Pharmacology

Local Anesthetics

Local anesthetics (LA):

Reversibly block impulse conduction along nerve axons and other excitable membranes that utilize sodium channels as the primary means of action potential generation.

Clinically, Local anesthetics are generally applied locally and **block nerve** conduction of sensory impulses from the **periphery to the CNS**, and at high conc. block also motor activity .

LA block sensation in limited area without producing unconsciousness (e.g. in dentistry , spinal anesthesia).

- The first local anesthetic introduced into medical practice, **Cocaine,** introduced into practice in1884 as an **ophthalmic anesthetic**. Despite the fact that its chronic use was associated with psychological dependence (addiction), cocaine was used clinically because it was the only local anesthetic drug available for 30 years.

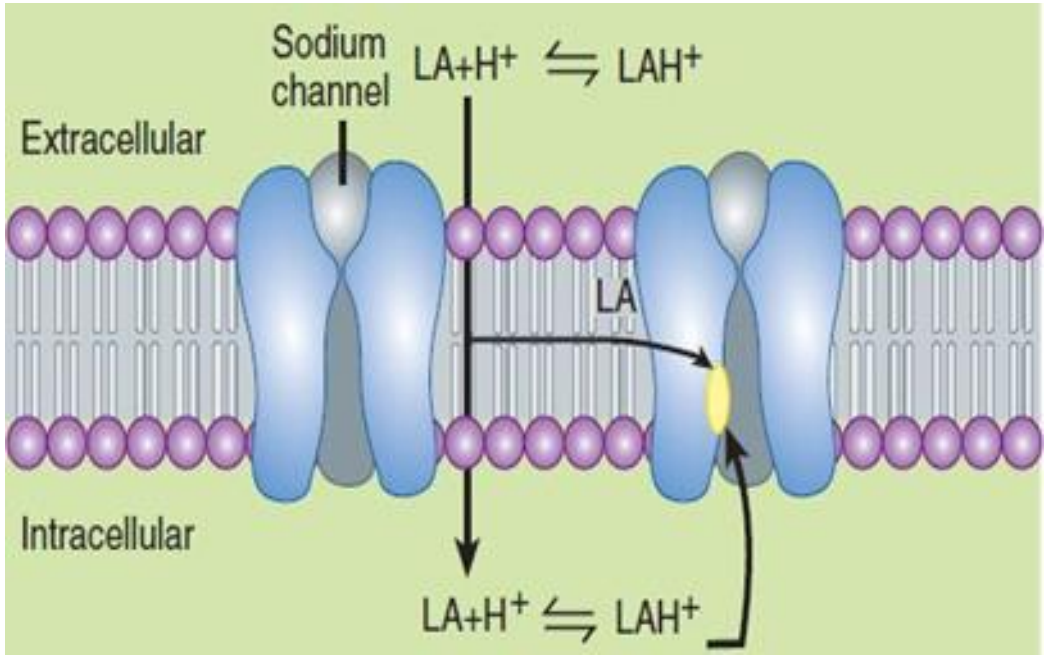
- In an attempt to improve upon the clinical properties of cocaine, Einhorn in 1905 synthesized **Procaine**, which became the dominant local anesthetic for the next 50 years.

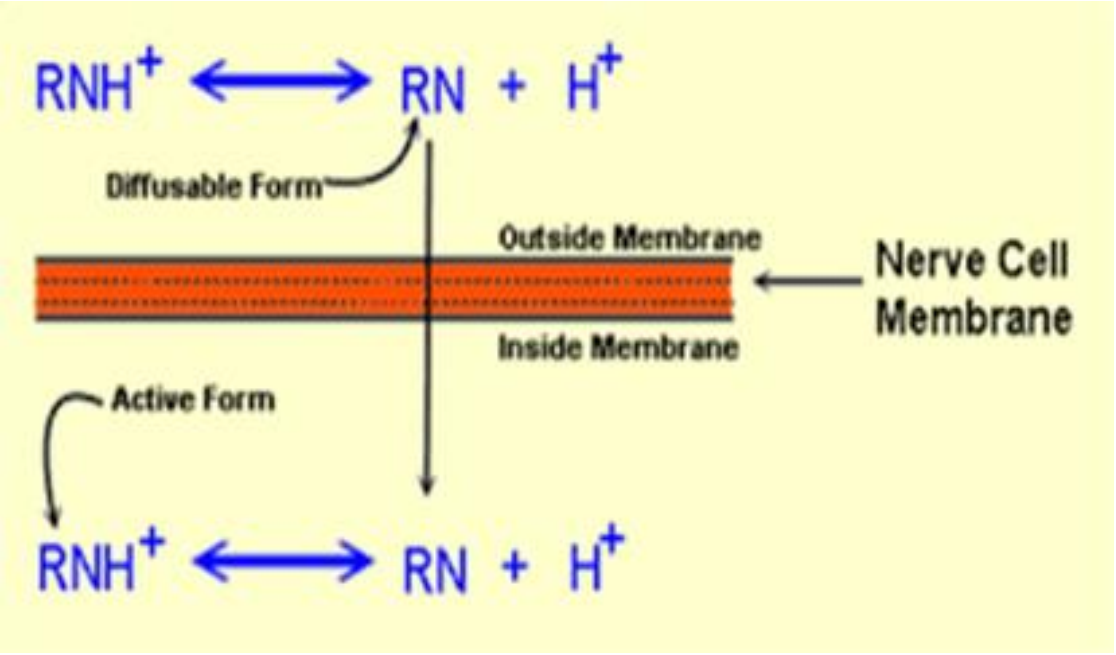
- Subsequently, **newer local anesthetics** were introduced with the goal of **reducing local tissue irritation**, minimizing systemic cardiac and central nervous system (CNS) toxicity, and achieving a faster onset and longer duration of action.
- **Lidocaine**, which is still the most widely used local anesthetic, was synthesized in 1943 .

Mechanism of Action

- Local anesthetics block voltage-dependent sodium channels and reduce the influx of sodium ions, thereby preventing depolarization of the membrane and blocking conduction of the action potential.
- Local anesthetics gain access to their receptors from the cytoplasm or the membrane (Figure 1).
- Because the drug molecule must cross the lipid membrane to reach the cytoplasm, the more lipid-soluble (nonionized, uncharged) form reaches effective intracellular concentrations more rapidly than does the ionized form.
- On the other hand, once inside the axon, the ionized (charged) form of the drug is the more effective blocking entity.
- Thus, both the nonionized and the ionized forms of the drug play important roles—the first in reaching the receptor site and the second in causing the effect.

Mechanism of Action





Subclass	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities
Amides				
Articaine Bupivacaine Levobupivacaine Lidocaine[a] Mepivacaine Prilocaine Ropivacaine	Blockade of Na^+ channels slows, then prevents axon potential propagation	Hepatic metabolism via CYP450 in part Half-lives: lidocaine, prilocaine < 2 h, others 3–4 h	Analgesia via topical use, or injection (perineural, epidural, subarachnoid); rarely IV	CNS: excitation, seizures CV: vasodilation, hypotension, arrhythmias (bupivacaine)
Esters				
Benzocaine[a] Cocaine[a] Procaine Tetracaine[a]	As above, plus cocaine has intrinsic sympathomimetic actions	Rapid metabolism via plasma esterases; short half-lives	Analgesia, topical only for cocaine and benzocaine	As above re CNS actions; cocaine vasoconstricts When abused has caused hypertension and cardiac arrhythmias

- **Benzocaine** :used topical for oral ulcer .but high conc. Cause methymoglobenemia (this is mostly common in children under 2years)
- **Tetracaine** mainly used topically in ophthalmology (topical local anesthesia for the eye).’
- **Lidocaine** (Xylocaine®)(lignocaine®)used systemic as an antiarrhythmic drug and locally as local anesthesia (dentistry), and sometimes used in epidural anesthesia ,topically in ophthalmology .
- **Mepivacaine** (Scandonest)local anesthesia (dentistry)rapid onset medium duration.
- **Bupivacaine** cardiotoxic
- **Ropivacaine** less cardiotoxic used for nerve block anesthesia and epidural anesthesia.
- **Articaine** (septocaine)used in dentistry more effective and safer than lidocaine.
- **Prilocaine** :combined with lidocaine as a topical preparation for dermal anesth.(EMLA®).

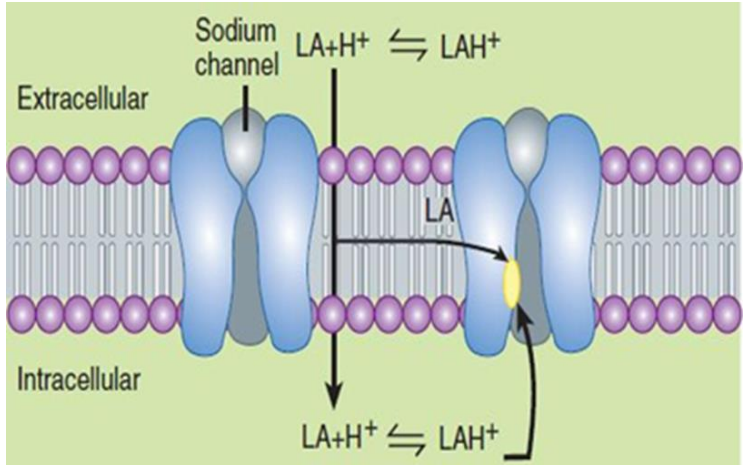
Chemistry

- Most local anesthetic agents consist of a lipophilic group (eg, an aromatic ring) connected by an intermediate chain via an ester or amide to an ionizable group that can become charged through the gain of a proton (H^+)
- Esters usually have a shorter duration of action because ester links are more prone to hydrolysis than amide link
- Local anesthetics are weak bases and are usually made available clinically as salts to increase solubility and stability.
- In the body, they exist either as the uncharged base or as a cation. The relative proportions of these two forms is governed by their pKa and the pH of the body fluids according to the Henderson-Hasselbalch equation:

Log (cation (charged)/ uncharged)= pKa - pH

Local anesthetics; Effect of lipophilicity

- LAs bind to receptor near the intracellular end of the channel. It is not readily accessible from the external side of the cell membrane.
- The uncharged form is more lipophilic and thus more rapidly diffuses through the membrane. However, the charged form has higher affinity for the receptor site of the sodium channel, because it cannot readily exit from closed channels.
- Therefore, LA are much less effective when they are injected into infected tissues because a larger % of the LA is ionized in an environment with a low extracellular pH and can not diffused across the membrane.



- At physiologic pH, these compounds are charged; it is this ionized form that interacts with the protein receptor of the Na+ channel to inhibit its function and, thereby, achieve local anesthesia
- With basic drugs (LA's) – as pH ↑, the nonionized (NI)fraction ↑
- Because the uncharged form is the more lipid-soluble, whereas more of a basic drug will be in the lipid-soluble form at alkaline pH.

Ineffective of LA in acidotic infected tissue. WHY??

- local anesthetics are much less effective when they are injected into infected tissues because a smaller percentage of the local anesthetic is nonionized and available for diffusion across the membrane in an environment with a low extracellular pH.
- Acidosis such as caused by inflammation reduces the action of LAs. This is partly because most of the anesthetic is ionized and therefore unable to cross the cell membrane to reach its cytoplasmic-facing site of action on the sodium channel.

STRUCTURE-ACTIVITY CHARACTERISTICS OF LOCAL ANESTHETICS

- The smaller and more lipophilic the local anesthetic, the faster the rate of interaction with the sodium channel receptor.
- Potency is also positively correlated with lipid solubility as long as the agent retains sufficient water solubility to diffuse to the site of action on the neuronal membrane. Lidocaine, procaine, and mepivacaine are more water-soluble than tetracaine, bupivacaine, and ropivacaine. The latter agents are more potent and have longer durations of local anesthetic action.

Pharmacokinetics

- Many shorter-acting local anesthetics are readily absorbed into the blood from the injection site after administration.
- The duration of local action is therefore limited unless blood flow to the area is reduced. This can be accomplished by administration of a vasoconstrictor (usually an α-agonist sympathomimetic) with the local anesthetic agent.
- Metabolism of ester local anesthetics is carried out by plasma cholinesterases (pseudocholinesterases) and is very rapid for procaine (half-life, 1–2 min), slower for cocaine, and very slow for tetracaine).
- The amides are metabolized in the liver, in part by cytochrome P450 isozymes.
- The half-lives of lidocaine and prilocaine are approximately 1.5 h.
- Bupivacaine and ropivacaine are the longest-acting amide local anesthetics with half-lives of 3.5 and 4.2 h, respectively.
- Liver dysfunction may increase the elimination half-life of amide local anesthetics (and increase the risk of toxicity).

By adding the vasoconstrictor to the local anesthetic:

- This is important for drugs with intermediate or short durations of action such as procaine, lidocaine, and mepivacaine
- Vasoconstrictors are less effective in prolonging anesthetic action of the more lipid-soluble, long-acting drugs (eg, bupivacaine and ropivacaine), possibly because these molecules are highly tissue-bound.

Vasoconstrictors like:

- **Adrenaline (Epinephrine)** is a medication and hormone. effects as agonist on alpha and beta receptors
- **Felypressin,** binds to the vasopressin receptor V1a. This causes contraction of the smooth muscle in the vascular bed, especially capillaries, small arterioles and venules.
- **Levonordefrin** is a sympathomimetic amine used as a vasoconstrictor in local anesthetic solutions. It has pharmacologic activity similar to that of Epinephrine but it is more stable than Epinephrine. Levonordefrin is less potent than Epinephrine in raising blood pressure, and as a vasoconstrictor.

Local anaesthetics are vasodilators(except cocaine), hence the addition of a vasoconstrictor provides the following advantages:

1.Reduce bleeding

2.Increase duration and quality of anesthesia (↓absorption)

3.↓amount of drug from reaching systemic circulation

Contra-Indications of Vasoconstrictor V.C.

1. Diabetics: As V.C. (uncontrolled) counteract the action of insulin i.e. (increase blood glucose level)

2. Heart disease

Unstable angina , recent myocardial infarction<6 month , refractory arrythmias ,uncontrolled congestive heart failure, uncontrolled severe hypertension As V.C. raises patient's blood pressure, stimulate the heart, produce tachycardia & increase Heart rate.

3. Pregnancy: Because the V.C. causes uterine contraction & may causes abortion(felypressin)

4. Hyperthyroidism (toxic goiter): Because V.C. specially adrenaline may cause thyroid crisis & sudden death. ↑ heart rate, ↑ blood pressure.

- Extreme care should be taken to avoid intravascular injection", and that "the minimum possible amount of vasoconstrictor should be used".
- An alternative is available; effective local anesthetic preparations without vasoconstrictor agents (e.g., 3% mepivacaine) have been shown to provide clinically effective local anesthesia, especially for nerve block procedures.

Precaution to use V.C in dentistry

- a patient who is taking medication that reduces the uptake or otherwise enhances the activity of adrenergic agents.

Toxicity

- **CNS Effects**

Including light-headedness or sedation, restlessness, nystagmus, and tonic-clonic convulsions. Severe convulsions may be followed by coma with respiratory and cardiovascular depression.

- **Neurotoxicity**

When applied at excessively high concentrations, all local anesthetics can produce direct neural toxicity. Chloroprocaine and lidocaine appear to be more neurotoxic than other local anesthetics when used for spinal anesthesia

Cardiovascular Effects

- Chest pain ,palpitation , hypotension, syncope , cardiac arrest – some of which may be due to hypoxemia secondary to respiratory depression.

Hematologic toxicity

- Methemoglobinemia (cyanosis life threatening condition in which the amount of O2 carried by blood is greatly reduced) ,frequently with benzocaine ,prilocaine, lidocaine.

Allergic reaction

- The ester-type local anesthetics are metabolized to *p*-aminobenzoic acid derivatives.. Allergic reactions may be encountered with procaine

- Mepivacaine should not be used in obstetric anesthesia due to its increased toxicity to the neonate.

The usual routes of administration include

- topical application (eg, nasal mucosa, wound [incision site] margins),
- injection in the vicinity of peripheral nerve endings (perineural infiltration)
- major nerve trunks (blocks),
- injection into the epidural or subarachnoid spaces surrounding the spinal cord
- Intravenous regional anesthesia (so-called Bier block) is used for short surgical procedures (< 60 minutes) involving the upper and/or lower extremities. This is accomplished by intravenous injection of the anesthetic agent into a distal vein while the circulation of the limb is isolated with a proximally placed tourniquet.

Table 1
INTERMEDIATE-DURATION OF ACTION LOCAL ANESTHETICS IN US

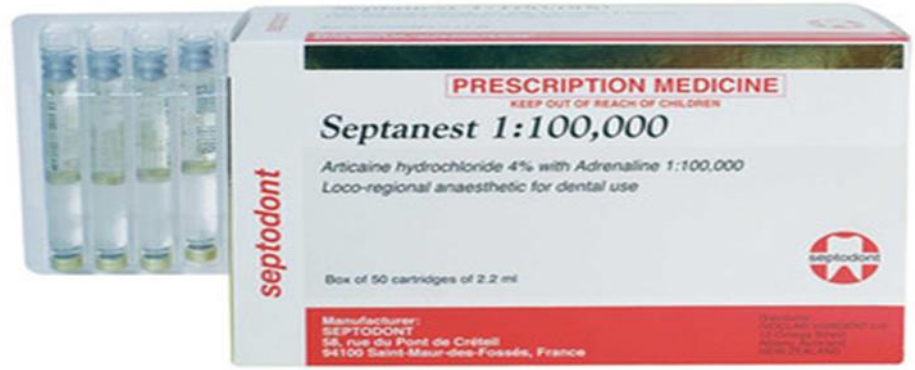
AGENT		ONSET	PULPAL	SOFT TISSUE
Articaine	*Epinephrine*			
4%	1:100,000	1-2 min	60-75 min	3-6 hrs
4%	1:200,000	1-2 min	45-60 min	2-5 hrs
Lidocaine	*Epinephrine*			
2%	1:100,000	2-3 min	60 min	3-5 hrs
Mepivacaine	*Levonordefrin*			
2%	1:20,000	1.5-2 min	60 min	3-5 hrs
Prilocaine	*Epinephrine*			
4%	1:200,000	2-4 min	60-90 min	3-8 hrs
4% plain	None	2-4 min	40-60 min (block)	2-4 hrs

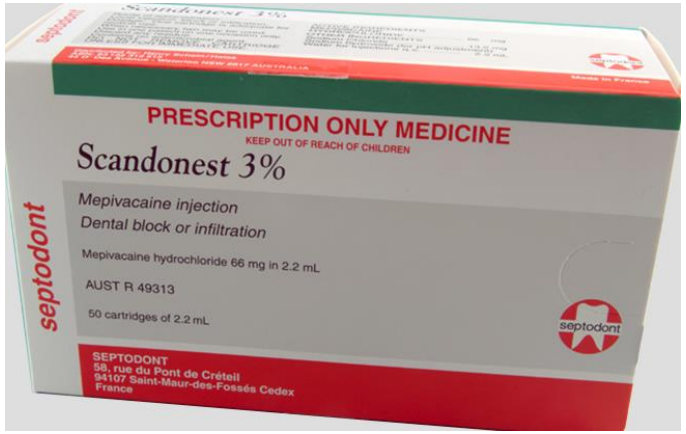
Drug	Preparation
Lidocaine 2%	1:50,000 epinephrine 1:100,000 epinephrine
Mepivacaine 3%	Plain (no vasoconstrictor)
Mepivacaine 2%	1:20,000 levonordefrin
Prilocaine 4%	Plain 1:200,000 epinephrine
Articaine 4%	1:100,000 epinephrine 1:200,000 epinephrine
Bupivacaine 0.5%	1:200,000 epinephrine

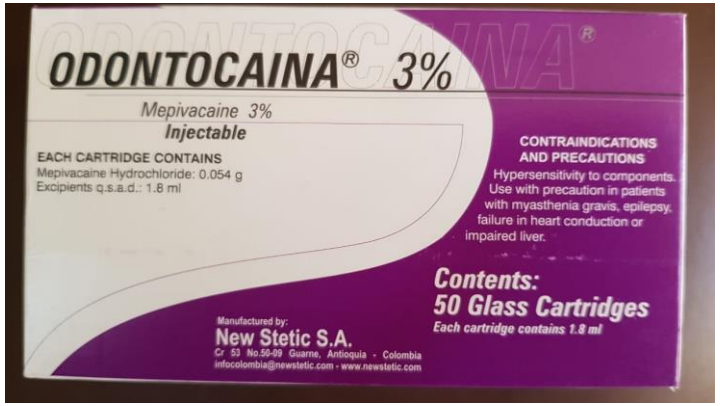
Table 1. Injectable Local Anesthetic Agents*			
Anesthetic Agent	**Agent/Formulation**	**Duration of Pulpal Anesthesia**	**Pregnancy Category****
Articaine *Brand Names:* Articadent Septocaine Ultracaine Zorcaine	4% articaine/1:100,000 epinephrine	Medium	C
	4% articaine/1:200,000 epinephrine	Medium	C
Bupivacaine *Brand Names:* Marcaine Sensorcaine Vivacaine	0.5% bupivacaine/1:200,000 epinephrine	Long	C
Lidocaine *Brand Names:* Xylocaine Lignospan Alphacaine Octocaine	2% lidocaine/1:100,000 epinephrine	Medium	B
	2% lidocaine/1:50,000 epinephrine	Medium	B
Mepivacaine *Brand Names:* Carbocaine Polocaine Scandonest	3% mepivacaine plain	Short	C
	2% mepivacaine/1:20,000 levonordefrin	Medium	C
Prilocaine *Brand Name:* Citanest	4% prilocaine plain	Short	B
	4% prilocaine/1:200,000 epinephrine	Medium	B


Lidocaine 2%
1:100,000 Epinephrine
Articaine 4%
1:100,000 Epinephrine
Prilocaine 4%
1:200,000 Epinephrine
Mepivacaine 3%


1.7 mL
LIDOCAINE HCl 2%
and EPINEPHRINE
1:100,000 INJECTION, USP
1.7 mL
LIDOCAINE HCl 2%
and EPINEPHRINE
1:50,000 INJECTION


PRESCRIPTION MEDICINE
KEEP OUT OF REACH OF CHILDREN
Septanest 1:100,000
Articaine hydrochloride 4% with Adrenaline 1:100,000
Loco-regional anaesthetic for dental use
septodont
Box of 50 cartridges of 2.2 ml
Manufacturer:
SEPTODONT
58, rue du Pont de Créteil
94100 Saint-Maur-des-Fossés, France


PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Scandonest 3%
Mepivacaine injection
Dental block or infiltration
Mepivacaine hydrochloride 66 mg in 2.2 mL
AUST R 49313
50 cartridges of 2.2 mL
septodont
SEPTODONT
58, rue du Pont de Créteil
94107 Saint-Maur-des-Fossés Cedex
France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EACH CARTRIDGE CONTAINS
Mepivacaine Hydrochloride: 0.054 g
Excipients q.s.a.d.: 1.8 ml
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AND PRECAUTIONS
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Use with precaution in patients
with myasthenia gravis, epilepsy,
failure in heart conduction or
impaired liver.
Contents:
50 Glass Cartridges
Each cartridge contains 1.8 ml
Manufactured by:
New Stetic S.A.
Cr 53 No.50-09 Guarne, Antioquia - Colombia
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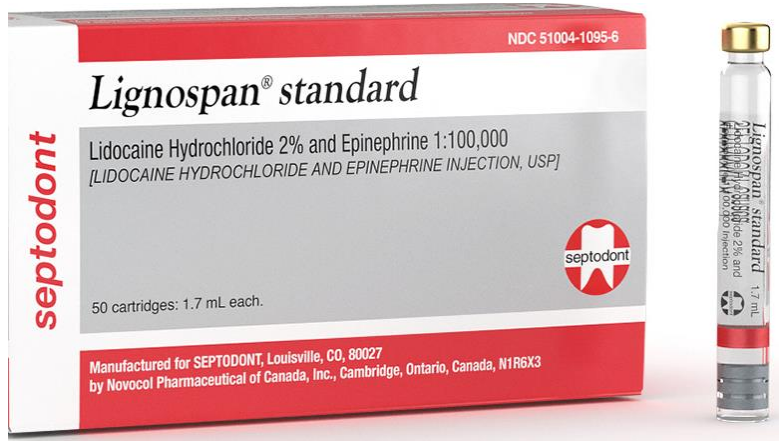
NDC 51004-1095-6
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Lidocaine Hydrochloride 2% and Epinephrine 1:100,000
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Lignospan standard
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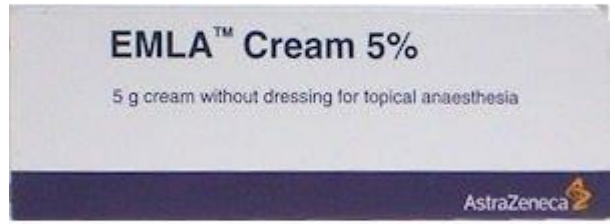
(10 mg/dose)
Pump spray for anaesthesia of mucous membranes
AstraZene
(10 mg/dose)


EMLA™ Cream 5%
5 g cream without dressing for topical anaesthesia
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