upon concentration and total dose administered, the specific site of application and duration of exposure. In general, the rate of absorption of local anesthetic agents following topical application to wound surfaces and mucous membranes is high, and occurs most rapidly after intratracheal and bronchial administration. Lidocaine is also well absorbed from the gastrointestinal tract, although little intact drug may appear in the circulation because of biotransformation in the liver.

Distribution:
Lidocaine has a total plasma clearance of 0.95 L/min and a volume of distribution at steady state of 91 L.

Following insertion of an endotracheal tube lubricated with a mean of 1.26 g (range 0.49-2.45) XYLOCAINE Ointment 5% in patients 18 to 80 years old, the mean peak venous plasma concentration of lidocaine was 0.45 (range 0.2-0.9) µg/mL and was usually observed within 15 min. A dose increase of 1 g ointment resulted in an average increase of 0.22 µg/mL.

Lidocaine readily crosses the placenta, and equilibrium in regard to free, unbound drug will be reached. Because the degree of plasma protein binding in the fetus is less than in the mother, the total plasma concentration will be greater in the mother, but the free concentrations will be the same.

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

Metabolism:
Lidocaine is metabolized 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. Only 2% of lidocaine is excreted unchanged. Most of it is metabolized first to monoethylglycinexylidide (MEGX) and then to glycinexylidide (GX) and 2,6-xylidine. Up to 70% appears in the urine as 4-hydroxy-2,6-xylidine.

Elimination
Lidocaine has an elimination half-life of 1.6 h and an estimated hepatic extraction ratio of 0.65. The clearance of lidocaine is almost entirely due to liver metabolism, and depends both on liver blood flow and the activity of metabolizing enzymes.

The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. The elimination half-life in neonates (3.2 h) is approximately twice that of adults. 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.

Special Populations and Conditions
Acidosis increases the systemic toxicity of lidocaine while the use of CNS depressants may increase the levels of lidocaine required to produce overt CNS effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 µg free base per mL.

11 STORAGE, STABILITY AND DISPOSAL

Store at 15-30°C. Protect from freezing.

12 SPECIAL HANDLING INSTRUCTIONS

On initial opening, do not use if the protective membrane of the tube is punctured.

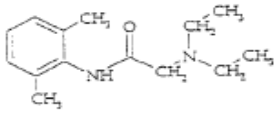
PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Lidocaine

Molecular formula and molecular mass: $C_{14}H_{22}N_2O$ and 234.3



Structural formula:

15 MICROBIOLOGY

No microbiological information is required for this drug product.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

XYLOCAINE® OINTMENT 5%

lidocaine ointment

Read this carefully before you start applying **XYLOCAINE Ointment 5%** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **XYLOCAINE Ointment 5%**.

What is XYLOCAINE Ointment 5% used for?

XYLOCAINE Ointment 5% is a topical ointment that is used in adults and children (2 years of age and older) to lubricate and numb (produce a temporary loss of feeling) the skin. It is used

- by your healthcare professional before certain types of medical procedures;
- to help relieve the pain from:
  - minor scrapes
  - sunburns or other minor burns
  - sore nipples
  - insect bites
  - hemorrhoids

How does XYLOCAINE Ointment 5% work?

XYLOCAINE Ointment 5% belongs to a group of medicines called topical anaesthetics. Topical anesthetics block nerve signals. This causes a temporary loss of feeling or numbness on the area where the ointment has been applied.

What are the ingredients in XYLOCAINE Ointment 5%?

Medicinal ingredients: lidocaine
Non-medicinal ingredients: polyethylene glycol, propylene glycol, and purified water

XYLOCAINE Ointment 5% comes in the following dosage forms:

Ointment: 50 mg/g
XYLOCAINE Ointment 5% is available in a 35 g tube.

Do not use XYLOCAINE Ointment 5% if:

- you are allergic to:
  - lidocaine or to any other type of anaesthetic ending in "-caine"
  - any of the other ingredients in XYLOCAINE Ointment 5%
- you have a blood disorder called methemoglobinemia
- you have a condition called glucose-6-phosphate dehydrogenase deficiency
- it is to be used for infants who are 12 months of age or younger who are taking medicines that may cause the blood disorder called methemoglobenima (e.g., sulphonamides)

To help avoid side effects and ensure proper use, talk to your healthcare professional before you apply XYLOCAINE Ointment 5%. Talk about any health conditions or problems you may have, including if you:

- have, or have had in the past, any health problems;
- take any medicines, including ones you can buy without a prescription;
- have problems with your heart, including:
  - A slower than normal heart rate (bradycardia)
  - Irregular heart beat (arrhythmia)
- have ever had a bad, unusual or allergic reaction to XYLOCAINE Ointment 5% or any other medicines ending with "caine";
- think you may be allergic or sensitive to any ingredients in XYLOCAINE Ointment 5%
- have bleeding hemorrhoids and wish to use the ointment in that area;
- if there is an infection, skin rash, cut or wound at or near the area you want to apply XYLOCAINE Ointment 5%;
- have a skin condition that is severe or that covers a large area;
- have problems with your liver or kidneys;
- have epilepsy;
- are experiencing severe shock;
- are pregnant, plan to become pregnant or are breastfeeding.

Other warnings you should know about:

Driving and operating machines: Know how you feel after using XYLOCAINE Ointment 5% before you drive or use heavy machines.

Use in children: Children are at greater risk for serious side effects. Always follow your healthcare professional's instructions for using XYLOCAINE Ointment 5%, especially in young children and infants. **It should not be used on the genitals of children or infants.**

Using XYLOCAINE Ointment 5% in the mouth: When applied in your mouth or throat, topical anesthetics may numb your tongue and the lining of your mouth and make swallowing difficult. This can increase your risk of chocking or accidently biting your tongue or the inside of your cheeks. You should avoid eating or drinking very hot or cold food or drinks or chewing gum until the numbness has worn off.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with XYLOCAINE Ointment 5%:

- Medicines you can buy without a prescription;
- Anti-arrhythmic medicines used to treat heart problems (e.g. mexiletine, amiodarone). Your healthcare professional should monitor you carefully and send you for an electrocardiogram (ECG) if you are taking this medicine and amiodarone.
- Other local anaesthetics;
- Erythromycin used to treat bacterial infections
- Itraconazole used to treat fungal infections

- If you are going to use high doses of this medicine for a long time, the following medications may interact with it:
  - Propranolol used to treat heart problems
  - Cimetidine used to treat gastrointestinal problems
  - Fluvoxamine used to treat depression
- Other medicines which may cause methemoglobinemia, including: sulfonamides, acetanilide, aniline dyes, benzocaine (or other "-caine" type anesthetics), chloroquine, dapsone, naphthalene, nitrates or nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine and high doses of acetaminophen.

How to apply XYLOCAINE Ointment 5%:

XYLOCAINE Ointment 5% can be:
- applied by your healthcare professional when you or your child arrive for the medical procedure
- for your own use to treat certain conditions such as:
  - minor scrapes
  - sunburns or other minor burns
  - sore nipples
  - insect bites
  - hemorrhoids

When used by a Healthcare Professional:
- Your dose or your child's dose will depend on:
  - what part of the body XYLOCAINE Ointment 5% will be applied; and
  - age, any health or medical conditions and medications you or child are taking

When treating yourself or your child:

- **Do NOT use more XYLOCAINE Ointment 5%; or more often or for a longer period of time than your healthcare professional ordered or than these package directions suggest. This may cause unwanted and serious side effects.**
- **ONLY** apply the ointment on unbroken skin. If you have a special skin condition or other conditions that require a healthcare professional's supervision, talk to your healthcare professional before you use XYLOCAINE Ointment 5%.
- XYLOCAINE Ointment 5% should start to work within 5 to 15 minutes after you apply it. The numbing effect usually last 20 to 30 minutes.
- You should:
  - clean the area well, before each application of ointment
  - apply a thin layer, using only enough to cover the affected area and reapply it only when you need it
  - avoid contact with your eyes
- For broken or burnt skin – avoid touching the affected area with your fingers. Apply the ointment to a sterile gauze pad and place the pad over the affected area. The pain relief effect lasts about 4 hours specifically for wounds caused by burning.
- If you are using the ointment on sore nipples, it is important that you clean the nipple area completely before each feeding. This will ensure that your baby does not take in any of the

medicine.

- Check with your doctor or pharmacist if you:
  - have any questions about how to apply or measure the amount of XYLOCAINE Ointment 5% you need to use
  - are treating yourself or your child and you do not see any improvement within 3 to 5 days
  - feel that the effect of XYLOCAINE Ointment 5% is too strong or too weak

Instructions for Use:

The tube has a special protective seal on the tube opening. If this seal is broken, do NOT use the ointment. Go to the pharmacy and exchange for a new tube.

To use the tube for the first time: break the protective seal by firmly pressing the pointed end of the white cap into the seal.

The ointment can easily be removed from the area where it was applied and from clothing by washing with water.

Usual dose:

Child dose (2 years of age and older): Follow the healthcare professional's instructions on how much of the ointment to use, how often it should be applied to the affected area and how to apply it.

The following are general directions for the maximum amount of XYLOCAINE Ointment 5% that should be used **without a healthcare professional's advice for adults**. These guidelines apply only to healthy people. If you have a special skin condition or other conditions that require a-healthcare professional's supervision, talk to your healthcare professional before you use XYLOCAINE Ointment 5%.

Adult dose: Apply no more than 1/3 of the tube (10 g) to the affected area. If you need to reapply the ointment, wait at least 8 hours before you reapply it again. Do NOT use more than 2/3 of the tube (20 g) in a 24-hour period.

Overdose:

Symptoms of an overdose with XYLOCAINE Ointment 5% may include:

- numbness of the lips and around the mouth
- feeling lightheaded
- dizziness
- blurred vision
- trembling
- seizures
- losing consciousness

If you think you, or a person you are caring for, have applied too much or accidently swallowed XYLOCAINE Ointment 5%, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using XYLOCAINE Ointment 5%?

These are not all the possible side effects you may have when applying XYLOCAINE Ointment 5%. If you experience any side effects not listed here, tell your healthcare professional.

XYLOCAINE Ointment 5% may cause skin irritation where it was applied.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			√
Methemoglobinemia (blood disorder): brownish or greyish skin especially around the lips and nails.			√
VERY RARE			
drowsiness, numbness of your tongue, light-headedness, ringing in your ears, blurred vision, vomiting, dizziness, unusually slow heart beat, fainting, nervousness, unusual sweating, trembling or seizures. These symptoms usually require large amounts of XYLOCAINE Ointment 5% over a long period of time**.**			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (15-30°C). Protect from freezing.
- Keep out of reach and sight of children.
- Do not use XYLOCAINE Ointment 5% after the expiry date marked on the package.

If you want more information about XYLOCAINE Ointment 5%:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website https://aspenpharma.ca/ , or by calling 1-844-330-1213.

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