Summary of Product Characteristics

For

Biogyl suspension

(Metronidazole)

1. NAME OF MEDICINAL PRODUCT Biogyl suspension

2. QUALITATIVE AND QUANTITATIVE DESCRIPTION

Each 5ml of the suspension contains

Metronidazole benzoate BP equivalent to Metronidazole BP 200mg

3. PHARMACEUTICAL FORM

A bright-yellow colored suspension with orange and lemon flavor in 60ml amber PET bottle with pilfer proof cap and a graduated dose measurement cap to facilitate easy dosing

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- In the treatment of urogenital trichomonaisis.
- In the treatment of acute ulcerative gingivitis.
- In the treatment of infections due to E. histolytica (including carrier states).
- In the treatment of infections due to G. Lamblia (including carrier states).
- In the prevention and treatment of infections due to anaerobic bacteria, particularly species of Bacteroides, anaerobic Streptococci, fusobacteria, clostridia, etc.
- In the treatment of acute dental infections.
- In the treatment of non-specific vaginitis. Metronidazole is indicated in adults only for the following indications:
- In the treatment of chronic pressure sores and ulcers with possible infection due to anaerobes

4.2 Posology and method of administration

Posology

The safety and efficacy of promethazine hydrochloride used in the formulation of Biothazine syrup has been established in adults and paediatric populations when taken at the prescribed doses

Method of Administration

Indications	**1 to 3 years**	**3 to 7 years**	**7 to 10 years**	**Duration of Dosage in Days**
Acute Ulcerative Gingivitis	2.5ml (100mg) once daily	2.5ml (100mg) twice daily	2.5ml (100mg) thrice daily	3
Amoebiasis (a) Invasive intestinal disease in susceptible subjects	5ml three times	5ml four times daily	10ml three times daily	5
(b) Intestinal disease in susceptible subjects	2.5ml three times daily	2.5ml four times daily	5ml three times daily	5-10

(c) Symptomless cyst passers	2.5ml three times daily	2.5-5ml four times daily	5-10ml three times daily	5
Urogenital Trichomoniasis where re-infection is likely. The consort should receive a similar course of treatment concurrently	1.2ml three times daily	2.5ml two times daily	2.5ml three times daily	7 or 2
Giardiasis	10ml once daily	15ml once daily	25ml once daily	3

Or as directed by the physician.

4.3 Contraindications

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological aggravation. Use in patients with known hypersensitivity to metronidazole

4.4 Special warnings and Precautions for Use

The use of Biogyl for prolonged treatment duration should be carefully weighed. If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible. It is recommended that haematological tests be carried out regularly and that patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, vertigo, convulsive seizures). High dosage regimens have been associated with transient epileptiform seizures. Caution is required in patients with active disease of the central nervous system except for brain abscess. Metronidazole and a metabolite have been shown to be mutagenic in some tests with non-mammalian cells. Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction. Metronidazole is removed during haemodialysis and should be administered after the procedure is finished. Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit using metronidazole to treat trichomoniasis in such patients should be carefully considered.
Flagyl should be administered with caution to patients with hepatic encephalopathy. Cases of severe bullous skin reactions, sometimes fatal, such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalised exanthematous pustulosis (AGEP) have been reported with metronidazole. The majority of cases of SJS reported occurred within 7 weeks of starting treatment with metronidazole. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms of SJS, TEN or AGEP (e.g. flu-like symptoms, progressive skin rash often with blisters or mucosal lesions) are present, treatment must be immediately discontinued. Patients should be warned that metronidazole may darken urine (due to metronidazole metabolite).

Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hour s afterwards. 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. This medicinal product contains 31.4 mg of ethanol in each 5 ml of suspension which is equivalent to 6.28 mg per ml (0.628% w/v). The amount in each 5 ml of this medicinal product is equivalent to less than 1 ml beer or 1 ml wine. The small amount of ethanol in this medicinal product will not have any noticeable effects. This medicinal product contains less than 1mmol sodium (23 mg) per 5ml, that is to say essentially 'sodium free'. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. 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 oxidized 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 Drug Interactions

Potentiation of the anticoagulant effect and increased hemorrhagic risk caused by decreased hepatic catabolism. In case of co-administration, prothrombin time should be more frequently monitored and anticoagulant therapy adjusted during treatment with metronidazole. Lithium retention observed by increased plasma lithium levels, accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole. Plasma levels of lithium may be increased by 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. Phenytoin or Phenobarbital: increased elimination of metronidazole resulting in reduced plasma levels. A similar effect may occur with other drugs which induces hepatic microsomal enzymes. Patients should be advised not to take alcohol, (or drugs containing alcohol) during metronidazole therapy and for at least 48 hours afterwards because of a disulfiram-like (antabuse effect) reaction (flushing, vomiting, tachycardia). Disulfiram: psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently. Cyclosporin: risk of elevation of the cyclosporin serum levels. Serum cyclosporin and serum creatinine should be closely monitored

when coadministration is necessary. 5-Fluorouracil: reduced clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil. 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 Pregnancy and Lactation

Metronidazole should only be used during pregnancy or lactation following careful evaluation and only if considered essential by the physician. Its effects on foetal organogenesis are not known. If used, high dosage regimens should be avoided. The drug crosses the placenta and is excreted in breast milk in which concentrations equal those in serum. Unnecessary exposure to the drug should be avoided.

4.7 Effects on ability to drive and use machine

Patients should be warned about the potential for confusion, dizziness, vertigo, hallucinations, convulsions or eye disorders and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

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

- epigastric pain, nausea, vomiting, malaise, diarrhea.
- oral mucositis, taste disorders, dry mouth, anorexia.
- reversible cases of pancreatitis.
- tongue discolouration/furry tongue. Immune system disorders
- angioedema anaphylactic shock.

Nervous system disorders

- peripheral sensory neuropathy, paraesthesia
- headache, convulsions, dizziness.
- reports of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve with discontinuation of the drug.
- aseptic meningitis, vertigo

Psychiatric disorders

• psychotic disorders including confusion, hallucinations

• depressed mood

Eye disorders

• transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision.

• Optic neuropathy/neuritis.

Ear and labyrinth disorders

• hearing impaired/hearing loss (including sensorineural)

• tinnitus Blood and lymphatic system disorders

• cases of agranulocytosis, neutropenia and thrombocytopenia have been reported.
Hepatobiliary disorders

• increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported.

• cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole mostly when used 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.

Skin and subcutaneous tissue disorders

• rash, pruritus, flushing, urticaria

• pustular eruptions, acute generalised exanthematous pustulosis

• fixed drug eruption

• Stevens-Johnson syndrome, toxic epidermal necrolysis.
General disorders and administration site conditions

• fever Cardiac disorders

• Frequency not known: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

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 overdosage, a symptomatic and supportive treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antiemetic

ATC code:

Pharmacodynamics effects

Metronidazole has antiprotozoal and antibacterial actions including activity against anaerobic bacteria and entamoeba histolytica.

5.2 Pharmacokinetics Properties

A nitroimidazole derivative well absorbed and widely distributed in the body. It is metabolised by hepatic acid oxidation, hydroxylation and glucuronidation and excreted in urine and faeces with a T½ of about 6-10 hours. After a 400 mg metronidazole (or equivalent) single oral dose, given either as metronidazole benzoate 6.4% suspension or metronidazole tablet to 10 healthy subjects in a cross-over study (Table 1), tmax is delayed by approximately 2 hours, Cmax decreased by 45% and AUC by 20% corresponding to a decrease in relative bioavailability of 20% of the metronidazole benzoate 6.4 % oral suspension compared to the tablet. No change in elimination half-life is reported. No metronidazole benzoate was found in plasma. These slight differences in the rate and extent of metronidazole absorption are due to the transformation of metronidazole benzoate to the active compound metronidazole by hydrolysation in the gastrointestinal tract.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Sucrose, Methyl paraben, Propylene glycol, Citric acid, Orange flavour, Lemon flavor, Tartrazine yellow, Polysorbate 80, Glycerol

6.2 Incompatibilities

None

6.3 Shelf life

3 years

6.4 Special Precautions for Storage

Biogyl suspension should be stored in a cool dry place at temperatures not more than 30^{o}C

6.5 Nature and Contents of Container

Plain Amber-coloured Polyethylene terephthalates (PET) bottle with ROPP cap placed inside a paperboard carton

6.6 Special Precautions for disposal

Container and/or any unused product should be disposed in accordance with the local requirement

7. MANUFACTURER

BIOMEDICAL LTD
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