SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxycycline 100mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains 100 mg doxycycline base

(as doxycycline hyclate)

For a full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Capsules

Hard gelatin capsules, containing spherical yellow to yellowish microgranules, intended for oral administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Doxycycline 100 mg 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 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 100 mg is also indicated in chancroid, granuloma inguinale and lymphogranuloma venereum. Doxycycline 100 mg is an alternative drug in the treatment of gonorrhoea and syphilis.

Skin infections: Acne vulgaris, when antibiotic therapy is considered necessary. Since Doxycycline 100 mg is a member of the tetracycline series 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. Trachoma, although the infectious agent, as judged by immunofluorescence, is not always eliminated. Inclusion conjunctivitis may be treated with oral Doxycycline 100 mg 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, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever, tularaemia glanders, melioidosis, chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides).

Doxycycline 100 mg is an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.

Doxycycline 100 mg is indicated for prophylaxis in the following conditions: Scrub typhus, travellers' diarrhoea (enterotoxigenic Escherichia coli), leptospirosis and malaria. Prophylaxis of malaria should be used in accordance to current guidelines, as resistance is an ever changing problem.

4.2 Posology and method of administration

Adults

The usual dosage of doxycycline for the treatment of acute infections in adults 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, 200 mg daily should be given throughout treatment.

Capsules are for oral administration only.

Doxycycline 100 mg capsules should be administered with adequate amounts of fluid. This should be done in the sitting or standing position and well before retiring at night

to reduce the risk of oesophageal irritation and ulceration. If gastric irritation occurs, it is recommended that Doxycycline 100 mg be given with food or milk. Studies indicate that the absorption of Doxycycline 100 mg is not notably influenced by simultaneous ingestion of food or milk.

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 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: 50 mg daily with food or fluid for 6 to 12 weeks.

Sexually transmitted diseases: 100 mg 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: Non-pregnant penicillin-allergic patients who have primary or secondary syphilis can be treated with the following regimen: doxycycline 200 mg orally twice daily for two weeks, as an alternative to penicillin therapy.

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

Treatment of chloroquine-resistant falciparum malaria: 200 mg 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 100 mg; quinine dosage recommendations vary in different areas.

Prophylaxis of malaria: 100 mg 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: 200 mg as a single dose.

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

Use for children: see under “contra-indications”.

Use in the elderly: Doxycycline 100 mg may be prescribed in the elderly in the usual dosages with no special precautions. No dosage adjustment is necessary in the presence of renal impairment.

Use in patients with impaired hepatic function: see under “special warnings and precautions for use”.

Use in patients with renal impairment: Studies to date have indicated that administration of Doxycycline 100 mg at the usual recommended doses does not lead to accumulation of the antibiotic in patients with renal impairment see under “special warnings and precautions for use”.

4.3 Contraindications

Persons who have shown hypersensitivity to doxycycline, any of its inert ingredients or to any of the tetracyclines.

This product also contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isornaltase insufficiency should not take this medicine.

The use of drugs of the tetracycline class during tooth development (pregnancy, infancy and childhood to the age of 12 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. Doxycycline 100 mg is therefore contra-indicated in these groups of patients.

Patients known to have, or suspected to have, achlorhydria or who have had surgery that bypasses or excludes the duodenum must not be prescribed doxycycline.

Pregnancy: Doxycycline 100 mg is contra-indicated 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 above

about use during tooth development).

Nursing mothers: Tetracyclines are excreted into milk and are therefore contra-indicated in nursing mothers. (see above about use during tooth development).

Children: Doxycycline 100 mg is contra-indicated in children under the age of 12 years. As with other tetracyclines, Doxycycline 100 mg forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracyclines in doses of 25mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. (See above about use during tooth development).

4.4 Special warnings and precautions for use

Use in patients with impaired hepatic function: Doxycycline 100 mg 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%/72h ours 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). 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 100 mg in patients with impaired renal function.

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.

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. Pseudo membranous 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. Agents inhibiting the peristalsis should not be employed in this situation.

Treatment with higher doses of Tetracyclines is associated with emergence of resistant intestinal bacteria, such as enterococci and enterobacteria. Although not observed during clinical studies with low dose doxycycline (40mg/day), the risk for

development of resistance in the normal micro flora cannot be excluded in patients treated with Doxycycline.

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.

Bulging fontanelles: in infants and benign intracranial hypertension in juveniles and adults have been reported in individuals receiving full therapeutic dosages. These conditions disappeared rapidly when the drug was discontinued.

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 betahaemolytic 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.

Doxycycline should not be used in patients with ocular manifestations of rosacea and/or blepharitis/meibomianitis) as there are limited efficacy and safety data in this population. If these manifestations appear during the course of the treatment Doxycycline should be discontinued and the patient should be referred to an ophthalmologist.

Systemic lupus erythematosus: Tetracyclines can cause exacerbation of SLE.

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

Methoxyflurane: caution is advised in administering tetracyclines with methoxyflurane. See section 4.5.

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(found for example in milk, diary products and calcium containing fruit juices), magnesium (found for example in antacids) or other drugs containing these cautions; oral zinc, iron salts, activated charcoal, cholestyramine, sucralfate or bismuth preparations. Therefore such medicinal products or food stuffs should be taken after a period of 2 to 3 hours following ingestion of doxycycline. Dosages should be maximally separated. Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving Doxycycline 100 mg in conjunction with penicillin.

Medicinal products which increase gastric pH may reduce the absorption of doxycycline, and should be taken at least 2 hours after doxycycline.

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

Quinapril may reduce the absorption of doxycycline due to the high magnesium content in Quinapril tablets.

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. If administered in combination of these agents, coagulation parameters including INR should be monitored. The possibility of increase of bleeding events should be borne in mind. 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 100 mg should be considered.
Alcohol may decrease the half-life of doxycycline.

Doxycycline has been shown to potentiate the hypoglycaemic effect of sulphonylurea oral antidiabetic agents. If administered in combination with these medicinal products, blood glucose levels should be monitored and, if necessary, doses of the sulphonylureas should be reduced.

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 cyclosporin. Co-administration should only be undertaken with appropriate monitoring. The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity. (See section 4.4)

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.

Laboratory test interactions

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

4.6 Pregnancy and lactation

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, doxycycline is contraindicated during the second and third trimesters of pregnancy (see section 4.3).

Low levels of tetracyclines are secreted into the milk of lactating women. Doxycycline can be used by breast-feeding mothers for short term use only. Long term use of doxycycline may result in significant absorption by the suckling infant and is therefore not recommended because of a theoretical risk of dental discolouration and decreased bone growth of the suckling child.

4.7 Effects on ability to drive and use machines

Doxycycline has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

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

MEDRA System organ class	Reaction
Infections and infestations:	Very rare: Anogenital candidiasis
Blood and lymphatic system disorders:	Rare: Thrombocytopenia, neutropenia, eosinophilia Very rare: Haemolytic anaemia Not known: porphyria
Immune system disorders:	Rare: Hypersensitivity reactions including anaphylaxis There have also been reports of: Anaphylactoid purpura
Endocrine disorders:	Very rare: Brown-black microscopic discolouration of thyroid tissue has been reported with long-term use of tetracyclines. Thyroid function is normal.

Nervous system disorders:	Rare: Benign intracranial hypertension Very rare: Bulging fontanelle in infants and benign intracranial hypertension in juveniles and adults have been reported in some individuals receiving full therapeutic dosages of tetracyclines. These are reversible on stopping the drug. Symptoms include blurring of vision, scotomata and diplopia. Permanent visual loss has been reported. Not known: Headache
Cardiac disorders:	Rare: Pericarditis
Vascular disorders	Intracranial hyper tension
Gastrointestinal disorders:	Common: Abdominal pain Rare: Nausea, vomiting, diarrhoea, anorexia Very rare: Glossitis, dysphagia, enterocolitis. 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. Not known: Stomatitis, dyspepsia
Hepatobiliary disorders:	Rare: Hepatotoxicity Not known: Transient increases in liver function tests, hepatitis, jaundice, hepatic failure and pancreatitis have been reported rarely.

Skin and subcutaneous tissue disorders:	Rare: Maculopapular and erythematous rashes, skin photosensitivity, urticaria Very rare: Exfoliative dermatitis, angioneurotic oedema Not known: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders:	Very rare: Exacerbation of systemic lupus erythematosus Not known: Arthralgia,Myalgia
Renal and urinary disorders:	Rare: Increased blood urea.
Ear and labyrinth disorders:	Tinnitus
Reproductive system and breast disordes:	Not known: Vaginitis

Other: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discolouration of thyroid tissue. No abnormalities of thyroid function are known to occur.

Tetracyclines may cause discoloration of teeth and enamel hypoplasia, but usually only after long-term use.

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

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 overdose there is, however, a risk of parenchymatous hepatic and renal damage and of pancreatitis.

Treatment:

In cases of significant overdose, doxycycline therapy should be stopped immediately and symptomatic measures undertaken as required.

Intestinal absorption of unabsorbed doxycycline should be minimised by administering magnesium or calcium salt-containing antacids to produce non-absorbable chelate complexes with doxycycline. Gastric lavage should be considered.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxycycline 100 mg is primarily bacteriostatic and is believed to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline 100 mg is active against a wide range of Gram-positive and Gram-negative bacteria and 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.

- 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
In adults, an oral dose of 200 mg results in :

- a peak serum concentration of more than 3µg/ml
- a residual concentration of more than 1µg/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. Major Metabilic pathways of doxycycline have not been identified but enzyme decrease the half life of doxycycline.

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.

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.

5.3 Preclinical safety data

Adverse reactions seen in repeat dose studies in animals include hyperpigmentation of the thyroid and tubular degeneration in the kidney. These effects were seen at exposure levels of 1.5 to 2 times those seen in humans administered EFRACEA at the proposed dose. The clinical relevance of these findings remains unknown.

Doxycycline showed no mutagenic activity and no convincing evidence of clastogenic activity. In a rat carcinogenicity study increases in benign tumours of the mammary gland (fibroadenoma), uterus (polyp) and thyroid (C-cell adenoma) were noted in females.

In rats, doses of 50 mg/kg/day doxycycline caused a decrease in the straight-line velocity of sperm but did not affect male or female fertility or sperm morphology. At this dose systemic exposure experienced by rats is likely to have been approximately 4 times that seen in humans taking the recommended dose of EFRACEA. At doses greater than 50 mg/kg/day fertility and reproductive performance were adversely affected in rats. A peri/postnatal toxicity study in rats revealed no significant effects at therapeutically relevant doses. Doxycycline is known to cross the placenta and literature data indicate that tetracyclines can have toxic effects on the developing foetus.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose and maize starch microgranules,

Crospovidone,

Polymethacrylate,

Talc.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

None stated

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.

Pack sizes are: 8, 10 and 50 capsules. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Relonchem Ltd

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London WC1 3XX

8 MARKETING AUTHORISATION NUMBER(S)

PL 20395 / 0011

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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