

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Metronidazole Tablets 400mg

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole Tablets 400mg.

Each tablet contains 400mg metronidazole.

Excipients with known effect

Metronidazole Tablets 400mg contains 100 mg of Lactose

Metronidazole Tablets 400mg contains approximately 0.260 mg of Sunset Yellow (E110)

For the full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Metronidazole Tablets 400mg.

Metronidazole 400mg tablets are presented as yellow, normal convex tablets, with the company logo on one side and 'A' breakline '321' on the other.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Metronidazole 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*.

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

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

2. The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and *anaerobic streptococci*.
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 dental infections (e.g. acute pericoronitis and acute apical infections).
8. Acute ulcerative gingivitis.
9. Anaerobically-infected leg ulcers and pressure sores

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 swallowed with water (not chewed). It is recommended that the tablets be taken during or after a meal.

##### *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.

##### **Children**

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.

Anaerobic infections: The duration of a course of Metronidazole tablets 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.

##### **Children**

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, therefore concentrations of metronidazole in serum should preferably be monitored after a few days therapy.

*Protozoal and other infections:*

<b>Dosage is given in terms of metronidazole or metronidazole equivalent</b>					
	<b>Duration of dosage in days</b>	<b>Adults and children over 10 years</b>	<b>Children</b>		
			7 to 10 years	3 to 7 years	1 to 3 years
<i>Urogenital trichomoniasis</i> (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 for 7 days; not to exceed 2g /dose	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 2g /dose	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 2g /dose
<i>Bacterial vaginosis</i>					
	5-7 or 1	400 mg twice daily or 2000 mg as a single dose	N/A		
<i>Amoebiasis</i>					
(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	5-10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily

hepatitis					
(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 50mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400 mg/day					
<i>Giardiasis</i>					
	3 or	2000 mg once daily or	1000 mg once daily	600 -800 mg once daily	500 mg once daily
	5 Or 7-10	400 mg three times daily or 500 mg twice daily			
Alternatively, as expressed in mg per kg of body weight: 15-40 mg/kg/day divided in 2-3 doses					
<i>Acute ulcerative gingivitis</i>					
	3	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
<i>Acute dental infections</i>					
	3-7	200 mg three times daily	N/A		
<i>Leg ulcers and pressure sores</i>					
	7	400 mg three times daily	N/A		
Children and infants weighing less than 10 kg should receive proportionally smaller dosages. Elderly: Metronidazole is well tolerated by the elderly but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.					

*Eradication of Helicobacter pylori in paediatric patients:*

As a part of a combination therapy, 20mg/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 Metronidazole tablets should be swallowed with water (not chewed). It is recommended that the tablets be taken during or after a meal.

#### **4.3 Contraindications**

Known hypersensitivity to nitroimidazoles, metronidazole or any of the ingredients listed in section 6.1.

#### **4.4 Special warnings and precautions for use**

Neuropathy (central and peripheral)

Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of Metronidazole 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).

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.

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

Patients should be warned that Metronidazole may darken urine. For information on renal and hepatic insufficiency, please see section 4.2.

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.

Hepatotoxicity in patients with Cockayne syndrome

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 not be used unless the benefit is considered to outweigh the risk and 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 (see section 4.8).

### Skin and subcutaneous tissue disorders

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 metronidazole. If symptoms or signs of SJS, TEN or AGEP are present, metronidazole must be immediately discontinued.

Metronidazole Tablets 400mg contains sunset yellow (E110) which may cause allergic reactions.

Metronidazole Tablets 200mg and 400mg contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### Interference with laboratory tests

Metronidazole may interfere with certain types of blood test determinations in blood (aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], triglycerides, glucose), which may lead to false negative or an abnormally low result. These analytical determinations are based on a decrease in ultraviolet absorbance, a fact that occurs when nicotinamide adenine dinucleotide hydrogen (NADH) is oxidised to nicotinamide adenine dinucleotide (NAD). The interference is due to the similarity in the absorption peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

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

**Alcohol:** 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 effect) reaction.

**Disulfiram:** Psychotic reactions have been reported in patients who were using Metronidazole and disulfiram concurrently.

**Oral anticoagulant therapy (warfarin type):** 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. There is no interaction with heparin.

**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 concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

**Phenytoin or phenobarbital:** Patients receiving phenobarbital or phenytoin metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.

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

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

Busulfan: Plasma levels of busulfan may be increased by Metronidazole which may lead to severe busulfan toxicity.

*Drugs that prolong QT interval:* QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

#### **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. Nevertheless metronidazole, like other medicines should not be given during pregnancy or lactation unless the physician considers it essential. In these circumstances, the short, high-dose regimens are not recommended.

#### **4.7 Effects on ability to drive and use machines**

Patients should be warned about the potential for drowsiness, dizziness, vertigo, 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, 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 (e.g. confusion, fever, vertigo, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, 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.
- aseptic meningitis.
- Vertigo

*Eye disorders:*

Very rare: vision disorders such as diplopia, 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.

*Cardiac disorders:*

*Not known:* QT prolongation has been reported particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

*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 metronidazole in combination with other antibiotic drugs.

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.4).

*Skin and subcutaneous tissue disorders:*

Very rare: skin rashes, pustular eruptions, acute generalised exanthematous pustulosis, pruritis, 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 at: [www.mhra.gov.uk/yellowcard](http://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 Metronidazole, 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 Metronidazole 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.

Metronidazole has antiprotozoal and antibacterial actions and is effective against *Trichomonas vaginalis* and other protozoa including *Entamoeba histolytica* and *Giardia lamblia* and against anaerobic bacteria.

**5.2 Pharmacokinetic properties**

Metronidazole is rapidly and almost completely absorbed on administration of Metronidazole tablets; peak plasma concentrations occur after 20 mins to 3 hours.

The half-life of Metronidazole is 8.5±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 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 other studies were negative

## **PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose  
Microcrystalline cellulose  
Pregelatinised starch  
Magnesium stearate

Metronidazole Tablets 400mg also contains:  
Quinoline Yellow Aluminium Lake E104  
Sunset Yellow Aluminium Lake E110

### **6.2 Incompatibilities**

None

### **6.3 Shelf life**

36 months in tablet containers

48 months in blister packs

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

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

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

1. Opaque plastic containers composed of polypropylene tubes and polyethylene made tamper evident closures in pack sizes of 9, 10, 14, 15, 20, 21, 28, 30, 50, 56, 84, 100, 250, 500 and 1000 tablets.

2. Opaque plastic container composed of either high density polypropylene or high density polyethylene with a tamper evident or child resistant tamper evident closure composed of high density polyethylene with a packing inclusion of standard polyether foam or polyethylene or polypropylene made filler in pack sizes of 9, 10, 14, 15, 20, 21, 28, 30, 50, 56, 84, 100, 250, 500 and 1000 tablets.
3. Blister packs of aluminium/white opaque PVC with PVDC coating in pack sizes of 9, 10, 14, 15, 20, 21, 28, 30, 56 and 84 tablets.

Not all pack sizes may be marketed.

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

None stated

### **7. MARKETING AUTHORISATION HOLDER**

Crescent Pharma Limited  
Key House, Sarum Hill,  
Basingstoke, RG21 8SR,  
United Kingdom

### **8 MARKETING AUTHORISATION NUMBER(S)**

PL 20416/0106

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

12/01/2004

### **10 DATE OF REVISION OF THE TEXT**

11/04/2025