Summary of Product Characteristics

1. Name of the medicinal product
METROGYL SUSPENSION
(Metronidazole Benzoate Oral suspension 125 mg/ 5mL)

2. Qualitative and quantitative composition
Each 5 mL (teaspoonful) contains:
Metronidazole Benzoate BP
Equivalent to Metronidazole 125 mg

For a full list of excipients, see section 6.1

3. Pharmaceutical form
Oral suspension.

4. Clinical particulars
4.1 Therapeutic indications
Amoebiasis, Giardiasis
Amoebic liver Abscess
Anaerobic Bacterial Infections

4.2 Posology and method of administration
Children: 35 to 50 mg/kg/24 hours, divided into three doses, orally for 10 days.

4.3 Contraindications
Metrogyl is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

4.4 Special warnings and precautions for use
General: Patients with severe hepatic disease metabolize Metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously.
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.
Mutagenicity studies: Although metronidazole has shown mutagenic activity in a number of *in vitro* assay systems. Studies in mammals (*in vivo*) have failed to demonstrate a potential for genetic damage. Due to inadequate evidence on the mutagenicity risk in humans, the use of Metronidazole for longer treatment than usually required should be carefully considered.

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 disulfiram concurrently.
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 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.
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 than those 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 / tacrolimus serum levels. Serum ciclosporin / tacrolimus and serum creatinine should be closely monitored when co-administration is necessary.
Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

4.6 Fertility, pregnancy and breastfeeding
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 (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in 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 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

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 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.

• 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:

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. Pharmaceutical properties

5.1 Pharmacodynamic properties

Metronidazole diffuses into aerobic and anaerobic bacteria equally well, but in the former it remains unchanged while in the latter it is reduced. As a result of biochemical reduction in the cell, the concentration of unchanged drug is reduced and this probably creates a gradient which promotes further uptake of the drug into anaerobic organisms. The nitro group of Metronidazole accepts electrons from electron-transport proteins and diverts them from normal energy yielding pathways. Oxygen markedly reduces the uptake of Metronidazole in experiments using certain anaerobic protozoa, suggesting that this process depends on reducing power inside the cell. The selective uptake and specificity of Metronidazole for anaerobes may be because their redox processes are different from those of aerobes; It has been assumed that the product of reduction of the nitro group of Metronidazole interacts with DNA with ultimate inhibition of nucleic acid synthesis and subsequent cell death. Moreover Metronidazole has been shown to inhibit DNA synthesis and degrade existing DNA in Clostridium bifermentans.

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

Sodium Methyl Hydroxy Benzoate BP

Sodium Propyl Hydroxy Benzoate BP

Sorbic Acid BP
Guar Gum BP
Polysorbate 80 BP
Sorbitol Soln 70% (Non-crystallizing) BP
Colour Sunset Yellow FCF
Essence Mix Fruit
Essence Peppermint
Sucrose BP
Sodium Citrate BP
Purified water BP

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C. Protect from light.

6.5 Nature and content of container
100 mL bottle

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing Authorization Holder

UNIQUE PHARMACEUTICAL LABORATORIES
(A Division of J.B. Chemicals & Pharmaceuticals Ltd.)
Neelam center, B Wing, 4th floor, Hind cycle road,
Worli, Mumbai 400 030, INDIA

8. Marketing Authorization Number
07037/08057/REN/2021

9. Date of First Authorization/Renewal of the Authorization
Date of First Authorization :20/01/2022

10. Date of revision of the text
27/07/2023