Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Xylocaine 2% with Adrenaline (Epinephrine) (1:200,000) Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains lidocaine hydrochloride equivalent to 20 mg of lidocaine hydrochloride anhydrous (400 mg per 20 ml vial) and adrenaline (epinephrine) tartrate equivalent to 5 micrograms of adrenaline (epinephrine) (100 micrograms per 20 ml vial).

Excipients with known effect:

Each ml of solution also contains 0.5 mg sodium metabisulphite (E223), 1 mg methyl parahydroxybenzoate (E218) and 2.49 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless, sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Xylocaine 2% with Adrenaline is indicated for local anaesthesia in adults and children above 12 years of age.

4.2 Posology and method of administration

Adults and children above 12 years of age

Route: Infiltration by injection

The dosage is adjusted according to the response of the patient and the site of administration. The lowest concentration and smallest dose producing the required effect should be given (see section 4.4). Individual variations in onset and duration occur. Solutions containing adrenaline may be used to prolong anaesthesia and reduce systemic absorption (see section 5.2). The risk of systemic effects of adrenaline with large volumes of adrenaline-containing solutions should be considered.

The maximum single dose of Xylocaine, when given with adrenaline, is 7 mg/kg or 500 mg total, whichever is the lower. Concomitant use of lidocaine via other routes should be borne in mind.

The following table is a guide to dosage for the more commonly used techniques in the average adult. The figures reflect the expected average dose range needed. Standard textbooks should be consulted for factors affecting specific block techniques and for individual patient requirements.

The clinician's experience and knowledge of the patient's physical status are of importance in calculating the required dose. Elderly or debilitated patients require smaller doses, commensurate with age and physical status.

Type of block	% Conc.	Each dose		Indication
		ml	mg	
Field Block (e.g. minor nerve blocks and infiltration)				
Infiltration	1	up to 30	up to 300	Surgical operations

Intercostals (per nerve) (maximal number of nerves blocked at same time should be = 8)	1	2-5 Max 30 ml	20-50 Max 300 mg	Surgical operations Postoperative pain and fractured ribs
Pudendal	1	10	100	Instrumental delivery
Major Nerve Block				
Paracervical (each side)	1	10	100	Surgical operations and dilatation of cervix Obstetric pain relief
Sciatic	2	15	300	Surgical operations
3 in 1 (femoral, obturator and lateral cutaneous)	1	30	300	Surgical operations

Xylocaine with adrenaline solution for injection contains methyl parahydroxybenzoate (methylparaben) as a preservative and should not be used for anaesthesia by the intrathecal, intracisternal or intra- or retro-bulbar routes.

In general, surgical anaesthesia requires the use of higher concentrations and doses. When blocking smaller nerves, or when a less intense block is required, the use of a lower concentration is indicated. The volume of drug used will affect the extent and spread of anaesthesia.

Care should be taken to prevent acute toxic reactions by avoiding intravascular injection. Careful aspiration before and during the injection is recommended. An accidental intravascular injection may be recognised by a temporary increase in heart rate. The main dose should be injected slowly, at a rate of 100–200 mg/min, or in incremental doses, while closely observing the patient's vital functions and maintaining verbal contact. If toxic symptoms occur, the injection should be stopped immediately.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to local anaesthetics of the amide type.

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

Hypersensitivity to sodium metabisulphite.

Use intravenously or intrathecally.

Solutions containing adrenaline or other vasoconstrictor agents should not be used in the production of end-organ anaesthesia e.g. fingers, toes, ear lobe and penis, or in spinal anaesthesia.

4.4 Special warnings and precautions for use

Regional anaesthetic procedures should always be performed in a properly equipped and staffed area. Equipment and drugs necessary for monitoring and emergency resuscitation should be immediately available. When performing major blocks, or using large doses, an IV cannula should be inserted before the local anaesthetic is injected. Clinicians should have received adequate and appropriate training in the procedure to be performed and should be familiar with the diagnosis and treatment of side effects, systemic toxicity or other complications (see sections 4.8 and 4.9).

Care should be taken to prevent acute toxic reactions by avoiding intravascular injection. Careful aspiration before and during the injection is recommended. An accidental intravascular injection may be recognised by a temporary increase in heart rate. The main dose should be injected slowly at a rate of 100–200 mg/min, or in incremental doses, while keeping in constant verbal contact with the patient. If toxic symptoms occur, the injection should be stopped immediately.

The effect of local anaesthetics may be reduced if an injection is made into an inflamed or infected area, absorption from these areas is also increased.

Attempts should be made to optimise the patient's condition before major blocks.

Although regional anaesthesia is frequently the optimal anaesthetic technique, some patients require special attention in order to reduce the risk of dangerous side effects:

- Patients with epilepsy.

- The elderly and patients in poor general condition.

- Patients with partial or complete heart conduction block - due to the fact that local anaesthetics may depress myocardial conduction.

- Patients with advanced liver disease or severe renal dysfunction.

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

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

Certain local anaesthetic procedures may be associated with serious adverse reactions, regardless of the local anaesthetic drug used, e.g.

- Injections in the head and neck regions may be made inadvertently into an artery, causing cerebral symptoms even at low doses.

- Paracervical block can sometimes cause foetal bradycardia/tachycardia, and careful monitoring of the foetal heart rate is necessary.

- There have been post-marketing reports of chondrolysis in patients receiving post-operative intra-articular continuous infusion of local anaesthetics. The majority of reported cases of chondrolysis have involved the shoulder joint. Due to multiple contributing factors and inconsistency in the scientific literature regarding mechanism of action, causality has not been established. Intra-articular continuous infusion is not an approved indication for Xylocaine.

Solutions containing adrenaline should be used with caution in patients with hypertension, cardiac disease, cerebrovascular insufficiency, hyperthyroidosis, advanced diabetes and any other pathological condition that may be aggravated by the effects of adrenaline.

Xylocaine with adrenaline contains sodium metabisulphite, which may cause allergic reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

The overall prevalence of sulphite sensitivity in the general population is unknown and probably low.

Sulphite sensitivity is seen more frequently in asthmatic than non-asthmatic people.

Xylocaine with adrenaline contains methyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed) and exceptionally, bronchospasm.

Xylocaine with adrenaline solution for injection contains methyl parahydroxybenzoate (methylparaben) as a preservative and should not be used for anaesthesia by the intrathecal, intracisternal or intra- or retro-bulbar routes.

4.5 Interaction with other medicinal products and other forms of interactions

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

Drugs that reduce the clearance of lidocaine (e.g. cimetidine or betablockers) may cause potentially toxic plasma concentrations when lidocaine is given in repeated high doses over a long time period. Such interactions should be of no clinical importance following short term treatment with lidocaine at recommended doses.

Solutions containing adrenaline should generally be avoided or used with care in patients receiving monoamine-oxidase inhibitors or tricyclic antidepressants since severe, prolonged hypertension may result. In addition, the concurrent use of adrenaline-containing solutions and oxytocic drugs of the ergot type may cause severe, persistent hypertension and possibly cerebrovascular and cardiac accidents. Phenothiazines and butyrophenones may oppose the vasoconstrictor effects of adrenaline giving rise to hypotensive responses and tachycardia.

Solutions containing adrenaline should generally be used with caution in patients undergoing general anaesthesia with inhalation agents such as halothane and enflurane, due to the risk of serious cardiac arrhythmias.

Non-cardioselective betablockers such as propranolol enhance the pressor effects of adrenaline, which may lead to severe hypertension and bradycardia.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although there is no evidence from animal studies of harm to the foetus, as with all drugs, Xylocaine should not be given during early pregnancy unless the benefits are considered to outweigh the risks.

The addition of adrenaline may potentially decrease uterine blood flow and contractility, especially after inadvertent injection into maternal blood vessels.

Foetal adverse effects due to local anaesthetics, such as foetal bradycardia, seem to be most apparent in paracervical block anaesthesia. Such effects may be due to high concentrations of anaesthetic reaching the foetus.

Breast-feeding
Lidocaine may enter the mother's milk, but in such small amounts that there is generally no risk of this affecting the neonate. It is not known whether adrenaline enters breast milk or not, but it is unlikely to affect the breast-fed child.

4.7 Effects on ability to drive and use machines

Besides the direct anaesthetic affect, local anaesthetics may have a very mild effect on mental function and co-ordination, even in the absence of overt CNS toxicity, and may temporarily impair locomotion and alertness.

4.8 Undesirable effects

In common with other local anaesthetics, adverse reactions to Xylocaine with adrenaline are rare and are usually the result of excessively high blood concentrations due to inadvertent intravascular injection, excessive dosage, rapid absorption or occasionally to hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. In such circumstances systemic effects occur involving the central nervous system and/or the cardiovascular system.

The adverse reaction profile for Xylocaine with adrenaline is similar to those of other amide local anaesthetics. Adverse reactions caused by the drug *per se* are difficult to distinguish from the physiological effects of the nerve block (e.g. decrease in blood pressure, bradycardia), events caused directly (e.g. nerve trauma) or indirectly by the needle puncture.

Tabulated list of adverse reactions

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) or not known (cannot be estimated from the available data).

The following table gives a list of the frequencies of undesirable effects:

System Organ Class	Frequency Classification	Adverse Drug Reaction
Immune system disorders	Rare	Allergic reactions, anaphylactic reaction

Nervous system disorders	Common	Paraesthesia, dizziness
	Uncommon	Signs and symptoms of CNS toxicity (convulsions, numbness of tongue and paraesthesia circumoral, tinnitus, tremor, dysarthria, hyperacusis, visual disturbances, CNS depression)
	Rare	Neuropathy, peripheral nerve injury, arachnoiditis
Eye disorders	Rare	Diplopia
Cardiac disorders	Common	Bradycardia
	Rare	Cardiac arrest, cardiac arrhythmias
Vascular disorders	Common	Hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Rare	Respiratory depression
Gastrointestinal disorders	Common	Nausea, vomiting

Acute systemic toxicity

Systemic toxic reactions primarily involve the central nervous system (CNS) and the cardiovascular system (CVS). Such reactions are caused by high blood concentrations of a local anaesthetic, which may appear due to (accidental) intravascular injection, overdose or exceptionally rapid absorption from highly vascularised areas (see section 4.9). CNS reactions are similar for all amide local anaesthetics, while cardiac reactions are more dependent on the drug, both quantitatively and qualitatively. Signs of toxicity in the central nervous system generally precede cardiovascular toxic effects, unless the patient is receiving a general anaesthetic or is heavily sedated with drugs such as benzodiazepine or barbiturate.

Central nervous system toxicity is a graded response with symptoms and signs of escalating severity. The first symptoms are usually, circumoral paraesthesia, numbness of the tongue, light-headedness, hyperacusis, tinnitus and visual disturbances. Dysarthria, muscular twitching or tremors are more serious and precede the onset of generalised convulsions. These signs must not be mistaken for a neurotic behaviour. 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 respiration and possible loss of functional airways. In severe cases apnoea may occur. Acidosis hyperkalaemia, hypocalcaemia and hypoxia increase and extend the toxic effects of local anaesthetics.

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

Cardiovascular system toxicity may be seen in severe cases and is generally preceded by signs of toxicity in the central nervous system. In patients under heavy sedation or receiving a general anaesthetic, prodromal CNS symptoms may be absent. Hypotension, bradycardia, arrhythmia and even cardiac arrest may occur as a result of high systemic concentrations of local anaesthetics, but in rare cases cardiac arrest has occurred without prodromal CNS effects.

In children, early signs of local anaesthetic toxicity may be difficult to detect in cases where the block is given during general anaesthesia.

Treatment of acute toxicity

If signs of acute systemic toxicity appear, injection of the local anaesthetic should be stopped immediately and CNS symptoms (convulsion, CNS depression) must promptly be treated with appropriate airway/respiratory support and the administration of anticonvulsant drugs.

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

If cardiovascular depression occurs (hypotension, bradycardia), appropriate treatment with intravenous fluids, vasopressor, chronotropic and or inotropic agents should be considered. Children should be given doses commensurate with age and weight.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected

adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie

4.9 Overdose

Accidental intravascular injections of local anaesthetics may cause immediate (within seconds to a few minutes) systemic toxic reactions. In the event of overdose, systemic toxicity appears later (15-60 minutes after injection) due to the slower increase in local anaesthetic blood concentration(see section 4.8).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): N01B B52

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

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

Central nervous system toxicity occurs at lower plasma concentrations (see section 4.8), and usually precedes the cardiovascular effects. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

5.2 Pharmacokinetic properties

Lidocaine has a pKa of 7.9, an oil/water partition coefficient of 2.9, and is 65% protein-bound (mainly to alpha-1-acid glycoprotein) in plasma.

The rate of absorption depends upon the dose, the route of administration and the vascularity of the injection site. Intercostal blocks give the highest peak plasma concentrations (approx. 1.5 micrograms/ml for every 100 mg injected), while abdominal subcutaneous injections give the lowest (approx. 0.5 micrograms/ml per 100 mg injected). Epidural and major nerve blocks are intermediate.

Absorption is considerably slowed by the addition of adrenaline, although it also depends on the site of injection.

Peak plasma concentrations are reduced by 50% following subcutaneous injection, by 30% following epidural injection and by 20% following intercostal block if adrenaline 5 micrograms/ml is added.

Lidocaine shows complete and biphasic absorption from the epidural space with half-lives in the order of 9.3 min and 82 min respectively. The slow absorption is rate-limiting in the elimination following epidural injection compared to intravenous injection.

Lidocaine has a total plasma clearance of 0.95 L/min, a volume of distribution at steady state of 91 L, 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 metabolising enzymes.

The elimination half-life in neonates (3.2 h) is approximately twice that of adults.

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 foetus is less that in the mother, the total plasma concentration will be greater in the mother, but the free concentrations will be the same.

Lidocaine is excreted in breast milk, but in such small quantities that there is no risk of affecting the child with therapeutic doses.

Only 2% of lidocaine is excreted unchanged. Most is metabolised 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.

5.3 Preclinical safety data

Genotoxictiy 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. The metabolite 2,6-dimethylaniline has been shown to have carcinogenicity potential in preclinical toxicological studies evaluating chronic exposure. Risk assessments comparing the calculated maximum human exposure from intermittent use of lidocaine, with the exposure used in preclinical studies, indicate a wide margin of safety for clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium metabisulphite (E223)
Methyl parahydroxybenzoate (E218)
Water for injections
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened: 2 years

Chemical and physical in-use stability has been demonstrated for 3 days at room temperature, 20-23°C. From a microbiological point of view, once opened, the product may be stored as long as the chemical-physical stability allows, i.e. 3 days at room temperature, 20-23°C. Other in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator between 2 and 8°C.

Keep the vials in the outer carton in order to protect from light.

For storage of product that has been opened please refer to section 6.3.

6.5 Nature and contents of container

Type I, Ph. Eur., clear colourless glass multidose vial with bromobutyl rubber stopper, containing 20 ml of solution.

Available as a single vial or a pack of 5 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/027/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1980

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10 DATE OF REVISION OF THE TEXT

February 2020