SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT:

LOX 2% - ADRENALINE (1:2,00,000)

Lidocaine and Adrenaline Injection B.P.

Strength:

21.3 mg/ml-50ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION :

Sr. No.	Particulars	Grade	Qty./ml	Function
1.	Lidocaine Hydrochloride Monohydrate	BP	21.3 mg	Active
2.	Adrenaline Acid Tartrate Equivalent to Adrenaline	BP	0.009 mg ≅ 0.005mg	Active

For full list of Excipients, see section 6.1.

3. PHARMACEUTICAL FORM :

Solution for Injection.

A clear, colourless solution.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Lidocaine Hydrochloride and Epinephrine Injection B.P. is indicated for production of local or regional anesthesia by infiltration techniques such as percutaneous injection, by peripheral nerve block techniques such as brachial plexus and intercostal and by central neural techniques such as lumbar and caudal epidural blocks, when the accepted procedures for these techniques as described in standard textbooks are observed.

4.2 Posology and method of administration:

Adults: For normal healthy adults, the individual maximum recommended dose of Lidocaine hydrochloride with adrenaline should not exceed 7 mg/kg (3.2 mg/lb) of body weight and in general it is recommended that the maximum total dose not exceed 500 mg in an adult of 70 kg body weight.

When used without adrenaline, the maximum individual dose should not exceed 4.5 mg/kg (2 mg per lb) of body weight, and in general it is recommended that the maximum total dose does not exceed 200 mg (in an adult of 70 kg body weight).

The maximum recommended dose per 90 minute period of Lidocaine hydrochloride for paracervical block in obstetrical patients and nonobstetrical patients is 200 mg total. One half of the total dose is usually administered to each side. Inject slowly, five minutes between sides.

Children: It is difficult to recommend a maximum dose of any drug for children, since this varies as a function of age and weight. For children over 3 years of age who have a normal lean body mass and normal body development, the maximum dose is determined by the child's age and weight. For example, in a child of 5 years weighing 50 lbs., the dose of Lidocaine hydrochloride should not exceed 75 – 100 mg (1.5 – 2 mg/lb). In order to guard against systemic toxicity the lowest effective concentration and lowest effective dose should be used at all times in some cases it may be necessary to dilute available concentrations with 0.9% sodium chloride injection in order to obtain the required final concentration.

Route of Administration: Local Anaesthetic

4.3 Contraindications:

Lidocaine is contraindicated in patients with a known history of hypersensitivity to local anaesthetics of the amide type.

Adrenaline is contraindicated in narrow angle (congestive) glaucoma, shock, during general anesthesia with halogenated hydrocarbons or cyclopropane and in individuals with organic brain damage. Adrenaline is also contraindicated with local anesthesia of certain areas, e.g. fingers, toes, because of the danger of vasoconstriction producing sloughing of tissue; in labor because it may delay the second stage, in cardiac dilation and coronary insufficiency.

4.4 Special warnings and precautions for use:

Lidocaine with adrenaline solutions contain potassium metabisulfite, a sulfite that may cause allergic–type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people. Administer with caution to elderly people; to those with cardiovascular disease, hypertension, diabetes, or hyperthyroidism; in psychoneurotic individuals; and in pregnancy. Patients with longstanding bronchial asthma and emphysema who have developed degenerative heart disease should be administered the drug with extreme cautions.

Overdosage or inadevertent intravenous injection of adrenaline may cause cerebrovascular hemorrhage resulting from the sharp rise in blood pressure. Product should be protected from exposure to light. Do not remove from carton until ready to use. The solution should not be used if it is pinkish or darker than slightly yellow or if it contains a precipitate. Adrenaline is readily destroyed by alkalies and oxidizing agents. In the latter category are oxygen, chlorine, bromine, iodine, permanganates, chromates, nitrites, and salts of easily reducible metals, especially iron.

4.5 Interaction with other medicinal products and other forms of interaction:

Use of adrenaline with excessive doses of digitalis, mercurial diuretics, or other drugs that sensitize the heart to arrhythmias is not recommended. Anginal pain may be induced when coronary insufficiency is present. The effects of adrenaline may be potentiated by tricyclic antidepressants; certain antihistamines, e.g., diphenhydramine, tripel-ennamine, d-chlorpheniramine; and sodium l-thyroxine.

Local anesthetic solutions containing antimicrobial preservatives (e.g., Methylparaben) should not be used for epidural or epinal anesthesia because the safety of these agents has not been established with regard to Intrathecal Injection, either intentional or accidental.

4.6 Fertility, pregnancy and lactation:

Usage in Pregnancy: Pregnancy Category C. adrenaline has been shown to be teratogenic in rats when given in dose about 25 times the human dose. There are no adequate and well controlled studies in pregnant women. Adrenaline should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Lignocaine 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:

Transient and minor side effects of anxiety, headache, fear, and palpitations often occur with therapeutic doses of adrenaline, especially in hyperthyroid individuals. Repeated local injections can result in necrosis at sites of injection from vascular constriction. "Adrenaline-fastness" or "Epinephrine fastness" can occur with prolonged use.

Systemic: Adverse experiences following the administration of Lidocaine are similar in nature to those observed with other amide local anaesthetic agents. These adverse experiences are in general, dose related and may result from high plasma levels caused by excessive dosage, rapid absorption or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient. Serious adverse experiences are generally systemic in nature. The following types are those most commonly reported.

Central Nervous System: CNS manifestations are excitatory and/ or depressant and may be characterised by light-headedness, nervousness, apprehension, euphoria, confusion, dizziness drowsiness, tinnitus, blurred or double vision, vomiting, sensations of heat cold or numbness, twitching, tremors, convulsions, unconsciousness, 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 blood level of the drug and may occur as a consequence of rapid absorption.

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

Allergic: Allergic reactions are characterised by cutaneous lesions, urticaria, edema or anaphylactoid reactions. Allergic reactions may occur as a result or sensitivity either to local anaesthetic agents or to the methylparaben used as a preservative in multiple dose vials. Allergic reactions as a result of sensitivity to Lidocaine are extremely rare and, if they occur, should be managed by conventional means. Allergic reactions may occur despite a negative result in skin testing for sensitivity.

4.9 Overdose:

Acute emergencies from local anaesthetics are generally related to high plasma levels encountered during therapeutic use of local anaesthetics.

5. PHARMACOLOGICAL PROPERTIES :

5.1 Pharmacodynamic properties :

Mechanism of Action:

Lidocaine stabilizes the neuronal membrane by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby effecting local anesthetic action.

Hemodynamics: Excessive blood levels may cause changes in cardiac output, total peripheral resistance, and mean arterial pressure. With central neural blockade these changes may be attributable to block of autonomic fibers, a direct depressant effect of the local anesthetic agent on various components of the cardiovascular system and/or the beta-adrenergic receptor stimulating action of epinephrine when present. The net effect is normally a modest hypotension when the recommended dosages are not exceeded.

5.2 Pharmacokinetic properties :

Information derived from diverse formulations, concentrations and usages reveals that lidocaine is completely absorbed following parenteral administration, its rate of absorption depending, for example, upon various factors such as the site of administration and the presence or absence of a vasoconstrictor agent. Except for intravascular administration, the highest blood levels are obtained following intercostal nerve block and the lowest after subcutaneous administration.

The plasma binding of lidocaine is dependent on drug concentration, and the fraction bound decreases with increasing concentration. At concentrations of 1 to 4 mcg of free base per mL, 60 to 80 percent of lidocaine is protein bound. Binding is also dependent on the plasma concentration of the alpha-1-acid glycoprotein. Lidocaine crosses the blood-brain and placental barriers, presumably by passive diffusion. Lidocaine is metabolized rapidly by the liver, and metabolites and unchanged drug are excreted by the kidneys. Biotransformation includes oxidative N-dealkylation, ring hydroxylation, cleavage of the amide linkage, and conjugation. N-dealkylation, a major pathway of biotransformation, yields the metabolites monoethylglycinexylidide and glycinexylidide.

The pharmacological/ toxicological actions of these metabolites are similar to, but less potent than, those of lidocaine. Approximately 90% of lidocaine administered is excreted in the form of various metabolites, and less than 10% is excreted unchanged. The primary metabolite in urine is a conjugate of 4-hydroxy-2, 6-dimethylaniline. The elimination half-life of lidocaine following an intravenous bolus injection is typically 1.5 to 2.0 hours. Because of the rapid rate at which lidocaine is metabolized, any condition that affects liver function may alter lidocaine kinetics.

The half-life may be prolonged two-fold or more in patients with liver dysfunction. Renal dysfunction does not affect lidocaine kinetics but may increase the accumulation of metabolites. Factors such as acidosis and the use of CNS stimulants and depressants affect the CNS levels of lidocaine required to produce overt systemic effects. Objective adverse manifestations become increasingly apparent with increasing venous plasma levels above 6.0 mcg free base per mL. In the rhesus monkey arterial blood levels of 18-21 mcg/mL have been shown to be threshold for convulsive activity.

5.3 Pre-clinical Safety Data:

Lignocaine and adrenaline are well-established active ingredients. In animal studies, the signs and symptoms of toxicity noted after high doses of lignocaine are the results of the effects on the central nervous and cardiovascular systems. No drug related adverse effects were seen in the reproduction toxicity studies, neither did lignocaine show any mutagenic potential in either in vitro or in vivo mutagenicity tests.

Cancer studies have not been performed with lidocaine, due to the area and duration of therapeutic use for this drug.

Genotoxicity tests with lignocaine 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:

Adrenaline Bitartrate B.P.
Sodium Chloride B.P.
Potassium Metabisulphite B.P.
Methylparaben B.P.
Disodium Edetate B.P.
Citric Acid Anhydrous B.P.
Water for Injection B.P.

6.2 Incompatibilities: None

6.3 Shelf – life: 24 Months

6.4 Special precautions for storage:
Store below 25°C., protected from light. Do not freeze

6.5 Nature and contents of container:
50ml flint USP Type-I victory vial stoppered with gray butyl rubber stopper and sealed with violet coloured flip off lacquered "NEON" embossed aluminium seal.

6.6 Special Precautions for Handling and Disposal:
Not applicable.

7. MARKETING AUTHORIZATION HOLDER:

M/s. NEON LABORATORIES LIMITED
140, Damji Shamji Industrial Complex,
28, Mahal Indl. Estate, Mahakali Caves Road,
Andheri (East), Mumbai - 400 093

8. MARKETING AUTHORIZATION NUMBER : NEON/IND/4154

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORISATION:
Date of first of the Authorisation: 17/05/2019

10. DATE OF REVISION OF THE TEXT: July, 2023

11. REFERENCE

- https://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=af24dd64-3d31-48b4-bc83-b1a21483486d