

AUSTRALIAN PRODUCT INFORMATION

ORAQIX® Periodontal Gel

(Lidocaine (Lignocaine) 25 mg/g and Prilocaine 25 mg/g)

1 NAME OF THE MEDICINE

Lidocaine (lignocaine)

Prilocaine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oraqix® periodontal gel contains lidocaine (lignocaine) (25 mg/g) and prilocaine (25 mg/g) as the active substances.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Oraqix® periodontal gel is a clear, colourless, oil-in-water microemulsion. Oraqix® is a low-viscosity fluid at room temperature and an elastic gel at the temperature in the periodontal pockets.

Oraqix® Periodontal Gel is supplied in dental cartridges that provide 1.7 g Oraqix® gel (corresponding to 42.5 mg lidocaine (lignocaine) and 42.5 mg prilocaine). Individually blister-packed cartridges of Oraqix® are distributed in a carton of 20. Each individual blister pack also contains a sterile blunt-tipped applicator.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oraqix® is indicated in adults for localised anaesthesia in periodontal pockets for probing, scaling and/or root planing.

4.2 DOSE AND METHOD OF ADMINISTRATION

DO NOT INJECT

Administer Oraqix® as a liquid. Oraqix® will gel upon contact with warm oral mucosa.

Oraqix® is not intended for use with standard dental anaesthetic syringes. This product should only be used with the Oraqix Dispenser™, which is available from Dentsply Sirona Pty Ltd.

Adults

On average, one cartridge (1.7 g) or less of Oraqix® will be sufficient for one quadrant of the dentition. The maximum recommended dose of Oraqix® at one treatment session is five cartridges, i.e. 8.5 g gel containing 212.5 mg lidocaine (lignocaine) base and 212.5 mg prilocaine base.

Clinicians should administer Oraqix® in the following sequence:

1. Apply Oraqix® gel around the gingival margin of 2 or 3 teeth. Gingivae will be anaesthetised after 30 seconds.
2. Insert blunt tipped cannula subgingivally and deposit Oraqix® directly into periodontal pockets of the same 2 or 3 teeth. Completely fill the pockets for optimal anaesthesia. Subgingival anaesthesia will be complete after 30 seconds (a longer waiting time does not enhance the anaesthesia).
3. You may now remove Oraqix® gel by having the patient rinse, though this is not necessary.
4. Commence scaling.
5. The Oraqix® gel will be removed from the periodontal pocket by the directional strokes of handscaling, and/or by the lavage and tip motion of an ultrasonic scaler. This is normal and will not affect the anaesthesia duration.
6. Gel should be suctioned from the mouth as it is removed from pockets.
7. Move onto the next 2 or 3 teeth once complete.

The duration of anaesthesia, as assessed by probing of pocket depths, is about 20 minutes. If the anaesthesia starts to wear off, re-apply Oraqix® as needed.

When administered, Oraqix® should be a liquid. If it has formed a gel, it should be placed in a refrigerator until it becomes a liquid again. The air bubble visible in the cartridge will then move if the cartridge is tilted.

The cartridge and applicator are intended for single use.

Discard any unused Oraqix®.

Oraqix® should not be used after the expiry date printed on the container.

4.3 CONTRAINDICATIONS

Oraqix® is contraindicated in patients with a known history of hypersensitivity to local anaesthetics of the amide type or to any other component of the product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ORAQIX® MUST NOT BE INJECTED.

Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methaemoglobinaemia are more susceptible to drug-induced methaemoglobinaemia (see Section 5.2 Pharmacokinetics Properties).

Care should be taken not to allow Oraqix® to come in contact with the eyes as it may cause eye irritation. Also the loss of protective reflexes may allow corneal irritation and potential abrasion. If eye contact occurs, immediately rinse the eye in water or sodium chloride solution and protect it until sensation returns.

When Oraqix® is used, the patient should be aware that its use may be accompanied by a block of all sensations in the treated area and, if inadvertently spread may induce numbness of the oral mucosa. Care should be taken to avoid excess Oraqix® gel from spreading to the oro-pharyngeal mucosa. The patient should avoid inadvertent trauma to

the treated area, exposure to extreme hot or cold temperatures and refrain from eating and drinking until complete sensation has returned.

Avoid contact with Oraqix® to prevent the development of possible allergy.

Do not use cartridge warmers with Oraqix®. The heat will cause the product to gel.

Oraqix® does not contain a preservative. The product and the blunt-tipped applicator are for single use in one patient only. Discard any unused portion.

Use in hepatic impairment

Due to the extensive liver metabolism the pharmacokinetics of lidocaine (lignocaine) and prilocaine is dependant on-liver function. The lidocaine (lignocaine) half-life may be doubled or more in patients with impaired liver function.

Use in renal impairment

Lidocaine (lignocaine) and prilocaine and their metabolites are known to be excreted by the kidney, and the metabolites may accumulate in patients with impaired renal function.

Use in the elderly

There is no data on plasma levels of lidocaine (lignocaine) and prilocaine following application of Oraqix® in elderly patients. However, data on EMLA cream (eutectic mixture of lidocaine (lignocaine) and prilocaine) used on intact skin do not indicate higher plasma levels in geriatric compared to non-geriatric patients.

Paediatric use

The use of Oraqix® in children and adolescents has not been assessed. Isolated cases of methaemoglobinaemia in children using the combination of lidocaine (lignocaine) and prilocaine in other drugs have been reported.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Oraqix®, i.e. lidocaine (lignocaine) and prilocaine, should be used with caution in combination with dental injection anaesthesia, other local anaesthetics or agents structurally related to amide-type local anaesthetics, e.g. antiarrhythmics such as mexiletine, since the toxic effects of these drugs are additive (See Section 4.9 Overdose).

In view of the low systemic exposure and short duration of Oraqix® application, metabolic drug-drug interactions of clinical significance with lidocaine (lignocaine) or prilocaine seem unlikely.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The potential effects of the lidocaine (lignocaine)/prilocaine combination on fertility have not been evaluated.

Use in pregnancy

Category A

Lidocaine (lignocaine) and prilocaine have been used by a large number of pregnant women and women of childbearing age without an increased incidence of malformations or other direct or indirect harmful effects on the foetus having been observed.

No embryofetal effects were observed in rats dosed subcutaneously with 40 mg/kg/day lidocaine (lignocaine) and 40 mg/kg/day prilocaine during organogenesis.

Use in lactation

Lidocaine (lignocaine), and in all probability, prilocaine are excreted in breast milk, though in such small quantities that there is generally no risk of the child being affected after therapeutic use of Oraqix®.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Oraqix® has no known influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

Although no major differences in adverse events between Oraqix® and placebo treated subjects were observed, all patients in the placebo controlled studies received either Oraqix® or a placebo gel (consisting of the vehicle in Oraqix® without lidocaine (lignocaine) or prilocaine). Therefore, it is not possible to determine if adverse events in each treatment group were attributable to the inactive ingredients comprising the Oraqix® vehicle or if adverse event rates were higher than expected background rates. Therefore, a causal relationship between the reported adverse reactions and Oraqix® could neither be established nor ruled out.

Following SRP treatment with Oraqix® in 391 patients, the most frequent adverse events were local reactions in the oral cavity (see *Table 1*). These events, which occurred in approximately 15% of patients, included pain, soreness, irritation, numbness, vesicles, ulcerations, oedema and/or redness in the treated area. Of the 391 patients treated with Oraqix®, five developed ulcerative lesions and two developed vesicles of mild to moderate severity near the site of SRP. In addition, ulcerative lesions in or near the treated area were also reported for three out of 168 patients who received placebo. Other symptoms reported in more than one patient were headache, taste perversion, nausea, fatigue, flu, respiratory infection, musculoskeletal pain and accident/injury.

Table 1. Frequency of patients with adverse events occurring in more than one patient in any of the treatment groups.

Each patient is counted only once per adverse event. The occurrence in a single patient is included in this table if the same symptom has been seen in at least one patient in another group.

System Organ Class Preferred Term	Oraqix® gel* N=391 %	Placebo (vehicle only) gel N=168 %	Lidocaine (lignocaine) injection* N=170 %
MUSCULO-SKELETAL SYSTEM DISORDERS			
Myalgia	<1	1	
Arthralgia and/or Arthropathy	<1	1	
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS			
Headache	2	2	3
Dizziness	<1	1	1
SPECIAL SENSES OTHER, DISORDERS			
Taste Perversion ¹	2	1	
GASTRO-INTESTINAL SYSTEM DISORDERS			
Nausea	1		1
RESPIRATORY SYSTEM DISORDERS			
Respiratory Infection	1		1
Rhinitis		1	
BODY AS A WHOLE – GENERAL DISORDERS			
Accident and/or Injury	1	1	
Fatigue	1		1
Flu-Like Disorder	1		
Pain (remote from application site)	<1	1	1
APPLICATION SITE DISORDERS**			
Anaesthesia local	1		
Application Site Reaction***	14	12	

¹includes complaints of bad or bitter taste lasting for up to 4 hours after administration of Oraqix®

* in a cross-over study, 170 subjects received either Oraqix® or lidocaine (lignocaine) injection 2% in each test period

** i.e. symptoms in the oral cavity

*** includes pain, soreness, irritation, numbness, ulcerations, vesicles, oedema, abscess and/or redness in the treated area

Allergic Reactions: Allergic and anaphylactic reactions associated with lidocaine (lignocaine) or prilocaine can occur. They may be characterized by urticaria, angioedema, bronchospasm, and shock. Most often the reactions manifest as skin rashes, gingival redness and swelling. Occasionally, severe reactions, including laryngeal oedema and anaphylactoid reactions have occurred. If they occur, they should be managed by conventional means.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia) and 0800 764 766 (New Zealand),

Oraqix® alone and used as recommended is not likely to cause toxic plasma levels (>5 mg/L). However if other local anaesthetics are administered at the same time, e.g. topically or by dental injection, the toxic effects are additive and may cause an overdose with systemic toxic reactions.

Should symptoms of systemic toxicity occur, the signs are anticipated to be similar in nature to those following the administration of local anaesthetics by other routes. Local anaesthetic toxicity is manifested by symptoms of nervous system excitation and, in severe cases, central nervous and cardiovascular depression.

Severe CNS symptoms (convulsions, CNS depression) or cardiovascular symptoms must be treated symptomatically by the administration of e.g. anticonvulsive drugs, respiratory support and/or cardiovascular resuscitation as necessary.

Prilocaine in high doses may cause an increase in the methaemoglobin level, particularly in conjunction with other methaemoglobin-inducing agents. Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylene blue.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lidocaine (lignocaine) and prilocaine belong to the amide class of local anaesthetic agents which produce a local blockade of nerve impulses. Local anaesthetics affect the micro-vascular bed, which may cause a transient paleness or redness.

Oraqix® is applied directly into the periodontal pockets to provide localised anaesthesia. The onset of local anaesthesia after application of Oraqix® in tooth pockets is rapid, about 30 seconds, and a longer waiting time does not seem to enhance the anaesthesia. The median duration of anaesthesia, as assessed by probing of pocket depths, is 20 minutes.

Clinical trials

A total of 337 patients (146 men and 191 women; 169 Oraqix® and 168 placebo) were studied in three randomised, double-blind, placebo-controlled trials. Subjects received a median dose of approximately 1 cartridge (1.7g gel), ranging from ¼ - 2½ cartridges per quadrant treated. The primary objective of these clinical studies was to estimate the analgesic effect of Oraqix® by asking subjects to rate their pain on a continuous visual analog scale (VAS) from 0 (no pain) to 100 mm (worst pain imaginable). Patients were asked to report overall procedural pain 5 minutes following manual scaling and/or root planing (SRP) in a single quadrant that had been pre-treated with Oraqix® or placebo (vehicle only, without lidocaine (lignocaine) or prilocaine). In all three studies, subjects who were given Oraqix® reported less pain during the procedure than those given placebo. Study B3 recruited patients with a known sensitivity to mechanical probing of dental pockets, whereas in studies B1 and B2, this was not a requirement. Results of B1, B2 and B3 are summarized below.

Table 2. Visual Analog Pain Scale (100 mm scale)

Visual Analog Pain Scale

	B1 (n=122)	B2 (n=130)	B3 (n=85)
Mean (SD)			
- Oraqix	11.6 (± 12.0)	12.8 (± 17.9)	17.3 (± 19.2)
- Placebo	25.4 (± 24.7)	19.2 (± 19.2)	28.5 (± 20.9)
Median			
- Oraqix	7	5	11
- Placebo	17	13	27
Range			
- Oraqix	0 – 48	0 – 85	0 – 83
- Placebo	0 – 94	0 – 79	3 – 100
Difference (95% CI)	8.0 (2.0 – 13.0)	4.0 (0.0 – 10.0)	10.0 (4.0 – 19.0)
P value	<0.0005	0.015	0.004

A secondary objective was to compare individual patient estimates of pain on a 5-step categorical Verbal Rating Scale (VRS) which included the following categories: no pain, mild pain, moderate pain, severe pain, and very severe pain. The results of those who reported no pain or mild pain are shown in the next table.

Table 3. Verbal Rating Scale

Number of Patients Reporting “no pain” or “mild pain” during SRP

Study (no of patients)	Oraqix®	Placebo
B1 (n=122)*	57 (90%)	38 (64%)
B2 (n=130)	49 (78%)	51 (76%)
B3 (n=85)*	30 (70%)	20 (48%)

* p<0.05 in the statistical test of the full five categorical scale

5.2 PHARMACOKINETIC PROPERTIES

Prilocaine base and lidocaine (lignocaine) base are both relatively hydrophilic amino-amides.

Absorption

Lidocaine (lignocaine) and prilocaine are absorbed from the oral mucous membranes to a similar extent. The systemic bioavailability after the highest recommended dose, 8.5 g, is estimated to be 20 to 40% (95% confidence interval) for both drugs. A low bioavailability is expected from the gel if swallowed, as both lidocaine (lignocaine) and prilocaine show a substantial first-pass hepatic elimination. The median t_{max} of both drugs is approximately 30 minutes.

Distribution

Lidocaine (lignocaine) and prilocaine have an intermediate degree of plasma binding, mainly to α_1 -acid glycoprotein, with protein binding of 70% and 40% respectively. The plasma concentration of lidocaine (lignocaine) is higher than that of prilocaine, with mean C_{max} values of 0.17 and 0.08 mg/L respectively after single application of 0.9-3.5 g, and of 0.28 and 0.11 mg/L after a cumulative dose of 8.5 g Oraqix® administered as repeated applications during 3 hours.

Metabolism

Lidocaine (lignocaine) is mainly metabolised in the liver and has a high hepatic extraction ratio (0.65). Prilocaine has a high clearance in excess of normal hepatic blood flow, which suggests extensive extrahepatic metabolism.

The main metabolism of lidocaine (lignocaine) is through N-dealkylation to monoethylglycinexylidide (MEGX) and glycinexylidide (GX), which is mainly mediated by CYP3A4. These are hydrolysed to 2,6-xylidine, which is converted to 4-hydroxy-2,6-xylidine, the major urinary metabolite in man. MEGX has an antiarrhythmic and convulsant activity similar to that of lidocaine (lignocaine) and GX has a weak antiarrhythmic effect but lacks convulsant activity.

Prilocaine is split at the amide linkage to *o*-toluidine, which is converted further to 4- and 6-hydroxytoluidine. The formation of methaemoglobin during treatment with prilocaine is related to the plasma concentration of *o*-toluidine and its metabolites. However, even after the maximum recommended dose of 8.5 g Oraqix®, individual maximum plasma concentrations of methaemoglobin were within the normal range (<2% of haemoglobin).

Excretion

Lidocaine (lignocaine) and prilocaine have mean total plasma clearances of 0.95 L/min and 2.37 L/min respectively. The terminal half-life of both drugs after IV administration is 1.6 h. After application of Oraqix®, the mean terminal half-life of lidocaine (lignocaine) is 3.6 h and of prilocaine 2.8 h, which indicates absorption-dependent elimination. However, the duration of anaesthesia at the application site is only 20 minutes.

Linearity

The increase in C_{max} of both lidocaine (lignocaine) and prilocaine is proportional to the dose; at the maximum recommended dose the increase is less than proportional.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There is equivocal evidence for genotoxic potential of the metabolites. See next paragraph Section 5.3 Preclinical Safety Data – Carcinogenicity.

Carcinogenicity

Carcinogenicity potential of the lidocaine (lignocaine)/prilocaine combination or each agent alone has not been studied. There is evidence that the major metabolites of these compounds, 2,6-xylydine and *o*-toluidine, have carcinogenic potential. In a rat Carcinogenicity study, carcinomas and adenomas of the nasal cavity and subcutaneous fibromas and/or fibrosarcomas were increased at high doses. In Carcinogenicity studies in mice and rats, the following tumours associated with *o*-toluidine administration were observed: hepatocarcinomas/adenomas in female mice, multiple occurrences of hemangiosarcomas/hemangiomas in both sexes of mice, sarcomas of multiple organs, transitional cell carcinomas/papillomas of urinary bladder in both sexes of rats, subcutaneous fibromas/fibrosarcomas and mesotheliomas in male rats, and mammary gland fibroadenomas/adenomas in female rates.

The carcinogenic potential of Oraqix® from infrequent use at low doses is likely to be low.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Excipients: poloxamer (containing butylated hydroxytoluene), hydrochloric acid for pH adjustment to pH 7.5-8.0 and purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 24°C to avoid gel forming in the cartridge. Refrigerate any gelled product to return it to the liquid state. Do not freeze. At temperatures below 5°C opaqueness may occur. This opaqueness will disappear when the cartridge is warmed to room temperature.

Keep out of reach of children.

6.5 NATURE AND CONTENTS OF CONTAINER

Each carton contains 20 x 1.7g blister-packed cartridges.

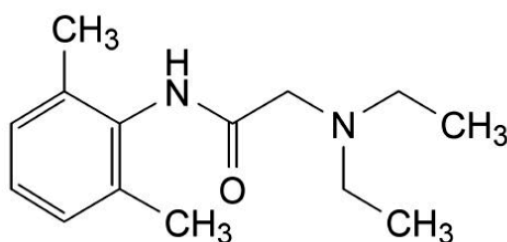
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

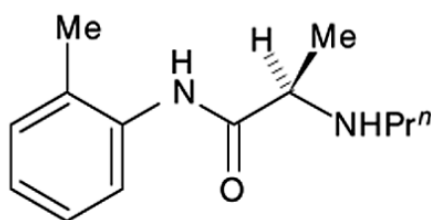
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structure of lidocaine (lignocaine) is:



The chemical structure of prilocaine hydrochloride is:



and enantiomer

CAS number

Lidocaine (lignocaine) has a molecular weight of 234.3. The CAS number for lidocaine (lignocaine) is 137-58-6.

Prilocaine has a molecular weight of 220.3. The CAS number for prilocaine is 721-50-6.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

New Zealand Medicine Classification: Prescription Medicine

8 SPONSOR

Australia

Dentsply Sirona Pty Ltd
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New Zealand

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9 DATE OF FIRST APPROVAL

6 June 2008

10 DATE OF REVISION

31 August 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	<ul style="list-style-type: none">• Updated PI format according to the new requirements• Updated expression of the Drug Substance to ensure consistency of the ingredient name with the Australian Approved Name for therapeutic substances
Section 8	Updated sponsor information