

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0943/012/001

Case No: 2076479

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Alliance Pharmaceuticals Ltd.

Avonbridge House, Bath Road, Chippenham, Wiltshire SN15 2BB, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Periostat 20 mg film-coated tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **03/03/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Periostat[®] 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 23.08 mg doxycycline hyclate equivalent to 20 mg doxycycline.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white round tablets imprinted on one side with PS-20.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For patients with adult periodontitis. PERIOSTAT is indicated as an adjunct to supra-gingival and sub-gingival scaling and root planing, with oral hygiene instruction, carried out by a dental practitioner or hygienist as appropriate.

4.2 Posology and method of administration

Adults and the elderly:

PERIOSTAT 20 mg should be administered twice daily, at least one hour before meals or before bedtime. Tablets should be swallowed whole with adequate fluids (at least 100ml of water) and should be taken in an upright sitting or standing position (see 4.4: Special warnings and Precautions for Use).

PERIOSTAT is indicated for treatment periods of 3 months. PERIOSTAT should not be administered for more than 3 consecutive three month periods.

No dosage modification is necessary in elderly patients.

Renal Impairment:

No dosage adjustment is necessary in the presence of renal impairment.

Children:

For use in children, see 'Contraindications'.

4.3 Contraindications

In common with other drugs of the tetracycline class, PERIOSTAT is contra-indicated in infants and children up to 12 years of age.

Doxycycline should not be administered to patients who have shown hypersensitivity to doxycycline hyclate, other tetracyclines or to any of the excipients.

Patients known to have, or suspected to have, achlorhydria should not be prescribed doxycycline.

Use of doxycycline is contra-indicated during pregnancy and lactation (See 4.6 Pregnancy and lactation).

4.4 Special warnings and precautions for use

Tablet forms of the tetracycline class of drugs may cause oesophageal irritation and ulceration. To avoid oesophageal irritation and ulceration, adequate fluids should be taken with this medication. PERIOSTAT should be swallowed whilst in an upright sitting or standing posture. Tablets taken in the evening should be taken well in advance of retiring (see 4.2: Posology and Method of Administration).

Whilst no overgrowth by opportunistic microorganisms such as yeast were noted during clinical studies, PERIOSTAT therapy may result in overgrowth of nonsusceptible microorganisms including fungi (with clinical symptoms of persistent bad breath, reddening of the gums, etc.). Periodic observation of the patient is essential. PERIOSTAT therapy has been associated with diarrhoea, colitis and vaginal moniliasis which may suggest overgrowth of non-susceptible micro-organisms. If overgrowth by resistant organisms appears, PERIOSTAT therapy should be discontinued and an appropriate treatment instituted.

PERIOSTAT should be used with caution in patients with a history of or predisposition to oral candidosis. The safety and effectiveness of PERIOSTAT has not been established for the treatment of periodontitis in patients with coexistent oral candidosis. Whilst not observed during clinical trials with PERIOSTAT, the use of tetracyclines may increase the incidence of vaginal candidosis.

The blood doxycycline levels in patients treated with PERIOSTAT are lower than in those treated with conventional antimicrobial formulations of doxycycline. As, however, there are no data to support safety in hepatic impairment at this lower dose, PERIOSTAT should be administered with caution to patients with hepatic impairment or to those receiving potentially hepatotoxic drugs.

Caution should be observed in the treatment of patients with myasthenia gravis who may be at risk of worsening of the condition.

All patients receiving doxycycline including PERIOSTAT should be advised to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (e.g., skin eruption etc.) occurs. Sunscreen or sunblock should be considered. Treatment should cease at the first sign of skin erythema.

In common with the use of antimicrobial drugs in general, there is a risk of the development of pseudomembranous colitis with doxycycline treatment. In the event of the development of diarrhoea during treatment with PERIOSTAT, the possibility of pseudomembranous colitis should be considered and appropriate therapy instituted. This may include the discontinuation of doxycycline and the institution of specific antibiotic therapy (e.g. vancomycin). Agents inhibiting peristalsis should not be employed in this situation.

In the event of a severe acute hypersensitivity reaction (e.g. anaphylaxis), treatment with PERIOSTAT must be stopped at once and the usual emergency measures taken (e.g. administration of antihistamines, corticosteroids, sympathomimetics and if necessary artificial respiration instituted).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

These recommendations regarding the potential interactions between doxycycline and other medications are based upon the larger doses generally used in antimicrobial formulations of doxycycline rather than with PERIOSTAT. However at the present time, insufficient data exist for reassurance that the interactions described with higher doses of doxycycline will not occur with PERIOSTAT.

The absorption of doxycycline from the gastro-intestinal tract may be inhibited by bi- or tri- valent ions such as aluminium, zinc, calcium (found for example in milk, dairy products and calcium-containing fruit juices), by magnesium (found for example in antacids) or by iron preparations, activated charcoal, cholestyramine, bismuth chelates and sucralfate. Therefore such medicines or foodstuffs should be taken after a period of 2 to 3 hours following ingestion of PERIOSTAT. Didanosine tablets may decrease the absorption of doxycycline due to the gastric pH increase as a consequence of the antacid content of the didanosine tablets. Didanosine should therefore be taken at least 2 hours after doxycycline. Quinapril may reduce the absorption of doxycycline due to the high magnesium content in quinapril tablets.

Doxycycline has been shown to potentiate the hypoglycaemic effect of sulfonylurea oral antidiabetic agents. If administered in combination with these drugs, blood sugar levels should be monitored and if necessary, the doses of the above drugs reduced.

Doxycycline has been shown to depress plasma prothrombin activity thereby potentiating the effect of anticoagulants of the dicoumarol type. If administered in combination with these agents, coagulation parameters, including INR, should be monitored and if necessary, the doses of the above drugs reduced. The possibility of an increased risk of bleeding events should be borne in mind.

When doxycycline is administered shortly before, during or after courses of isotretinoin, there is the possibility of potentiation between the drugs to cause reversible pressure increase in the intracranial cavity (pseudotumour cerebri). Concomitant administration should therefore be avoided.

Bacteriostatic drugs including doxycycline may interfere with the bacteriocidal action of penicillin and betalactam antibiotics. It is advisable that PERIOSTAT and betalactam antibiotics should not therefore be used in combination.

Rifampicin, barbiturates, carbamazepine, diphenylhydantoin, primidone, phenytoin, and chronic alcohol abuse, may accelerate the decomposition of doxycycline due to enzyme induction in the liver thereby decreasing its half-life. Sub-therapeutic doxycycline concentrations may result. Doxycycline used concurrently with cyclosporin has been reported to decrease the half-life of doxycycline.

Tetracyclines and methoxyflurane used in combination have been reported to result in fatal renal toxicity.

Tetracyclines used concurrently with oral contraceptives have in a few cases resulted in either breakthrough bleeding or pregnancy.

4.6 Pregnancy and lactation

Use in Pregnancy:

Studies in animals have not demonstrated a teratogenic effect. In humans, the use of tetracyclines during a limited number of pregnancies has not revealed any specific malformation to date. The administration of tetracyclines during the second and the third trimesters results in permanent discolouration of the deciduous teeth in the offspring.

As a consequence, PERIOSTAT is contraindicated during pregnancy (see 4.3: Contraindications).

Use in Lactation:

Tetracyclines are secreted into the milk of lactating women. PERIOSTAT should therefore not be used in breast-feeding mothers.

4.7 Effects on ability to drive and use machines

PERIOSTAT therapy has been associated with nausea and dizziness. Those affected should not drive or operate machinery.

4.8 Undesirable effects

The most commonly reported adverse reactions in Phase III trials were headache (26%) and common cold (22%). The following table lists those adverse reactions occurring in four Phase III trials conducted in 213 patients.

Organ System	Undesirable Effect	Very Common (>1/10)	Common (>1/100, <1/10)	Uncommon (>1/1000,<1/100)	Rare (>1/10000,<1/1000)
Infections & Infestations	Infection Periodontal Abscess		4 8		
Respiratory	Common Cold Flu Symptoms Sinusitis Coughing Bronchitis	47 24	18 9 7		
Gastrointestinal	Dyspepsia Diarrhoea Acid Indigestion		13 12 8		
Skin Disorders	Rash		8		
Musculoskeletal	Toothache Joint Pain Back Pain Pain Muscle Pain Gum Pain		14 12 11 8	2 1	
Reproductive	Menstrual Cramps		9		
General	Headache Nausea Tooth Disorder Sore Throat Sinus Headache	55	17 13 11 8		
Injury	Accidental Injury		11		

The following adverse reactions have been observed in patients receiving tetracyclines, including doxycycline:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhoea, glossitis, dysphagia, enterocolitis and inflammatory lesions with monilial overgrowth in the anogenital region. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Oesophagitis and oesophageal ulceration have been reported, most often in patients administered the hyclate salt in capsule form. Most of these patients took medication just prior to going to bed.

Skin: Maculo popular, erythematous rashes and Stevens-Johnson syndrome. Skin photosensitivity can occur. Exfoliative dermatitis has been reported but is uncommon.

Renal: An apparently dose related increase in blood urea has been reported with tetracyclines.

Blood: Thrombocytopenia, neutropenia, haemolytic anaemia, eosinophilia and porphyria have been reported with tetracyclines.

Hypersensitivity reactions: Exacerbation of systemic lupus erythematosus, anaphylaxis, anaphylactoid purpura, pericarditis, urticaria and angioneurotic oedema.

Musculoskeletal: Arthralgia.

Other: Bulging fontanelles in infants and benign intracranial hypertension in adults has been reported with the use of tetracyclines. Treatment should cease if evidence of raised intracranial pressure develops. These conditions disappeared rapidly when the drug was discontinued. Brown-black microscopic discolouration of thyroid tissue has been reported with long-term use of tetracyclines. Thyroid function is normal.

Adverse reactions typical of the tetracycline class of drugs are less likely to occur during medication with PERIOSTAT, due to the reduced dosage and the relatively low serum levels involved. This assertion is supported by several clinical trials which suggest that no significant differences exist with regard to frequency of adverse events between active and placebo groupings. However, the clinician should always be aware of the possibility of adverse events occurring and should monitor patients accordingly.

The following adverse events have been reported during post-marketing: (Frequency estimate: very common > 1 in 10; common >1 in 100 to <1 in 10; uncommon >1 in 1000 to <1 in 100; rare >1 in 10,000 to <1 in 1000; very rare <1 in 10,000):

Infections

Rare: Vaginal moniliasis, Anogenital moniliasis.

Immune system disorders

Rare: Mild allergic reactions.

Nervous system disorders

Rare: Headache.

Very rare: Dizziness.

Gastrointestinal disorders

Rare: Nausea, diarrhoea, dyspepsia.

Very rare: Abdominal pain, constipation, dry mouth, superficial tooth discolouration.

There have been isolated case reports of bloody diarrhoea, colitis and pseudomembranous colitis.

Skin and subcutaneous tissue disorders

Rare: Rash.

Very rare: Urticaria, pruritus, skin photosensitivity.

Musculoskeletal disorders

Very rare: Arthralgia.

General disorders

Very rare: Asthenia.

4.9 Overdose

To date no significant acute toxicity has been described in the case of a single oral intake of a multiple of therapeutic doses of doxycycline. In case of overdosage there is, however, a risk of parenchymatous hepatic and renal damage and of pancreatitis.

The usual dose of PERIOSTAT is low when compared with the usual doses for doxycycline when used for antimicrobial therapy. Therefore clinicians should bear in mind that a significant proportion of overdoses are likely to produce blood concentrations of doxycycline within the therapeutic range of antimicrobial treatment, for which there is a large quantity of data supporting the safety of the drug. In these cases observation is recommended. In cases of significant overdosage, doxycycline therapy should be stopped immediately; and symptomatic measures undertaken as required. Intestinal absorption of unabsorbed doxycycline should be minimised by producing non-absorbable chelate complexes by the administration of magnesium or calcium salt containing antacids.

Gastric lavage should be considered.

Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tetracyclines.

ATC code: J01A A02.

The active ingredient of PERIOSTAT, doxycycline, is synthetically derived from oxytetracycline, with a molecular formula of $C_{22}H_{24}N_2O_8 \cdot HCl \cdot \frac{1}{2} C_2H_5OH \cdot \frac{1}{2} H_2O$.

PERIOSTAT is an inhibitor of collagenase activity. Studies have shown that at the proposed 20 mg b.i.d. dose level, PERIOSTAT reduces the elevated collagenase activity in the gingival crevicular fluid of patients with chronic adult periodontitis, whilst not demonstrating any clinical evidence of anti-microbial activity.

Susceptibility

The dosage achieved with this product during administration is well below the concentration required to inhibit microorganisms commonly associated with adult periodontitis. Clinical studies with this product demonstrated no effect on total anaerobic and facultative bacteria in plaque samples from patients administered this dose regimen for 9 to 18 months. This product **SHOULD NOT** be used for reducing the numbers of, or eliminating, those microorganisms associated with periodontitis.

5.2 Pharmacokinetic properties

Absorption:

Doxycycline is almost completely absorbed after oral administration. Following ingestion of 20 mg doxycycline twice daily, mean maximum plasma concentrations were 0.79 micrograms/ml. Peak levels were generally achieved 2 hours after administration. Food intake reduced the extent of absorption by 10% and decreased and delayed the peak plasma levels.

Distribution:

Doxycycline is greater than 90% bound to plasma proteins and has an apparent volume of distribution of 50L.

Metabolism:

Major metabolic pathways of doxycycline have not been identified, however, enzyme inducers decrease the half-life of doxycycline.

Elimination:

Doxycycline is excreted in the urine and faeces as unchanged drug. Between 40% and 60% of an administered dose can be accounted for in the urine by 92 hours, and approximately 30% in the faeces. The terminal half-life after a single 20 mg doxycycline dose averaged 18h.

Special populations:

The half-life is not significantly altered in patients with severely impaired renal function. Doxycycline is not eliminated to any great extent during haemodialysis.

5.3 Preclinical safety data

The carcinogenic potential of doxycycline has been investigated and no changes indicative of a direct carcinogenic effect were seen. Increases in benign tumours of the mammary gland (fibroadenoma), uterus (polyp) and thyroid (C-cell adenoma), which are consistent with a hormonal effect, were observed in treated females. Doxycycline has shown no mutagenic activity and no convincing evidence of clastogenic activity.

Effects on fertility and reproductive performance and on pre- and post-natal toxicity have been assessed in rats over the dose range 50 to 500 mg/kg/day. At 50 mg/kg/day (88 times the human dose) there was a decrease in the straight-line velocity of sperm, but there was no apparent effect on male or female fertility or on sperm morphology. Maternal toxicity at 500 mg/kg/day was shown by noisy breathing, loose faeces, and transient reductions in both body weight gain and food consumption after parturition with a slight increase in the duration of gestation. No maternal toxicity was apparent at or below 100 mg/kg/day and there was no effect on the F1 generation at 50 mg/kg/day during parturition, lactation or post-weaning. Developmental toxicity studies have not been conducted, but doxycycline is known to cross the placenta.

Hyperpigmentation of the thyroid following administration of members of the tetracycline class has been observed in rats, minipigs, dogs and monkeys and thyroid hyperplasia has occurred in rats, dogs, chickens and mice. The anticipated human dose for doxycycline, 20 mg b.i.d. is equivalent to ~0.5 mg/kg/day for a 70 kg man. At this dose plasma C_{max} and AUC₀₋₂₄ were 780 ng/ml and 10954 ng*h/ml respectively.

Toxicity following repeated oral administration has been evaluated in rats and cynomolgus monkeys. Discolouration of the thyroid was a finding common to rats exposed at 25 mg/kg/day for 13 weeks or 20 mg/kg/day for 26 weeks, and to cynomolgus monkeys at 30 mg/kg/day for 1 year.

C_{max} and AUC₀₋₂₄ following a single oral dose of 25 mg/kg were 2.2 and 1.6 times respectively the values recorded in man. Dose-related increases in both the incidence and severity of tubular degeneration/regeneration in the kidney were seen following administration to cynomolgus monkeys for 28 days or 52 weeks. At 5 mg/kg/day, focal lesions were present after 28 days, but no lesions were present in monkeys treated for 52 weeks. Mean plasma C_{max} and AUC₀₋₂₄ values at 28 days in monkeys receiving 5 mg/kg/day were 1235 ng/ml and 11600 ng*h/ml respectively and there was no evidence of accumulation.

In humans the use of tetracyclines during tooth development may cause permanent discolouration of the teeth (yellow-grey-brown). This reaction is more common during long-term use of the drug but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. As for other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Magnesium stearate
Microcrystalline cellulose

Film coating:

Lactose monohydrate
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

PVC Aclar/aluminium foil blisters containing 14 tablets. Carton pack sizes: 28 and 56 tablets.

A 120ml white high density polyethylene tablet container with child resistant polypropylene closure. Each HDPE container contains 60 tablets.

Not all pack sizes may be marketed.

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

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Limited
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Chippenham
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8 MARKETING AUTHORISATION NUMBER

PA 943/12/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 May 2002

Date of last renewal: 20 December 2005

10 DATE OF REVISION OF THE TEXT

September 2006