Summary of Product Characteristics
AVDOX 100
(Doxycycline Capsules BP 100 mg)

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1. Name of the medicinal product

AVDOX 100

Doxycycline Capsules BP 100 mg

2. Qualitative and quantitative composition

Each hard gelatin capsule contains doxycycline hyclate corresponding to 100 mg of doxycycline.

Excipient with known effect

Each hard gelatin capsule contains 67.00 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Capsule, hard.

A hard gelatin capsule with a green cap and green body, containing a yellow powder.

4. Clinical particulars

4.1 Therapeutic indications

AVDOX 100 is indicated for the treatment of infections caused by doxycycline-susceptible Gram-positive and Gram-negative organisms and certain other micro-organisms, including:

Respiratory tract infections

Pneumonia and other lower respiratory tract infections due to susceptible strains of Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae and Mycoplasma pneumoniae; chronic bronchitis and sinusitis.

Urinary tract infections

Caused by susceptible strains of Klebsiella species, Enterobacter species, Escherichia coli and other organisms.

Sexually transmitted infections

Uncomplicated urethral, endocervical or rectal infections due to Chlamydia trachomatis; non-gonococcal urethritis caused by Ureaplasma urealyticum; lymphogranuloma venereum, granuloma inguinale and chancroid. Doxycycline is an alternative agent in the treatment of gonorrhoea and of syphilis in penicillin-allergic patients.

Skin infections

Acne vulgaris, when antibacterial therapy is considered necessary.

Ophthalmic infections

Due to susceptible strains of gonococci, staphylococci and Haemophilus influenzae; trachoma and inclusion conjunctivitis.

Rickettsial and other infections

Rocky Mountain spotted fever, typhus group infections and Q fever; psittacosis, brucellosis (with an aminoglycoside), cholera, louse- and tick-borne relapsing fever, and chloroquine-resistant falciparum malaria (in combination with a rapid-acting schizonticide such as quinine); acute intestinal amoebiasis as an adjunct to amoebicides.

Prophylaxis
Prophylaxis of malaria, travellers' diarrhoea (enterotoxigenic Escherichia coli), leptospirosis and scrub typhus. Malaria prophylaxis should follow current guidelines, as resistance patterns change over time.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults and children aged 12 to less than 18 years
The usual dose for acute infections is 200 mg on the first day (as a single dose or in two divided doses), followed by a maintenance dose of 100 mg daily. In the management of more severe infections, 200 mg daily should be given throughout treatment.

Children aged 8 to less than 12 years
Use in this age group should be carefully justified and reserved for situations where other agents are unavailable, unlikely to be effective, or contraindicated (see section 4.4). For children 45 kg or less: initial dose 4.4 mg/kg (as a single dose or two divided doses) followed by a maintenance dose of 2.2 mg/kg; in more severe infections up to 4.4 mg/kg daily may be given throughout treatment. Children over 45 kg should receive the adult dose.

Children aged from birth to less than 8 years
Doxycycline should not be used in children younger than 8 years because of the risk of permanent tooth discolouration, except in severe or life-threatening conditions (e.g. Rocky Mountain spotted fever) where no adequate alternative therapy is available (see sections 4.3 and 4.4).

Dosage in specific infections

- Acne vulgaris: 50 mg daily with food or fluid for 6 to 12 weeks.
- Uncomplicated gonococcal infections (except anorectal infections in men), and uncomplicated urethral, endocervical or rectal infection due to Chlamydia trachomatis or non-gonococcal urethritis due to Ureaplasma urealyticum: 100 mg twice daily for 7 days.
- Acute epididymo-orchitis due to Chlamydia trachomatis or Neisseria gonorrhoeae: 100 mg twice daily for 10 days.
- Primary and secondary syphilis (penicillin-allergic, non-pregnant patients): 200 mg twice daily for 14 days.
- Streptococcal infections: therapy should continue for 10 days to prevent rheumatic fever or glomerulonephritis.
- Chloroquine-resistant falciparum malaria (treatment): 200 mg daily for at least 7 days, together with a rapid-acting schizonticide such as quinine.
- Malaria prophylaxis: 100 mg daily in adults and children over 12 years; begin 1–2 days before travel, continue during travel and for 4 weeks after leaving the malarial area.
- Prophylaxis of travellers' diarrhoea: 200 mg on the first day (as a single dose or 100 mg every 12 hours) followed by 100 mg daily throughout the stay; data are not available beyond 21 days.

Special populations

Elderly
Doxycycline may be prescribed in the elderly at the usual dosage with no special precautions.

Renal impairment
No dose adjustment is required; doxycycline does not accumulate in patients with renal impairment (see section 4.4).

Hepatic impairment
Doxycycline should be administered with caution to patients with hepatic impairment or those receiving potentially hepatotoxic medicinal products (see section 4.4).

Method of administration
For oral use only. The capsules should be swallowed whole with plenty of water, in the sitting or standing position and well before retiring to bed, to reduce the risk of oesophageal irritation and ulceration. If gastric irritation occurs, the capsules may be taken with food or milk; the absorption of doxycycline is not notably affected by food or milk. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.

4.3 Contraindications

- Hypersensitivity to doxycycline or to other tetracyclines, or to any of the excipients listed in section 6.1.
- Pregnancy (see sections 4.4 and 4.6).
- Breast-feeding (see section 4.6).
- Children under 8 years of age (during the period of tooth development), except in severe or life-threatening infections where no adequate alternative therapy is available (see sections 4.2 and 4.4).

4.4 Special warnings and precautions for use

Paediatric population and effects on teeth and bone
The use of tetracyclines during tooth development (the second half of pregnancy, infancy and childhood up to 8 years of age) may cause permanent discolouration of the teeth (yellow-grey-brown) and enamel hypoplasia. This reaction is more common with long-term use but has been observed after repeated short courses. Doxycycline should be used in children younger than 8 years only when the potential benefits outweigh the risks in severe or life-threatening conditions and no adequate alternative exists.

Serious skin reactions
Serious skin reactions such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which may be life-threatening, have been reported. If serious skin reactions occur, doxycycline should be discontinued immediately and appropriate treatment instituted.

Photosensitivity
Photosensitivity, manifesting as an exaggerated sunburn reaction, has been observed. Patients likely to be exposed to direct sunlight or ultraviolet light should be advised of this risk, and treatment should be discontinued at the first sign of skin erythema. Photo-onycholysis has also been reported.

Benign intracranial hypertension
Benign intracranial hypertension (pseudotumor cerebri) has been associated with tetracyclines, including doxycycline, and bulging fontanelles have been reported in infants. It is usually transient,

but cases of permanent visual loss have occurred. If visual disturbance occurs during treatment, prompt ophthalmological evaluation is warranted and treatment should be discontinued; intracranial pressure may remain elevated for weeks after cessation. Concomitant use of isotretinoin or other systemic retinoids should be avoided (see section 4.5).

Clostridium difficile-associated diarrhoea and microbial overgrowth

Use of antibacterial agents, including doxycycline, may lead to overgrowth of non-susceptible organisms including Candida. Pseudomembranous colitis and Clostridium difficile-associated diarrhoea, ranging from mild to fatal colitis, have been reported and must be considered in any patient presenting with diarrhoea during or after treatment; CDAD has occurred more than two months after antibacterial use.

Oesophagitis

Oesophagitis and oesophageal ulceration have been reported, most frequently when capsules were taken immediately before lying down or with inadequate fluid (see section 4.2).

Hepatic and renal effects

Abnormal hepatic function has been reported rarely with tetracyclines, including doxycycline; caution is advised in hepatic impairment. Doxycycline does not accumulate in renal impairment, and the anti-anabolic effect that may raise blood urea with other tetracyclines does not appear to occur with doxycycline.

Other precautions

Tetracyclines may exacerbate systemic lupus erythematosus and, owing to potential weak neuromuscular blockade, should be used with care in patients with myasthenia gravis. Rare reports of porphyria have occurred. Caution is advised when tetracyclines are given with methoxyflurane owing to reports of fatal renal toxicity (see section 4.5). A Jarisch-Herxheimer reaction may occur shortly after treatment of spirochaete infections and is usually self-limiting. When treating venereal disease where co-existent syphilis is suspected, appropriate diagnostic procedures, including dark-field examination and serological testing, should be performed.

Excipients

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

- Antacids and cation-containing products (aluminium, calcium, magnesium), oral zinc, iron salts and bismuth preparations impair the absorption of doxycycline; administration should be maximally separated.
- Penicillins: bacteriostatic agents may interfere with the bactericidal action of penicillin; concurrent use is not advised.
- Anticoagulants: tetracyclines depress plasma prothrombin activity; prolonged prothrombin time has been reported with warfarin, and reduced anticoagulant doses may be required.
- Barbiturates, carbamazepine and phenytoin may shorten the serum half-life of doxycycline; alcohol may also decrease its half-life. An increase in the daily dose of doxycycline may be considered.
- Oral contraceptives: rare cases of contraceptive failure or breakthrough bleeding have been attributed to concurrent use of tetracyclines.
- Ciclosporin: doxycycline may increase ciclosporin plasma concentrations; appropriate monitoring is advised.

- Methoxyflurane: concurrent use with tetracyclines has been reported to result in fatal renal toxicity (see section 4.4).
- Isotretinoin and other systemic retinoids: concomitant use should be avoided owing to the risk of benign intracranial hypertension (see section 4.4).
- Laboratory tests: false elevations of urinary catecholamines may occur due to interference with the fluorescence test.

4.6 Fertility, pregnancy and lactation

Pregnancy

Doxycycline is contraindicated in pregnancy. The risks associated with tetracyclines during pregnancy relate predominantly to effects on the developing teeth and skeleton of the foetus.

Breast-feeding

Doxycycline is contraindicated during breast-feeding, as tetracyclines are excreted in breast milk.

Fertility

No data on the effect of doxycycline on human fertility are available.

4.7 Effects on ability to drive and use machines

The effect of doxycycline on the ability to drive or operate machinery has not been studied, and there is no evidence to suggest it affects these abilities. Patients experiencing visual disturbances, dizziness or other central nervous system effects should refrain from driving or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions are gastrointestinal (nausea and vomiting), headache, hypersensitivity reactions and photosensitivity. Serious but less frequent reactions include severe cutaneous reactions, hepatic disorders, benign intracranial hypertension and Clostridium difficile-associated colitis.

Tabulated list of adverse reactions

Adverse reactions observed with tetracyclines, including doxycycline, are listed below by system organ class and frequency, defined as: common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data).

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known
Infections and infestations		Vaginal infection	Candida infection	
Blood and lymphatic system disorders			Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia	
Immune system disorders	Hypersensitivity (including anaphylactic shock, anaphylactic and anaphylactoid reactions, angioedema, exacerbation of systemic lupus erythematosus,		Drug reaction with eosinophilia and systemic symptoms (DRESS), Jarisch-Herxheimer reaction	

System Organ Class	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Not known
	pericarditis, serum sickness, Henoch-Schönlein purpura, hypotension, dyspnoea, tachycardia, peripheral oedema and urticaria)			
Endocrine disorders			Brown-black microscopic discolouration of thyroid glands	
Metabolism and nutrition disorders			Porphyria, decreased appetite	
Nervous system disorders	Headache		Anxiety, benign intracranial hypertension (pseudotumor cerebri), fontanelle bulging	
Ear and labyrinth disorders			Tinnitus	
Eye disorders			Visual disturbance	
Vascular disorders			Flushing	
Gastrointestinal disorders	Nausea / vomiting	Dyspepsia (heartburn / gastritis)	Pancreatitis, pseudomembranous colitis, Clostridium difficile colitis, oesophageal ulcer, oesophagitis, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, dysphagia, abdominal pain, diarrhoea, glossitis, stomatitis	Tooth discolouration
Hepatobiliary disorders			Hepatic failure, hepatitis, hepatotoxicity, jaundice, hepatic function abnormal	
Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash (including maculopapular and erythematous rashes)		Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, fixed drug eruption, photo-onycholysis, skin hyperpigmentation	
Musculoskeletal, connective tissue and bone disorders			Arthralgia, myalgia	
Renal and urinary disorders			Blood urea increased	

Benign intracranial hypertension may present with headache, vomiting and visual disturbances (blurred vision, scotoma, diplopia or, rarely, permanent visual loss); treatment should be discontinued if it is suspected. Reversible, superficial discolouration of permanent teeth has also been reported, with a frequency that cannot be estimated from the available data.

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. Healthcare professionals are asked to report any suspected adverse reactions to the National Regulatory Authority.

4.9 Overdose

Acute overdosage with doxycycline is rare. In the event of overdosage, treatment should be discontinued and gastric lavage together with appropriate supportive treatment instituted; any gastrointestinal upset should be treated symptomatically. As tetracyclines form insoluble complexes with cations, antacids may be administered where appropriate. Dialysis does not alter the serum half-life of doxycycline and is therefore of no benefit in overdose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tetracyclines. ATC code: J01AA02.

Mechanism of action

Doxycycline is a second-generation tetracycline that is primarily bacteriostatic. It exerts its antimicrobial effect by binding reversibly to the 30S ribosomal subunit of susceptible micro-organisms, thereby inhibiting bacterial protein synthesis.

Spectrum of activity

Doxycycline is active against a wide range of Gram-positive and Gram-negative bacteria and against certain other micro-organisms, including Mycoplasma, Chlamydia, Rickettsia and Plasmodium species. The prevalence of acquired resistance may vary geographically and with time, and local information on resistance is desirable, particularly when treating severe infections.

5.2 Pharmacokinetic properties

Absorption

Doxycycline is virtually completely absorbed after oral administration, and its absorption is not notably influenced by food or milk. Following a 200 mg dose, adult volunteers achieved mean peak serum concentrations of approximately 2.6 micrograms/mL at 2 hours, declining to about 1.45 micrograms/mL at 24 hours.

Distribution

Doxycycline has a high degree of lipid solubility, a low affinity for calcium and is extensively bound to plasma proteins. It is widely distributed into body tissues and fluids.

Biotransformation

Doxycycline is highly stable in normal human serum and does not degrade into an epianhydro form; it does not undergo significant metabolism.

Elimination

Doxycycline is concentrated in bile by the liver and is excreted largely unchanged, in a biologically active form, in the urine and faeces. Its serum half-life is not significantly altered in renal impairment, and haemodialysis does not affect it.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans beyond effects consistent with the pharmacological class. Tetracyclines, including doxycycline, cross the placenta and are deposited in developing bone and teeth; studies in animals have shown effects on skeletal and dental development, which underlie the contraindications in pregnancy and in children under 8 years of age.

6. Pharmaceutical particulars

6.1 List of excipients

- Lactose monohydrate BP

- Maize Starch BP
- Hard gelatin capsule shell (green cap / green body)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from light and moisture. Keep out of the reach of children.

6.5 Nature and contents of container

10 × 10 capsules (100 capsules) packed in a printed carton together with a package insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorisation Holder

AVEO PHARMACEUTICALS PVT LTD

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Manufacturer
ZAIN PHARMA LTD

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8. Marketing Authorisation Number

9. Date of first authorisation / renewal of the authorisation

10. Date of revision of the text