Summary of Product Characteristics

1. Name of the Medicinal Product: Metronidazole oral suspension BP 125 mg/5ml

2. Qualitative and Quantitative Composition

Each 5 ml contains:

Metronidazole Benzoate BP Equivalent to

Metronidazole BP .....125 mg

Flavoured syrupy Base ..... q.s.

Colour: Sunset Yellow

3. Pharmaceutical Form

Oral Suspension

Yellowish orange colour suspension.

4. 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 Trichomonas vaginalis, Entamoeba histolytica, Giardia lamblia, Balantidium coli and other species of bacteroides, fusobacteria, eubacteria, clostridia, Gardnerella vaginalis and anaerobic cocci. Metronidazole an antibiotic that is used to treat bacterial infections of the vagina, stomach, liver, skin, joints, brain and spinal cord, lungs, heart, or bloodstream.

Metronidazole is also used to treat trichomoniasis, a sexually transmitted disease caused by a parasite. Usually both sexual partners are treated at the same time, even if one has no symptoms.

Do not use metronidazole to treat any condition that has not been checked by your doctor.

It is indicated in

- Adults, Children and New-borns 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:
- Giardiasis
- Acute ulcerative gingivitis.
- Children for
- Eradication of Helicobacter pylori

4.2 Posology and Method of Administration

ROUTE OF ADMINISTRATION: Oral

Shake the oral suspension (liquid). Measure a dose with the supplied measuring device (not a kitchen spoon). Oral suspension (Bottle of 100 ml). A measuring spoon (5 ml) corresponds to 125mg of metronidazole. (Metronidazole benzoate 200 mg Equivalent to Metronidazole 125 mg).

A: Prophylaxis: against anaerobic infectionchiefly 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.

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

B: Treatment of established anaerobic infection:

800mg followed by 400mg at 8 hourly intervals.

Children > 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.

4.3 Contraindications

Known hypersensitivity to Metronidazole, nitroimidazoles and/or hydroxybenzoates or any of the excipients.

4.4 Special warnings and precautions for use

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). There is the 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 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 encephalopathy. Metronidazole should be administered with caution to patients with hepatic encephalopathy. The daily dosage may be reduced to one third and may be administered once daily. 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. Patients should be

warned that metronidazole may darken urine. Due to inadequate evidence on the mutagenicity risk in humans, 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.

4.5 Interactions with other medicinal products and other forms of interaction

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.

Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently. Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the anticoagulant may require reducing. Prothrombin time should be monitored. No interactions have been reported of the heparin type. 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. Patients receiving phenobarbital or phenytoin metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately three hours. Increased serum carbamazepine levels and toxicity have been seen in patients given concomitant metronidazole.

4.6 Fertility, 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 Effect on ability to drive and 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 (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight andmovement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus andtremor) 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

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, acute generalised exanthematous pustulosis, pruritus, flushing
Not known:	Erythema multiforme may occur, which may be reversed on drug withdrawal. 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 the urine (due to metronidazole metabolite)

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

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. Pharmaceutical Particulars

6.1 List of Excipients

Sr. No.	Name of Ingredients	Specification
1.	Sodium Benzoate	British Pharmacopoeia
2.	Sugar (sucrose)	British Pharmacopoeia
3.	Sodium Methyl Hydroxybenzoate	British Pharmacopoeia
4.	Sodium Propyl Hydroxybenzoate	British Pharmacopoeia
5.	Disodium EDTA	British Pharmacopoeia
6.	Xanthan gum	British Pharmacopoeia
7.	Sorbitol 70% (Non- crystalline)	British Pharmacopoeia
8.	Polysorbate 80 (Tween 80)	British Pharmacopoeia
9.	Citric Acid Monohydrate	British Pharmacopoeia
10.	Silicon dioxide	British Pharmacopoeia
11.	Sodium Metabisulphite	British Pharmacopoeia
12.	Colour sunset yellow	In House Specifications
13.	Flavour orange sweet	In House Specifications
14.	Purified Water	British Pharmacopoeia

6.2 Incompatibilities

None known

6.3 Shelf Life

36 months

6.4 Special precautions for Storage

Store in a dry place, below 30ºC. Protect from light.

6.5 Nature and Contents of Container

100 ml Glass bottle with ROPP cap, packed in carton along with leaflet.

6.6 Special Precautions for disposal and other handling

Not applicable.

7.0 Marketing Authorisation Holder

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8.0 Marketing Authorisation Number

9.0 Date of First Authorisation

10.0 Date of revision of the Text: June 2022