SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

PerioChip®, 2.5 mg Periodontal Insert

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each periodontal insert contains chlorhexidine digluconate 2.5 mg.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Periodontal insert (chip).

Bullet shaped, orange brown periodontal insert.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The PerioChip is indicated for reduction and/or elimination of pathogenic periodontal pocket microbiota, delaying and/or arresting recolonization of the subgingival microflora, reduction and/or elimination of inflammatory lesions in the periodontal pockets, and as an adjunct to mechanical treatment in periodontitis.

4.2 Posology and method of administration

Dosage

Adults including the elderly: Following mechanical debridement, a PerioChip is placed in each of the periodontal pockets to be treated. One PerioChip is inserted into a periodontal pocket with probing pocket depth (PD) 5 mm or greater. Up to 8 chips may be inserted in a single visit. Retreatment with PerioChip following mechanical plaque removal at 3 month intervals may provide additional benefit if pocket depth remains ≥ 5mm.

The PerioChip biodegrades in the periodontal pocket over about a 7-day period and no return visit to the dental clinic to remove the periodontal insert is necessary. The patient should be instructed to continue normal oral hygiene procedures. No restrictions on dietary habits are needed.

Children and adolescents: PerioChip is not indicated in children and adolescents, since data on safety and efficacy in this age group have not been established.

Method of administration

Isolate the periodontal pocket and dry the periodontal pocket and the surrounding area. Open a blister cavity containing one PerioChip. Pick up the periodontal insert with a pair of forceps so that the rounded end points away from the forceps. Rapidly insert the periodontal insert, curved end first, into the periodontal pocket to its maximum depth and release. The periodontal insert can be further manoeuvred into position using the tips of the forceps or a flat plastic instrument. After proper insertion, PerioChip should rest subgingivally at the base of the pocket.
PerioChip insertion into periodontal pockets is rapid. The periodontal insert's consistency allows placement into the pocket with little discomfort to the patient.

In the unlikely event of PerioChip dislodgement, several actions are recommended, depending on the day of PerioChip loss. If dislodgement occurs 7 days or more after placement, the dentist should consider the subject to have received a full course of treatment. If dislodgement occurs within 48 hours after placement, a new PerioChip should be inserted. If dislodgement occurs more than 48 hours after placement, the dentist should not replace the PerioChip, but reevaluate the patient at 3 months and insert a new PerioChip if the pocket depth has not been reduced to less than 5 mm.

4.3 Contraindications

Hypersensitivity to chlorhexidine digluconate or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There have been individual reports of systemic hypersensitivity following placement of PerioChip. Local hypersensitivity reactions such as gingival swelling are common.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving products containing chlorhexidine. These usually occur from within minutes to a few hours of dosing.
Patients should therefore be instructed to seek immediate medical attention if they develop allergic symptoms such as skin rash, itch, generalised swelling, breathing difficulties, light headedness, rapid heart rate, upset stomach or diarrhoea after exposure to chlorhexidine (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Chlorhexidine is known to be incompatible with anionic agents which may be present in some toothpastes and with sucrose in the diet. Such interactions do not impact significantly on the efficacy of PerioChip. Treatment remained effective with PerioChip during clinical studies in which patients continued with regular toothbrushing and their normal diet.

Nystatin is known to be antagonistic to the efficacy of chlorhexidine. Concomitant use of medicinal products containing this active substance should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data or limited data (less than 300 pregnancies) on the use of chlorhexidine in pregnant women.
Studies in animals have not shown any direct or indirect harmful effects (under normal conditions of use) on reproduction (see section 5.3).
As a precaution PerioChip should be avoided during pregnancy.

Breast-feeding
It is not known if chlorhexidine is excreted in human milk.
A risk for newborns/infants cannot be excluded.
PerioChip should not be administered to nursing women.

Fertility
Studies in animals have not shown any effect on fertility (within normal conditions of use).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Approximately one third of patients experience adverse reactions, usually transient, during the first few days after chip insertion. These may also be due to the mechanical placement of the periodontal insert in the periodontal pocket or as a result of the preceding scaling procedure. The most commonly reported are gastrointestinal system disorders: dental, gingival or oral soft tissue reactions or are otherwise described as application site reactions.

Adverse reactions have been ranked under headings of frequency using the following convention:
very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); frequency not known (cannot be estimated from the available data):

System Organ Class	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Not Known (cannot be estimated

				from the available data)
Infections and infestations			Upper respiratory tract infection	
Blood and lymphatic system disorders			Lymphadenopathy	
Immune disorders				Hypersensitivity including anaphylactic shock* (see sections 4.3 and 4.4.)
Nervous system disorders			Dizziness, neuralgia	
Gastrointestinal disorders	Toothache	Gingival swelling, gingival pain, gingival bleeding	Gingival hyperplasia, gingival recession, gingival pruritus, mouth ulceration, sensitivity of teeth	
Skin disorders				Allergic skin reactions such as dermatitis, pruritus, erythema, eczema, rash, urticaria, skin irritation, and blisters
General disorders and administration site conditions			Malaise, influenza like illness, pyrexia	

* Patients should be instructed to seek immediate medical attention if they develop allergic symptoms such as skin rash, itch, generalised swelling, breathing difficulties, light headedness, rapid heart rate, upset stomach or diarrhoea after exposure to chlorhexidine.

The following adverse reactions have been derived from post-marketing reports on PerioChip: systemic hypersensitivity, anaphylactoid reaction, soft tissue necrosis, cellulitis and abscess related to the application site, loss of taste and gingival discoloration.

Reporting of 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Stomatological preparations; Antiinfectives and antiseptics for local oral treatment.
ATC code: A01AB03.

General properties

Chlorhexidine digluconate is an antimicrobial agent active against a wide spectrum of Gram-positive and Gram-negative organisms, yeast, fungi, facultative anaerobes and aerobes. Chlorhexidine is predominately a “membrane-active” agent; it damages the outer membrane in the bacteria.

In an *ex vivo* study of plaque samples, taken from 25 patients with periodontal disease, exposure to escalating doses of chlorhexidine, resulted in elimination of 99% of subgingival bacteria at concentrations of 125 µg/mL or more. The MIC values for various oral cavity micro-organisms to chlorhexidine are tabulated below:

Micro-organisms	**MIC (µg/mL)**
Porphyromonas gingivalis	62
Prevotella intermedia	62
Campylobacter concisus	31
Capnocytophaga ochracea	250
Hemophilus aphrophilus	8
Streptococcus mutans	8
Actinobacillus actinomycetemcomitans	62
Bacteroides forsythus	125
Bacteroides melaninogenious	62
Eikenella corrodens	62
Streptococcus intermedia	125
Streptococcus sanguis	125
Veilonella parvule	62
Bacteroides fragilis	250
Capnocytophaga sp.	500

Other information

Clinical microbiology studies with chlorhexidine mouthrinse have demonstrated the efficacy of chlorhexidine in reducing the numbers of periodontopathic bacteria, with a minimal risk of developing resistance. These studies, demonstrating the use of chlorhexidine for 6 months and up to 2 years, did not result in overgrowth of pathogenic bacteria or changes in the antimicrobial susceptibility of the oral flora.

Chlorhexidine resistance to bacteria usually results from either changes in the bacterial cell membrane, limiting chlorhexidine uptake, or low-level plasmid-encoded resistance. However, since neither of these mechanisms have been associated with the Bacteroides sp., major pathogens in periodontal pockets, and since the concentrations of chlorhexidine delivered by the PerioChip are relatively high, there is no concern about the development of chlorhexidine resistance following PerioChip administration.

PerioChip

In a 6-month study of the PerioChip, microbiological examination by DNA probe of bacteria from periodontal pockets, showed a sharp decrease in micro-organisms.

5.2 Pharmacokinetic properties

In order to maintain a therapeutically effective concentration, PerioChip delivers a sustained release of chlorhexidine from the gelatin matrix of the periodontal insert over a period of seven days. This release is most rapid within the first 24 hours after periodontal insert placement with a peak concentration of about 2000 µg/mL at 2 hours, followed by a slow reduction in the concentration of chlorhexidine over a period of seven days. A microbiologically effective dose of at least 125 µg/mL is maintained during the release period.

There was no evidence of any systemic absorption following periodontal insert insertion. In addition, low systemic absorption of chlorhexidine has been demonstrated in studies conducted in animals and humans employing high oral doses of chlorhexidine.

5.3 Preclinical safety data

PerioChip has been tested for cytotoxicity *in vitro*, for mutagenicity using the mouse micronucleus assay, for oral mucosal irritation potential using a Hamster cheek pouch model and for subchronic oral toxicity in a 30 day ingestion study in rats.

Cytotoxicity

In Chinese Hamster lung cells (V79), PerioChip showed marked *in vitro* cytotoxicity. The cytotoxicity of the PerioChip was considerably less than that of chlorhexidine digluconate alone and was reduced by the addition of a rat liver-derived, metabolic activation system. Thus, the cytotoxicity of the active, chlorhexidine digluconate, is reduced when incorporated into the PerioChip.

Mutagenicity

The potential of PerioChip to induce chromosomal or other damage was assessed *in vivo* by evaluating the formation of micronuclei in immature bone marrow erythrocytes in mice. No significant chromosomal or other damage was observed with the PerioChip for any test dose up to and including 1240 mg/kg chlorhexidine digluconate compared to the vehicle control.

Oral mucosal irritation

The potential of PerioChip to induce irritation was evaluated through surgical insertion into Hamster cheek pouches for either 7 or 14 days. Mucosal irritation was observed after removal of the PerioChips and, through comparison with sites treated with placebo periodontal inserts, was considered to be caused by the chlorhexidine digluconate. There were few instances of significant differences in erythema and oedema. The effects were transitory and the animals had recovered seven days after periodontal insert removal, indicating either that the initial localised effects were biologically insignificant or that the healing process was rapid.

Oral toxicity

Daily dosing for 30 days with up to 37.5 mg/kg of PerioChip powder containing chlorhexidine digluconate caused no adverse reactions in rats.

Reproductive toxicity

In reproduction and fertility studies with chlorhexidine digluconate, no evidence of impaired fertility was observed in rats at doses up to 100 mg/kg/day, and no evidence of harm to the fetus was observed in rats and rabbits at doses up to 300 mg/kg/day and 40 mg/kg/day, respectively.

Animal studies using rats have shown no evidence of toxic effects to suckling pups when chlorhexidine was administered to dams. The chlorhexidine doses used were greater than 100 times the amount administered to a person treated with twelve PerioChips.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrolysed gelatin (cross-linked with glutaraldehyde)
Glycerol
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30˚C.

6.5 Nature and contents of container

Blister (laminated aluminium foil blister packs), each containing 10 or 20 periodontal inserts.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Dexcel Pharma Technologies Ltd.,
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8 MARKETING AUTHORISATION NUMBER

062-94-27005-00

Revised in July 2024 according to MOH guidelines.