SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxycycline Capsules BP 50mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Doxycycline Hyclate BP equivalent to 50mg doxycycline.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxycycline is clinically useful in the treatment of a variety of infections caused by susceptible strains of gram-positive and gram-negative bacteria and certain other micro-organisms. These include:

Respiratory tract infections: Lower respiratory tract infections including pneumonia, due to susceptible strains of *Haemophilus influenzae, Klebsiella pneumoniae, Streptococcus pneumoniae,* and other organisms. *Mycoplasma pneumoniae* pneumonia. The treatment of chronic bronchitis and sinusitis.

Dermatological infections: Doxycycline can be used in the treatment of acne vulgaris in cases where antibiotic therapy is considered necessary.

Urinary infections: Infections caused by susceptible strains of Klebsiella, Enterobacter, *Escherichia coli, Streptococcus faecalis* and other organisms.

Sexually transmitted diseases: Infections including uncomplicated urethral, endocervical or rectal infections due to *Chlamydia trachomatis,* non-gonococcal urethritis, caused by *ureaplasma urealyticum* (t-mycoplasma). Doxycycline can also be used to treat

chancroid and infections due to *Calymmatobacterium granulomatis* or as an alternative drug for the treatment of gonorrhoea and syphilis.

As a member of the tetracycline group of antibiotics, Doxycycline may be useful in the treatment of infections due to other tetracycline-sensitive micro-organisms such as:

Ophthalmic infections: Due to *Haemophilus influenzae* and susceptible strains of gonococci and staphylococci. Doxycycline is indicated in the treatment of trachoma. Inclusion conjunctivitis may be treated with oral doxycycline alone, or in combination with topical medication.

Rickettsial infections: Tick fevers, Q fever, Rocky mountain spotted fever, Coxiella endocarditis and typhus group.

Prophylaxis: Doxycycline is also indicated in the prophylactic treatment of leptospirosis, scrub typhus, travellers' diarrhoea (entero-toxigenic *Escherichia coli*) and malaria. Malarial prophylaxis is indicated in accordance with current guidelines due to the continuously changing problem of resistance.

Miscellaneous: Psittacosis, leptospirosis, cholera, meliodosis, other infections due to susceptible strains of yersinia species, brucella species (in combination with streptomycin), clostridium species, *francisella tularensis* and chloroquine -resistant falciparum malaria.

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

4.2 Posology and method of administration

Adults aged 12 years to less than 18 years: The usual dosage of Doxycycline capsules for the treatment of acute infections in adults and children aged 12 years to less than 18 years is 200mg on the first day (administered as a single dose or divided into two equal doses with a 12 hour interval) followed by a maintenance dose of 100mg/day. For more severe infections (particularly chronic infections of the urinary tract) 200mg should be given throughout the treatment.

Children aged 8 years to less than 12 years. (Section 4.4)
The use of doxycycline for the treatment of acute infections in children aged 8 years to less than 12 years should be carefully justified in situations where other drugs are not available, are not likely to be effective or are contraindicated.
In such circumstance, the doses for the treatment of acute infections are:
For children 45 kg or less- Initial dose: 4.4 mg/kg (in single or 2 divided doses) with maintenance dose: 2.2 mg/kg (in single or 2 divided doses). In the management of more severe infections, up to 4.4 mg/kg should be given throughout treatment.
For children, over 45 kg - Dose administered for adults should be used.

Children aged from birth to less than 8 years.
Doxycycline should not be used in children aged younger than 8 years due to the risk of teeth discolouration. (Section 4.4 and 4.8)

Elderly: Doxycycline may be prescribed in the usual dose with no special precautions. No dosage adjustment is necessary in the presence of renal impairment.

It is recommended that patients over 70 years of age are specifically instructed regarding the administration of Doxycycline.

An adequate volume of fluid should be taken when administering Doxycycline capsules; this should preferably be taken in an upright position and not immediately before going to bed.

If gastric irritation occurs Doxycycline should be given with food or milk.

Treatment should be continued at least 24 to 48 hours after fever and symptoms have subsided. When used in Streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulo-nephritis.

Specific Infections: Acne vulgaris: 50mg daily with food or fluid for 6 to 12 weeks.

Sexually transmitted diseases: for the treatment of uncomplicated gonococcal infections (except anorectal infections in males), uncomplicated urethral, endocervical or rectal infections caused by *Chlamydia trachomatis*, or non-gonococcal urethritis caused by *Ureaplasma urealyticum*, 100mg should be taken twice daily for 7 days.

For the treatment of acute epididymo-orchitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae;* 100mg twice daily for 10 days.

For the treatment of primary and secondary syphilis: 300mg a day in divided doses for at least 10 days.

Louse and tick-borne relapsing fevers: A single dose of 100mg or 200mg according to severity.

Chloroquine - resistant falciparum malaria: 200mg to be taken daily for at least 7 days. A quick acting schizonticide such as quinine should be used in conjunction with Doxycycline because of the potential severity of the infection. Recommended dosages for quinine vary in different areas.

Prophylaxis: For the prevention of travellers' diarrhoea in adults: 200mg on the first day of travel (administered as a single dose or as 100mg every 12 hours), followed by 100mg daily throughout the stay in the area.

For the prevention of scrub typhus: 200mg to be taken as a single dose.

For the prevention of leptospirosis: 200mg to be taken once a week throughout the stay in the area and 200mg at the end of the trip.

For the prophylaxis of malaria: 100mg daily in adults and children over the age of 12 years. Treatment should commence 1-2 days before travelling to a malarial area and continue daily whilst travelling in malarial areas. On leaving a malarial area the traveller should continue treatment for 4 weeks. To ensure appropriate chemoprophylaxis and for current information on geographical resistance patterns, the current guidelines or the Malarial Reference Laboratory should be consulted, details of which can be found in the current version of the British National Formulary (BNF).

Method of administration: oral.

4.3 Contraindications

Doxycycline should not be administered to patients who have shown hypersensitivity to tetracyclines or to any of the excipients listed in section 6.1.

Pregnancy: Doxycycline capsules is contraindicated in pregnancy. It appears that the risks associated with the use of tetracyclines during pregnancy are predominantly due to effects on teeth and skeletal development. (See Section 4.4 regarding use during tooth development).

Nursing mothers: Tetracyclines are excreted into milk and are therefore contraindicated in nursing mothers. (See Section 4.4 regarding use during tooth development).

4.4 Special warnings and precautions for use

Paediatric population

The use of drugs of the tetracycline class during tooth development (last half of pregnancy; infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses.

Enamel hypoplasia has also been reported. Use doxycycline in paediatric patients aged younger than 8 years only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g. Rocky Mountain spotted fever), only when there are no adequate alternative therapies.

Although the risk of permanent teeth staining is rare in children aged 8 years to less than 12 years, the use of doxycycline should be carefully justified in situations where other drugs are not available, are not likely to be effective or are contraindicated.

Use in patients with impaired hepatic function

Doxycycline should be administered with caution to patients with hepatic impairment or those receiving potentially hepatotoxic drugs.

Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline.

Use in patients with renal impairment Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function. This percentage excretion may fall to a range as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10ml/min). Studies have shown no significant difference in the serum half-life of doxycycline in individuals with normal and severely impaired renal function. Haemodialysis does not alter the serum half-life of doxycycline. The anti-anabolic action of the tetracyclines may cause an increase in blood urea. Studies to date indicate that this anti-anabolic effect does not occur with the use of Doxycycline in patients with impaired renal function.

Serious skin reactions

Serious skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving doxycycline (see section 4.8). If serious skin reactions occur, doxycycline should be discontinued immediately, and appropriate therapy should be instituted.

Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines, including doxycycline (see section 4.8).

Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs and treatment should be discontinued at the first evidence of skin erythema.

Photoonycholysis has also been reported in patients receiving doxycycline (see section 4.8).

Benign intracranial hypertension

Bulging fontanelles in infants have been reported in individuals receiving tetracyclines. Benign intracranial hypertension (pseudotumor cerebri) has been associated with the use of tetracyclines including doxycycline. Benign intracranial hypertension (pseudotumor cerebri) is usually transient, however cases of permanent visual loss secondary to benign intracranial hypertension (pseudotumor cerebri) have been reported with tetracyclines including doxycycline. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

Concomitant use of isotretinoin or other systemic retinoids and doxycycline should be avoided because isotretinoin is also known to cause benign intracranial hypertension (pseudotumor cerebri). (See section 4.5).

Microbiological overgrowth

The use of antibiotics may occasionally result in the overgrowth of non-susceptible organisms including Candida. If a resistant organism appears, the antibiotic should be discontinued and appropriate therapy instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and has ranged in severity from mild to life-threatening. It is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including doxycycline, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD.

Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Oesophagitis

Instances of oesophagitis and oesophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class, including doxycycline. Most of these patients took medications immediately before going to bed or with inadequate amounts of fluid.

Porphyria

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

Venereal disease

When treating venereal disease, where co-existent syphilis is suspected, proper diagnostic procedures including dark-field examinations should be utilised. In all such cases monthly serological tests should be made for at least four months.

Beta-haemolytic streptococci infections

Infections due to group A beta-haemolytic streptococci should be treated for at least 10 days.

Myasthenia gravis

Due to a potential for weak neuromuscular blockade, care should be taken in administering tetracyclines to patients with myasthenia gravis.

Systemic lupus erythematosus

Tetracyclines can cause exacerbation of SLE (see section 4.8).

Methoxyflurane

Caution is advised in administering tetracyclines with methoxyflurane. See section 4.5.

Jarisch-Herxheimer reaction

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.

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

The absorption of doxycycline may be impaired by concurrently administered antacids containing aluminium, calcium, magnesium or other drugs containing these cations; oral zinc, iron salts or bismuth preparations. Dosages should be maximally separated.

Since bacteriostatic drugs may interfere with the bacteriocidal action of penicillin, Doxycycline should not be administered in conjunction with penicillins.

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Tetracyclines depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary.

The serum half-life of doxycycline may be shortened when patients are concurrently receiving barbiturates, carbamazepine or phenytoin. An increase in the daily dosage of Doxycycline should be considered.

Alcohol may decrease the half-life of doxycycline.

A few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent use of tetracycline antibiotics with oral contraceptives.

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

Absorption of tetracyclines is impaired by food, milk and milk products.

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity. See section 4.4.

Concomitant use of isotretinoin or other systemic retinoids and doxycycline should be avoided. Each of these agents used alone has been associated with benign intracranial hypertension (pseudotumor cerebri). (See section 4.4).

Laboratory test interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

4.6 Fertility, pregnancy and lactation

Doxycycline is contra-indicated during pregnancy and lactation.

Tetracyclines taken during pregnancy may affect fetal skeletal development and cause permanent discolouration and malformation of teeth.
Tetracyclines are also found in the milk of lactating women receiving Doxycycline therapy and should therefore not be used in nursing mothers (see contra-indications about tooth development).

4.7 Effects on ability to drive and use machines

The effect of doxycycline on the ability to drive or operate heavy machinery has not been studied. There is no evidence to suggest that doxycycline may affect these abilities.

4.8 Undesirable effects

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

System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1000 to <1/100**	**Rare ≥1/10,000 to <1/1000**	**Not known Cannot be estimated from the available data.**
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 reaction, anaphylactoid		Drug reaction with eosinophilia and systemic symptoms (DRESS), Jarisch-Herxheimer reaction[b] (see section 4.4)	

	reaction, angioedema, exacerbation of systemic lupus erythematosus (see section 4.4), pericarditis, serum sickness, Henoch-Schonlein 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)[a], fontanelle bulging	
Ear and labyrinth disorders			Tinnitus	
Eye disorders			Visual disturbance[d]	
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[e]

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, dermatitis exfoliative, fixed eruption, skin hyperpigmentation[c], photoonycholysis	
Musculoskeletal, connective tissue and bone disorders			Arthralgia, myalgia	
Renal and urinary disorders			Blood urea increased	

[a] In association with tetracyclines, including doxycycline, benign intracranial hypertension has been reported with possible symptoms of headache, vomiting, visual disturbances including blurred vision, scotoma, diplopia or permanent loss of vision. The manifestation of clinical symptoms, including headache or visual disturbances, should suggest a possible diagnosis of intracranial hypertension. If an increase in intracranial pressure is suspected during treatment with tetracyclines, administration should be discontinued.
[b] in the setting of spirochete infections treated with doxycycline.
[c] with chronic use of doxycycline.
[d] Associated with Benign intracranial hypertension (pseudotumor cerebri).
[e] Reversible and superficial discolouration of permanent teeth has been reported with the use of doxycycline but frequency cannot be estimated from 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 via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdosage with antibiotics is rare. In the event of overdosage discontinue medication, gastric lavage and other supportive measures are indicated.

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: J01AA02

Doxycycline is primarily bacteriostatic and is believed to exert its anti-microbial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative bacteria and certain other micro-organisms.

5.2 Pharmacokinetic properties

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and faeces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration. Studies reported to date indicate that the absorption of doxycycline, unlike certain other tetracyclines, is not notably influenced by the ingestion of food or milk. Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 micrograms/ml of doxycycline at 2 hours decreasing to 1.45 micrograms/ml at 24 hours. Doxycycline has a high degree of lipid solubility and a low affinity for calcium. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Children and Adolescents (2 to 18 years of age)

Population pharmacokinetic analysis of sparse concentration-time data of doxycycline following standard of care intravenous (IV) and oral dosing in 44 paediatric patients (2-18 years of age) showed that allometrically-scaled clearance (CL) of doxycycline in paediatric patients ≥2 to ≤8 years of age (median [range] 3.58 [2.27-10.82] L/h/70 kg, N=11) did not differ significantly from paediatric patients >8 to 18 years of age (3.27 [1.11-8.12] L/h/70 kg, N=33). For paediatric patients weighing ≤45 kg, body weight normalized doxycycline CL in those ≥2 to ≤8 years of age (median [range] 0.071 [0.041-0.202] L/kg/h, N=10) did not differ significantly from those >8 to 18 years of age (0.081 [0.035-0.126] L/kg/h, N=8). In paediatric patients weighing >45 kg, no clinically significant differences in body weight normalized doxycycline CL were observed between those ≥2 to ≤8 years (0.050 L/kg/h, N=1) and those >8 to 18 years of age (0.044 [0.014-0.121] L/kg/h, N=25). No clinically significant difference in CL between oral and IV dosing was observed in the small cohort of paediatric patients who received the oral (N=19) or IV (N=21) formulation alone.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber, which are additional to those already included in other sections of the SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, magnesium stearate, talc, lactose. Capsule Shell: Green cap: yellow iron oxide (E172), indigotine (E132), titanium dioxide (E171) gelatin. White body: titanium dioxide (E171), gelatin.

6.2 Incompatibilities

Not known.

6.3 Shelf life

3 years: Blister strips composed of 300µm polypropylene, 16mm aluminium foil or blister strips composed of 20µm aluminium foil and 250µm PVC coated with 40gm^2 PVdC.

24 months: Blister strips composed of 240µm polypropylene laminated cyclo-olefin-copolymer (COC) film, laminated both sides with 30µm polypropylene.

6.4 Special precautions for storage

Store in a dry place.

6.5 Nature and contents of container

Blister strips composed of 300 µm polypropylene or 240µm polypropylene laminated cyclo-olefin-copolymer (COC) film, laminated both sides with 30µm polypropylene, 16 mm aluminium foil or 250µm PVC coated with 40gm^2 PVdC, 20µm aluminium foil packed in outer cartons.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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