SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Finished Pharmaceutical Product:

1.1 Product Name : **DOXYZIM 100** (Doxycycline Capsules BP 100 mg)

1.2 Strength : 100 mg/Capsule

1.3 Pharmaceutical Form : Hard Gelatin Capsule

2. Qualitative and Quantitative Composition:

Each hard gelatin capsule contains:

Doxycycline Hyclate BP

Eq. to Doxycycline 100 mg

3. Pharmaceutical Form

"Hard gelatin capsule"

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 pneumonia*, *Haemophilus influenza*, *Klebsiella pneumonia* and other organisms. *Mycoplasma 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.
Rickettsial infections:
Rocky Mountain spotted fever, typhus group, Q fever, *Coxiella endocarditis* and tick fevers.
Other infections:
Psittacosis, cholera, meliodosis, leptospirosis, other infections due to susceptible strains of Yersinia species, Brucella species (in combination with Streptomycin), Clostridium species, *Francisella tularensis* and chloroquine-resistant falciparum malaria.
Doxycycline Capsules are indicated for prophylaxis in the following conditions: Scrub typhus, travellers diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis.

4.2 Posology and method of administration

Posology:

Adults: The usual dosage of Doxycycline for the treatment of acute infections in adults is 200 mg on the first day (as a single dose or in divided doses) followed by a maintenance dose of 100 mg/day. In the management of more severe infections (particularly chronic infections of the urinary tract), 200 mg 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: 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* 100 mg twice daily for 10 days.
Primary and secondary syphilis: 300 mg 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: 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; 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.
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 100 mg 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 200 mg at the completion of the trip.
Children: Not recommended.
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.
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.

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.

4.3 Contraindication
• Hypersensitivity to the active substance, any of the Tetracyclines or to any of the excipients used in the formulation.
• 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 is contraindicated in these groups of patients.
• *Pediatric Population:* Doxycycline is contraindicated in children under the age of 12 years. As with other tetracyclines, Doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature infants given oral tetracyclines in doses of 25mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

4.4 Special warnings and special precautions for use
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.
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).

Microbiological overgrowth:

The use of antibiotics may occasionally result in 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.*

Oesophagitis: Instances of oesophagitis and oesophageal ulcerations have been reported in patients receiving 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: 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 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).

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.

Methoxyflurane: Caution is advised in administering tetracyclines with methoxyflurane.

4.5 Interaction with other medicinal products and other forms of interaction

Prolonged prothrombin time in patients taking warfarin and doxycycline.

Tetracyclines depress plasma prothrombin activity and reduced dosage of concomitant anti-coagulants may be necessary

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

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.

Phenobarbital, carbamazepine, primidone and phenytoin may increase the metabolism of doxycycline (reduced half-life). An increase in the daily dosage of doxycycline should be considered.

Alcohol may decrease the half-life of doxycycline.

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

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.

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

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

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

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

4.6 Pregnancy and lactation

Pregnancy: Doxycycline 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.

Nursing mothers: Tetracyclines are excreted into milk and are therefore contraindicated in nursing mothers.

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.

Hypersensitivity reactions, including anaphylactic shock, anaphylaxis, anaphylactoid reaction, anaphylactoid purpura, hypotension, pericarditis, angioneurotic oedema, exacerbation of systemic lupus erythematosus, dyspnoea, serum sickness, peripheral oedema, tachycardia and urticaria.

Infections and infestations: As with all antibiotics, overgrowth of non-susceptible organisms may cause candidiasis, glossitis, staphylococcal enterocolitis, pseudomembranous colitis (with *Clostridium difficile* overgrowth) and inflammatory lesions (with candidal overgrowth) in the anogenital region.

Blood and lymphatic system disorders: Haemolytic anaemia, thrombocytopenia, neutropenia, porphyria, and eosinophilia with tetracyclines.

Immune system disorders: Jarisch-Herxheimer reaction

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

Nervous system disorders: Headache. Bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported in individuals receiving full therapeutic dosages of tetracyclines. These are reversible on stopping the drug. Symptoms included blurring of vision, scotomata diplopia and permanent visual loss has been reported.

Ear and labyrinth disorders: Tinnitus

Gastrointestinal disorders: Gastrointestinal symptoms are usually mild and seldom necessitate discontinuation of treatment. They include abdominal pain, stomatitis, anorexia, nausea, vomiting, diarrhoea, dyspepsia and rarely dysphagia. Oesophagitis and oesophageal ulceration have been reported in patients receiving doxycycline. A significant proportion of these cases occurred with the hydrochloride salt in the capsule form. Tetracyclines may cause discoloration of teeth and enamel hypoplasia, but usually only after long-term use. Black hairy tongue

Hepatobiliary disorders: There have been rare reports of hepatotoxicity with transient increases in liver function tests, hepatitis, jaundice, hepatic failure and pancreatitis.

Skin and subcutaneous tissue disorders: Rashes including maculopapular and erythematous rashes, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Photosensitivity and photo-onycholysis. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Musculoskeletal and connective tissue disorders: Arthralgia and myalgia

Renal and urinary system disorders: Increased blood urea
Reproductive system and breast disorders: Vaginitis

5. Pharmacological Properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Tetracyclines.

ATC Code: J01AA02.

Doxycycline is primarily a bacteriostatic antibiotic.

Mechanism of action:

The main mechanism of action of doxycycline is on protein synthesis. Doxycycline passes directly through the lipid bilayer of the bacterial cell wall and an energy dependent active transport system pumps the drug through the inner cytoplasmic membrane. Once inside the cell doxycycline inhibits protein synthesis by binding to 30S ribosomes and prevents the addition of amino acids to the growing peptide chain. Doxycycline will impair protein synthesis in mammalian cells at very high concentrations but these cells lack the active transport system found in bacteria.

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: Doxycycline is almost completely absorbed and is not subject to presystemic metabolism, the mean bioavailability being approximately 93%.

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: Tissue distribution is good and Doxycycline has a strong affinity for renal and lung tissue. The volume of distribution for doxycycline ranges from 0.9-1.8 lkg-1.

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.

Biotransformation: No significant metabolism occurs.

Elimination: Doxycycline is cleared intact by renal and biliary mechanisms

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
Not Applicable.

6. Pharmaceutical Particulars
6.1 List of excipients
Colloidal Anhydrous Silica
Maize Starch
Purified Talc
Empty hard gelatin capsules Size “2”

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
24 months from the date of Manufacture.

6.4 Special precautions for storage
Store at a temperature not exceeding 30°C, protect from moisture.
Keep out of the reach of children.

6.5 Nature and contents of container
1 x 10 Capsules in Alu-Alu blister pack. Such 10 blisters are packed in a carton along with Insert.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
ZIM Laboratories Limited
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441 501,
Maharashtra State, India

8. Number(S) In the National Register of Finished Pharmaceutical Products

04865/07298/NMR/2019

9. Date of First Authorization/Renewal of the Authorization
Dec 25, 2019

10. Date of Revision of the Text

Not Applicable