Summary of Pharmaceutical Products

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1. Name of the medicinal product

Metronidazole Oral Suspension BP 125mg/5ml

2. Qualitative and quantitative composition

Product Name:

Each 5 ml suspension contains:

Metronidazole Benzoate BP

Eq. to Metronidazole 125 mg

3. Pharmaceutical form

Oral Suspension
Yellow coloured viscous suspension

4. Clinical particulars

4.1 Therapeutic indications

Metronidazole Oral Suspension is indicated in the prophylaxis and treatment of infections in which anaerobicbacteria 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.

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 bacteroidesand 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

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

4.2 Posology and method of administration

Posology

A: ***Prophylaxis****:* against anaerobic infection- chiefly in the context of abdominal (especially colorectal) andgynaecological 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 informationavailable on modification of drug.

Anaerobic infections: The duration of a course of Metronidazole treatment is about 7 days but it will dependupon 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 dividedinto 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:***

(See Table).

	Duration of dosage in days	**Adults and children over 10 years****	**Children***		
			7-10 years	**3-7 years**	**1-3 years**
Urogenital Trichomoniasis Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently	7 or	125mg three times daily	40mg/kg orally as a single dose or 15 – 30mg/kg/day divided in 2 – 3 doses not to exc 2000mg/dose		
	5 - 7 or	400mg twice daily			
	1	2000mg as a single dose			
Bacterial Vaginosis	5 - 7 or	400mg twice daily			
	1	2000mg as a single dose			
Amoebiasis (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 hepatitis	5-10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
(c) Amoebic liver abscess also other forms of extra-intestinal amoebiasis	5	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily

(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 d
	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 bo weight: 15 – 40mg/kg/day divided in 2 – 3 doses.		
Acute Ulcerative Gingivitis	3	125mg three times daily	100mg three times daily	100mg twice daily	50mg three ti
Acute Dental Infections	3-7	125mg three times daily			
Leg Ulcers and Pressure Sores	7	400mg three times daily			

Dosage is given as

Alternative

f 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 highdosage 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. Officialguidelines should be consulted before initiating therapy.

Method of administration

For oral administration only.

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, convulsiveseizures).

There is the possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection mightpersist.

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 centralnervous 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 (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 liverinjury to their physician and stop taking metronidazole.

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, treatment with metronidazole must be immediately discontinued

Excipient Warnings

This medicine contains 113.7 mg sorbitol (E420) in each ml.

• The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products fororal use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

• Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

This medicine contains 220mg of glucose and 125mg of sucrose in each ml. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency shouldnot take this medicine.

This medicine contains 31.1 mg propylene glycol (E1520) in each ml.

• Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effectsin children less than 5 years old.

• While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or
humans, it may reach the foetus and was found in milk. As a consequence,

administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.

• Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.

This medicine contains methyl, ethyl and propyl hydroxybenzoates are contained in this product which maycause allergic reactions (possibly delayed).

4.5 Interaction 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 disulfiramconcurrently.

Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anti-coagulants. 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 treatedsimultaneously 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 concomitantmetronidazole.

Aspartate amino transferase assays may give spuriously low values in patients taking metronidazole,depending on the method used.

Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods no longer thanthose recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

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

increased toxicity of 5-fluorouracil.

Patients receiving ciclosporin or tacrolimus with metronidazole are at risk of elevated ciclosporin / tacrolimusserum levels. Serum ciclosporin / tacrolimus and serum creatinine should be closely monitored when coadministration is necessary.

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

4.6 Pregnancy and lactation

There is inadequate evidence of the safety of metronidazole in pregnancy. Metronidazole should not thereforebe 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 alarge 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 symptomsoccur.

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 hasalways 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 hallucinationsNot known: depressed mood

Nervous system disorders:

Very rare:

• Encephalopathy (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbancesin sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) have been reported very rarely which may resolve on discontinuationof the drug

• Drowsiness, dizziness, convulsions, headache, ataxia, inco-ordination of movementNot 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 reportedNot known:

Ear and labyrinth disorders:

Not known: hearing impaired/hearing loss (including sensorineural), tinnitus

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 ormixed 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 metronidazolein 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)

Metronidazole Oral Suspension contains glycerol, which can cause headache, gastro-intestinal disturbanceand diarrhoea.

The para hydroxy benzoate used in Metronidazole Oral Suspension may cause immediate or delayedhypersensitivity reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allowscontinued monitoring of the benefit/risk balance of the medicinal product.

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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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

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 supportivetreatment 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 reactivedrug 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 inplasma 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 breastmilk. Therapeutic concentrations are also achieved in cerebrospinal fluid.

Unchanged metronidazole and several metabolites are excreted in the urine, the liver is the main site ofmetabolism 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 studieshave 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 cellsin 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

Sucrose, Sodium Methyl Hydroxybenzoate, Sodium Propyl Hydroxybenzoate, Sodium Benzoate, Citric Acid Monohydrate, Sodium Citrate, Disodium Edetate, Polysorbate-80, Colloidal Anhydrous Silica, Xanthum Gum, Colour Quinoline

Yellow Supra, Flavor Mango (Liquid)

6.2 Incompatibilities

None known

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.

6.5 Nature and contents of container

Pet bottle 100ml.

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing Authorisation Holder

MEDICAMEN BIOTECH LIMITED

SP-1192 A & B, Phase-IV,
Industrial Area, Bhiwadi-301019,
Distt Alwar, Rajasthan India

8. Number(s) in the national register of finished pharmaceutical products

Certificate No: 06011/07813/REN/2021

9. Date of first authorisation/renewal of the authorisation

May 26, 2021

10. Date of revision of the text

July 2023