DOXYVARD-200 TABLETS
(Vardhman Exports),

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DOXYVARD-200 TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Doxycycline Hyclate USP eq. to Doxycycline 200mg

Excipients with known effects:

Each tablet contains 130 mg of Microcrystalline Cellulose BP102, 8mg of Magnesium Stearate.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Light Yellow coloured circular biconvex film coated tablets with embossing "DOXYVARD" & "200" and central breakline on one side and plain on other side of each tablet.

The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOXYVARD 200mg Tablet is indicated as an adjunct to supra-gingival and sub-gingival scaling and root planning, with oral hygiene instruction, carried out by a dental practitioner or hygienist as appropriate.

4.2 Posology and method of administration

Posology

Adults and the elderly

DOXYVARD should be administered once daily, at least one hour before meals or before bedtime.

No dosage modification is necessary in elderly patients.

Renal Impairment

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

Paediatric population

DOXYVARD is contraindicated in children up to 12 years of age (see section 4.3).

Method of administration

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).

4.3 Contraindications

Hypersensitivity to the active substance, tetracyclines or to any of the excipients listed in section 6.1.

In common with other drugs of the tetracycline class, DOXYVARD is contraindicated in infants and children up to 12 years of age.

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

Use of doxycycline is contraindicated 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. DOXYVARD 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, DOXYVARD therapy may result in overgrowth of non-susceptible microorganisms including fungi (with clinical symptoms of persistent bad breath, reddening of the gums, etc.). Periodic observation of the patient is essential. DOXYVARD 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, DOXYVARD therapy should be discontinued and an appropriate treatment instituted.

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

The blood doxycycline levels in patients treated with DOXYVARD are lower than in those treated with conventional antimicrobial formulations of doxycycline. However, as there are no data to support the safety in hepatic impairment at this lower dose, DOXYVARD 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 DOXYVARD 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 DOXYVARD, 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 DOXYVARD 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, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline treatment is started. Patients should be reassured that this is a usually self-limiting consequence of antibiotic treatment of spirochete infections.

There have been rare reports of porphyria in patients receiving tetracyclines.

Tetracyclines can cause exacerbation of systemic Lupus Erythematosus (SLE).

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 DOXYVARD. However, at the present time, insufficient data exist for reassurance that the interactions described with higher doses of doxycycline will not occur with DOXYVARD.

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 DOXYVARD. 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 DOXYVARD 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.

Doxycycline may increase the plasma concentration of ciclosporin. Co-administration should only be undertaken with appropriate monitoring.

4.6. Fertility, Pregnancy and lactation

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, DOXYVARD is contraindicated during pregnancy (see 4.3: Contraindications).

Breast-feeding

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

Fertility

There are no clinical data regarding the potential effect of DOXYVARD on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in Phase III trials were headache (26%) and common cold (22%).

Tabulated list of adverse reactions

The following listing of adverse reactions is based on clinical trial experience from four Phase III trials conducted in 213 patients, and/or post-marketing use. The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known".

Undesirable effects are listed by MedDRA System Organ Classes and use the following conventions for frequency:

Very common: ≥1/10

Common: ≥1/100 to <1/10

Uncommon: ≥1/1,000 to <1/100

Rare: ≥1/10,000 to <1/1,000

Very rare: <1/10,000

Not known: cannot be estimated from the available data

System Organ Class	**Adverse Drug Reactions**
Infections and infestations	*Common* Infection Periodontal Abscess *Rare* Vaginal moniliasis Anogenital moniliasis
Immune system disorders	*Rare*

	Allergic reaction *Not known* Jarisch-Herxheimer reaction (see section 4.4)
Psychiatric disorders	*Rare* Anxiety
Nervous system disorders	*Very common* Headache *Common* Sinus headache *Very rare* Dizziness
Respiratory, thoracic and mediastinal disorders	*Very common* Common Cold Flu Symptoms *Common* Sore Throat Sinusitis Cough Bronchitis
Gastrointestinal disorders	*Common* Dyspepsia Diarrhoea* Nausea Tooth Disorder Toothache *Very rare* Abdominal pain Constipation Dry mouth Superficial tooth discolouration
Skin and subcutaneous tissue disorders	*Common* Rash *Very rare* Urticaria Pruritus Skin photosensitivity *Unknown* Photo-onycholysis
Musculoskeletal and connective tissue disorders	*Common* Arthralgia Back Pain Pain *Uncommon* Muscle Pain Gum Pain
Reproductive system and breast disorders	*Common* Menstrual cramps
General disorders and administration site conditions	*Very rare* Asthenia
Injury, poisoning and procedural complications	*Common* Accidental Injury

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

Description of selected adverse reactions

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. Hepatotoxity 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 papular, 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 DOXYVARD, 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.

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.

4.9 Overdose

Symptoms

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 DOXYVARD 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.

Management

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 Pharmacodynamics properties

Pharmacotherapeutic group: Tetracyclines,

ATC code: J01A A02

The active ingredient of DOXYVARD, doxycycline, is synthetically derived from oxytetracycline, with a molecular formula of $C_{22}H_{24}N_2O_8$•HCl•½ C_2H_5OH•½ H_2O.

DOXYVARD is an inhibitor of collagenase activity. Studies have shown that at the proposed 20 mg b.i.d. dose level, DOXYVARD 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 µg/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.

Biotransformation

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.

Other 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.

Linearity/non-linearity

No data provided.

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 AUC_{0-24} 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 AUC_{0-24} 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 AUC_{0-24} 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

Microcrystalline Cellulose BP 102,
Colloidal Silicon Dioxide,
Kyron T-314,
Magnesium Stearate,
Purified Talc,
Pregel,
Lactose D.C.,
Carnuaba wax,
Titanium Dioxide,
Yellow Iron Oxide,
Black Iron Oxide JPE.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store in a cool and dry place and protect from light. Keep all medicines out of reach of children.

6.5 Nature and contents of container

10 Tablets are packed in a blister using printed aluminium foil with clear PVC.
1 Blisters of 10 Tablets is packed in a carton with one literature.

6.6 Special precautions for disposal and other handling

No special requirements.

7. APPLICANT/MANUFACTURER

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