SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 Name of the Medicinal Product

Brand Name : Metronidazole Oral Suspension 125 mg/5ml

Generic Name : Metronidazole Oral Suspension 125 mg/5ml

1.2 Strength : 125 mg/5 ml

1.3 Pharmaceutical Form: Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole Benzoate* (Eq. to Metronidazole 125 mg/5 ml)
Xanthan Gum
Colloidal Anhydrous Silica
Disodium Edetate
Sodium Chloride
Sodium Methyl Hydroxybenzoate
Citric Acid Monohydrate
Anhydrous Disodium Hydrogen Phosphate
Saccharin Sodium

Colour Sunset Yellow Supra
Orange Flavour (Dry)
Sucrose

3. PHARMACEUTICAL FORM

White to off white granular powder, forming orange coloured suspension after reconstitution with water.

4.0 Clinical particulars

4.1 Therapeutic Indications

Metronidazole Oral Suspension is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected as the pathogen.

Metronidazole Oral Suspension is active against a wide range of pathogenic micro-organisms, notably Trichomonasvaginalis, Entamoebahistolytica, Giardia lamblia, Balantidium coli and other species of bacteroides, fusobacteria, eubacteria, clostridia and anaerobic cocci.

It is indicated in

Adults, Children and Newborns with a gestation age of over 40 weeks for:

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

• The prevention of post-operative infections caused by anaerobic bacteria particularly species of bacteroides and anaerobic streptococci.

Adults and Children over 10 years only for:

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

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

• Anaerobically infected leg ulcers and pressure sores.

Adults and Children for:

• The treatment of urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male.

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

• Giardiasis

• Acute ulcerative gingivitis.

Children for

• Eradication of Helicobacter pylori

4.2 Posology and method of Administration

For oral administration only

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

Dosage: 400mg at 8 hourly intervals during the 24 hours preceding the operation followed by postoperative intravenous or rectal administration until the patient is able to take Metronidazole Oral Suspension by mouth.

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

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

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

B: Treatment of established anaerobic infection:

800mg followed by 400mg at 8 hourly intervals.

Children below 8 weeks to 12 years of age: The usual daily dose is 20 – 30mg/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 treatment is usually 7 days.

Children < 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 <40 weeks, accumulation of metronidazole can occur during the first week of life, which is why the concentrations of metronidazole in serum should preferably be monitored after a few days therapy.

C: Treatment of Protozoal and Other Infections:

<table>
<tr><th></th><th>Duration of dosage in days</th><th>Adult and Children over 10 years**</th><th colspan="3">Children*</th></tr>
<tr><th></th><th></th><th></th><th>7-10 years</th><th>3-7 years</th><th>1-3 years</th></tr>
<tr><td rowspan="3">Urogenital Trichomoniasis Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently</td><td>7 or</td><td>200mg three times daily</td><td colspan="3">40mg/kg orally as a single dose or15 – 30mg/kg/day divided in 2 – 3 doses not to exceed 2000mg/dose</td></tr>
<tr><td>5-7 or</td><td>400mg twice daily</td><td></td><td></td><td></td></tr>
<tr><td>1</td><td>2000mg as a single dose</td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Bacterial Vaginosis</td><td>5-7 or</td><td>400mg twice daily</td><td></td><td></td><td></td></tr>
<tr><td>1</td><td>2000mg as a single dose</td><td></td><td></td><td></td></tr>
<tr><td>Amoebiasis</td><td>5-10</td><td>400 – 800mg three</td><td>200 – 400mg three times</td><td>100 – 200mg four times daily</td><td>100 – 200mg three times</td></tr>
</table>

		times daily	daily		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 2400mg/day		
Giardiasis	3 or	2000mg once daily	1000mg once daily	600-800mg once daily	500mg once daily
	5 or	400mg three times daily			
	7 - 10	500mg twice daily			
			Alternatively, as expressed in mg per kg of body weight: 15 – 40mg/kg/day divided in 2 -3 doses.		
Acute Ulcerative Gingivitis	3	200mg three times daily	100mg three times daily	100mg twice daily	50mg three times
Acute Dental Infections	3-7	200mg three times daily			
Leg Ulcers and Pressure Sores	7	400mg three times daily			

Dosage is given in terms of metronidazole or metronidazole equivalent.

* Children and babies weighing less than 10Kg should receive proportionally smaller doses.

** Metronidazole is well tolerated by the elderly, but a pharmacokinetic study suggests cautious use of high dosage regimen in this age group.

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. Official guidelines should be consulted before initiating therapy.

4.3 Contraindications

Known hypersensitivity to Metronidazole and/or hydroxybenzoates.

4.4 Special warnings and precautions for use

Regular clinical and laboratory monitoring are advised if administration of Metronidazole for more than 10 days is considered to be necessary.

There is a possibility that after Trichomonasvaginalis 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 (IDP) 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. 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.

4.5 Interaction with other medicinal products and other forms of interaction.

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when Metronidazole is prescribed for patients on this type of anticoagulant therapy.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of Metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of Metronidazole. In patients stabilized on relatively high doses of lithium, short-term therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum cre-atinine levels should be obtained several days after beginning Metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

Alcoholic beverages should not be consumed during Metronidazole therapy and for at least one day afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

4.6 Pregnancy and Lactation

There is inadequate evidence of the safety of metronidazole in pregnancy. Metronidazole should not therefore be given during pregnancy or during lactation unless the physician considers it essential, in these circumstances short, high dosage regimes are not recommended.

A significant amount of metronidazole is found in breast milk and breast feeding should be avoided after a large dose. This could 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 (≥ 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).

Frequency, type and severity of adverse reactions in children are the same as in adults.
Serious adverse reactions occur very rarely with standard recommended regimens. However, 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, often reversible on drug withdrawal, although fatalities have occurred.
Not known: A moderate leucopenia has been reported in some patients but the white cell count has always returned to normal before or after treatment has been completed.

Immune system disorders:
Rare: Anaphylaxis
Not known: urticaria, angioedema and 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, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysathria, gait impairment, nystagmus and tremor) have been reported very rarely which may resolve on discontinuation of the drug.

• Drowsiness, dizziness, convulsions, headache, ataxia, inco-ordination of movement

Not known:

• During intensive and/or prolonged metronidazole therapy a few instances of peripheral neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.

• Aseptic meningitis has been reported

Eye disorders:

Very rare: transient visual disorders such as diplopia and myopia have been reported

Not known: Optic neuropathy/neuritis has been reported

Gastrointestinal disorders:

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

Hepatobiliary disorders:

Very rare:

• Abnormal liver function tests, increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis, and hepatocellular liver injury, jaundice and pancreatitis, reversible on drug withdrawal have been reported.

• 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 may occur, which may be reversed on drug withdrawal. Stevens-Johnson syndrome or toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders:
Very rare: myalgia, arthralgia

Renal and urinary disorders:
Very rare: Darkening of the urine (due to metronidazole metabolite)
Metronidazole Oral Suspension contains glycerol, which can cause headache, gastro-intestinal disturbance and diarrhoea.
The parahydroxybenzoates used in Metronidazole Oral Suspension may cause immediate or delayed hypersensitivity reactions.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important.

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.

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties

The selective action of this compound against anaerobes and anoxic and hypoxic cells is due to the mode of action. The nitro group of metronidazole acts as electron acceptor and is thus reduced to a chemically reactive drug form. This produces biochemical lesions in the cells, thus causing death. The major site of action is believed to be DNA, where it causes loss of the helical structure and inhibits synthesis.

5.2 Pharmacokinetic Properties

It is readily absorbed from the gastro-intestinal tract and widely distributed in body tissues. Half life in plasma is about 8-10 hours. About 10% is bound to plasma proteins.

It penetrates well into body tissues and fluids, including vaginal secretions, seminal fluid, saliva and breast milk. Therapeutic concentrations are also achieved in cerebrospinal fluid.

Unchanged metronidazole and several metabolites are excreted in the urine, the liver is the main site of metabolism and the major metabolites are as a result of side chain oxidation, forming glucuronides.

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.

6.0 Pharmaceutical Particulars

6.1 List of Excipients

- Xanthan Gum BP
- Colloidal Anhydrous Silica BP

- Disodium Edetate BP
- Sodium Chloride BP
- Sodium Methyl Hydroxybenzoate BP
- Citric Acid Monohydrate BP
- Anhydrous Disodium Hydrogen Phosphate BP
- Saccharin Sodium BP
- Colour Sunset Yellow Supra
- Orange Flavour (Dry)
- Sucrose BP

6.2 Incompatibilities

None reported

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at a temperature not exceeding 30 °C in a dry place. Protect from light. Use the reconstituted oral suspension within 7 days of preparation.

6.5 Nature and contents of container

HDPE bottle 100 ml

6.6 Special precautions for disposal

No special requirements

7.0 Marketing Authorization holder

MEDICAMEN Biotech Ltd.

SP-1192 A & B, Phase-IV,

Industrial Area, Bhiwadi-301019,

Distt Alwar, Rajasthan

INDIA

8.0 Number(s) in the National Register of Finished Pharmaceutical Products

Old Registration No.:

MED/IND/009

New: 06011/07813/REN/2021

9.0 Date of First Authorization/Renewal of the Authorization]

Approval Date: 19/05/2017

Last renewal: May 26, 2021

10.0 Date of revision of the text

Shall be provided based after registration