PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrXYLOCARD®

Lidocaine hydrochloride
Solution, 20 mg/mL, Intravenous

(Ph Eur)

Antiarrhythmic ATC CO1BB01

Aspen Pharmacare Canada Inc.
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RECENT MAJOR LABEL CHANGES

1 Indications, 1.1 Pediatrics	05/2021
1 Indications, 1.2 Geriatrics	05/2021
3 Dosage and Administration, 3.1 Dosing Considerations	05/2021
3.2 Dosage and Administration, Recommended Dose and Dosage Adjustment	05/2021
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6 Warnings and Precautions	05/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

XYLOCARD (lidocaine hydrochloride) by intravenous administration is indicated for:

- the treatment of ventricular tachycardia occurring during cardiac manipulation (such as surgery or catheterization) or during acute myocardial infarction, digitalis toxicity, or other cardiac diseases.

This drug requires administration by experienced health professionals, with emergency resuscitative equipment and drugs immediately available (see WARNINGS AND PRECAUTIONS).

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

A reduction in dosage may be necessary for elderly patients, particularly those with compromised cardiovascular and/or hepatic function (see WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

XYLOCARD 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.

XYLOCARD is contraindicated in patients:

- With known hypersensitivity to local anesthetics of the amide type, such prilocaine, mepivacaine, or bupivacaine;
- With Adams-stokes syndrome, or severe degrees of sinoatrial, atrioventricular, or intraventricular block.
- With supraventricular arrhythmias
- With severe myocardial depression

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

- The onset of action following a single intravenous injection varies from 45 to 90 seconds. Duration of action is 10 to 20 minutes.
- No more than 200 to 300 mg of XYLOCARD should be administered during a one-hour period (see WARNINGS AND PRECAUTIONS - General, Pharmacodynamics, and General Toxicology).
- Intravenous infusions should be terminated as soon as the patient's basic cardiac rhythm appears to be stable or at the earliest signs of toxicity. It is rarely necessary to continue intravenous infusion beyond 24 hours. As soon as possible, and when indicated, patients should be changed to an oral antiarrhythmic agent for maintenance therapy.
- Intravenous infusions of XYLOCARD must be administered under constant ECG and blood pressure monitoring and with meticulous regulation of infusion rate, in order to avoid potential overdosage and toxicity.

3.2 Recommended Dose and Dosage Adjustment

Single Intravenous Injection

The usual dose is 50 to 100 mg XYLOCARD (lidocaine hydrochloride) administered under ECG and blood pressure monitoring. This dose may be administered at the rate of approximately 25 to 50 mg/min. Sufficient time should be allowed to enable a slow circulation to carry the drug to the site of action. If the initial injection of 50 to 100 mg does not produce a desired response, a second dose may be repeated after 10 minutes. Elderly patients and those with congestive heart failure or cardiogenic shock may require smaller bolus doses.

Continuous Intravenous Infusion

Following intravenous injection, XYLOCARD may be administered by intravenous infusion at a rate of 1-2 mg/min (approximately 15-30 µg/kg/min in the average 70 kg patient) in those patients in whom the arrhythmia tends to recur, and who are incapable of receiving oral antiarrhythmic therapy.

Health Canada has not authorized an indication for pediatric use.

3.3 Administration

XYLOCARD is for intravenous administration (injection, infusion) only.

In the treatment of ventricular arrhythmias, an intravenous injection should be given initially, followed by an intravenous infusion.

Continuous infusion: XYLOCARD should be diluted to the desired concentration in an appropriate infusion solution using aseptic technique (see Reconstitution).

When administering XYLOCARD, careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness is required. At the first sign of change, oxygen should be administered.

3.4 Reconstitution

Table 1 – Reconstitution

Desired concentration of lidocaine hydrochloride	Suggested dilution (Each ampoule contains 5 mL = 100 mg)	Actual final concentration of lidocaine hydrochloride
1 mg/mL	10 ampoules added to 1 L (1000 mL)	1000 mg in 1050 mL = 0.95 mg/mL (~ 1 mg/mL)
2 mg/mL	10 ampoules added to 500 mL	1000 mg in 550 mL = 1.8 mg/mL (˜2 mg/mL)

5% dextrose in water is the preferred diluent for continuous intravenous infusion.

Solution for intravenous infusion may be prepared by adding one gram of XYLOCARD (i.e., contents of ten 5 mL ampoules) to one litre of an appropriate infusion solution. Approximately a 0.1% solution will result from this procedure; that is, each mL will contain approximately 1 mg of XYLOCARD.

In those cases in which fluid restriction is medically desirable, a more concentrated solution may be prepared by adding one gram of XYLOCARD (i.e., contents of ten 5 mL ampoules) to 500 mL of diluent. Approximately a 0.2% solution will result from this procedure; that is, each mL will contain approximately 2 mg of XYLOCARD.

Solutions should be prepared using aseptic technique. As with all intravenous admixtures, dilution should be made just prior to administration. Prepared solutions should be used within 12 hours (see STORAGE, STABILITY AND DISPOSAL).

4 OVERDOSAGE

Symptoms of idiosyncratic reactions are described under ADVERSE REACTIONS.

Toxicity is initially manifested as CNS excitation and may result in a slow onset of nervousness, dizziness, delirium, blurred vision and tremors followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest.

Cardiovascular toxic effects are generally preceded by signs of toxicity in the central nervous system, unless the patient is receiving a general anaesthetic or is heavily sedated with medicines such as a benzodiazepine or a barbiturate. Toxic cardiovascular reactions are usually depressant in nature, may occur rapidly and with little warning and can lead to peripheral vasodilation, severe hypotension, conduction defects, bradycardia, asystole, arrhythmias, including ventricular tachycardia/fibrillation, cardiovascular collapse which may lead, to cardiac arrest, apnea, seizures, coma, respiratory arrest and death. In rare cases, cardiac arrest has occurred without prodromal CNS effects.

Treatment of Overdose

Discontinue administration of XYLOCARD. Maintain a patent airway and support ventilation with oxygen and assisted or controlled respiration as required. Should a convulsion persist despite ventilation therapy, small increments of a benzodiazepine (e.g. diazepam) or an ultra-short-acting barbiturate (e.g. thiopentone) may be given intravenously, bearing in mind that anticonvulsant drugs may also depress respiration and the circulation. Use of intravenous lipid emulsion should be considered.

Cardiovascular depression may require circulatory assistance in the form of elevation of legs, intravenous fluids and/or vasopressor agents, volume expanders and, if necessary, cardiac massage.

Lidocaine toxicity may appear at serum concentrations greater than 8 mg/L.
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.
Recovery is due to redistribution and metabolism of the drug. Recovery may be rapid unless large amounts of the drug (>5 µg/mL) have been administered.

If the convulsions do not stop spontaneously in 15-20 seconds, an anticonvulsant should be given intravenously. Intravenous administration of thiopental 100-150 mg will abort the convulsions rapidly. Alternatively, diazepam 5-10 mg i.v. may be used, although its action is slower.

Hypotension may be counteracted by giving sympathomimetic drugs (e.g., epinephrine). Adrenergic agents of both α-adrenoceptor stimulating and β-adrenoceptor stimulating type are generally effective. The bradycardia may be treated with parasympatholytic agents.

Should circulatory arrest occur, immediate cardiopulmonary resuscitation should be instituted. Continued optimal 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.

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

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	20 mg/ mL	Sodium chloride, sodium hydroxide and/or hydrochloric acid, water for injection

XYLOCARD 100 mg is available in a 5 mL glass ampoule (contains 20 mg/mL, a 2% solution). Each carton contains 10 ampoules with a leaflet.

See DOSAGE AND ADMINISTRATION section for instructions regarding preparation of solutions for continuous intravenous infusion.

6 WARNINGS AND PRECAUTIONS

General

This drug requires administration by experienced healthcare professionals.

Constant ECG monitoring is essential for the proper administration of XYLOCARD intravenously. Signs of excessive depression of cardiac conductivity, such as prolongation of PR interval and QRS complex, and the appearance of aggravation of arrhythmias, should be followed by prompt cessation of the intravenous infusion.

It is mandatory to have emergency resuscitative equipment and drugs immediately available to manage possible adverse reactions involving the cardiovascular, respiratory, or central nervous systems.

In emergency situations, when a ventricular rhythm disorder is suspected, and ECG equipment is not available, a single dose may be administered when the physician in attendance has determined that the potential benefits outweigh the possible risks. If possible, emergency resuscitative equipment and drugs should be available.

XYLOCARD should be used with caution in patients with:

- bradycardia,
- severe digitalis intoxication,
- first or second-degree heart block in the absence of a pacemaker
- hypokalaemia
- impaired hepatic function
- porphyria
- epilepsy
- impaired cardiac conduction
- impaired renal function
- severe shock
- cardiac decompensation
- hypotension
- posterior diaphragmal infarction with a tendency towards development of heart block.

Lower doses should be used in patients with congestive cardiac failure and following cardiac surgery.

Since CNS effects may not be apparent as an initial manifestation of toxicity, circulatory collapse should be monitored in unconscious patients.

Intravenous administration of XYLOCARD is sometimes accompanied by a hypotensive response, and, in overdosage, this may be precipitous. For this reason the intravenous dose should not exceed 100 mg in a single injection, and no more than 200-300 mg in a one hour period (see DOSAGE and ADMINISTRATION). When high doses are used and the patient's myocardial function is impaired, combination with other drugs which reduce the excitability of cardiac muscle requires caution.

Repeated doses of XYLOCARD may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites. Tolerance to elevated blood levels varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with their age and physical condition. XYLOCARD should also be used with caution in patients with epilepsy, impaired cardiac conduction, bradycardia, impaired hepatic function or renal function and in severe shock.

Carcinogenesis and Mutagenesis
Long term studies in animals to evaluate the carcinogenic and mutagenic potential or the effect on fertility of lidocaine HCl have not been conducted.

Hematologic
Theoretical evidence suggests that lidocaine may have porphyrogenic properties. The clinical significance of this is unknown. Caution should be exercised if intravenous lidocaine (XYLOCARD) is administered to patients with acute porphyria.

Hepatic/Biliary/Pancreatic
Caution should be employed in the repeated use of XYLOCARD in patients with severe liver disease, since possible accumulation of lidocaine or its metabolites may lead to toxic phenomena.

Renal
Caution should be employed in the repeated use of XYLOCARD in patients with severe renal disease, since possible accumulation of lidocaine or its metabolites may lead to toxic phenomena.

Sexual Health

Fertility: Studies of lidocaine in animals to evaluate the effect on fertility have not been conducted.

6.1 Special Populations

6.1.1 Pregnant Women

Lidocaine crosses the placenta. Animal studies have revealed no evidence of harm to the fetus. Although lidocaine has been used extensively for surgical procedures during pregnancy with no reports of ill effects to mother or fetus, there are no adequate and well-controlled studies in pregnant women of the effects of lidocaine on the developing fetus. XYLOCARD should not be administered during pregnancy, particularly at early stage, unless the benefits are considered to outweigh the risks.

6.1.2 Breast-feeding

Lidocaine passes into breast milk. One case report calculated that breastmilk contained ~40% of the maternal serum concentration after two boluses and seven hours of infusion, potentially resulting in a dose up to ~1.5 mg of lidocaine per day in the infant. The amount of lidocaine appearing in breast milk from the nursing mother receiving parenteral lidocaine is therefore unlikely to lead a significant accumulation of the parent drug in the breast fed infant. The remote possibility of an idiosyncratic or allergic reaction in the breast fed infant from lidocaine remained to be determined.

6.1.3 Geriatrics

A reduction in dosage may be necessary for elderly patients, particularly those with compromised cardiovascular and/or hepatic function and/or prolonged infusion. The doses should be adjusted individually to the patients' age and body weight. Dosages may need adaptation as cardiac output and hepatic blood flow decrease with advanced age indicating a decreased clearance of lidocaine

6.1.4 Population with impaired organ functions

Use in patients with impaired hepatic function

Patients with reduced hepatic blood flow or function have a longer lidocaine half-life and lower clearance and may therefore require a reduction in dosage.

Use in patients with impaired renal function

Impairment of renal function is unlikely to affect lidocaine clearance in the short term (24 hours). However, toxicity due to accumulation of lidocaine and its metabolites may develop with prolonged or repeated administration.

7 ADVERSE REACTIONS

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

Common adverse reactions are those from the central and peripheral nervous system. They occur in 5-10% of the patients and are mostly dose-related. The following definitions of frequencies are used: Very common (≥ 10%), common (1 – 9.9%), uncommon (0.1 – 0.9%), rare (0.01 – 0.09%) and very rare (< 0.01%).

Systemic reactions of the following types have been reported from post-marketing data:

Central Nervous System
CNS manifestations are excitatory and/or depressant. Common adverse reactions are circumoral paresthesia, dizziness and drowsiness. Rare adverse reactions would include: persistent dizziness, lightheadedness, nervousness, apprehension, euphoria, confusion, hyperacusis, tinnitus, blurred vision, vomiting, and sensations of heat, cold or numbness, twitching, tremors, convulsions, unconsciousness, apnea, respiratory depression and arrest. The excitatory manifestations 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
Rare cardiovascular manifestations are usually depressant and are characterized by bradycardia, hypotension, asystole and cardiovascular collapse which may lead to cardiac arrest. Arrhythmias, including ventricular tachycardia/ventricular fibrillation have also been reported.

Hematologic System
Very rarely, neonatal methaemoglobinaemia can occur (see WARNINGS AND PRECAUTIONS).

Immune System
Allergic reactions are characterized by cutaneous lesions, urticaria, edema, or in the most severe and very rare instances, hypersensitivity including anaphylactic shock. Allergic reactions of the amide type are rare and may occur as a result of sensitivity either to the drug itself, or to other components of the formulation.

Idiosyncratic reactions have been reported at low doses in some patients. Cross-sensitivity between XYLOCARD and procainamide or XYLOCARD and quinidine have not been reported.

8 DRUG INTERACTIONS

8.1 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Lidocaine is mainly metabolized in the liver by CYP1A2 and CYP3A4 (see Pharmacokinetics). Since the affinity of lidocaine to CYP1A2 and CYP3A4 is very low compared to therapeutic plasma concentrations, it is less likely that the metabolism of substrates for these enzymes will be inhibited when coadministered with lidocaine. However, there is a potential for influence of other drugs on the plasma levels/effect of lidocaine, e.g. strong inhibitors or inducers of CYP1A2 and/or CYP3A4 and drugs that affect liver blood flow (see Table 3).

Table 3 - Established or Potential Drug-Drug Interactions

Name	Reference	Effect	Clinical comment
Strong inhibitors of CYP1A2 (fluvoxamine)	CT	Coadministration of fluvoxamine reduced [41%] the elimination of lidocaine in healthy subjects. Given concomitantly with lidocaine, strong inhibitors of CYP1A2 can cause a metabolic interaction leading to increased lidocaine plasma concentrations.	Therefore, coadministration of lidocaine should be avoided in patients treated with strong inhibitors of CYP1A2, such as fluvoxamine.
CYP1A2 inducers (Phenytoin)	T	During concomitant administration of lidocaine and CYP1A2 inducers, plasma levels/effect of lidocaine may decrease.	Higher dose of lidocaine may be required.
Strong inhibitors of CYP3A4 (erythromycin, itraconazole)	CT	Erythromycin and itraconazole have each been shown to have a **modest** or no effect on the pharmacokinetics of intravenous lidocaine (0-18% decreased elimination with erythromycin but no effect with itraconazole).	No dose adjustment seems required.
CYP3A4 inducers (carbamazepine , phenobarbital, phenytoin, primidone)	CT	Concomitant administration with carbamazepine, phenobarbital, phenytoin, and primidone, may slightly decrease plasma levels of lidocaine (<10%).	No dose adjustment seems required.

Beta-blockers (propranolol, metoprolol, nadolol)	CT	Propranolol, metoprolol, and nadolol have been reported to reduce intravenous lidocaine clearance, probably through effects on hepatic blood flow and/or metabolism, and may increase the plasma concentration of lidocaine by about 30%, less with metoprolol.	Therefore, concomitant administration of beta-blockers with lidocaine should be avoided. If not possible, close monitoring and dose adjustment may be required.
Cimetidine	CT	Cimetidine has an unspecific inhibitory effect on CYP (including CYP1A2 and CYP 3A4) mediated metabolism and reduces hepatic blood flow. Clinical experiments showed that the concomitant administration of cimetidine reduces the systemic clearance of lidocaine and increases lidocaine serum concentration by as much as 50%. Thus, therapeutic serum levels of lidocaine may rise to toxic levels when cimetidine is used concomitantly. Ranitidine has not displayed this effect.	Therefore, concomitant administration with lidocaine should be avoided. If not possible, close monitoring and dose adjustment of lidocaine and/or cimetidine may be required.
Amiodarone	CT, C	Like cimetidine, amiodarone has an unspecific inhibitory effect on CYP mediated metabolism. Concomitant administration has resulted in increased plasma levels of lidocaine and may result in toxic effects.	Therefore, concomitant administration with lidocaine should be avoided. If not possible, close monitoring and dose adjustment of lidocaine and/or amiodarone may be required.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

8.2 Drug-Food Interactions

Interaction with food have not been established

8.3 Drug-herb interactions

Interaction with herbal products have not been established

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

The mode of action of the antiarrhythmic effect of XYLOCARD (lidocaine hydrochloride) appears to be similar to that of procaine, procainamide, and quinidine. Ventricular excitability is depressed and the stimulation threshold of the ventricle is increased during diastole. The sinoatrial node is, however, unaffected. In contrast to the latter three drugs, XYLOCARD in therapeutic doses does not produce a significant decrease in arterial pressure or in cardiac contractile force. In larger doses, XYLOCARD may produce circulatory depression, but the magnitude of the change is less than that found with comparable doses of procainamide. Neither drug appreciably affects the duration of the absolute refractory period.

9.2 Pharmacodynamics

Lidocaine hydrochloride is a well-known anesthetic agent which has been used for many years for regional and topical anesthesia. However, it has been demonstrated to exert an antiarrhythmic effect by increasing the electrical stimulation threshold of the ventricle during diastole.

In decerebrated, vagotomized cats with stellate ganglia destroyed, lidocaine hydrochloride intravenous suppressed cardiac arrhythmias induced by faradic stimulation, barium chloride and epinephrine. The minimal effective dose was 0.5 mg per kg. This was 4 and 5 times less than the minimal doses of procaine and procainamide respectively.

In anesthetized open-chest dogs, lidocaine hydrochloride 5 mg per kg intravenously reduced the duration of methacholine-induced auricular arrhythmias by 55.5%. The effect of quinidine sulphate at the same dose was a reduction 46.5%. Ventricular arrhythmias induced by coronary ligation were controlled by total intravenous doses of 50 mg/kg. Convulsions and vomiting were produced and death occurred in 1 of 6 dogs at 75.5 mg/kg. In the same preparation, interruption of the arrhythmia was obtained by an injection of 15 mg/kg directly into the ventricle. In normothermic or hypothermic dogs the same effect was obtained in ventricular fibrillation induced by mechanical stimulation.

In anesthetized dogs, intravenous infusions of 40-80 mg converted digitalis-induced ventricular arrhythmia to sinus rhythm. Also, acetylstrophanthidin-induced ventricular tachycardia was suppressed at a minimal effective dose of lidocaine hydrochloride of 1 mg/kg intravenously. Digitalis-induced ventricular tachycardia, which failed to respond to electro- shock was converted to normal sinus rhythm by intravenous injection of lidocaine hydrochloride 100 mg and ventricular tachycardia, induced by ouabain was converted to supraventricular tachycardia by intravenous injection of 1-2 mg/kg.

In unanesthetized dogs with ventricular arrhythmia induced by coronary occlusion, intravenous injections of 5-10 mg/kg suppressed the arrhythmia. This effect could be maintained by intravenous infusion with calculated lidocaine hydrochloride blood levels of 1-3 µg/mL.

Other effects in anesthetized intact dogs were depression of myocardial contractile force, heart rate and femoral arterial pressure with lidocaine hydrochloride 0.5 to 6 mg/kg intravenously. At 2.0 mg/kg intra-arterially the same effects were obtained but there was less diminution of contractile force. In both anesthetized and conscious dogs, lidocaine hydrochloride in rapid intravenous injection of 2, 4 and 8 mg/kg caused transient decrease of systolic arterial pressure, venous pressure, cardiac output, mean ejection rate, rate of development of arterial pressure, stroke work and calculated peripheral resistance. Heart rate was slightly increased. Effects were greatest at 8 mg/kg and were more pronounced and of longer duration in anesthetized dogs. There was return to basal levels in 3-5 minutes.

9.3 Pharmacokinetics

The pharmacokinetics of lidocaine hydrochloride has been studied in normal subjects and in patients.

Following a single intravenous injection, or termination of a continuous intravenous infusion, declining plasma concentration follows a biphasic curve. Plasma half-lives of 8 to 15 minutes have been reported for the initial phase. Various studies have reported the mean half-life at the terminal phase to be in the range 1.2 to 1.9 hours. The minimum effective antiarrhythmic plasma concentration of lidocaine hydrochloride has been reported to be in the range of 1.0 to 1.2 µg/mL; concentrations higher than 5-6 µg/mL are associated with an increased risk of toxicity.

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 (3%) of lidocaine is excreted unchanged in the urine. The hepatic clearance of lidocaine is expected to depend largely on blood flow.

Absorption, Distribution, Metabolism, and Excretion

Absorption: In rats which received 14C-labelled lidocaine hydrochloride by intravenous injection, rapid uptake by all tissues was noted. Tissue distribution studies in monkeys have indicated: high affinity for lung, spleen, kidney, stomach and adipose tissue; moderate affinity for brain and most gastrointestinal organs; and low affinity for musculoskeletal tissue and skin. Similar distribution has been observed in the dog.

Distributions: Studies on plasma binding in monkey and man have indicated approximately 60% plasma binding within the plasma concentration range usually seen in clinical use. However, plasma binding was markedly reduced at concentrations of lidocaine hydrochloride exceeding 10 µg/mL, presumably due to saturation of the binding sites.

Metabolism: Studies in rabbit and rat have demonstrated that the liver is the principal site of metabolism. In man, hepatic clearance studies have shown that approximately 70% of the lidocaine hydrochloride passing through the liver was extracted. Microsomal enzyme systems are primarily responsible for hepatic metabolism. The major degradative pathway appears to be

by conversion to monoethylglycinexylidide, followed by hydrolysis to 2,6,-xylidine; further conversion to 4-hydroxy-2,6-xylidine appears to occur in man.

Excretion: Up to 10% of administered lidocaine hydrochloride may be excreted in the urine as unchanged drug. Although biliary secretion and intestinal absorption of lidocaine hydrochloride metabolites have been reported in rats, there is no evidence of biliary secretion in man.

10 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15 – 25°C).

XYLOCARD solutions are preservative free and are for single use. Discard unused portion after a maximum of 12 hours.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

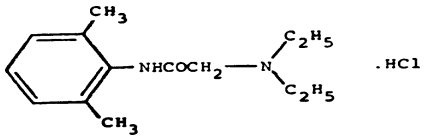
Drug Substance

Proper name: Lidocaine hydrochloride

Chemical name: 2-(Diethylamino)-2',6'-acetoxylidide monohydro-chloride monohydrate

Molecular formula and molecular mass: $C_{14}H_{22}N2O•H_2O$ and 288.82 Daltons (Da).

Structural formula:



Physicochemical properties: Lidocaine hydrochloride is a white, odourless, crystalline powder which has a slightly bitter taste. It is very soluble in water and in alcohol, soluble in chloroform and insoluble in ether.

12 NON-CLINICAL TOXICOLOGY

Acute Toxicity

SPECIES	SEX	ROUTE	LD_{50}(mg/kg)
mice	F	i.v.	17.9
mice	F	i.p.	164
mice	F	i.m.	200
mice	M	i.m.	154
rat	F	i.v.	19.7
rat	M	i.v.	21.4
dog	M & F	i.m.	100
guinea pig	F	i.m.	73
guinea pig	M	i.m.	67
rabbit	M	i.m.	450

Acute intravenous studies were performed in rabbits which received six serial injections of 1, 2, 3, 4 or 5 mg/kg at 15 minute intervals. At the 2 mg/kg dose level, slight depression was seen, beginning with the third injection. At 3 mg/kg there was depression and rigid extension of limbs after the last 5 injections. At 5 mg/kg there was severe depression and rigid limb extension after each injection; loss of righting reflex and convulsions began with the second injection and there was gasping for breath after each of the last injections.

Dogs were given intravenous incremental doses at 30 minute intervals until death occurred. Doses of 0.1 to 3.0 mg/kg were tolerated with minimal CNS or cardiovascular effects. Convulsions, mydriasis, salivation, urination and defecation were observed after 10 mg/kg.

Respiratory arrest and death occurred in one dog after 30 mg/kg; cardiovascular collapse, respiratory arrest and death occurred in remaining animals after 100 mg/kg. Mean arterial blood pressure and heart rate increased briefly, beginning at 3.0 mg/kg, and decreased after 100 mg/kg. Myocardial conduction time was not significantly changed prior to 100 mg/kg administration.

Acute local responses were studied in rats and rabbits following single intramuscular injections of 2%, 4%, 6%, 8% and 10% solutions of lidocaine hydrochloride. Microscopic examination revealed inflammatory changes with all solutions. In general, reactions produced by 2% solutions were least, although lesions seen with all other concentrations were of similar degree. In rabbits sacrificed seven days after intramuscular administration, there was evidence of marked muscle fiber regeneration; after 30 days there was virtually complete resolution of inflammatory changes at the site of injection.

Subacute Toxicity

In one study, dogs received daily intravenous injections according to the following schedule:

0.1 mg/kg for 7 days, 0.3 mg/kg for 7 days, 1 mg/kg for 7 days and 3 mg/kg for 21 days. Mild transient convulsions were seen in one dog at the high dose level. No other signs of toxicity were observed. Gross and microscopic examination at autopsy did not reveal any drug related effects.
In a second study, dogs received daily intravenous injections of 2.5, 5 or 10 mg/kg for 28 days. No overt symptoms were observed at the low dose level. At the 5 mg/kg level there was transient sedation, ataxia, head tremor, prostration and emesis. At the 10 mg/kg level there were severe tremors, muscular weakness, ataxia, prostration and convulsions, although animals recovered within 5-10 minutes. No ECG or hemochemistry changes were seen. No evidence of drug-related pathology was seen at autopsy. Injection sites showed inflammatory changes in drug and saline-treated animals.

In rats which received daily intravenous doses of 1.5, 4.5 or 15.0 mg/kg for 14 days, overt effects were observed only at the 15.0 mg/kg level, at which convulsions and death occurred. Increased blood glucose levels were seen in male rats at all dose levels. At autopsy, no changes were attributed to drug treatment. Mild inflammatory changes were seen at injection sites.

12.2 Carcinogenicity and Mutagenicity

Studies of lidocaine in animals to evaluate the carcinogenic and mutagenic potential have not been conducted.

12.3 Reproductive and Developmental Toxicology

Studies of lidocaine in animals to evaluate the effect on fertility have not been conducted.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrXYLOCARD®
lidocaine hydrochloride injection

Read this carefully before you start taking **XYLOCARD** 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 **XYLOCARD**.

What is XYLOCARD used for?

XYLOCARD is used to treat abnormally fast heart rhythms that may occur during:

- heart surgery or other procedures
- a heart attack or other heart conditions.

How does XYLOCARD work?

XYLOCARD is an antiarrhythmic drug. It works to reduce the number of heartbeats per minute and helps return the heartbeat to normal.

What are the ingredients in XYLOCARD?

Medicinal ingredients: lidocaine hydrochloride
Non-medicinal ingredients: Sodium chloride, sodium hydroxide (and/or hydrochloric acid) and water for injection

XYLOCARD comes in the following dosage forms:

Solution: 20 mg/mL

Do not use XYLOCARD if you:

- are allergic or sensitive to lidocaine hydrochloride, to any of the nonmedicinal ingredients in XYLOCARD or other local anaesthetics (e.g. prilocaine, mepivacaine or bupivacaine).
- have a heart condition such as, Adams-Stokes syndrome, or severe degrees of sinoatrial, atrioventricular or intraventricular block.
- have supraventricular arrhythmias
- have severe myocardial depression

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

- have a slow heartbeat.
- have low levels of potassium in your blood.
- have been taking a drug called digitalis.
- have epilepsy.
- have low blood pressure.
- have problems with your heart, liver or kidneys.
- have been diagnosed with porphyria.
- are experiencing severe shock.
- are pregnant or plan to become pregnant.
- are breastfeeding or planning to breastfeed.

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 XYLOCARD:
- Antiarrhythmic drugs used to treat heart problems such as; mexiletine, amiodaraone.
- Cimetidine used for stomach problems.
- Fluvoxamine used to treat depression.
- Beta-blockers, used to treat heart problems, such as; metoprolol, nadolol, propranolol.
- Drugs used to treat epilepsy and seizures such as; carbamazepine, phenobarbital, phenytoin, primidone.

How to take XYLOCARD?:
- XYLOCARD will be given as an intravenous injection by a healthcare professional.
- Your heart rate and blood pressure will be monitored while you are receiving XYLOCARD.
- Your doctor may give you one single injection of XYLOCARD. Depending on your condition, you may need a continuous infusion of XYLOCARD.

Usual dose:
The doctor will determine your dose based on your individual needs.

Overdose:
Serious side effects can occur if you are given too much XYLOCARD. Early signs that you have been given too much XYLOCARD include:
- numbness of the lips and around the mouth,
- lightheadedness or dizziness,
- blurred vision,
- hearing problems and/ or ringing in the ears.

If you think you, or a person you are caring for, have been given too much XYLOCARD, 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 XYLOCARD?

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

Side effects may include:
- nausea, vomiting
- dizziness, lightheadedness
- drowsiness
- sensations of heat, cold or numbness
- sensitivity to sounds, ringing in the ears

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	
COMMON **Abnormal sensations:** pins and needles, numbness around the mouth and/or of the tongue		√	
Slow or irregular heartbeat		√	
Low blood pressure: dizziness, fainting, lightheadedness, fatigue May occur when you go from lying or sitting to standing up.		√	
RARE **Prolonged dizziness**		√	
Heart attack: severe crushing chest pain, irregular heartbeat, shortness of breath			√
Allergic reaction: rash, hives, swelling of the face, lips, tongue or throat, anaphylactic reactions, difficulty swallowing or breathing			√
Nerve injury: tingling of the arms and legs		√	
Blurred vision		√	
Nervous system disorders: nervousness, apprehension, euphoria, confusion, twitching, tremors, convulsions, unconsciousness			√
Respiratory arrest: severe trouble breathing, unconsciousness			√

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 (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 - 25ºC).
Keep out of reach and sight of children.

If you want more information about XYLOCARD:

- 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 www.aspenpharma.ca, or by calling 1- 844-330-1213.

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