1. Name of the medicinal product

Metronidazole Tablets 250 mg

2. Qualitative and quantitative composition

Each tablet contains metronidazole 250 mg

Excipients with known effect: lactose monohydrate

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Tablets

4. Clinical particulars

4.1 Therapeutic indications
Metronidazole is active against a wide range of pathogenic micro-organisms, notably species of *Bacteroids, Fusobacteria, Clostridia, Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.

It is also active against *Trichomonas vaginalis, Entamoeba histolytica, Gardia lamblia*, *Balantidium coli* and *Helicobacter pylori*.

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

1) Prevention of post-operative infections due to anaerobic bacteria, particularly species of *bacteroids* 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 (T*richomonas vaginalis*), and in man.

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

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

6) Giardiasis.

7) Acute ulcerative gingivitis.

8) Acute dental infections (*eg* acute pericoronitis and acute apical infections)

9) Anaerobically-infected leg ulcers and pressure sores.

10) Treatment of *Helicobacter pylori* infection associated with peptic ulcer as part of triple therapy.

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

4.2 Posology and method of administration
Posology

Metronidazole Tablets should be taken during or after meals, swallowed with water and NOT CHEWED.

Elderly: Caution is advised in the elderly, particularly at high doses, although there is limited information available on modification of dosage.

Hepatic impairment: Caution is advised in patients with hepatic encephalopathy. One third of the daily dose given once a day should be considered (see section 4.4).

1) Anaerobic infections:

Treatment for 7 days should be satisfactory for most patients but, depending upon clinical and bacteriological assessments, the physician may decide to prolong treatment, *eg* for eradication of infection from sites which cannot be drained or are liable to endogenous recontamination by anaerobic pathogens from the gut, oropharynx or genital tract.

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.

In newborns with a gestation age <40 weeks, accumulation of metronidazole can occur during the first week of life, why the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.

Children under 10 years: A more suitable dosage form should be used for this age group.

Prophylaxis against anaerobic infection - chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.

Adults: 1g stat dose 24 hours pre-operatively, followed by 400mg at 8 hourly intervals during the 24 hours preceding operation followed by post-operative iv or rectal administration until the patient is able to take tablets.

Children < 12 years: 20-30 mg/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.

Children under 10 years: A more suitable dosage form should be used for this age group.

2) Treatment of established infections:

Adults and children over 10 years: 800mg followed by 400mg 8 hourly.

Children under 10 years: A more suitable dosage form should be used for this age group.

3) Urogenital trichomoniasis:

Where reinfection is likely, sexual partners should be treated concomitantly.

Adults and adolescents: 2000 mg as a single dose or 200 mg 3 times daily for 7 days or 400 mg twice daily for 5-7 days.

Children < 10 years: 40 mg/kg orally as a single dose or 15 – 30 mg/kg/day divided in 2-3 doses for 7 days; not to exceed 2000 mg/dose.

Children under 10 years: A more suitable dosage form should be used for this age group.

4) Bacterial vaginosis

Adults: 400mg twice daily for 7 days, or 2g as a single dose for one day only.

Adolescents: 400 mg twice daily for 5-7 days or 2000 mg as a single dose.

5) Amoebiasis

Adults> 10 years: 400 to 800 mg 3 times daily for 5-10 days.

Children 7 to 10 years: 200 to 400 mg 3 times daily for 5-10 days.

Children 3 to 7 years: 100 to 200 mg 4 times daily for 5-10 days.

Children 1 to 3 years: 100 to 200 mg 3 times daily for 5-10 days.

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.

Children under 7 years: A more suitable dosage form should be used for this age group.

6) Giardiasis:

Adults > 10 years: 2000 mg once daily for 3 days, or 400 mg. three times daily for 5 days, or 500 mg twice daily for 7 to 10 days.

Children 7 to 10 years: 1000 mg once daily for 3 days.

Children 3 to 7 years: 600 to 800 mg once daily for 3 days.

Children 1 to 3 years: 500 mg once daily for 3 days.

Alternatively, as expressed in mg per kg of body weight:

15-40 mg/kg/day divided in 2-3 doses.

Children under 7 years: A more suitable dosage form should be used for this age group.

7) Acute ulcerative gingivitis (for 3 day duration):

Adults and children over 10 years: 200mg three times daily.

Children under 10 years: A more suitable dosage form should be used for this age.

8) Acute dental infections (for 3-7 day duration):

Adults and children over 10 years: 200mg three times daily.

9) Leg ulcers and pressure sores (for 7 day duration):

Adults and children over 10 years: 400mg three times daily.

10) Treatment of Helicobacter pylori in infected 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.

<u>Method of Administration</u>

For oral administration.

4.3 Contraindications
• Known hypersensitivity to nitroimidazoles, metronidazole or to any of the excipients listed in 6.1.

• Pregnancy - metronidazole should not be used in the first trimester in patients with trichomoniasis or bacterial vaginosis (see section 4.6).

• Breast feeding should be discontinued for 12-24 hours when single high dose (e.g. 2g) therapy is used (see section 4.6).

4.4 Special warnings and precautions for use
• Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take metronidazole as this product contains lactose.

• Patients should abstain from alcohol for at least 48 hours following discontinuation of therapy with metronidazole. A disulfiram-like reaction with hypotension and flushing has occurred (see section 4.5).

• Caution is advised in patients with porphyria.

• Metronidazole tablets should not be used in patients with blood dyscrasias or with active non-infectious disease of the central nervous system. High doses of metronidazole may mask the presence of syphilis.

• Caution in patients with epilepsy or those who have had seizures as high doses of Metronidazole can induce seizures.

• Use with caution in the second and third trimester when used to treat trichomoniais or bacterial vaginosis (see section 4.6.)

• Regular clinical and laboratory surveillance are advised if treatment continues for more than 10 days.

• Consideration of the therapeutic benefit against the risk of peripheral neuropathy is advised with continuous therapy for chronic conditions.

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

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

• In patients undergoing haemodialysis metronidazole and metabolites are efficiently rmoved during an eight-hour period of dialysis. Metronidazole should, therefore, be readministered immediately after haemodialysis.

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

• Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Signficant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to symptoms of the encephalopathy. Therefore, metronidazole should be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

• 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 metronidazole for systemic use. In this population, metronidazole 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. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

• Patients should be warned that metronidazole may darken urine.

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

4.5 Interaction with other medicinal products and other forms of interaction
<u>Interactions to be used with caution:</u>

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

• *Anticoagulants:* Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. No interactions have been reported with anticoagulants of the heparin type. However, anticoagulant activity should be routinely monitored with these products.

• *Alcohol:* Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours after because of the possibility of a disulfiram-like reaction.

• *Disulfiram:* Psychotic reactions have been reported.

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

Pharmacokinetic interactions:

• *Antiepileptics:* Patients receiving phenobarbital metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours. Metronidazole inhibits metabolism of phenytoin (increases plasma-phenytoin concentration). Primidone accelerates the metabolism of Metronidazole causing reduced plasma concentrations.

• *Cytotoxics:* Metronidazole inhibits metabolism of fluorouracil. Therefore, increased toxicity of fluorouracil can result. Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

• *Ulcer-healing drugs:* Cimetidine inhibits the metabolism of metronidazole (increases plasma-metronidazole concentration).

• *Oestrogens:* broad spectrum antibiotics possibly reduce the contraceptive effect. See local/national guidelines or BNF for specific advice.

• *Drug-lab modifications:* Aspartate amino transferase assays may give spuriously low values in patients taking metronidazole, depending on the method used.

4.6 Fertility, pregnancy and lactation
There is inadequate evidence of the safety of metronidazole in pregnancy but it has been in wide use for many years without apparent ill consequence. As with all medicines, metronidazole should not be given during pregnancy or during lactation unless it is considered essential, and in these circumstances the short, high-dosage regimens are not recommended.

Pregnancy

Metronidazole is contraindicated in the first trimester (see section 4.3) and should be used with caution in the second and third trimester when used to treat trichomoniais or bacterial vaginosis (see section 4.4).

For all other indications Metronidazole should only be used if the benefits outweight the risks or no other alternative is available especially in the first trimester.

Breast-feeding

It is advisable to stop breast feeding until 12 – 24 hours after Metronidazole therapy has been discontinued (see section 4.3).

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
Frequency type and severity of adverse reactions in children are the same as in adults.

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.

Frequency, type and severity of adverse reactions in children are the same as in adults.

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.

Blood and lymphatic system disorders:	
Very rare	Agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
Not known	Leucopenia, bone marrow depression disorders such as aplastic anaemia
Immune system class:	
Rare	Anaphylaxis
Not known	Angiodema, 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, 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

	in discontinuation of the drug, drowsiness, dizziness, convulsions, headaches
Not known	Depression, paraesthesia, during intensive and-or prolonged metronidazole 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. Incoordination of movement, aseptic meningitis
Eye disorders:	
Very rare	Diplopia, myopia
Not known	Optic neuropathy/neuritis
Ear and labyrinth disorders:	
Not known	Hearing impaired/hearing loss (including sensorineural), tinnitus
Gastrointestinal disorders:	
Not known	Unpleasant taste in the mouth, taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances, diarrhoea, abdominal pain, anorexia
Hepatobiliary disorders:	
Very rare	Abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis which is reversible on drug withdrawal, cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs
Skin and subcutaneous tissue disorders:	
Very rare	Skin rashes, pustular eruptions, pruritus, flushing
Not known	Erythema multiforme, Stevens-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 metronidazole 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: website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose
Features:

Nausea, vomiting, diarrhoea, anorexia, metallic taste, headache, dizziness and occasionally insomnia and drowsiness. Transiently increased liver enzyme activities have been reported rarely.

Transient epileptiform seizures have been reported following intensive or prolonged therapy. Other adverse effects occurring in these circumstances include peripheral motor neuropathy, blood dyscrasias and liver damage.

The combination of alcohol and metronidazole has been said to cause disulfiram type reactions in about 10% of individuals with sudden onset of excitement, giddiness, flushing, nausea, headache, hypotension and dyspnoea. However the mechanism of this reaction has been questioned.

Treatment:

Unlikely to be required.

Disulfiram type reactions should be treated with intravenous fluids and plasma expanders if necessary. Symptomatic and supportive.

In more serious cases:

1. Single brief convulsions do not require treatment. If frequent or prolonged control with intravenous diazepam (10-20mg in adults; 0.1-0.3mg/kg body weight) or lorazepam (4mg in an adult and 0.05mg/kg in a child). Give oxygen and correct acid base and metabolic disturbances as required.

2. Other measures as indicated by the patient's clinical condition.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: *Nitroimidazole derivatives*

ATC Code: P01A B01

Mechanism of action

Metronidazole has antiprotozoan and antibacterial effects. It is effects against *Trichomonas vaginalis, Gardnerella vaginalis* and other protazoa including *Entamoeba histolytica, Gardia lamblia* and anaerobic bacteria.

5.2 Pharmacokinetic properties
Absorption

Metronidazole is readily absorbed following administration by mouth and bioavailability is 90-100%. Peak plasma concentrations occur after 20 minutes to 3 hours. Absorption may be delayed, but is not reduced overall, by administration with food.

Distribution

Metronidazole is widely distributed. It appears in most body tissues and fluids. It also crosses the placenta and rapidly enters foetal circulation. No more than 20% is bound to plasma proteins.

Biotransformation

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. The half-life of metronidazole is 6.5 ± 2.9 hours. The half-life of metronidazole is reported to be longer in neonates and in patients with severe liver disease.

Elimination

The majority of a dose of metronidazole is excreted in the urine, mainly as metabolites; a small amount appears in the faeces. Metronidazole can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis. Metronidazole 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
Metronidazole 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.

Metronidazole 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 metronidazole, with some studies reporting mutagenic effects, while others studies were negative.

6. Pharmaceutical particulars

6.1 List of excipients
Lactose, maize starch, povidone, magnesium stearate, carmellose sodium, microcrystalline cellulose, purified water, methylhydroxypropylcellulose, macrogol 400, titanium dioxide (E-171).

6.2 Incompatibilities
None.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store below 25°C. Protect from light.

6.5 Nature and contents of container
Polyethylene container with pilfer-proof polyethylene closure,

pack sizes of 50, 100, 250 and 500 tablets.

Amber glass bottles,

pack sizes of 50, 100, 250 and 500 tablets.

Blister pack (aluminium (20 µm)/PVC (250 µm)),

pack sizes of 14 and 21 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling
Not applicable.

7. Marketing authorisation holder

Emzor Pharmaceutical Industries Limited

Sagamu/Benin Expressway, Makun, Sagamu Local Govt, Sagamu

Manufacturer
Emzor Pharmaceuticals Ind. Ltd,
Lagos.

8. Marketing authorisation number(s)

N/A

9. Date of first authorisation/renewal of the authorisation

N/A

10. Date of revision of the text

07/10/2020