

**LIDOCAINE 10% W/W LOCAL ANAESTHETIC SPRAY
PL 20165/0009**

UKPAR

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**LIDOCAINE 10% W/W LOCAL ANAESTHETIC SPRAY
PL 20165/0009**

LAY SUMMARY

The MHRA has granted INyX Pharma Ltd, a Marketing Authorisation (licence) for the medicinal product Lidocaine 10% w/w Local Anaesthetic Spray (PL 20165/0009). This is a pharmacy-only medicine (P) used to help prevent pain during medical examinations and operations involving the nose, throat and sinuses; during childbirth and after childbirth if stitches are required and during dental procedures.

Lidocaine 10% w/w Local Anaesthetic Spray contains the active ingredient lidocaine, which works by stopping the nerves that sense pain from working temporarily and as a result the area that is to be treated becomes numb for a short time..

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of using Lidocaine 10% w/w Local Anaesthetic Spray outweigh the risks; hence a Marketing Authorisation has been granted.

**LIDOCAINE 10% W/W LOCAL ANAESTHETIC SPRAY
PL 20165/0009**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Lidocaine 10% w/w Local Anaesthetic Spray (PL 20165/0009) on 6th March 2007. The product is a pharmacy-only medicine.

This application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, as amended, referring to the original product Xylocaine Spray 10mg/dose pump spray (PL 14229/0021) granted to AstraZeneca UK Ltd (formerly Astra Pharmaceuticals Ltd) on 25th August 1989..

The products contain the active ingredient lidocaine, a local amide-type anaesthetic that interacts with voltage-sensitive sodium channels on the cell membrane. Topically, lidocaine is used as a surface anaesthetic and is rapidly and extensively absorbed following application to mucous membranes or damaged skin. It is, however, poorly absorbed systemically through intact skin.

Lidocaine 10% w/w Local Anaesthetic Spray is indicated for the prevention of pain during medical examinations and operations involving the nose, throat and sinuses; during childbirth and after childbirth if stitches are required and during dental procedures.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Lidocaine Base (Ph Eur)

Lidocaine Base (Ph Eur) is supplied as a white or almost white, crystalline powder, practically insoluble in water, very soluble in alcohol and methylene chloride, and freely soluble in ether. The melting point is between 66°C and 70°C, determined without previous drying.

It does not appear to exhibit polymorphism.

The drug substance specification provided is acceptable.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active lidocaine base is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated that support the retest period for the drug substance when stored in the proposed packaging.

Certificates of analysis for the reference standards and impurities have been provided.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely propylene glycol, saccharin sodium, absolute ethanol, purified water and banana flavour P473-1N1.

All excipients used comply with their respective British Pharmacopoeial monograph, with the exception of banana flavour P473-1N1 which complies with an in-house specification. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on the product. The results appear satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is package in clear Type I glass bottles of 60ml capacity with a metered pump and a polyethylene / polypropylene dip tube, which is crimped onto the neck of the bottle. The pump assembly is protected by a white polypropylene overcap. The polypropylene nozzle actuator (for directing the spray to the target surface area) is supplied separately inside the carton and replaces the overcap prior to use.

Specifications and certificates of analysis for all packaging have been provided. These are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are “Do not store above 30 degrees”.

Summary of Product Characteristics

This is satisfactory.

Labelling

This is satisfactory

Patient Information Leaflet

This is satisfactory.

The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

MAA Form

This is satisfactory.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.

CLINICAL ASSESSMENT

1. BACKGROUND

Lidocaine (lignocaine) has been in clinical use as a local anaesthetic and as an anti-arrhythmic agent since the 1940s. In local anaesthesia, lidocaine may be injected or applied topically to skin or mucous membranes in creams, ointments, suppositories, and sprays.

Lidocaine is used clinically as a local anaesthetic and as an antiarrhythmic, predominantly for ventricular tachycardias. In both instances, the therapeutic action of lidocaine depends on its ability to impair the generation and conduction of nerve impulses by interference with sodium channels. For antiarrhythmic uses, lidocaine is given intravenously because oral bioavailability is poor due to first pass metabolism in the liver. An intravenous infusion is usually employed, often after a bolus dose, to achieve and maintain blood levels required for the desired anti-arrhythmic effect (approximately 2-5 µg/mL).

Measurable concentrations of lidocaine in the blood also occur following local infiltration or topical application to achieve local anaesthesia. The rate of distribution of the drug away from the application site may be reduced when lidocaine is injected with a vasoconstricting agent. However, vasoconstriction is potentially hazardous in some types of local anaesthesia (eg. ring blocks) and is not applicable to topical applications.

Most of the adverse effects seen in association with use of the drug for local anaesthesia are related to actions which follow systemic distribution to sites distant from the area of local infiltration or topical application. For these reasons it is imperative that the dose of lidocaine applied for anaesthesia is metered, and that consideration is given to the likely extent of distribution and resulting concentrations which may be achieved in blood and tissues. Direct delivery of the drug to mucous membranes or to broken skin both result in much higher concentrations in blood compared with applications to intact skin. Thus, the amounts of drug which may be applied safely to various surfaces may be very different.

Nevertheless, lidocaine has been used extensively in local anaesthesia and is available in many different formulations. Apart from local infiltration in dentistry and minor surgery, the drug has proved useful for the topical anaesthetisation of mucous membranes prior to drainage and diagnostic procedures. In the latter areas of use, application of the drug in solution, sprayed over the target surface, has become a popular mode of delivery.

2. INDICATIONS

The indications proposed are identical to those approved for the reference product:

For the prevention of pain associated with the following procedures:

Otorhinolaryngology: *puncture of the maxillary sinus and minor surgical procedures in the nasal cavity, pharynx, and epipharynx. Paracentesis.*

Obstetrics: *During the final stages of delivery and before episiotomy and perineal suturing as supplementary pain control.*

Introduction of instruments and catheters into the respiratory and digestive tract: *provides surface anaesthesia for the oropharyngeal and tracheal areas to reduce*

reflex activity, attenuate haemodynamic response, and to facilitate inserion of the tube or the passage of instruments during endotracheal intubation, laryngoscopy, bronchoscopy and oesophagoscopy.

Dental practice: *Before injections, dental impressions, X-ray photography, removal of calculus, seating or adjustment of dentures.*

3. DOSE AND DOSE SCHEDULE

The recommendations are identical to those for the reference product and equate with maximum doses of 30 mg for maxillary sinus puncture, 50 mg in dental uses, and up to 200 mg for obstetric and instrumentation uses.

No mention is made of any dose adjustment which might be appropriate for children.

4. TOXICOLOGY

The pharmacological/toxicological expert report was prepared by an appropriately qualified consultant retained by the applicant.

The pharmacodynamics of lidocaine have been extensively studied in a variety of animal models and are reviewed with respect to local anaesthesia, cardiovascular and CNS effects. In summary, lidocaine is generally regarded as a classical local anaesthetic. Actions in the cardiovascular system include decelerator activity in heart lung preparations, and a potential to depress myocardial contraction and increase pulmonary vascular resistance. At high doses, CNS stimulation may be followed by depression and respiratory failure. Pharmacokinetic studies have been conducted in several species and the drug is used in veterinary medicine. While the predominant metabolites vary between species, the drug is handled in a similar manner in man and other mammals.

All the toxicological studies on lidocaine pre-date the introduction of GLP.

Single dose toxicity studies indicated that lidocaine is quite toxic when moderate systemic exposure occurs. The LD₅₀ for rodents was approximately 20 mg/kg by the IV route and 120-335 mg/kg by the subcutaneous route.

Repeated dose studies are not available in the literature. Since neither area of clinical use of the drug requires long term administration, it would not seem necessary to obtain such data.

A variety of studies in different species have failed to demonstrate a teratogenic effect; no information is available on the mutagenic or carcinogenic potential of the drug. It would not seem to be necessary to obtain such data since the drug has been used for nearly 50 years and its structure would make any such problem unlikely.

The inactive ingredients and impurities have been reviewed.

- The ethanol content of Lidocaine Spray (38.88-47.52 %) will be slightly higher than that in Xylocaine; the expert states that, despite efficient absorption through gut and lung mucosae, it would not be likely that this concentration will result in any notable CNS effects. Topical administration of >50% w/w solutions may cause local irritation.

- The propylene glycol concentration in Xylocaine Spray is 14.5% w/w. The concentration in Lidocaine Spray (6% w/w) is usually well-tolerated; higher concentrations are employed in many preparations. Topical applications may be accompanied by local irritation. When used as a solvent for oral preparations, stupor, tachypnoea and diaphoresis have been reported in children, and seizures have been recorded after parenteral administration.

- Neither the saccharin nor the banana flavouring ingredients should cause problems at the concentrations to be used.
- In addition, it seems very unlikely that the omission of two ingredients from Lidocaine Spray (cineole oil and menthol), compared with the reference product should result in any changes in the degree of absorption of other constituents. The expert has concluded that the new and reference products may be considered to be essentially similar with respect to any potential for toxicity.

5. CLINICAL PHARMACOLOGY

5.1 Pharmacodynamics

The pharmacodynamics of lidocaine have been reviewed many times over and are summarised by the clinical expert with respect to actions on peripheral nerve conduction, transmission of impulses within the CNS and myocardium, and its weak neuromuscular blocking activity. When used for its antiarrhythmic actions, lidocaine is infused intravenously to achieve plasma concentrations between 1-5 µg/mL. Concentrations below this range do not seem to be effective, and concentrations above the range may be associated with CNS toxicity, followed by adverse cardiovascular effects.

A local anaesthetic action is demonstrable following topical application of solutions at concentrations of 4% lidocaine to the tongue. In one comparative study of several agents at various concentrations, 4% lidocaine application was followed by a 2 minute latent period before the onset of 15 minutes of anaesthesia. The paper referred to omits the volume in which the drug was applied, and the clinical expert omits to justify the use of a 10% solution; the latter is clearly an advantage of reduced surface liquid.

5.2 Pharmacokinetics

The clinical expert has summarised the pharmacokinetics of lidocaine in man. Once in the systemic circulation, lidocaine is rapidly distributed to all tissues, with Vd at 100 L. Approximately 65 % is plasma protein bound. Lidocaine crosses the blood brain barrier freely, crosses the placenta, and is detectable in breast milk. Lebedevs *et al.* measured milk concentrations of lidocaine after injection of 20 mg doses for dental anaesthesia and found up to 66 ng/mL. They concluded that the resulting dose to the infant would be very low.

The serum elimination half life is around 1.6 hours.

Plasma concentrations of lidocaine which may follow topical application have been measured in several studies in man (see 6.4).

Lidocaine is extensively metabolised in the liver such that only 3% appears unchanged in urine. Both the de-ethylation metabolites have antiarrhythmic activity. Severe hepatic disease may reduce the rate of metabolism. Clearance of lidocaine is reduced by approximately 9% when patients are pretreated with cimetidine or ranitidine, thought to be due to reduced hepatic blood flow, and by 40% when co-administered with propranolol, mainly due to direct inhibition of metabolism. Lidocaine prolongs the duration of action of suxamethonium. Inhibition of plasma cholinesterase activity does not seem to have clinical relevance.

5.3 Special groups

There are no specific recommendations for dose adjustment when applying lidocaine topically. However, it has been demonstrated that the skin of neonates, and especially that of premature infants, is much more permeable to lidocaine than is mature skin. In addition, infants are more sensitive to lidocaine because the degree of plasma protein binding is less.

Furthermore, as described above, severe hepatic impairment could be expected to reduce the metabolism of lidocaine.

5.4 Bioavailability

No formal bioequivalence studies have been submitted and none are required for an application of this type.

As described, lidocaine is poorly bioavailable when given by the oral route due to first pass metabolism. This route is not used clinically.

The plasma concentrations of lidocaine which may be attained after topical application of the drug as a spray have been studied and reported on in several references provided by the applicant.

- In a comparative study with cocaine, Davies *et al.* gave 3.0 mL of a 4% solution (equivalent to 120 mg of lidocaine) into the larynx after induction of general anaesthesia and prior to intubation of 30 patients. The highest plasma concentration reported was 2.83 µg/mL, at 10 minutes, but mean C_{max} was 0.7 µg/mL. All patients had levels below 1 µg/mL after 60 minutes. No effects on cardiovascular functions were noted.
- Scott *et al.* performed a similar study with 5% and 10% (50 mg and 100 mg doses were given in 10 sprays) solutions and found that plasma concentrations after 100 mg doses were higher in paralysed (mean C_{max} 1.6 µg/mL) vs spontaneously breathing patients (mean C_{max} 1.03 µg/mL). Peak concentrations were seen at 15-25 minutes post dose, and plasma concentrations reached more than 2 µg/mL in some patients.
- Prior to endoscopic bronchoscopy, Mc Burney *et al.* administered a total of 2 mL 4% to the URT or 6 mL 2% lidocaine to the LRT (total 80 mg or 120 mg doses). Administration to the LRT gave peak levels below 2 µg/mL for 8/10 patients, but levels of 3 and 4 µg/mL were seen in the other two, at 25 and 30 minutes post dose, respectively. Other studies have recorded plasma concentrations between 2 and 5 µg/mL after several different administration regimens.
- For example, Labedzki *et al.* found that mean C_{max} after doses in excess of 500 mg lidocaine sprayed into the nasopharyngeal/laryngeal areas were between 3 and 4 µg/mL, and occurred at up to 40 minutes post dose.
- Jameson *et al.*, using the 10% Xylocaine Spray, randomised 60 patients due for upper GI endoscopy to 50, 100, or 200 mg doses of lidocaine to the pharyngeal area. The study concluded that 100 mg doses of lidocaine were optimal. Plasma lidocaine levels were not assayed within the first 20 minutes of dosing and, thus, the peak may have been missed in some patients. Nevertheless, the maximum concentration

recorded was 1 µg/mL, seen at 20 minutes after a 200 mg dose, and the graph below shows that most values were below the range for antiarrhythmic effects.

6. EFFICACY

No new studies of the efficacy of lidocaine have been performed. Given that the actions of the drug are well known, and that the efficacy of the drug when administered as a 4-10% spray has been demonstrated in clinical studies and by long clinical usage, it would seem unnecessary to require new data.

7. SAFETY

Adverse events following local or topical application of lidocaine have been reviewed by the clinical expert. With respect to topical applications, local hypersensitivity reactions may occur, urticarial reactions have been described, and anaphylaxis may be triggered when the drug is absorbed from the target site. However, considering the widespread use of lidocaine, hypersensitivity reactions do not appear to be at all common.

The local anaesthetic effect itself may cause temporary problems such as inadvertent biting of anaesthetised mouth tissues, swallowing difficulties, and undetected local trauma to an anaesthetised area. Other local problems include irritation, which may be due to excipients.

As stated above, most other adverse events are related to absorption of drug from the site of application and distribution in blood and tissues. From the data provided on blood levels, it would not seem too likely that problems of this nature will occur if the dosing limits are followed and if attention is paid to the possibility of unexpectedly high absorption (eg. when the spray is applied to breached mucosae).

The adverse effects of lidocaine are mainly in the CNS (eg. drowsiness, confusion, agitation, hallucination, psychosis, leading to seizures, coma, and respiratory arrest), which usually precede cardiac toxicity (at highest blood concentrations, a depression of conduction and contractility leads to arrhythmias and circulatory collapse). Deaths have occurred with plasma levels between 6-33 µg/mL.

While unwanted CNS and cardiovascular effects are usually not seen until blood levels exceed 5-6 µg/mL, nausea and vomiting may be seen at doses within the therapeutic range for control of ventricular arrhythmias.

Special groups

While healthy elderly patients do not seem to have a higher incidence of adverse events, those with chronic cardiac problems may be more susceptible to circulating lidocaine, and patients with impaired cardiac conduction and bradycardia are more sensitive to the cardiac depressant action of the drug. The potential for toxicity is increased in those with a severe impairment of hepatic metabolism.

There is a possibility that lidocaine may reduce the convulsive threshold in epileptics. Topical application of lidocaine to infants, followed by unexpectedly efficient absorption, has been associated with adverse events at plasma levels of 4-10 µg/mL.

Interactions

Plasma levels of lidocaine may be increased in patients on beta-blocker therapy due to reductions in clearance and in metabolism. Cimetidine is also known to reduce hepatic metabolism and may reduce clearance due to a reduction in hepatic blood flow.

Patients taking other antiarrhythmic agents may be expected to be more susceptible to the cardiac actions of lidocaine.

The other constituents of Lidocaine Spray would not seem to pose a significant additional hazard. The ethanol content of approximately 43% should not result in intoxication; twenty doses of the spray would deliver 860 mg of ethanol to the target surface - about 1/7th of that in an average glass of wine.

8. EXPERT REPORTS

The pharmacological/toxicological expert report is discussed in 4 above. The clinical expert report was prepared by an independent consultant retained by the company, who was formerly employed for many years within the pharmaceutical industry. The report provides a comprehensive review of the literature.

9. SUMMARY OF PRODUCT CHARACTERISTICS

This closely resembles the current version of the reference product and is satisfactory.

10. PATIENT INFORMATION LEAFLET

This is satisfactory.

11. LABELLING

The labelling proposed for the bottle is provided and may be acceptable but a final mock-up of this and of the carton enclosure must be reviewed. "PL" should appear in front of the number.

12. DISCUSSION

The desirable and unwanted pharmacological actions of lidocaine are well known. Local or topical applications carry a low risk to the patient provided that care is taken to limit the amount of drug which may reach the systemic circulation. Plasma levels which may result from drug absorption from mucous membranes have been described and suggest that maximum levels may be expected to be at the low end of the therapeutic range in the vast majority of recipients. The correlation between plasma levels and CNS and cardiac toxicity has been well documented due to the intravenous use of the drug in the treatment of arrhythmias. For these reasons, it would seem to be unnecessary to require additional clinical data for Lidocaine Spray.

The applicant has demonstrated that Lidocaine 10% Local Anaesthetic Spray is therapeutically equivalent to the previously granted application for Xylocaine Spray 10mg/dose pump spray.

13. RECOMMENDATIONS

Based on the evidence provided, the medical assessor recommends that marketing authorisation for Lidocaine 10% Local Anaesthetic Spray may be granted.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Lidocaine 10% w/w Local Anaesthetic Spray are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for applications of this type.

EFFICACY

Lidocaine has been approved as a local anaesthetic since the 1940s and has been used to manage and treat pain during medical procedures. This applicant has demonstrated that Lidocaine 10% w/w Local Anaesthetic Spray is therapeutically equivalent to the previously granted application for Xylocaine Spray 10mg/dose pump spray (PL 14229/0021).

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK-BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with lidocaine is considered to have demonstrated the therapeutic value of the compound. There does not appear to be an important safety concern and thus the risk-benefit appears positive.

**LIDOCAINE 5% W/W LOCAL ANAESTHETIC SPRAY
PL 20165/0009**

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 29 th February 1996
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 22 nd June 2006.
3	Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 22 nd June 2006.
4	The applicant responded to the MHRA's requests, providing further information 12 th December 2006.
5	The application was determined on 6 th March 2007

**LIDOCAINE 10% W/W LOCAL ANAESTHETIC SPRAY
PL 20165/0009**

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

LIDOCAINE 10% W/W LOCAL ANAESTHETIC SPRAY
PL 20165/0009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lidocaine 10% w/w local anaesthetic spray

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

<u>Active Ingredient</u>	<u>% w/w</u>
Lidocaine Base	10.0

Each actuation delivers 0.1ml spray, containing 10mg lidocaine.

For full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Local anaesthetic spray

Lidocaine Spray is a clear, colourless liquid contained within a clear glass bottle fitted with a silver metering pump.

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**

For the prevention of pain associated with the following procedures:

Otorhinolaryngology: Puncture of the maxillary sinus and minor surgical procedures in the nasal cavity, pharynx and epipharynx. Paracentesis.

Obstetrics: During the final stages of delivery and before episiotomy and perineal suturing as supplementary pain control.

Introduction of instruments and catheters into the respiratory and digestive tract:

Provides surface anaesthesia for the oropharyngeal and tracheal areas to reduce reflex activity, attenuate haemodynamic response and to facilitate insertion of the tube or the passage of instruments during endotracheal intubation, laryngoscopy, bronchoscopy and oesophagoscopy.

Dental Practice: Before injection, dental impressions, X-ray photography, removal of calculus, seating or adjustment of dentures.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

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

Each activation of the metered dose valve delivers 10mg lidocaine base. It is necessary to dry the site prior to application. No more than 20 spray applications should be used in any adult to produce the desired anaesthetic effect.

The number of sprays is dependent on the extent of the area to be anaesthetised.

Otorhinolaryngology: 3 applications for puncture of the maxillary sinus.

During delivery: Up to 20 applications (200mg lidocaine base)

Introduction of instruments and catheters into the respiratory and digestive tract: Up to 20 applications (200mg lidocaine base) for procedures in the pharynx, larynx and trachea.

Dental Practice: 1-5 applications to the mucous membrane.

4.3 CONTRAINDICATIONS

Contraindicated in known hypersensitivity to local anaesthetics of the amide type or to other components of the spray solution.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Avoid contact with the eyes.

Absorption from wound surfaces and mucous membranes is relatively high, especially in the bronchial tree. Lidocaine Spray should be used with caution in patients with traumatised mucosa and / or sepsis in the region of the proposed application.

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

The oropharyngeal use of topical anaesthetic agents may interfere with swallowing and thus enhance the danger of aspiration. This is particularly important in children because of their frequency of eating. Numbness of the tongue or buccal mucosa may increase the danger of biting trauma.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Lidocaine should be used with caution in patients receiving anti-arrhythmic drugs such as tocainide, since the toxic effects are additive.

Significant increases in plasma lidocaine concentrations have occurred during concomitant therapy with beta-blockers, such as propranolol, metoprolol or nalodol, owing to a reduction in the clearance of lidocaine from plasma and possibly a direct inhibition of hepatic metabolism.

Cimetidine appears to reduce the hepatic metabolism of lidocaine although it may also reduce its clearance by decreasing hepatic blood flow.

4.6 PREGNANCY AND LACTATION

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

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

In multiple or higher doses, local anaesthetics may have an effect on mental function and temporarily impair locomotion and co-ordination.

4.8 UNDESIRABLE EFFECTS

In rare cases local anaesthetic preparations have been associated with allergic reactions (in most severe instances anaphylactic shock).

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

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

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

4.9 OVERDOSE

The treatment of a patient with toxic manifestations consists of ensuring adequate ventilation and arresting convulsions. Ventilation should be maintained with oxygen by assisted or controlled respiration as required. If convulsions occur, they should be treated rapidly by the intravenous administration of succinylcholine 50-100mg and / or 5-15mg diazepam. As succinylcholine will arrest respiration, it should only be used if the clinician has the ability to perform endotracheal intubation and to manage a totally paralysed patient.

Thiopentone may also be used to abort convulsions in the dosage 100-200mg. If ventricular fibrillation or cardiac arrest occurs, effective cardiovascular resuscitation must be instituted. Adrenaline in repeated doses and sodium bicarbonate should be given as rapidly as possible.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC Code: C05 AD01

Lidocaine is a potent local anaesthetic of the amide type. Like other local anaesthetics, it prevents both the generation and conduction of nerve impulses by slowing depolarisation. This results from blocking of the large transient increase in permeability of the cell membrane to sodium ions that follows initial depolarisation of the membrane. Its mechanism of action is a reversible blockade of impulse propagation by prevention of sodium flux.

Lidocaine may have similar effects on the brain and myocardium and symptoms and signs of toxicity may appear as a results of the drug reaching the systemic circulation, and thus the brain and heart.

Lidocaine also acts as an anti-arrhythmic agent.

5.2 PHARMACOKINETIC PROPERTIES

Lidocaine is readily absorbed from mucous membranes, the respiratory tract, the gastrointestinal tract and through damaged skin. Only about 30-35% of lidocaine is systemically bioavailable after oral administration because of pre-systemic metabolism. Uptake of lidocaine from tissues into the blood is influenced by the site of application or injection and its vascularity.

Absorption may be particularly high from the tracheobronchial tree. Application of 10mg lidocaine from a 10% spray during laryngoscopy has produced mean maximum plasma concentrations of 1.03 (+/- 0.25) mcg/ml within about 20 minutes. Application of 50, 100 and 200mg lidocaine during upper endoscopy has resulted in maximum plasma levels of 0.49, 0.77 and 1.0 mcg/ml respectively 20 minutes after application by means of a 10% spray. Mean maximum plasma levels of 0.657 – 3.63 mcg/ml have been reported following application of doses of 118 – 572 mg lidocaine (as 2 of 4% nebulisers) during bronchoscopy.

Following absorption, there is rapid distribution to all body tissues; the volume of distribution being approximately 100 litres. Plasma protein binding is variable but approximately 65% is bound to plasma protein including alpha-1-acid glycoprotein. Lidocaine crosses the blood-brain barrier. It is excreted in breast milk.

Lidocaine has an elimination half-life of 1.6 hours. About 80% of lidocaine is metabolised in the liver with only about 3% being found unchanged in the urine.

Lidocaine is N-de-ethylated to monoethylglycinexylidide (MEGX) and glycinexylidide. Hydrolysis of glycinexylidide results in 2,6-xylidine, the main excretion product in the urine being 4-hydroxy-2,6-xylidine. 5-hydroxylation of the benzene ring of both lidocaine and MEGX results in the formation of 5-hydroxy MEGX and 5-hydroxylicocaine. Both de-ethylation metabolites have anti-arrhythmic activity, MEGX being 33-83% as active lidocaine and glycinexylidide being 10-42% as active. Only MEGX has convulsive activity, being approximately 88% that of lidocaine.

As lidocaine is largely metabolised in the liver, any alteration in liver function or hepatic blood flow may have a significant effect on its metabolism. Reduced clearance of lidocaine has been found in patients with heart failure, alcoholic liver disease or chronic or viral hepatitis.

Concomitant therapy with agents that alter hepatic blood flow or induce drug-metabolising microsomal enzymes can also effect the clearance of lidocaine.

Signs of toxicity are observed with plasma levels greater than 5mcg/ml.

5.3 PRECLINICAL SAFETY DATA

No relevant data

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Propylene Glycol
Sodium Saccharin
Absolute Ethanol
Purified Water
Banana Flavour P473-1N1

6.2 INCOMPATIBILITIES

No relevant incompatibilities

6.3 SHELF LIFE

3 Years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

A clear Type I glass bottle of 60ml capacity with a metered pump and a polyethylene / polypropylene dip tube, which is crimped onto the neck of the bottle. The pump assembly is protected by a white polypropylene overcap. The polypropylene nozzle actuator (for directing the spray to the target surface area) is supplied separately inside the carton and replaces the overcap prior to use.

The bottle contains 50ml lidocaine spray. Each actuation delivers 0.1ml spray, containing 10mg lidocaine.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

INyX Pharma
Innovation House
6 Seymour Court
Manor Park
Runcorn, Cheshire
WA7 1SY

8 MARKETING AUTHORISATION NUMBER(S)

PL 20165/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/03/2007

10 DATE OF REVISION OF THE TEXT

06/03/2007

LIDOCAINE 10% W/W LOCAL ANAESTHETIC SPRAY

PL 20165/0009

PATIENT INFORMATION LEAFLET

WHAT YOU SHOULD KNOW ABOUT LIDOCAINE SPRAY

Read all of this leaflet carefully because it contains important information for you.

A doctor or dentist will usually apply this medicine to you while you are having treatment in the surgery, clinic or hospital. Sometimes, a doctor or dentist will prescribe this medicine for you to use at home or tell you to buy it from a pharmacy. Always follow the instructions of your doctor or dentist.

- Keep this leaflet in a safe place. You may need to read it again.
- Ask your doctor, dentist or pharmacist if you need any more information or advice.
- You must see a doctor or dentist if your symptoms worsen.

In this leaflet:

1. What Lidocaine Spray
2. What it is used for.
3. Possible Side Effects.
4. Before you use Lidocaine Spray
5. Taking Other Medicines
6. How to use Lidocaine Spray
7. Storing Lidocaine Spray.

1. WHAT LIDOCAINE SPRAY

- The name of your medicine is Lidocaine Spray.
- The active ingredient is Lidocaine. Each spray action (squirt) contains 10 mg of lidocaine.
- Other ingredients are ethanol, propylene glycol, banana essence, sodium saccharin and purified water.
- Lidocaine Spray is available in glass bottles of 50ml. Each bottle contains approximately 500 doses of Lidocaine Spray.

Lidocaine Spray is one of a group of medicines known as local anaesthetics. Lidocaine is also known as lignocaine. It works by stopping the nerves that sense pain from working properly. As a result, the area that is treated with the spray becomes numb for a short time.

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Manufacturer:
INyX Pharma Ltd
9 Arkwright Road
Astmoor Industrial Estate
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WA7 1NU

2. WHAT IT IS USED FOR

Lidocaine Spray can be used to help prevent pain in the following cases:

- During medical examinations and operations involving the nose, throat and sinuses.
- During childbirth and after the birth if stitches are required.
- During dental procedures, for example to numb the gum before injection.

3. POSSIBLE SIDE EFFECTS

Like all medicines Lidocaine Spray can have side effects. If any of the following happen, stop using Lidocaine Spray and tell your doctor or dentist immediately or go to the casualty department at your nearest hospital. You may need urgent medical attention:

- Rash
- Swelling of the hands, feet, ankles, face, lips, mouth or throat.
- Difficulty breathing (may go on to stopping breathing)
- Fainting or losing consciousness.
- Fitting
- Changes in the way your heart beats, for example if you notice it beating slower.

These are all very serious but rare side effects. Sometimes, but not always, some of these side effects occur because of an allergic reaction to lidocaine or to one of the other ingredients in the liquid. Sometimes they occur because more lidocaine than usual has entered the body. Sometimes there is no obvious reason why someone has one or more of these effects. All of these very serious side effects are rare

Other possible side effects are:

- Feeling nervous
- Dizziness
- Drowsiness
- Drop in blood pressure

If you have any side effects not mentioned in this leaflet please inform your doctor, dentist or pharmacist.

4. BEFORE YOU USE LIDOCAINE SPRAY:

Do not use Lidocaine Spray

- If you are allergic to Lidocaine (also known as lignocaine) or any of the other ingredients in Lidocaine Spray.
- If you have ever had an allergic reaction to any other local anaesthetic.

Take special care with Lidocaine Spray

Although lidocaine is sprayed on to a part of your body, some of the lidocaine will enter your body. The amount that enters depends on where the spray is being used and how many squirts are used. In some people, the presence of lidocaine in the body can cause problems. Therefore, special care is needed:

- If you suffer from epilepsy, because lidocaine may increase the risk of having a fit.
- If you have any problems with your heart, particularly a slow heart beat, or have ever been told that you have a heart rhythm problem, because lidocaine can affect the heart rhythm.
- If you have any problems with your liver. Lidocaine is broken down in the liver so liver problems can cause lidocaine to stay in the body for longer than usual and cause side effects.
- If you are very seriously ill, do not use lidocaine spray unless you have asked your doctor if it is suitable for you.
- If you have any ulcers, sores, cuts or infection in or near the site where the spray is going to be used (for example in your throat,

mouth or nose), because more lidocaine than usual may enter your body with a higher chance of side effects.

Please consult your doctor, dentist or pharmacist, even if these statements were applicable to you in the past.

Using Lidocaine Spray with food or drink

Care should be taken after using Lidocaine Spray in the mouth and throat as chewing and swallowing may be difficult for a while due to numbness/loss of feeling. Choking and biting of gums and tongue are all possible due to local numbness. These problems are particularly likely to happen in children.

Pregnancy

Ask your doctor, dentist or pharmacist for advice before using this medicine.

Breast Feeding

Ask your doctor, dentist or pharmacist for advice before using this medicine.

Driving and Using Machines

Care should be taken when using Lidocaine Spray as very occasionally it may affect your ability to drive or operate machinery. This is because lidocaine in your body may slow down your thinking and interfere with your muscle control for a short time after treatment.

5. TAKING OTHER MEDICINES

Please inform your doctor, dentist or pharmacist if you are taking or have recently taken any other medicines even those not prescribed. Special care is needed if:

- You are taking any medicines used for the treatment of problems with your heart rhythm because lidocaine in your body may affect the heart rhythm
- You are taking medicines for your blood pressure called beta-blockers (such as propranolol and atenolol) because these may increase the amount of time after treatment that lidocaine stays in your body.
- You are taking certain medicines for stomach acidity or ulcers such as cimetidine because it may increase the amount of time after treatment that lidocaine stays in your body.

6. HOW TO USE LIDOCAINE SPRAY

Lidocaine Spray will usually be given to you by your doctor or dentist. If you are given Lidocaine Spray to take home, use the dose recommended by your doctor or dentist and apply the spray only to the area as instructed. In all cases you should use as few sprays as possible to produce the desired effect.

Before an injection or other treatment, the usual dose is between 1 and 20 sprays, depending on the size of the area that has to be numbed.

- Adults should never use more than 20 sprays before an injection or other treatment.
- The elderly, children and people who are feeling unwell should receive fewer sprays depending on their age and how unwell they feel. Your doctor or dentist will decide how much is needed or will tell you how much to use.

If you are using Lidocaine Spray near the face it is important not to get Lidocaine Spray in the eyes.

Follow these instructions unless your doctor or dentist tells you otherwise:

1. Remove the cap and attach the spray nozzle onto the top of the bottle.
2. Direct the spray nozzle at the area to be numbed and press the button down firmly.
3. Keep the button held down until all the spray has been released.
4. Repeat the above steps, until the number of sprays, advised by your doctor or dentist have been used.
5. Remove the spray nozzle and replace the cap onto the bottle.
6. The spray nozzle can be removed and cleaned by boiling in water for 5 minutes.

If you use more Lidocaine Spray than you should:

If you have used more Lidocaine Spray than you should, or if someone accidentally swallows some of the liquid from the bottle, you must get advice from your doctor or dentist as soon as possible or you should go to the nearest accident and emergency department.

If large amounts of lidocaine enter the body, there may be effects on heart rhythm that can lower blood pressure and even stop the heart beating. Lidocaine also interferes with the normal working of the brain and nerves so fits, dizziness, drowsiness, loss of consciousness and mental problems can occur.

7. STORING LIDOCAINE SPRAY

- Keep Lidocaine Spray out of the reach and sight of children.
- Do not use after the expiry date printed on the bottle
- The bottle should be kept at room temperature (not more than 30°C)

Leaflet Last Revised: November 2005

**LIDOCAINE 10% W/W LOCAL ANAESTHETIC SPRAY
PL 20165/0009
LABELLING**

<p>Each spray contains 10mg lidocaine. Also contains ethanol, purified water, propylene glycol, banana essence and sodium saccharin.</p>	<p>LIDOCAINE SPRAY 10%w/w local anaesthetic spray 50ml (Approx. 500 sprays)</p>	<p><u>Marketing Authorisation Holder</u> INyX Pharma Ltd Innovation House 6 Seymour Court, Manor Park Runcorn, Cheshire. WA7-1SY</p>
<p>To be used as a topical spray to help prevent pain during certain medical examinations and operations involving the nose and throat, during and after childbirth and in dentistry. Maximum adult dosage: 20 spray doses (200mg Lidocaine)</p>	<p>PL 20165/0009 Do not store above 30°C</p>	<p>Batch No: Expiry Date: P</p>

LIDOCAINE SPRAY 10%w/w local anaesthetic spray 50ml

Must not be sprayed in or near the eyes

Keep out of the reach and sight of children

Marketing Authorisation Holder:
INyX Pharma UK Ltd
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Manor Park
Runcorn
Cheshire
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PL20165/0009 P

Batch Number:
Expiry Date:

LIDOCAINE SPRAY 10%w/w local anaesthetic spray 50ml

PLASTIC SPRAY NOZZLE

The plastic spray nozzle can be cleaned by boiling in water for 5 minutes. It should not be autoclaved.

Do not cut or shorten the spray nozzle, as this will render it ineffective.

Do not store above 30°C

LIDOCAINE SPRAY 10%w/w local anaesthetic spray 50ml (Approx. 500 sprays)

Also contains ethanol, purified water, propylene glycol, banana essence and sodium saccharin.

To be used as a topical spray to help prevent pain during certain medical examinations and operations involving the nose and throat, during and after childbirth and in dentistry.

Maximum adult dosage:
20 spray doses (200mg lidocaine)

Each spray contains 10mg lidocaine.

LIDOCAINE SPRAY 10%w/w local anaesthetic spray 50ml

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