1. Name of the medicinal product

Emgyl Tablets BP 200mg

2. Qualitative and quantitative composition

Each tablet contains Emgyl 200mg.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablet.

Off-white coloured, round, biconvex uncoated tablets engraved “MZ 200” & break line on one side and plain on other.

4. Clinical particulars

4.1 Therapeutic indications

Emgyl is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Emgyl is active against a wide range of pathogenic micro-organisms notably species of *Bacteroides*, *Fusobacteria*, *Clostridia*, *Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.

It is also active against *Trichomonas*, *Entamoeba histolytica*, *Giardia lamblia* and *Balantidium coli*.

Emgyl is indicated in adults and children for the following indications:

1. The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci.

2. The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated.

3. Urogenital trichomoniasis in the female (*Trichomonal vaginitis*) and in the male.

4. Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or *Gardnerella vaginitis*).

5. All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers).

6. Giardiasis.

7. Acute ulcerative gingivitis.

8. Anaerobically-infected leg ulcers and pressure sores.

9. Acute dental infections (e.g. acute pericoronitis and acute apical infections).

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

4.2 Posology and method of administration

Posology

1. Prophylaxis against anaerobic infection:

Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.

Adults: 400 mg 8 hourly during 24 hours immediately preceding operation followed by postoperative intravenous or rectal administration until the patient is able to take tablets.

Paediatric population

Children < 12 years: 20-30mg/kg as a single dose given 1-2 hours before surgery

Newborns with a gestation age < 40 weeks: 10 mg/kg body weight as a single dose before operation.

2. Anaerobic infections:

The duration of a course of Emgyl treatment is about 7 days but it will depend upon the seriousness of the patient's condition as assessed clinically and bacteriologically.

Treatment of established anaerobic infection:

Adults: 800 mg followed by 400 mg 8 hourly.

Paediatric population

Children > 8 weeks to 12 years of age: The usual daily dose is 20-30 mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.

Children < 8 weeks of age: 15 mg/kg as a single dose daily or divided into 7.5 mg/kg every 12 hours.

Newborns with a gestation age <40 weeks: accumulation of Emgyl can occur during the first week of life, therefore the concentrations of Emgyl in serum should preferable be monitored after a few days therapy.

3. Protozoal and other infections:

Dosage is given in terms of Emgyl or Emgyl equivalent					
	Duration of dosage in days	Adults and children over 10 years	Children		
			7 – 10 years	3 – 7 years	1 – 3 years
Urogenital trichomoniasis (Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently)					
	7 Or 5 – 7	2000 mg as a single dose Or 200 mg three times daily or 400 mg twice daily	40 mg/kg orally as a single dose Or 15 – 30 mg/kg/day divided in 2 – 3 doses; not to exceed 2000 mg/kg dose		
Bacterial vaginosis					
	5 – 7 Or	400 mg twice daily	N/A		

	1	Or 2000 mg as a single dose			
Amoebiasis					
(a) Invasive intestinal disease in susceptible subjects	5	800 mg three times daily	400 mg three times daily	200 mg four times daily	200 mg three times daily
(b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis	5 – 10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
(c) Amoebic liver abscess also other forms of extra-intestinal amoebiasis	5				
(d) Symptomless cyst passers	5 – 10	400 – 800 mg three times daily	200 – 400 mg three times daily	100 – 200 mg four times daily	100 – 200 mg three times daily
	Alternatively, doses may be expressed by body weight: 35 to 50 mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400 mg/day				
Giardiasis					
	3 Or 5 Or 7 – 10	2000 mg once daily Or 400 mg three times daily Or 500 mg twice daily	1000 mg once daily	600 – 800 mg once daily	500 mg once daily
	Alternatively, as expressed in mg per kg of body weight: 15 – 40 mg/kg/day divided in 2 – 3 doses.				
Acute ulcerative gingivitis					
	3	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
Acute dental infections					
	3 – 7	200 mg three times daily	N/A		
Leg ulcers and pressure sores					
	7	400 mg three times daily	N/A		
Children and infants weighing less than 10 kg should receive proportionally smaller dosages. *Elderly:* Flagyl is well tolerated by the elderly but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.					

4. Eradication of *Helicobacter pylori* in paediatric patients:

As a part of a combination therapy, 20 mg/kg/day not to exceed 500 mg twice daily for 7 – 14 days. Official guidelines should be consulted before initiating therapy.

Method of administration

Oral administration. Emgyl tablets should be swallowed (not chewed). It is recommended that the tablets be taken during or after a meal.

4.3 Contraindications
Known hypersensitivity to nitroimidazoles, Emgyl or any of the excipients.

4.4 Special warnings and precautions for use
Emgyl has no direct activity against aerobic or facultative anaerobic bacteria.

Regular clinical and laboratory monitoring (especially leukocyte count) are advised if administration of Emgyl for more than 10 days is considered to be necessary and patients should be monitored for adverse reactions, such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures).

Emgyl should be used with caution in patients with active or chronic severe peripheral and central nervous system disease due to the risk of neurological aggravation.

The elimination half-life of Emgyl remains unchanged in the presence of renal failure. The dosage of Emgyl therefore needs no reduction. Such patients however retain the metabolites of Emgyl. The clinical significance of this is not known at present.

In patients undergoing haemodialysisEmgyl and metabolites are efficiently removed during an eight hour period of dialysis. Emgyl should therefore be re-administered immediately after haemodialysis.

No routine adjustment in the dosage of Emgyl need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

Emgyl is mainly metabolised by hepatic oxidation. Substantial impairment of Emgyl clearance may occur in the presence of advanced hepatic insufficiency.

Significant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of Emgyl may contribute to the symptoms of the encephalopathy. Emgyl should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

Patients should be warned that Emgyl may darken urine.

Due to inadequate evidence on the mutagenicity risk in humans (see section 5.3), the use of Emgyl for longer treatment than usually required should be carefully considered.

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing Emgyl for systemic use. In this population, Emgyl should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalised exanthematous pustulosis (AGEP) have been reported with Emgyl. If symptoms or signs of SJS, TEN or AGEP are present, Emgyl treatment must be immediately discontinued.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking Emgyl.

There is a possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might persist.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should be advised not to take alcohol during Emgyl therapy and for at least 48 hours afterwards because of the possibility of a disulfiram-like (antabuse effects) reaction. Psychotic reactions have been reported in patients who were using Emgyl and disulfiram concurrently.

Some potentiation of anticoagulant therapy has been reported when Emgyl has been used with the Warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.

Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and Emgyl. Lithium treatment should be tapered or withdrawn before administering Emgyl. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive Emgyl.

Patients receiving phenobarbital or phenytoin metaboliseEmgyl at a much greater rate than normally, reducing the half-life to approximately 3 hours.

Emgyl reduces the clearance of 5-fluorouracil and can therefore result in increased toxicity of 5-fluorouracil.

Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Plasma levels of busulfan may be increased by Emgyl which may lead to severe busulfan toxicity.

4.6 Fertility, pregnancy and lactation

There is inadequate evidence of the safety of Emgyl in pregnancy, but it has been in wide use for many years without apparent ill consequence.

Nevertheless Emgyl, like other medicines, should not be given during pregnancy or during lactation unless the physician considers it essential; in these circumstances the short, high-dosage regimens are not recommended.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:

Very common (≥1/10); 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), not known (cannot be estimated from the available data).

Serious adverse reactions occur rarely with standard recommended regimens. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

<u>Blood and lymphatic system disorders:</u>

Very rare: agranulocytosis, neutropenia, thrombocytopenia, and pancytopenia

Not known: leucopenia.

Immune system disorders:

Rare: anaphylaxis,

Not known: angioedema, urticaria, fever.

Metabolism and nutrition disorders:

Not known: anorexia.

Psychiatric disorders*:*

Very rare: psychotic disorders, including confusion and hallucinations.

Not known: depressed mood

Nervous system disorders:

Very rare:

• encephalopathy (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug.

• drowsiness, dizziness, convulsions, headaches

Not known:

• during intensive and/or prolonged Emgyl therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.

• aseptic meningitis

Eye disorders:

Very rare: vision disorders such as diplopia and myopia, which, in most cases, is transient.

Not known: optic neuropathy/neuritis

Ear and labyrinth disorders:

Not known: hearing impaired/hearing loss (including sensorineural), tinnitus

Gastrointestinal disorders:

Not known: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea.

Hepatobiliary disorders:

Very rare:

• increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, jaundice and pancreatitis which is reversible on drug withdrawal.

• cases of liver failure requiring liver transplant have been reported in patients treated with Emgyl in combination with other antibiotic drugs

Skin and subcutaneous tissue disorders:

Very rare: skin rashes, pustular eruptions, acute generalised exanthematous pustulosis, pruritis, flushing

Not known: erythema multiforme, Steven-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption.

Musculoskeletal, connective tissue and bone disorders:

Very rare: myalgia, arthralgia.

Renal and urinary disorders:

Very rare: darkening of urine (due to Emgyl metabolite).

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. or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
Single oral doses of Emgyl, up to 12g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation. There is no specific antidote for Emgyl overdosage. In cases of suspected massive overdose, symptomatic and supportive treatment should be instituted.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, ATC code: J01X D01

Emgyl has antiprotozoal and antibacterial actions and is effective against a wide range of pathogenic micro-organisms notably species of *Bacteroides, Fusobacteria, Clostridia, Eubacteria, anaerobic cocci* and *Gardnerella vaginalis*. It is also active against *Trichomonas vaginalis, Entamoeba histolytica, Giardia lamblia, Balantidium coli and against anaerobic bacteria.*

5.2 Pharmacokinetic properties
Emgyl is rapidly and almost completely absorbed on administration of Emgyl tablets; peak plasma concentrations occur after 20 min to 3 hours.

The half-life of Emgyl is 8.5 ± 2.9 hours. Emgyl can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis. Emgyl is excreted in milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants.

5.3 Preclinical safety data
Emgyl has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in the hamster have given negative results. Epidemiological studies have provided no clear evidence of an increased carcinogenic risk in humans.

Emgyl has been shown to be mutagenic in bacteria *in vitro*. In studies conducted in mammalian cells *in vitro* as well as in rodent or humans *in vivo*, there was inadequate evidence of a mutagenic effect of Emgyl, with some studies reporting mutagenic effects, while other studies were negative.

6. Pharmaceutical particulars

6.1 List of excipients
Povidone

Magnesium Stearate

Colloidal Anhydrous Silica

Maize Starch

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
White polypropylene container with tamper evident polyethylene closure: 3 years.

Amber polypropylene bottle with polyethylene closure: 3 years.

PVC/Aluminium blisters: 2 years.

PVdC coated PVC/Aluminium blisters: 3 years.

6.4 Special precautions for storage
Containers: Do not store above 25°C. Store in the original container. Keep the container tightly closed.

Bottle: Do not store above 25°C. Store in the original container. Keep the container tightly closed.

Blisters: Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container
*White polypropylene container with tamper evident polyethylene closure:*1000, 500, 250, 100, 84, 70, 56, 42, 28, 21, 15, 14 and 7 tablets.

Amber polypropylene bottle with polyethylene closure: 50 tablets.

PVC/Aluminium blisters: 7, 14, 15, 21, 28, 42, 56, 70 and 84 tablets.

PVdC coated PVC/Aluminium blisters: 7, 14, 15, 21, 28, 42, 56, 70 and 84 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorisation holder

Emzor Pharmaceutical Industries Limited located at located at No 13 Richfield Avenue,Ajao Estate,Lagos

8. Marketing authorisation number(s)

NA

9. Date of first authorisation/renewal of the authorisation

NA

10. Date of revision of the text

NA