Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vibramycin Capsules 50 mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vibramycin capsules contain 50 mg doxycycline as doxycycline hyclate.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule
Vibramycin capsules 50 mg are green and ivory hard capsules containing a yellow powder. The capsules are printed with 'Pfizer' and 'VBM 50'.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Vibramycin 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-organism.

Respiratory tract infections:
Pneumonia and other lower respiratory tract infections due to susceptible strains of *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Moraxella catarrhalis* 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). Vibramycin is also indicated in infections due to *Calymmatobacterium granulomatis.* Vibramycin is an alternative drug in the treatment of gonorrhoea and syphilis.

Dermatological infections:
Acne vulgaris and acne conglobata.

Since Vibramycin 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:
Vibramycin is indicated in the treatment of trachoma, although the infections agent is not always eliminated, as judged by immunofluorescence. Inclusion conjunctivitis may be treated with oral Vibramycin alone or in combination with topical agents.

Rickettsial infections:
Rocky Mountain spotted fever, typhus group, Q fever and Coxiella endocarditis.

Other infections:
Psittacosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever including stage 1 and stage 2 Lyme disease, leptospirosis, tularaemia glanders, chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides).

Infections due to susceptible strains of Bacteroides species, Listeria species and *Bacillus anthracis.*

Vibramycin is an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.

Vibramycin is indicated for prophylaxis in the following conditions: Scrub typhus traveller's diarrhoea (enterotoxigenic *Escherichia coli*) leptospirosis, malaria and cholera.

4.2 Posology and method of administration

The usual dose of Vibramycin for the treatment of acute infections in adults is 200mg on the first day (administered as a single dose or divided into two equal doses with a 12 hour interval), followed by a maintenance dose of 100mg/day. In the management of more severe infections (particularly chronic infections of the urinary tract), 200mg daily should be given throughout the treatment period.

Vibramycin capsules should be taken with adequate amounts of fluid (at least 100 mls of water). This should be done in the sitting or standing position and the patient should be advised to remain upright for at least thirty minutes after taking a dose. Vibramycin capsules should be taken well before bedtime to reduce the risk of oesophageal irritation and ulceration. If gastric irritation occurs, it is recommended that Vibramycin be given with food or milk. Studies indicate that the absorption of Vibramycin 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 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 urethral, endocervical or rectal infection caused by *Chlamydia trachomatis,* non-gonococcal urethritis caused by *Ureaplasma urealyticum.*

Uncomplicated gonococcal infections (except anorectal infections in men) Doxycycline 100 mg twice daily for 7 days together with intramuscular ceftriaxone.

Acute epididymo-orchitis caused by Chlamydia trachomatis or Neisseria gonorrhoea Doxycycline 100 mg twice daily for 10 days together with intramuscular ceftriaxone.

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

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

Early Lyme Disease (Stage 1 and 2) 100 mg twice daily for 10-30 days according to clinical signs, symptoms and response.

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 Vibramycin; quinine dosage recommendations very in different areas.

Prophylaxis of malaria 100 mg daily in adults. Prophylaxis can begin 1-2 days before travel to malarious areas. It should be continued daily during travel in the malarious areas and for 4 weeks after the traveller leaves the malarious area.

For the treatment and selective prophylaxis of cholera in adults 300 mg as a single dose.

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

For the prevention of traveller's 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 treatment of leptospirosis 100 mg twice daily for 7 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. Data on the use of the drug prophylactically are not available beyond 21 days.

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

Use in patients with impaired hepatic function Vibramycin should be administered with caution to patients with hepatic impairment or those receiving potentially hepatotoxic drugs.

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

4.3 Contraindications

Vibramycin is contra-indicated in persons who have shown hypersensitivity to doxycycline, any of its inert ingredients or to any of the tetracyclines.

Obstructive oesophageal disorders, such as stricture or achalasia.

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. Vibramycin is therefore, contraindicated in these groups of patients.

Pregnancy Vibramycin 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 Vibramycin is contra-indicated in children under the age of 12 years. As with other tetracyclines, Vibramycin 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 use during tooth development).

4.4 Special warnings and precautions for use

Use in Patients with Impaired Hepatic Function Vibramycin 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 Vibramycin in patients with impaired renal function.

Use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose – galactose malabsorption. Vibramycin capsules should not be taken as they contain lactose.

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 over-growth of non susceptible organisms. Constant observation of the patient is essential. 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.

Oesophagitis Cases of oesophageal injuries (oesophagitis and ulceration), sometimes serious, have been reported. Patients should be instructed to take doxycycline capsules with plenty of water (at least 100ml), remain upright and not take their treatment before going to bed (see section 4.2). Withdrawal of doxycycline and investigation of oesophageal disorder should be considered if symptoms such as dyspepsia or retrosternal pain occur. Caution is required in the treatment of patients with known oesophageal reflux disorders.

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.

Veneral 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 a group A beta-haemolytic streptococci should be treated for at least 10 days.

4.5 Interaction with other medicinal products and other forms of interaction

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving Vibramycin in conjunction with penicillin.
The absorption of doxycycline is impaired by concurrently administered antacids containing aluminium, calcium,

magnesium or other drugs containing these cations; oral zinc, iron salts or bismuth preparations.

The serum half-life of doxycycline is shortened when patients are concurrently receiving alcohol, barbiturates, carbamazepine or phenytoin.

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

Usage in Pregnancy
Vibramycin has not been studied in pregnant patients. It should not be used in pregnancy unless, in the judgement of the physician, it is essential for the welfare of the patient. (See Contra-indications section about use during tooth development).
Results of animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage in Nursing Mothers
Tetracyclines are present in the milk of lactating women who are taking a drug of this kind and should therefore not be used in nursing mothers (See Contraindications section about use during tooth development).

4.7 Effects on ability to drive and use machines

The effect of doxycycline on the ability to drive and 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.

Gastro-intestinal: Abdominal pain, anoerexia, nausea, vomiting, diarrhoea, glossitis, dysphagia, dyspepsia, enterocolitis, pseudomembranous colitis, C.*difficile* diarrhoea and inflammatory lesions (with candidal overgrowth) in the anogenital region. Oesophagitis and oesophageal ulcerations (see section 4.4).

Hearing/Vestibular: Tinnitus.

Hepatic Toxicity: Abnormal hepatic function and hepatitis.

Musculo-Skeletal: Arthralgia and myalgia.

Skin: 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).

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

Body as a Whole: 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.

With tetracyclines allergic reactions are less than half as common as to penicillins. For this reason tetracyclines may be suitable for patients with allergic reactions to one or more other antibiotics.

Haemopoietic: Haemolytic anaemia, thrombocytopenia, neutropenia, and eosinophilia have been reported with tetracyclines but are extremely rare.

Central and peripheral nervous system: Headache. Bulging fontanelles in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages of tetracycline but are extremely rare. These conditions disappeared rapidly when the drug was discontinued.

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.

4.9 Overdose

Acute overdosage with antibiotics 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

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

Vibramycin has a high degree of lipid solubility and a low affinity for calcium. It is highly stable in normal human serum. Vibramycin will not degrade into an epianhydro form.

5.2 Pharmacokinetic properties

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and faeces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration. Studies reported to date indicate that the absorption of doxycycline, unlike certain other tetracyclines, is not notably influenced by the ingestion of food or milk.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 micrograms/ml of doxycycline at 2 hours decreasing to 1.45 micrograms/ml at 24 hours.

Studies have shown no significant difference in serum half-life of Vibramycin (range 18 to 22 hours) in individuals with normal or severely impaired renal function.

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

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Alginic Acid

Lactose Monohydrate
Magnesium Stearate
Maize Starch
Sodium Laurilsulfate

Cap:
Gelatin
Patent Blue V(E131)
Quinoline Yellow (E104)
Titanium Dioxide (E171)

Body:
Gelatin
Indigotine (E132)
Titanium Dioxide (E171)
Yellow Iron Oxide (E172)

Printing ink:
Black Iron Oxide (E172)
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

4 years.

6.4 Special precautions for storage

Store below 25^{o}C.

6.5 Nature and contents of container

Vibramycin Capsules 50 mg are available as:

Calendar Packs of 28 Capsules.
Aluminium/PVC blister strips, 14 capsules per strip, 2 strips in a box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 19/13/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 March 1985

Date of last renewal: 25 March 2005

10 DATE OF REVISION OF THE TEXT

November 2005