

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1 NAME OF THE MEDICINAL PRODUCT**

Metronidazole 400mg Tablets BP

### **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 400mg Metronidazole.

Also contains lactose, for a full list of excipients, see section 6.1

### **3 PHARMACEUTICAL FORM**

Tablet

Yellow, biconvex and embossed 'M/400' on one side and 'PV' on the other side. Diameter 12.5mm.

### **4 CLINICAL PARTICULARS**

#### **4.1 Therapeutic indications**

Metronidazole 400mg tablets BP is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause. Metronidazole is active against a wide range of pathogenic microorganisms 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 and Helicobacter pylori.

Metronidazole 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).

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

For oral administration.

Metronidazole 400mg Tablets BP is a round shaped biconvex tablet. Take with or after food. Swallow whole with plenty of water. Do not chew. Duration of treatment will depend upon the clinical and bacteriological response to treatment.

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).

### **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, or pharynx or genital tract.

### **Treatment of established anaerobic infection:**

Adults: 800mg initially followed by 400mg every 8 hours, usually for 7 days.

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

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

In newborns with a gestation age over the 40 weeks, accumulation of metronidazole can occur during the first week of life, why the concentrations of metronidazole in serum should preferably 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 postoperative infections caused by anaerobic bacteria:**

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

Adults: 1g start 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 under 12 years: 20-30mg/kg as a single dose given 1-2 hours before surgery

Newborns with a gestation age under 40 weeks: 10mg/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.

**Bacterial vaginosis:**

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

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

**Urogenital Trichomoniasis:**

Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently

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

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

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

**Giardiasis:**

Adults, elderly and Children over 10 years: 2000mg once daily for 3 days, or 400mg three times daily for 5 days, or 500mg twice daily for 7-10 days.

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

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

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

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

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

Alternatively, 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.

**Amoebiasis:**

Adults and children over 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 2400mg/day.

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

**Acute ulcerative gingivitis:**

Adults, elderly and children over 10 years: 200mg 3 times daily for 3 days

Children 7 to 10 years: 100mg 3 times daily for 3 days

Children 3 to 7 years: 100mg 2 times daily for 3 days

Children 1 to 3 years: 50mg 3 times daily for 3 days

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

**Acute dental infection:**

Adults, elderly and children over 10 years: 200mg 3 times daily for 3-7 days

**Leg ulcers pressure sores:**

Adult, elderly and children over 10 years: 400mg 3 times daily for 7 days.

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

As a part of combination therapy, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days.

Children and infants weighing less than 10kg should receive proportionally smaller dosages.

Use in the elderly: Metronidazole is well tolerated by the elderly, but a pharmacokinetic study suggests cautions use of high dosage regimens in this age group.

Official guidelines should be consulted before initiating therapy.

### **4.3 Contraindications**

Known hypersensitivity to nitroimidazoles, metronidazole or any of the excipients.

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 mal-absorption should not take metronidazole as this product contains lactose.

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 trichomoniasis or bacterial vaginosis (see section 4.6.)

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

Metronidazole 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.

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 removed during an eight-hour period of dialysis. Metronidazole should therefore be re-administered 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 may produce abnormal liver function tests.

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole 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 metronidazole may contribute to the symptoms of the encephalopathy. Metronidazole 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.

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.

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.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Lithium retention accompanied by evidence of possible renal damages 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.

Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the later may require reducing. Prothrombin times should be monitored. There is no interaction with heparin. However, anticoagulant activity should be routinely monitored with these products.

Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards because of the possibility of a Disulfiram-like (antabuse effects) reaction. Psychotic reactions have been reported with Disulfiram.

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

Patients receiving phenobarbital or phenytoin metabolize 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.

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

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

Cimetidine inhibits the metabolism of metronidazole.

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 an inadequate evidence of the safety evidence of the safety of metronidazole in pregnancy but it has been in wide use for many years without apparent ill consequence. Nevertheless Metronidazole, 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.

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 trichomoniasis or bacterial vaginosis (see section 4.4).

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

A significant amount of metronidazole is found in breast milk and therefore breast-feeding should be avoided after a large significant dose. It may give a bitter taste to the milk.

#### **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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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.

##### **Blood and lymphatic system disorders:**

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 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, in most cases transient

Not known: optic neuropathy/neuritis

**Gastrointestinal disorders:**

Not known: unpleasant taste in the mouth, taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances like epigastric pain, diarrhoea, abdominal pain.

**Hepatobiliary disorders:**

Very rare: abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis which are 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, pruritis, flushing.

Not known: erythema multiforme.

**Musculoskeletal, connective tissue and bone disorders:**

Very rare: myalgia, arthralgia.

**Renal and urinary disorders:**

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

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

**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](http://www.mhra.gov.uk/yellowcard).

**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. Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation.

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.

Early gastric lavage is recommended following oral over dosage. Metronidazole is readily removed from plasma by haemodialysis. Treatment is symptomatic.

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

#### ATC Code: P01A B01

Metronidazole is a 5-nitroimidazole derivative with activity against anaerobic bacteria and protozoa whose method of action is thought to involve interference with DNA by a metabolite in which the nitro group of metronidazole has been reduced.

Metronidazole has an antibiotic action that is based on the modification of the genetic substance of micro-organisms. Its spectrum contains anaerobic bacteria (*Bacteroides fragilis*, clostridia, fusobacteria, peptococci, peptostreptocci), certain other bacteria (e.g. *Gardnerella vaginalis*) and protozoas (*Giardia lamblia*, *Entamoeba histolytica*, *Trichomonas vaginalis*). Bactericidal tissue concentrations are achieved in the central nervous system, in the liver and the bile ducts, in vaginal secretions, and in the pelvic organs.

Metronidazole is also used against resistant *Helicobacter pylori*. Known or previously unrecognised candidates may present more prominent symptoms during therapy with metronidazole and requires treatment with a candididal agent.

### 5.2 Pharmacokinetic properties

Metronidazole is rapidly and almost completely absorbed on administration of metronidazole tablets and bioavailability approaches 100%. Peak plasma concentration occurs after 20 minutes to 3 hours. Metronidazole appears in most body tissues. It is metabolised mainly in the liver. Both unchanged metronidazole and several metabolites are excreted in the urine. It crosses the placental barrier and rapidly enters the foetal circulation. It is secreted in breast milk.

The half-life of metronidazole is  $8.5 \pm 2.9$  hours. 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 sucking 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 other studies were negative.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of excipients**

- 1) Lactose monohydrate
- 2) Macrogol 4000
- 3) Maize starch
- 4) Povidone
- 5) Magnesium stearate
- 6) Colloidal anhydrous silica
- 7) Sodium starch glycollate
- 8) Microcrystalline cellulose
- 9) Aluminium lake Quinoline Yellow (E104)

### **6.2. Incompatibilities**

Not applicable.

### **6.3. Shelf life**

5 years.

### **6.4. Special precautions for storage**

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

### **6.5 Nature and contents of container**

Polypropylene securitainer, in pack sizes of 14, 21, 100, 250 and 500. Blister packs of 0.25 thick PVC and Aluminium foil of thickness 20 microns. Not all pack sizes may be marketed.

### **6.6 Special precautions for disposal**

None

## **7. MARKETING AUTHORISATION HOLDER**

Pharmvit Limited  
Unit 13, Metropolitan Centre  
Derby Road  
Greenford  
Middlesex  
UB6 8UJ  
United Kingdom

**8.     MARKETING AUTHORISATION NUMBER**

PL 04556/0011

**9.     DATE OF FIRST AUTHORISATION/RENEWAL OF THE  
AUTHORISATION**

13 January 2003

**10    DATE OF REVISION OF THE TEXT**

26/04/2017