SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxycycline 50mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxycycline base …….50 mg
(as doxycycline hyclate)
Excipients q.s. for …… …….. 1 capsule

3 PHARMACEUTICAL FORM

Capsules

Hard gelatin capsules, containing spherical yellow to yellowish microgranules, intended for oral administration to human beings with the markings “50mg” printed with black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxycycline has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro- organisms.

Respiratory tract infections
Pneumonia and other lower respiratory tract infections due to susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and other organisms. *Mycoplasma pneumoniae* pneumonia.Treatment of chronic bronchitis, sinusitis.

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

Sexually transmitted diseases
Infections due to *Chlamydia trachomatis* including uncomplicated urethral, endocervical or rectal infections. Non-gonococcal urethritis caused by *Ureaplasma urealyticum* (T-mycoplasma). Doxycycline is also indicated in

chancroid, granuloma inguinale and lymphogranuloma venereum. Doxycycline is an alternative drug in the treatment of gonorrhoea and syphilis.

Dermatological infections
Acne vulgaris when antibiotic therapy is considered necessary.

Since Doxycycline is a member of the tetracycline group of antibiotics, it may be expected to be useful in the treatment of infections which respond to other tetracyclines such as:

Ophthalmic infections
Due to susceptible strains of gonococci, staphylococci and *Haemophilus influenzae*. Doxycycline Capsules are indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence. Inclusion conjunctivitis may
be treated with oral ByMycin alone or in combination with topical agents.

Rickettsial infections
Rocky Mountain spotted fever, typhus group, Q fever, *Coxiella endocarditis* and tick fevers.

Other infections
Psittacosis, cholera, bubonic plague, meliodosis, leptospirosis, other infections due to susceptible strains of Yersinia species, tularaemia glanders, Brucella species (in combination with Streptomycin), Clostridium species, *Francisella tularensis* and chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides).

Doxycycline Capsules are indicated for prophylaxis in the following conditions: Scrub typhus, traveller's diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis.

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

4.2 Posology and method of administration

The capsules should be swallowed with plenty of fluid in either the resting or standing position and well before going to bed for the night to reduce the likelihood of oesophageal irritation and ulceration.

If gastric irritation occurs, it is recommended that Doxycycline Capsules be given with food or milk. Studies indicate that the absorption of doxycycline is not notably influenced by simultaneous ingestion of food or milk.

Posology

Adults and children aged 12 years to less than 18 years

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

Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued for at least 24 to 48 hours after the symptoms and fever have subsided.
When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Dosage recommendations in specific infections:

*Acne vulgaris*50mg daily with food or fluid for 6 to 12 weeks.

Sexually transmitted diseases
100mg twice daily for 7 days is recommended in the following infections: uncomplicated gonococcal infections (except anorectal infections in men); uncomplicated urethral, endocervical or rectal infection caused by *Chlamydia trachomatis*; non-gonococcal urethritis caused by *Ureaplasma urealyticum*. Acute epididymo-orchitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoea* 100mg twice daily for 10 days.

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.

Treatment of chloroquine-resistant falciparum malaria
200mg daily for at least 7 days. Due to the potential severity of the infection, a rapid-acting schizonticide such as quinine should always be given in conjunction with Doxycycline; quinine dosage recommendations vary in different areas.

Prophylaxis of malaria
100mg daily in adults and children over the age of 12 years. Prophylaxis can begin 1-2 days before travel to malarial areas. It should be continued daily during travel in the malarial areas and for 4 weeks after the traveller leaves the malarial area. For current advice on geographical resistance patterns and appropriate chemoprophylaxis, current guidelines or the Malaria Reference Laboratory should be consulted, details of which can be found in the British National Formulary (BNF).

For the prevention of scrub typhus
200mg as a single dose.

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. Data on the use of the drug prophylactically are not available beyond 21 days.

For the prevention of leptospirosis
200mg once each week throughout the stay in the area and 200mg at the completion of the trip. Data on the use of the drug prophylactically are not available beyond 21 days.

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

Renal impairment: Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Rocky Mountain spotted fever

Adults: 100 mg every 12 hours.

Children: weighing less than 45 kg: 2.2 mg/kg body weight given twice a day. Children weighing 45 kg or more should receive the adult dose (see section 4.4 paediatric population).

Patients should be treated for at least 3 days after the fever subsides and until there is evidence of clinical improvement. Minimum course of treatment is 5-7 days.

The anti-anabolic action of the tetracyclines may cause an increase in blood urea. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Haemodialysis does not alter the serum half-life of doxycycline.

4.3 Contraindications

Persons who have shown hypersensitivity to doxycycline or any of the excipients listed in section 6.1 or to any of the tetracyclines.

Sucrose intolerance
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrose-isomaltase insufficiency should not take doxycycline.

Pregnancy
Doxycycline is contraindicated in pregnancy (see section 4.6). 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 8years) 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. 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).

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 antibiotics, including doxycycline, and has ranged 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 should be considered in all patients who present with diarrhoea after antibiotic treatment. 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.

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).

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 such cases monthly serological tests should be performed 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 systemic lupus erythematosus (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.

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.

Ergotamine and methysergide
There is an increased risk of ergotism when doxycycline is co-administered with ergotamine and methysergide.

Methotrexate
Doxycycline increases the risk of methotrexate toxicity; prescribe with caution to patients on methotrexate.

Kaolin and sucralfate may reduce the absorption of doxycycline.

Quinapril contains magnesium carbonate and may interfere with the absorption of doxycycline.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving Doxycycline in conjunction with penicillin.

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

The serum half-life of doxycycline may be shortened when patients are concurrently receiving barbiturates, carbamazepine, primidone 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.

Drugs that induce hepatic enzymes such as rifampicin may accelerate the decomposition of doxycycline, thereby decreasing its half-life. Sub-therapeutic doxycycline concentrations may result. Monitoring concurrent use is advised and an increase in doxycycline dose may be required.

There is a possible increased risk of benign intra-cranial hypertension when doxycycline given with retinoids. Concomitant use should be avoided. Each of these agents used alone has been associated with benign intracranial hypertension (pseudotumor cerebri).

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

Antibacterials inactivate oral typhoid vaccines. Avoid administration of vaccine during treatment with doxycycline.

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 contraindicated in pregnancy and lactation.

See section 4.3.

4.7 Effects on ability to drive and use machines

Visual disturbances such as blurring of vision may occur during treatment with doxycycline and in such cases, patients must be informed to refrain from driving or operating machinery.

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 reactions (*including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, Henoch-Schonlein purpura,hypotension, pericarditis, angioedema, exacerbation of systemic lupus erythematosus, (see section 4.4) dyspnoea, serum sickness, peripheral oedema, tachycardia and urticaria.)*		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Jarisch-Herxheimer reaction [B] (*see Section 4.4*)	
Endocrine disorders			Brown-black microscopic discolouration of thyroid glands	
Metabolism and nutrition disorders			porphyria, decreased appetite	
Nervous system disorders	Headache		Anxiety, fontanelles Bulging benign intracranial hypertension (pseudotumor cerebri [A])	
Ear and labyrinth disorders			Tinnitus	
Eye disorders			Visual disturbance	

			[D]	
Vascular disorders			flushing	
Gastrointestinal disorders	nausea, vomiting	dyspepsia (heartburn/ gastritis)	pancreatitis, glossitis, pseudomembranous colitis, *Clostridium difficile colitis, oesophageal ulcer, oesophagitis, enterocolitis,* inflammatory lesions (with monilial overgrowth) in the anogenital region dsysphagia, abdominal pain, diarrhoea, glossitis, stomatitis	Tooth discolouration[E]
Hepatobiliary disorders			Hepatotoxicity, hepatic function abnormal, hepatitis, jaundice, hepatic failure	
Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash including maculopapular and erythematous rashes,		Skin Hyperpigmentation [C] erythema multiforme, dermatitis exfoliative, Stevens-Johnson syndrome and toxic epidermal necrolysis and photo-onycholysis have been reported.	
Musculoskeletal and connective tissue disorders			Arthralgia, myalgia	
Renal and urinary system disorders			Blood urea increased (see section4.4).	

[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 adversereactions
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.

There is no specific antidote but in the event of overdosage, discontinue medication. Gastric lavage plus appropriate supportive treatment is 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: J01 AA02.

As antibiotic, doxycycline exerts its antimicrobial effect by the inhibition of protein synthesis and is considered to be primarily bacteriostatic.

Doxycycline is clinically effective in the treatment of a variety of infections caused by a wide range of gram-negative and gram-positive bacteria, as well as certain other micro-organisms.

5.2 Pharmacokinetic properties

Absorption
Absorption is rapid (effective concentrations are attained as from the first

hour), and the peak serum concentration occurs after 2 to 4 hours. 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.

Almost all of the product is absorbed in the upper part of the digestive tract. Absorption is not modified by administration with meals, and milk has little effect.

Distribution
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.

In adults, an oral dose of 200 mg results in;

- A peak serum concentration of more than 3 μg/ml
- A residual concentration of more than 1 μg/ml after 24 hours
- A serum half-life of 16 to 22 hours.
- Protein binding varying between 82 and 93% (labile binding) intra- and extracellular diffusion is good.

With usual dosages, effective concentrations are found in the ovaries, uterine tubes, uterus, placenta, testicles, prostate, bladder, kidneys, lung tissue, skin, muscles, lymph glands, sinus secretions, maxillary sinus, nasal polyps, tonsils, liver, hepatic and gallbladder bile, gallbladder, stomach, appendix, intestine, omentum, saliva and gingival fluid. Doxycycline is transferred into breast milk.
Only small amounts are diffused into the cerebrospinal fluid.

Excretion
The antibiotic is concentrated in the bile. About 40% of the administered dose is eliminated in 3 days in active form in the urine and about 32% in the faeces.

Urinary concentrations are roughly 10 times higher than plasma concentrations at the same time. In the presence of impaired renal function, urinary elimination decreases, faecal elimination increases and the half-life remains unchanged. The half-life is not affected by haemodialysis.

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

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose and Maize starch microgranules
Crospovidone
Basic Butylated Methacrylate Copolymer (Eudragit E100)
Purified Talc

Capsule
Titanium Dioxide (E171)
Indigocarmine (E132)
Quinoline yellow (E104)
Gelatin
Iron oxide (E172)

Ink
Shellac
Black iron oxide (E172)
Propylene glycol
Potassium hydroxide

6.2 Incompatibilities

Nil

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Doxycycline capsules are packed in blister packs made of one sheet of 200 micron rigid, opaque white polyvinyl chloride and a second sheet of 20 micron aluminium.

Ethypharm Doxycycline 50 mg is presented in boxes of 28 capsules.

6.6 Special precautions for disposal

See Part 4.2 « Posology and method of administration ».

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited,
2nd Floor, Connect 38,
1 Dover Place,
Ashford, Kent,
England, TN23 1FB.

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