PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrXYLOCAINE® JELLY 2%

Lidocaine hydrochloride

20 mg/mL

USP

Topical Anesthetic

Aspen Pharmacare Canada Inc.
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

XYLOCAINE Jelly 2% (lidocaine hydrochloride) is indicated for:

- Surface anesthesia and lubrication for:
  - The male and female urethra during cystoscopy, catheterization, exploration by sound and other endourethral operations;
  - Nasal and pharyngeal cavities in endoscopic procedures such as gastroscopy and bronchoscopy;
  - Proctoscopy and rectoscopy;
  - Tracheal intubation.

- Symptomatic treatment of pain in connection with cystitis and urethritis.

1.1 Pediatrics

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

1.2 Geriatrics

Geriatrics (> *65* years of age): Evidence from experience suggests that use in the geriatric population is associated with differences in safety. Elderly patients should be given reduced doses commensurate with their age and physical condition (see DOSAGE AND ADMINISTRATION-Special Populations and WARNINGS AND PRECAUTIONS-Special Populations).

2 CONTRAINDICATIONS

XYLOCAINE Jelly 2% 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 Dosage Forms, Strengths, Composition and Packaging.

- Patients with a known history of hypersensitivity to local anesthetics of the amide type or to other components in the formulation (see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
- Patients with a known hypersensitivity to methylparaben and/or propylparaben (preservatives used in the tube format of XYLOCAINE Jelly 2%), or to their metabolite para amino benzoic acid (PABA).
- Formulations of lidocaine containing parabens should also be avoided in patients with a history of allergic reactions to ester local anesthetics, which are metabolized to PABA.

- Patients with congenital or idiopathic methemoglobinemia.
- Infants who require treatment with methemoglobin-inducing agents, e.g., sulfonamides and are 12 months of age or younger (see DRUGS INTERACTIONS).

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

When XYLOCAINE Jelly 2% (lidocaine hydrochloride) is used concomitantly with other products containing lidocaine, the total dose contributed by all formulations must be kept in mind.

- XYLOCAINE Jelly 2% in the plastic syringe is preservative-free, and intended for single use only. The syringe is graduated, i.e., a 3 mm line of jelly is equivalent to approximately 1 mL of jelly (20 mg lidocaine hydrochloride).
- The tube presentation of XYLOCAINE Jelly 2% contains preservatives.

The absorption of lidocaine jelly from the nasopharynx is usually lower than with other lidocaine products. Blood concentrations of lidocaine after instillation of the jelly in the intact urethra and bladder in doses up to 800 mg are fairly low and below toxic levels.

3.2 Recommended Dose and Dosage Adjustment

Urethral Anesthesia

Surface Anesthesia of the Male Adult Urethra

For adequate analgesia in males, 20 mL (400 mg lidocaine hydrochloride) jelly is usually required. The jelly is instilled slowly until the patient has a feeling of tension (approximately 10 mL) (200 mg). A penile clamp is then applied for several minutes at the corona, after which the rest of the jelly is instilled.

When anesthesia is especially important, e.g., during sounding or cystoscopy, a larger quantity of jelly (e.g., 30-40 mL) may be instilled in 3-4 portions and allowed to act for 10-12 minutes before insertion of the instrument. The jelly instilled into the bladder is also effective for procedures in this region.

To anesthetize only the anterior male urethra, e.g., for catheterization, small volumes (5-10 mL, i.e., 100-200 mg lidocaine HCl) are usually adequate for lubrication.

For Surface Anesthesia of the Female Adult Urethra

Instill 5-10 mL of jelly in small portions to fill the whole urethra. If desired, some jelly may be deposited on the orifice and covered with a cotton swab. In order to obtain adequate anesthesia, several minutes should be allowed prior to performing urological procedures.

Endoscopy

The instillation of 10-20 mL is recommended for adequate analgesia and a small amount may be applied to the lubricating instrument. When combined with other lidocaine products (e.g., for bronchoscopy), the total dose of lidocaine should not exceed 400 mg.

Proctoscopy and Rectoscopy

Up to 20 mL can be used for anal and rectal procedures. The total dose should not exceed 400 mg lidocaine.

Lubrication for Endotracheal Intubation

Apply approximately 2 mL of jelly to the external surface of the endotracheal tube just prior to insertion. Care should be taken to avoid introducing the product into the lumen of the tube (see WARNINGS AND PRECAUTIONS). Do not use the jelly to lubricate endotracheal stylettes. It is also recommended that the use of endotracheal tubes with dried jelly on the external surface be avoided for lack of lubricating effect.

Maximum Dosage

Adults
The dose of XYLOCAINE Jelly 2% depends on the application site. A safe dose for oral use is 400 mg (20 mL). A safe dose for use in the urethra and bladder is 800 mg (40 mL). A maximum single dosage for XYLOCAINE Jelly 2% is not established. No more than four doses should be given during a 24-hour period.

Children
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. The maximum amount per dose of XYLOCAINE Jelly 2% should not exceed 6 mg/kg of body weight or 3 mL per 10 kg weight. No more than four doses should be given during a 24-hour period.

- 12-18 Years
  For children over 12 years of age doses should be commensurate with weight and physical condition.

Dosage Adjustment

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.

4 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 ADVERSE REACTIONS and 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 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, 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 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, hyperkalaemia, hypocalcaemia and hypoxia increase and extend 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 Jelly 2% 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

CONTRAINDICATIONS, 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.

5 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	20 mg/mL jelly in 10 mL syringe	Hydroxypropyl methylcellulose, purified water, and sodium hydroxide and/or hydrochloric acid.
Topical	20 mg/mL jelly in 30 mL tube	Methylparaben, propylparaben, hydroxypropyl methylcellulose, purified water, and sodium hydroxide and/or hydrochloric acid.

Packaging

XYLOCAINE Jelly 2% is available in 10 mL prefilled, single-use plastic syringes and 30 mL aluminum tubes with an applicator cone.

The syringe contains no preservatives and is intended for single use only.

6 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-TREATENING ADVERSE EFFECTS, including methemoglobinemia. Absorption from 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 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 Jelly 2% 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 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 used for endotracheal tube lubrication, care should be taken to avoid introduction of the jelly into the lumen of the tube. If allowed into the inner lumen, the jelly may dry on the inner surface leaving a residue which tends to clump with flexion, narrowing the lumen. There have been rare reports in which this residue has caused the lumen to occlude. Similarly, do not use the jelly to lubricate the endotracheal stylettes.

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 Part III: Consumer Information.

XYLOCAINE Jelly 2% is ineffective when applied to intact skin.

Lidocaine has been shown to be porphyrinogenic in animal models. XYLOCAINE Jelly 2% should only be prescribed to patients with acute porphyria on strong or urgent indications, when they can be closely monitored. Appropriate precautions should be taken for all porphyric patients.

Carcinogenesis and Mutagenesis

Genotoxicity tests with lidocaine showed no evidence of mutagenic potential. A metabolite of lidocaine, 2,6-dimethylaniline, showed weak evidence of activity in some genotoxicity tests. A chronic oral toxicity study of the metabolite 2,6-dimethylaniline (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-dimethylaniline for 2 years. The lowest tumor-inducing dose tested in animals (135 mg/kg) corresponds to approximately 50 times the amount of 2,6-dimethylaniline to which a 50 kg subject would be exposed following the application of 20 g of lidocaine jelly 2% for 24 hours on the mucosa, assuming the highest theoretical extent of absorption of 100% and 80% conversion to 2,6-dimethylaniline. Based on a yearly exposure (once daily dosing with 2,6-dimethylaniline in animals and 5 treatment sessions with 20 g lidocaine jelly 2% in humans), the safety margins would be approximately 3400 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 amid-type local anesthetics.

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

Driving and Operating Machinery

With the recommended doses, XYLOCAINE Jelly 2% 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 DOSAGE AND ADMISTRATION).

***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-dimethylaniline (see ACTION AND 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 Jelly 2% is used for short treatment durations, according to dosage instructions (see 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 DOSAGE AND ADMINISTRATION).

Sensitivity/Resistance

Lidocaine should be used with caution in persons with known drug sensitivities.

XYLOCAINE Jelly 2% is contraindicated in patients with known hypersensitivities to local anesthetics of the amide type, to other components in the formulation, methylparaben and/or propylparaben (preservatives of the tube) and their metabolite para amino benzoic acid (PABA). The use of paraben-containing lidocaine preparations should also be avoided in patients who are allergic to ester local anesthetics (see CONTRAINDICATIONS).

6.1 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 Jelly 2% 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 CONTRAINDICATIONS).

6.1.1 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.

***Labor and Delivery*:** Lidocaine is not contraindicated in labor and delivery. Should XYLOCAINE Jelly 2% be used concomitantly with other products containing lidocaine during labor and delivery, the total dose contributed by all formulations must be kept in mind.

6.1.2 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.

6.1.3 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 Jelly 2% 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 DOSAGE AND ADMINISTRATION).

XYLOCAINE 2% should not be applied to the genital mucosa of children or infants due to insufficient data on absorption.

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

Pediatrics (2-18 Years): 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 DOSAGE AND ADMINISTRATION).

Pediatrics (< 2 Years): Xylocaine Jelly 2% 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. XYLOCAINE Jelly 2% is contraindicated for infants 12 months of age or younger who require treatment with methemoglobin-inducing drugs (see also CONTRAINDICATIONS).

6.1.4 Geriatrics

Elderly patients may be more sensitive to systemic effects due to increased blood levels of lidocaine following repeated doses and may require dose reductions.

7 ADVERSE REACTIONS

7.1 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.

An increased incidence of postoperative sore throat has been reported following endotracheal tube lubrication with lidocaine jelly.

Serious adverse experiences are generally systemic in nature. The following types 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 DOSAGE FORM, COMPOSITION AND PACKAGING).

8 DRUG INTERACTIONS

8.1 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 WARNINGS AND PRECAUTIONS, General; 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 Jelly 2% 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 JELLY 2% and other methemoglobin-inducing agents to patients 12 months of age or younger may result in clinical signs of methemoglobinemia (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, ADVERSE REACTIONS)

8.2 Drug-Drug Interactions

<u>Local anesthetics and agents structurally related to amide-type local anesthetics</u>

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.

<u>Antiarryhythmic Drugs</u>

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 Jelly 2% 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 Jelly 2% may induce the formation of methemoglobin and result in overt clinical signs of methemoglobinemia (see CONTRAINDICATIONS and 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.

8.3 Drug-Food Interactions

Interactions of lidocaine with food have not been established.

8.4 Drug-Herb Interactions

Interactions of lidocaine with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions of lidocaine with laboratory tests have not been established.

8.6 Drug-Lifestyle Interactions

Interactions of lidocaine with lifestyle have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 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.

9.2 Pharmacodynamics

Onset of Action

Anesthesia is achieved within 5 minutes, depending on the area of application. Duration of anesthesia is approximately 20-30 minutes. XYLOCAINE Jelly 2% (lidocaine hydrochloride) 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 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.

9.3 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. The absorption of lidocaine jelly from the nasopharynx is usually lower than with other lidocaine products. Blood concentrations of lidocaine after instillation of the jelly in the intact urethra and bladder in doses up to 800 mg are fairly low and below toxic levels. 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.

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

Metabolism: Lidocaine is metabolized rapidly by the liver, and its metabolites and the 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-dimethylaniline. Up to 70% appears in the urine as 4-hydroxy- 2,6-dimethylaniline. The pharmacological/toxicological actions of MEGX and GX are similar to, but less potent than those of lidocaine. GX has a longer half-life (about 10 h) than lidocaine and may accumulate during long-term administration.

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. Approximately 90% of the lidocaine administrated intravenously is excreted in the form of various metabolites, and less than 10% is excreted unchanged in the urine. The primary metabolite in urine is a conjugate of 4-hydroxy- 2,6-dimethylaniline, accounting for about 70-80% of the dose excreted in the urine.

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.

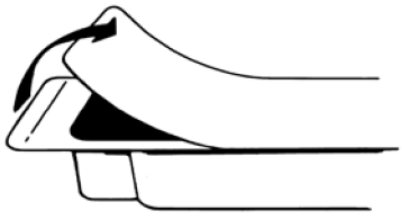
10 STORAGE, STABILITY AND DISPOSAL

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

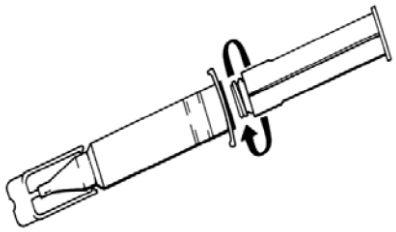
11 SPECIAL HANDLING INSTRUCTIONS

Instructions for Use – XYLOCAINE Jelly 2%, Syringe

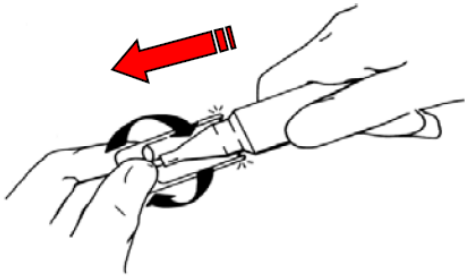
1. Tear off the paper cover.



2. Screw plunger rod clockwise into grey rubber until rubber rotates.

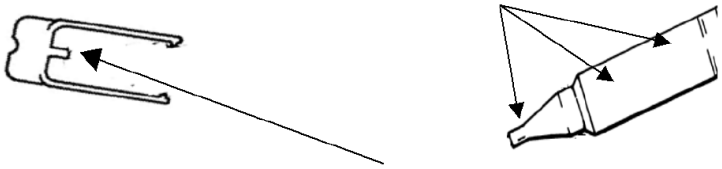


3. Twist the protective tab and **then, without bending, pull slightly** to break the seal.



4. **Extrude a small amount (i.e. 1 cm) of Jelly. Inspect the syringe to ensure that there is no plastic fragment present in the Jelly.**

   Note: upon visual inspection, a clear plastic fragment in clear jelly may be difficult to detect and may look like an air pocket.



If the protective tab is broken, do not use the syringe.

5. **The syringe must not be used and must be discarded if there is any suspicion of a broken plastic fragment.**

6. **If the protective tab is intact and no plastic fragment is found in the Jelly, the syringe is ready for use.**

For further assistance please contact Aspen Pharmacare Canada Inc. at 1-(844)-330-1213.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

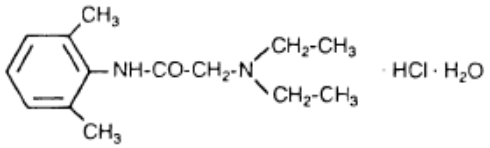
Drug Substance

Proper name: Lidocaine Hydrochloride

Chemical name: 2-(Diethylamino)-N-(2,6-dimethylphenyl) acetamide hydrochloride monohydrate

Molecular formula and molecular mass: $C_{14}H_{22}N_2OHClH_2O$ (288.8)

Structural formula:



Physicochemical properties: White or almost white crystals or crystalline powder. Lidocaine hydrochloride contains no asymmetric carbon, and has therefore no optical activity. Very soluble in water. Freely soluble in alcohol.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

XYLOCAINE® Jelly 2%
Lidocaine hydrochloride Jelly

Read this carefully before you start taking **XYLOCAINE® Jelly 2%** 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® Jelly 2%**.

What is XYLOCAINE® Jelly 2% used for?
XYLOCAINE Jelly 2% is a topical jelly 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 doctor before certain types of medical procedures;
- to help relieve the pain from inflammation of the bladder and the urethra

How does XYLOCAINE® Jelly 2% work?
XYLOCAINE Jelly 2% 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 jelly has been applied.

What are the ingredients in XYLOCAINE® Jelly 2%?
Medicinal ingredients: lidocaine hydrochloride 2%
Non-medicinal ingredients: hydroxypropyl, methylcellulose, purified water, and sodium hydroxide and/or hydrochloride acid (to adjust pH).

XYLOCAINE Jelly 2% in tubes also contain the preservatives methylparaben and propylparaben.

XYLOCAINE® Jelly 2% comes in the following dosage forms:
Jelly: 20 mg /mL

XYLOCAINE® Jelly 2% is available:

- in a 30 mL tube with applicator nozzle that contains a total of 600 mg of lidocaine hydrochloride / tube
- as a single-use 10mL syringe that contains a total of 200 mg of lidocaine hydrochloride / syringe

Do not use XYLOCAINE® Jelly 2% if:

- you are allergic to:
  - lidocaine, prilocaine or to any other type of anaesthetic ending in “-caine”
  - any of the other ingredients in XYLOCAINE Jelly 2% (see list of Non-medicinal ingredients above)
  - methylparaben and/or propylparaben (preservatives used tube format) or to para amino benzoic acid (PABA) – a substance that is made from the breakdown of methylparaben and propylparaben
- you have a blood disorder called methemoglobinemia
- 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 take XYLOCAINE® Jelly 2%. Talk about any health conditions or problems you may have, including if you:

- Take other medications, including ones you can buy without prescription;
- Have problems with your heart including:
  - A slower than normal heart rate (bradycardia);
  - Irregular heart beat (arrhythmia);
- Ever had a bad, unusual, or allergic reaction to XYLOCAINE Jelly 2% or any other medicines ending with "-caine";
- Think you may be allergic or sensitive to any ingredients in XYLOCAINE Jelly 2% (see list of ingredients above);
- Have an infection, skin rash, cut, or wound at or near the area you want to apply XYLOCAINE Jelly 2%;
- Have a skin condition that is severe or that covers a large area;
- Have problems with your liver or kidneys;
- Have epilepsy;
- You or someone in your family has been diagnosed with a disorder that can cause nerve or skin problems (porphyria);
- Are experiencing 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 Jelly 2% before you drive or use heavy machines.

Use in children: Children are at greater risk for serious side effects. Always follow your doctor's instructions for using XYLOCAINE Jelly 2%, especially in young children and infants. It **should not be used on the genitals of children or infants.**

Using XYLOCAINE Jelly 2% 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® Jelly 2%:

- Drugs you can buy without a prescription;
- Anti-arrhythmic drugs used to treat heart problems (e.g. mexiletine, amiodarone). Your doctor should monitor you carefully and send you for an electrocardiogram (ECG) if you are taking XYLOCAINE Jelly 2% 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 problem
  - 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 use XYLOCAINE® Jelly 2%:

XYLOCAINE Jelly 2% can be:
- applied by your doctor when you or your child arrive for the medical procedure
- for your own use to treat certain conditions such as:
  - pain caused by inflammation of the urethra or urinary bladder, or
  - self-catheterization

When used by a Healthcare Professional:
- Your dose or your child's dose will depend on:
  - what part of the body XYLOCAINE Jelly 2% 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 Jelly 2%; or more often or for a longer period of time than your doctor ordered or than these package directions suggest. This may cause unwanted and serious side effects.**
- **ONLY** apply the jelly on unbroken skin. If you have a special skin condition or other conditions that require a doctor's supervision, talk to your doctor before you use XYLOCAINE Jelly 2%.
- XYLOCAINE Jelly 2% should start to work within 5 to 15 minutes after you apply it. The numbing effect usually lasts 20 to 30 minutes.
- You should:
  - clean the area well, before each application of jelly
  - use the smallest amount of the jelly to control your symptoms
  - avoid contact with your eyes
- Check with your doctor or pharmacist if you:
  - have any questions about how to apply or measure the amount of XYLOCAINE Jelly 2% you need to use
  - are treating yourself and your condition does not seem to improve within 3 to 5 days
  - feel that the effect of XYLOCAINE Jelly 2% is too strong or too weak

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

Instructions for Use - XYLOCAINE Jelly 2%, Tube

The following are general directions for the maximum amount of XYLOCAINE Jelly 2% that

should be used **without a doctor's advice for adults**. These guidelines apply only to healthy people. If you have a special skin condition or other conditions that require a doctor's supervision, talk to your doctor before you use XYLOCAINE Jelly 2%.

Adult dose:

- For oral use: a dose of 20 mL (about 2/3 of the tube) is recommend as usually safe
- For use in the urethra before insertion of urinary catheters: 5 to 20 mL (up to about 2/3 of a tube) is recommended as usually safe
- For use in the urethra and bladder: 40 mL (about 1 full tube plus 1/3 of another tube) is recommended as usually safe.

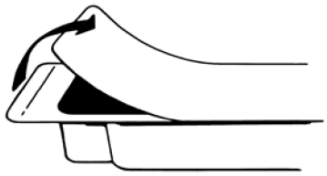
Do not use more than 4 doses in a 24-hour period.

Instructions for Use – XYLOCAINE Jelly 2%, Syringe

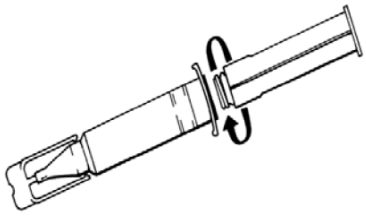
Adult dose (Pre-filled syringe): If you are using the pre-filled syringe to treat your condition, follow the **Instructions for Use – XYLOCAINE Jelly 2%, Syringe** (below) and your doctor or pharmacist's instructions on how much to use.

- The syringe is graduated (there are lines on it that indicate the volume of jelly in the syringe). A 3 mm line of the jelly is equal to about 1 mL of jelly (20 mg lidocaine hydrochloride).

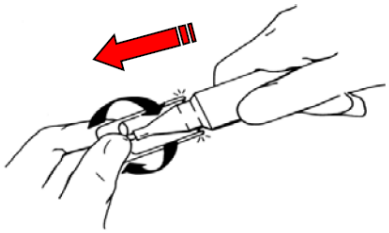
1. Tear off the paper cover.



2. Screw plunger rod clockwise into grey rubber until the rubber rotates.

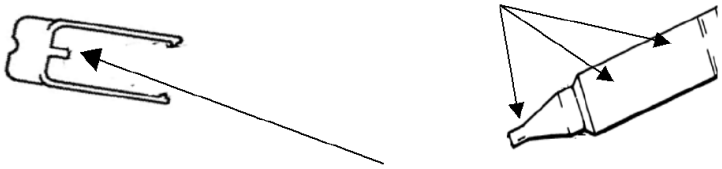


3. Twist the protective tab and **then, without bending, pull slightly** to break the seal.



4. **Force a small amount (i.e. about 1 cm) of jelly out of the syringe. Inspect the syringe to ensure that there are no pieces of plastic in the jelly.**

Note: when you inspect the syringe, a clear piece of plastic may be difficult to see in clear jelly. It may look like an air pocket.



If the protective tab is broken, do not use the syringe.

5. **Throw the syringe away and do NOT use it if you think that the jelly contains any broken pieces of plastic.**

6. **If the protective tab is intact and there are no plastic pieces found in the jelly, the syringe can be used.**

If you have any questions or concerns contact Aspen Pharmacare Canada Inc. at 1-(844)-330-1213.

Overdose:

If you think you have used too much XYLOCAINE Jelly 2%, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Symptoms of an overdose include:
- numbness of the lips and around the mouth
- feeling lightheaded
- dizziness and
- blurred vision
- trembling
- seizures or
- loosing consciousness

What are possible side effects from using XYLOCAINE® Jelly 2%?

These are not all the possible side effects you may feel when taking XYLOCAINE® Jelly 2%. If you experience any side effects not listed here, contact your healthcare professional.

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.	**X**		**X**
RARE **Methemoglobinemia** Brownish or greyish skin especially around lips and nails			**X**
EXTREMELY 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 can occur when too much XYLOCAINE 2% Jelly is used at one time and when large amounts are used over a long period of time.			**X**

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

- 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.

Store:

At room temperature (15-30°C). Protect from freezing. Store it in its original package. Keep out of the reach and sight of children.

Do not use XYLOCAINE Jelly 2% after the expiry date marked on the package.

If you want more information about XYLOCAINE® Jelly 2%:

- 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://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://aspenpharma.ca/, or by calling 1-844-330-1213.

This leaflet was prepared by Aspen Pharmacare Canada Inc.

Last Revised: September 10, 2020