Reg. No.: SIN15172P

Antibiotic Product for Dental Use <Therapeutic Agent for Periodontitis>

Periocline® Periodontal Ointment

Minocycline 2% w/w as hydrochloride dihydrate

Regulatory classification: Prescription Only Medicine [Caution: Use only as directed by a dentist]

Storage	Expiration date
Store in a refrigerator (2-8℃), in a light-proof package.	3 years (The final expiration date is indicated on the aluminum pouch and outer package.)

CONTRAINDICATIONS

- Allergy to tetracycline antibiotics.
- The use of this drug should be avoided for children less than 8 years of age due to the risk of permanent teeth discoloration and of dental enamel hypoplasia.
- Pregnancy and lactation.
- Use in association with retinoids.

DESCRIPTION

Periocline® Periodontal Ointment contains 10 mg (potency) of minocycline hydrochloride in each syringe (0.5g). This drug also contains 25 mg of magnesium chloride, hydroxyethylcellulose, aminoalkylmethacrylate copolymer RS, triacetine, and concentrated glycerin as inactive ingredients.
(Product Description)
This drug is pale yellow ointment filled in a syringe for dental use.

INDICATIONS

Periocline® is indicated for the treatment of severe chronic periodontitis in adults. It should be used as an adjunct to conventional scaling and root planing.

DOSAGE AND ADMINISTRATION

Insert the tip of the applicator in periodontal pockets of each tooth as deeply as possible prior to injecting a sufficient amount of gel to fill the pockets. Approximately 25 mg of gel is administered into pockets of 5 to 7 mm in depth.
The treatment starts with applications every 14 days, up to a total of 3 or 4 applications (over 4 to 6 weeks). Then the applications will be made every 3 months.

PRECAUTIONS

1. Important Precautions

1) Because of the potential for the development of sensitization, the treatment area should be observed carefully. If signs of sensitization (itching, redness, swelling, papules, vesicles, etc.) develop, administration should be discontinued.
2) Hypersensitivity symptoms may occur. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) including fatal cases have been reported with minocycline use. If such symptoms occur, administration should be discontinued immediately.
3) If an infection caused by minocycline-resistant or non-susceptible bacteria occur, administration should be discontinued.
4) As a general rule, the duration of administration of this drug should be limited to the minimum period required for the treatment of the patient's condition, after susceptibility of the microorganism to the drug has been confirmed, in order to prevent the emergence of drug-resistant microorganisms.

2. Precautions concerning Use

1) This drug should be used only for dental treatment.
2) In administration of this drug, the following cautions should be taken.
   a) This drug should be applied following supragingival plaque control by brushing or other means.
   b) Scaling before administration is recommended.
   c) In order the drug to reach the bottom of the gingival pocket, this product should be administered after inserting the tip of the syringe to the sufficient depth.
   d) Vigorous mouthwashing, drinking or eating should be avoided immediately after administration.
3) Caution is required as transient pain or irritation may occur at the treated site when applicating this drug.
4) If the improvement is not observed, this drug should not be used aimlessly.

ADVERSE REACTIONS

Adverse reactions to this drug were observed in 39 (1.19%) of 3,291 patients evaluated in the postmarketing surveillance. The major adverse reaction was the application site pain in 34 patients (1.03%).

(1) Clinically significant adverse reactions

Shock and anaphylaxis (incidence unknown): Since shock or anaphylaxis may occur, patients should be carefully monitored. If any abnormal reaction such as urticaria, itching, generalized flushing, laryngeal oedema, dyspnea, hypotension, etc. are observed, administration should be discontinued and appropriate therapeutic measures taken.

(2) Other adverse reactions

If any of following adverse reactions develop, appropriate measures should be taken.

	Incidence ≥ 1%	Incidence < 1%	Incidence unknown*
Oral cavity/ oral mucous	Pain	Irritation (redness, etc.), sensory abnormality (elongated feeling of teeth)	
	Incidence ≥ 1%	Incidence < 1%	Incidence unknown*
Others		Migraine, rash	Malaise, fever, nausea, vomiting, hypersensitivity reactions (Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS))

*Incidence is unknown because the reactions are observed in spontaneous reports.

USE DURING PREGNANCY DELIVERY OR LACTATION

This drug should not be used in pregnant women, women who may possibly be pregnant, and nursing mothers only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The safety of this product in pregnant or possibly pregnant women has not been established.]

PEDIATRIC USE

Safety of this drug in children has not been established (no clinical experience).

PHARMACOKINETICS

1. Drug concentration in periodontal pockets[1)]

When this drug was administered in periodontal pockets of patients with periodontitis in dose of about 0.05 ml [1.3 mg (potency) as minocycline hydrochloride] per tooth, the concentration of minocycline in periodontal pockets sustained for a long time, showing 0.1 μg/ml, 168 hrs after administration.

2. Drug concentration in serum

When this drug was orally administered one time in healthy adults in dose of 0.5 g [10 mg (potency) as minocycline hydrochloride], the maximum serum concentration of minocycline reached 0.19 μg/ml, 2 hrs after administration. When this drug was administered in periodontal pockets of patients with periodontitis in dose of 0.5 g [10 mg (potency) as minocycline hydrochloride] once a week for 4 weeks, the serum concentration of minocycline showed about 0.1 μg/ml 4 hrs after the first and 4th applications. However, the serum concentration was not detected immediately before the 4th application.

CLINICAL STUDIES

1. Clinical effect[2)]

The probing pocket depth (PPD) reduction from baseline treated with Periocline® was statistically significantly greater than treated with vehicle after scaling and root planing (SRP).

	PPD reduction mm (%)	
	Week 4	Week 12
SRP + Periocline®	1.4 (23)	1.7 (29)
SRP + Vehicle	1.1 (18)	1.4 (25)
P value	0.0001	0.0018

2. Susceptible pathogen[3)]

Minocycline susceptible *Porphyromonas gingivalis*, *Prevotella intermedia*, *Campylobacter rectus*, *Treponema denticola*, *Aggregatibacter actinomycetemcomitans*, *Fusobacterium nucleatum*, and *Eikenella corrodens*.

3. Undesirable Effects[2)]

Gingival irritation, local pain, ecchymosis, gingival swelling, dental abscess, diarrhea and stomach pain.

PHARMACOLOGY

1. Antibacterial activity

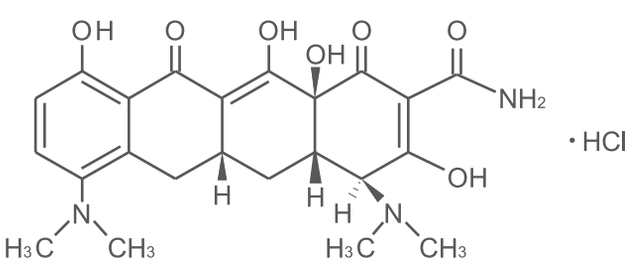
Minocycline hydrochloride exhibits a broad antibacterial activity against gram-positive bacteria, such as *Staphylococcus* and *Pneumococcus spp.* and gram-negative bacteria, such as *Escherichia coli*, *Klebsiella* and *Enterobacter spp*[4)]. The antibacterial activity is demonstrated through the mechanism of protein synthesis inhibition in bacteria. Nakashima, et al.[5)], Ueda, et al.[6)] and Ishikawa, et al.[7)] reported on the antibacterial activity of minocycline hydrochloride in the dental field that this drug showed strong antibacterial activity against pathogens of periodontitis, such as *Prevotella spp.* and those present in subgingival plaque. By using an experimental model of periodontitis in dogs, therapeutic effect of Periocline® Periodontal Ointment has been proved, clinically and bacteriologically.

2. Other pharmacological action (inhibitory effect on collagenolytic activity)

Minocycline hydrochloride inhibits the collagenolytic activity involving in the destruction of periodontal tissues and formation of periodontal pockets (*in vitro*). This drug inhibited about 50 % of the collagenolytic activity of *Porphyromonas gingivalis* at the concentration of 50 μg/ml and about 65 % of it of human neutrophils at the concentration of 100 μg/ml[8)].

PHYSICOCHEMISTRY

Nonproprietary name: Minocycline (INN)
Chemical name: (4*S*, 4a*S*, 5a*R*, 12a*S*)-4, 7-Bis (dimethylamino)-3, 10, 12, 12a-tetrahydroxy-1, 11-dioxo-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydrotetracene-2-carboxamide monohydrochloride
Molecular formula: $C_{23}H_{27}N_3O_7 \cdot HCl$
Molecular weight: 493.94
Structural formula:



Description: Minocycline Hydrochloride occurs as yellow crystals or crystalline powder. It is odorless, and has a bitter taste. It is freely soluble in methanol, sparingly soluble in water and in ethanol, and practically insoluble in acetone, ether or chloroform.

PRECAUTIONS FOR HANDLING

Precautions

This is a disposable product that each syringe should be discarded after being used once for single patient.

PACKAGING

1 syringe (0.5 g)×5

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS

Not recommended combinations

+ Retinoids (systemic administration)

Risk of intracranial hypertension.

Combinations requiring precautions

+ Oral anticoagulants

Enhancement of the effect of oral anticoagulants and increased risk of hemorrhaging. More frequent control of the prothrombin levels and INR monitoring: possible adjustment of the dosage of oral anticoagulants during the anti-infective treatment and after its completion.

+ Salt, oxides, hydroxides of magnesium, aluminum and calcium (gastrointestinal topical medications)

Decrease of the gastrointestinal absorption of cyclins. Spread out taking of gastrointestinal topical medications and cyclins (more than 2 hours, if possible).

+ Iron salts (oral administration)

Decrease of the gastrointestinal absorption of cyclins (formation of complexes). Iron salts and cyclins should not be taken simultaneously (more than 2 hours apart, if possible).

Specific problems of INR imbalance

Many cases of enhancement of the effect of oral anticoagulants have been reported in patients taking antibiotics. The acute infectious or inflammatory context, the age and general condition of the patient appear as risk factors. In these circumstances, it is difficult to differentiate between the infectious pathology and its treatment in the occurrence of INR imbalance. However, certain classes of antibiotics are more involved: in particular fluoroquinolones, macrolides, cyclins, cotrimoxazole and certain cephalosporins.

OVERDOSE

In case of overdose, a gastric lavage must be performed.
There is no specific antidote.

REFERENCES

1) Ayako Satomi et al.: *J. Jpn. Soc. Periodontol.* 1987, 29 (3), p.937.
2) Daniel van Steenberghe et al.: *J Periodontol.* 1993, 64,p.637.
3) Daniel van Steenberghe et al.: *J Periodontol.* 1999, 70, p.657.
4) Minoru Kobayashi et al.: *Jpn. J. Antibiotics.* 1972, 25 (5), p.283.
5) Koichi Nakashima et al.: *J. Jpn. Soc. Periodontol.* 1987, 29 (2), p.463.
6) Masatoshi Ueda et al.: *J. Jpn. Soc. Periodontol.* 1988, 30 (1), p.223.
7) Isao Ishikawa et al.: *Jpn. J. Conservative Dentistry*. 1988, 31 (2), p.636.
8) Reiko Maehara et al.: *J. Jpn. Soc. Periodontol.* 1988, 30 (1), p.182.

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