Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oraqix 25/25 mg per g Periodontal gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g contains 25 mg lidocaine and 25 mg prilocaine.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Periodontal gel. Clear, colourless gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Oraqix is indicated in adults for localised anaesthesia in periodontal pockets for diagnostic and treatment procedures such as probing, scaling and/or root planing.

4.2 Posology and method of administration

Adults including the elderly

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 base and 212.5 mg prilocaine base.

Fill the periodontal pockets with Oraqix, by means of a dental syringe or the Oraqix Dispenser and the blunt-tipped applicator included with the pack, until the gel becomes visible at the gingival margin. Wait half a minute before starting treatment (a longer waiting time does not enhance the anaesthesia). 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.

If additional local anaesthesia is needed in combination with Oraqix, please refer to the specific Summary of Product Characteristics of each adjunctive anaesthetic. Because the systemic toxic effects are additive (see section 4.5 and 4.9) it is not recommended to give any further local anaesthetics at the same treatment session, if the amount of Oraqix administered corresponds to the maximum recommended dose of five cartridges.

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 use of Oraqix in children and adolescents has not been assessed and therefore its use is not recommended in patients less than 18 years old.

Method of administration

Periodontal use. Oraqix must not be injected.

4.3 Contraindications

Oraqix is contraindicated in patients with a history of hypersensitivity to lidocaine, to prilocaine, to local anaesthetics of the amide type or to any excipients.

Oraqix is contraindicated in patients with congenital or idiopathic methaemoglobinaemia.

Oraqix is contraindicated in patients with recurrent porphyria.

4.4 Special warnings and precautions for use

Oraqix must not be injected.

Oraqix should be used with caution in patients with severe impairment of renal or hepatic function. With short-term treatment it is unlikely that either lidocaine, prilocaine or their respective metabolites will accumulate significantly.

Oraqix should also be used with caution in patients with severe impairment of impulse initiation and conduction of the heart (e.g. grade II and III AV block, pronounced bradycardia). Similarly, it should be used with caution in patients who are in remission from porphyria or who are asymptomatic carriers of the mutated genes that are responsible for the development of porphyria.

Patients with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methaemoglobinaemia are more susceptible to drug-induced methaemoglobinaemia (See 5.2 Pharmacokinetics). The use of Oraqix in children and adolescents has not been assessed. Isolated cases of methaemoglobinaemia in children using the combination of lidocaine and prilocaine in other medicinal products have been reported.

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.

Oraqix should not be applied to ulcerative lesions or during acute infections of the oral cavity.

Persons applying or removing the gel should ensure that contact is avoided in order to prevent the development of hypersensitivity.

This product contains an active ingredient that may interfere with tests for substances prohibited in sportswomen and sportsmen. This may make them falsely positive.

4.5 Interaction with other medicinal products and other forms of interactions

Oraqix, i.e. lidocaine 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 medicinal products are additive (see sections 4.2 and 4.9).

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

Methaemoglobinaemia may be accentuated in patients already taking drugs known to induce the condition, e.g. sulphonamides.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of Oraqix in pregnant women. Animal studies are incomplete with respect to effects on pregnancy, embryonic and fetal development, parturition and postnatal development (see section 5.3). Lidocaine and prilocaine cross the placenta and may be absorbed by the fetal tissues. The potential risk for humans is unknown. Oraqix should not be used in pregnancy unless clearly necessary.

Lidocaine, and in all probability, prilocaine are excreted in breast milk in small amounts. However it is unlikely that effects will be seen in the child following treatment with Oraqix. Thus breast-feeding can be continued following treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

No adverse reactions could be ascribed specifically to Oraqix. The most frequent adverse events in all clinical trials were local reactions in the oral cavity. The frequency and type of reactions were very similar for Oraqix and placebo. For patients exposed to Oraqix and the placebo, 15% reported adverse events of mild intensity. For both groups, 4% reported adverse events of moderate intensity.

The local reactions reported, such as soreness, ulceration, irritation and redness, represent a pattern of symptoms normally found after scaling and root planning therapy. Similar symptoms may also be associated with periodontal disease.

Table 1. Summary of adverse reactions

Common (>1/100 - <1/10)	*Nervous system disorders*	Headache
	Administration site conditions [1]	Local pain, soreness, numbness, ulcer, irritation, redness, reaction
	Gastrointestinal disorders	Taste perversion[2]
Uncommon (>1/1,000 - <1/100)	*Nervous system disorders*	Dizziness
	Administration site conditions [1]	Local anaesthesia, pulsation, vesicles, oedema, burning
	Gastrointestinal system	Nausea

[1] i.e. symptoms in the oral cavity.
[2] includes complaints of bad or bitter taste lasting for up to 4 hours after Oraqix administration.

Methaemoglobinaemia: Prilocaine can cause elevated methaemoglobin levels (see 4.4 and 5.2 for additional information) causing cyanosis. Methaemoglobinaemia was not reported during clinical studies with Oraqix.

In rare cases local anaestheticshave been associated with allergic reactions (in the most severe instances anaphylactic shock). Allergic reactions were not reported during clinical studies with Oraqix.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

4.9 Overdose

Oraqix alone and used as recommended is not likely to cause toxic plasma levels (>5mg/L). However if other local anaesthetics are administered concomitantly to enhance anaesthesia the 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 e.g. infiltration and nerve-block anaesthesia. 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. A patient showing signs of toxicity should be kept under observation for several hours following emergency treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anaesthetics, local, amides, combinations

ATC code N01BB20.

Lidocaine and prilocaine belong to the amide class of local anaesthetics which produce a local blockade of nerve impulses through inhibition of voltage dependent sodium channels on the nerve fibre membrane. 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.

5.2 Pharmacokinetic properties

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

Absorption: Lidocaine 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 and prilocaine show a substantial first-pass hepatic elimination. The median Tmax of both drugs is 30 minutes after administration of a single dose and 200 minutes after a cumulative dose of 8.5 g Oraqix, administered as repeated applications during 3 hours.

Distribution: Lidocaine 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 is higher than that of prilocaine, with mean Cmax 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.

Biotransformation: Lidocaine 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 is through N-dealkylation to monoethylglycinexylidide (MEGX) and glycinexylidide (GX), which is mainly mediated by CYP3A4. These are hydrolyzed 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 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).

Elimination: Lidocaine 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 hours. After application of Oraqix, the mean terminal half-life of lidocaine is 3.6 hours and of prilocaine 2.8 hours, which indicates absorption-dependent elimination.

Linearity: The increase in C_{max} of both lidocaine and prilocaine is proportional to the dose, whereas at the maximum recommended dose the increase is less than proportional.

Paediatrics: The pharmacokinetics of Oraqix has not been studied in children.

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

Special populations: Lidocaine and prilocaine and their metabolites are known to be excreted by the kidney, and the metabolites may accumulate in patients with impaired renal function. Due to the extensive liver metabolism the pharmacokinetics of lidocaine and prilocaine is dependent on the liver function. The lidocaine half-life may be doubled or more in patients with impaired liver function.

5.3 Preclinical safety data

Reproduction toxicology

Lidocaine: No teratogenic effects were noted in embryo-foetal development studies in which rats or rabbits were treated during the period of organogenesis. Embryotoxicity was seen in rabbits, at maternally toxic doses. In rats, decreased pup survival was seen for dams treated during late pregnancy and lactation, at a dose that was maternally toxic and affected the duration of gestation.

Prilocaine: Studies on fertility and embryofetal development are lacking. In a peri-post natal study in rats, no effects on pups survival or development were observed.

Lidocaine and prilocaine: No effects on embryo-foetal development were seen in a study in which lidocaine and prilocaine were given in combination, during organogenesis.

As no data for systemic exposure in rats and rabbits are available in these studies, it is not possible to perform a comparison with the exposure in humans.

Genotoxicity and carcinogenicity

Lidocaine: Genotoxicity tests with lidocaine were negative. However, genotoxicity tests with 2,6-xylidine indicated an *in vitro* genotoxic potential of this metabolite of lidocaine. In a rat carcinogenicity study with both *in utero* and life-long post-natal exposure to 2,6-xylidine, tumours in the nasal cavity, subcutis and liver were observed.

Prilocaine: Genotoxicity tests of prilocaine were negative. However, genotoxicity tests with o-toluidine indicated an *in vitro* genotoxic potential of this metabolite of prilocaine. In life-long mouse and rat carcinogenicity studies, as well as a limited hamster study, o-toluidine induced tumours in various organs.

High doses of 2,6-xylidine or o-toluidine were required to induce tumours in animal studies. The clinical relevance of the observed tumorigenicity of these metabolites of lidocaine and prilocaine following intermittent use for local anaesthesia is unknown. Frequent use of high doses of lidocaine and/or prilocaine is not recommended.

No other preclinical safety data relevant for the safety assessment are available besides those already taken into consideration in the other sections of the summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poloxamer 188 purified
Poloxamer 407 purified
Dilute hydrochloric acid to adjust pH
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and contents of container

Type I glass cartridge with a bromobutyl rubber stopper (plunger) and a combination cap made of aluminium with a bromobutyl rubber membrane. One cartridge contains 1.7 g gel.

Pack size: 20 individual cartridges. One stainless steel single-use dental applicator with a hub of polypropylene or high-density polythene will be provided for each cartridge.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Oraqix is a fluid at room temperature and an elastic gel at the temperature in the periodontal pockets. The glass cartridge and blunt applicator fit into standard dental syringes with metric threads or the Oraqix Dispenser.

At temperatures below +5°C opaqueness may occur. This disappears when warming up at room temperature. Do not use cartridge warmers with this medicinal product.

The cartridge and the blunt-tipped applicator are for single use only. Any unused periodontal gel should be discarded.

7 MARKETING AUTHORISATION HOLDER

DENTSPLY DeTrey GmbH

De-Trey-Strasse 1
78467 Konstanz
Germany

8 MARKETING AUTHORISATION NUMBER

PA1045/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd July 2005
Date of last renewal: 1st March 2008

10 DATE OF REVISION OF THE TEXT

September 2016