SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Remycin 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains doxycycline hyclate equivalent to 100 mg doxycycline.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Remycin 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 stains 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, *Escherichiacoli, 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 Ureaplasmaurealyticum (T-mycoplasma). Remycin is also indicated in chancroid, granuloma inguinale and lymphogranuloma venereum. Remycin is an alternative drug in the treatment of gonorrhoea and syphilis.

Since Remycin 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 Remycin 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 plaque, louse and tick-borne relapsing fever, tularaemia glanders, melioidosis, chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides).
Remycin is an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.
Remycin is indicated for prophylaxis in the following conditions: Scrub typhus, travelers diarrhea (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 Remycin for the treatment of acute infections in adults is 200 mg on the first day (as a single dose or in divided doses) followed bya maintenance dose of 100 mg/day. In the management of more severe infections, 200 mg daily should be given throughout treatment.
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 Remycin be given with food or milk. Studies indicate that the absorption of doxycycline 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:
Sexually transmitted diseases100 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 Ureaplasmaurealyticum. Acute epididymo-orchitis caused by Chlamydia trachomatis or Neisseria gonorrhoea 100 mg 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 for two weeks, as an alternative to penicillin therapy.

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

Treatment of chloroquine-resistant falciparum malaria200 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 Remycin; 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 malaria areas. It should be continued daily during travel in the malarial areas and for 4 weeks after the traveler 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 typhus200 mg as a single dose.

Forthe prevention of travelers' diarrhea in adults200 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 leptospirosis200 mg once each week throughout the stay in the area and 200 mg at the completion of the trip. Data on the use of the drug prophilactically are not available beyond 21 days.

Use for childrensee under "Contraindications".

Use in the elderlyRemycin 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 functionSee under "Special warnings and precautions for use".

Use in patients with renal impairmentStudies to date have indicated that administration of Remycin 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".

Method of administration
Oral administration.

4.3 Contraindications

Persons who have shown hypersensitivity to doxycycline, any of its inert ingredients or to any of the tetracyclines.
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 hypoplasiahas also been reported. Remycin is therefore contra-indicated in these group of patients.

Pregnancy:Remycin 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 toothdevelopment).

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

Children: Remycin is contra-indicated 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 prematures given oral tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued. (See above about the use during tooth development).

4.4 Special warnings andprecautions for use

Use in patients with impaired hepatic function
Remycin 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 10 ml/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 Remycin 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.
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.

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 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.

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, 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 bactericidal action of penicillin, it is advisable to avoid giving Remycin 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 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 Remycin 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 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.

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

4.6 Fertility, pregnancy and lactation

See “Contraindications”.

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:

Autonomic nervous system Flushing.

Body as a wholeHypersensitivity 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.

Central and Peripheral nervous system Headache. Bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported in individuals receiving full therapeutic dosages of tetracyclines. In relation to benign intracranial hypertension, symptoms included blurring of vision, scotomata and diplopia. Permanent visual loss has been reported.

Gastro-intestinalGastro-intestinal symptoms are usually mild and seldom necessitate discontinuation of treatment. Abdominal pain, anorexia, nausea, vomiting, diarrhoea, dyspepsia and rarely dysphagia. Oesophagitis and oesophageal ulceration have been reported in patients receiving Remycin. A significant proportion of these occurred with the hyclate salt in the capsule form. (See 'Special warnings and precautions for use' section).

Hearing/VestibularTinnitus.

HaemopoieticHaemolyticanaemia, thrombocytopenia, neutropenia, porphyria, and eosinophilia have been reported with tetracyclines.

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

Musculo-SkeletalArthralgia and myalgia.

Skin and Subcutaneous Tissue Disorders Rashes including maculopapular and erythematous rashes, exfoliative dermatitis, erythema multiforme, Steven-Johnson syndrome and toxic epidermal necrolysis, photosensitivity skin reactions (see 'Special warnings and precautions for use' section) and photo-onycholysis.

SuperinfectionAs 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. Similarly there have been reports for products in the tetracycline class of stomatitis and vaginitis.

Urinary system Increased blood urea. (See 'Special warnings and precautions for use' section.)

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 national reporting system.

4.9 Overdose

Acute overdosage with Remycin is rare.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: Antibacterials for systemic use; Tetracyclines,
ATC code: J01AA02

Remycin is primarily bacteriostatic and is believed to exert its antimicrobial effect by the inhibition of protein synthesis. Remycin 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 200mg 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.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Core</u>
Magnesium stearate
Talc
Microcrystalline cellulose
Povidone
Sodium starch glycollate
Croscarmellose sodium

Coating
Hypromellose
Polyethylene glycol 400
Titanium dioxideE171
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 25ºC. Protect from light and moisture.

6.5 Nature and contents of container

PVC/Aluminium blisters. Pack-sizes of 10, 100 and 1000 film-coated tablets.
PP containers with PE closures. Pack-sizes of 1000 film-coated tablets.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Remedica Ltd.
Aharnon Str., Limassol Industrial Estate,
3056 Limassol, Cyprus

8. MARKETING AUTHORISATION NUMBER(S)

06637/08168/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: 19-10-2021

10. DATE OFREVISION OF THE TEXT

04/07/2023