# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Metrolyl* (Metronidazole) Suppositories 500mg

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 500mg suppository contains metronidazole BP 500mg

For a full list of excipients, see section 6.1

## 3 PHARMACEUTICAL FORM

Suppository
White opaque suppository

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Metrolyl* is indicated in adults and children for the following indications:
Treatment of infections in which anaerobic bacteria have been identified or are suspected as pathogens, particularly *Bacteroides fragilis* and other species of *Bacteroides* and including other species for which metronidazole is bactericidal e.g.: *Fusobacteria, Eubacteria, Clostridia* and anaerobic *cocci.*

Metrolyl* can be used in septicaemia, bacteraemia, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, peritonitis and post operative wound infection from which one or more of these anaerobes have been isolated.

Prevention of post operative infections due to anaerobic bacteria,particularly species of *Bacteroides* and anaerobic Streptococci.

## 4.2 Posology and method of administration

Route of administration: Rectal

*Treatment of Anaerobic Infections:*

Adults and children over 10 years of age: 1 g suppository inserted into the rectum 8 hourly for 3 days. Oral medication with 400 mg 3 times a day should be substituted as soon as feasible. If rectal medication has to be continued for more than 3days then the suppositories should be inserted at 12 hourly intervals.

Children (5 -10 years): As for adults but with 500 mg suppositories and oral medication with 7.5 mg/kg bodyweight 3 times a day.

Infants and children under 5 years: As for children of 5-10 years but with a reducted dose of suppositories (1½ of a 500 mg suppository for 1-5 years and ¼ of a 500 mg suppository for under 1 year).

*Prevention of Anaerobic Infections:*

Used in appendectomy and post-operative medication for elective colonic surgery.

Adults and children over 10 years of age: 1 g suppository inserted into the rectum 2 hours before surgery and repeat at 8 hourly intervals until oral medication (200-400 mg 3 times a day) can be given to complete a 7day course.

If rectal medication is necessary after the third post-operative day, the frequency of administration should be reduced to 12 hourly.

Children (5-10 years): 500 mg suppositories administered as for adults until oral medication, 3.7 to 7.5 mg/kg bodyweight three times daily becomes a possibility.

## 4.3 Contraindications

Known sensitivity to metronidazole or any of the excipients.

## 4.4 Special warnings and precautions for use

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 (see section 4.8).

Metronidazole has no direct activity against aerobic or facultative anaerobic bacterium.

Clinical and laboratory monitoring e.g. leucocyte count, are advised if administration with Metrolyl for more than 10 days is considered to be necessary. Patients should be monitored for adverse reactions, such as peripheral or central neuropathy e.g. paraesthesia, ataxia, dizziness, convulsive seizures.

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.

There is a possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might be persistant.

The half-life elimination of metronidazole remains the same in patients with renal failure, therefore there is no needs for dose reduction. However, such patients retain the metabolites of metronidazole, the clinical significance of this is not known.

In patients undergoing haemodialysis metronidazole and its metabolites are efficiently removed during an eight hour dialysis period. Therefore, Metronidazole should be re-administered immediately after haemodialysis.

No adjustment in the dosage of Metrolyl is required 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, resulting in high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Therefore, Metrolyl should, be administered with caution in patients with

hepatic encephalopathy, the daily dosage should be reduced to one third and administered once daily.

Metronidazole may cause darkened urine.

Due to inadequate evidence, the mutagenicity risk in humans (see section 5.3), with the use of Metrolyl for longer treatment than usually required should be carefully considered.

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

Alcohol
The consumption of alcohol during metronidazole therapy should be avoided since there could be a disulfiram-like reaction. Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.
Anticoagulant
Potentiation of warfarin-type anticoagulant therapy (except with heparin) has been reported so that dose adjustment of the anticoagulant may be needed.
Barbiturates
Phenobarbitone: The half-life of metronidazole is reduced from 7-8 hours to about 3 hours in patients receiving phenobarbitone.
In patients taking metronidazole, the assay of aspartate amino transferase may give spuriously low values; this depends on the method used.
Lithium
Lithium retention with evidence of possible renal damage has been reported where this compound and metronidazole have been used concurrently. Preferably, apart from monitoring lithium, creatinine and electrolyte concentrations, lithium therapy should be tapered and or withdrawn before use of metronidazole.

Anti-epileptics

Patients taking phenobarbital or phenytoin metabolise metronidazole at a much greater rate than normally reducing the half-life to approximately 3 hours.

Primidone: accelerates the metabolism of metronidazole resulting in a reduced plasma concentration.
Cytotoxics:
Busulfan: Increased risk of toxicity due to increased busulfan plasma concentration levels which may lead to severe busulfan toxicity.
Fluorouracil: Metronidazole reduces the clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil.
Ulcer-healing drugs:
Cimetidine increases the plasma concentration of metronidazole by inhibiting its metabolism.
Disulfiram
Administration of metronidazole may lead to psychoses and confusion.

Ciclosporin: Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

## 4.6 Pregnancy and lactation

There is inadequate data of the safety of metronidazole in pregnancy. Metrolyl should not be given during pregnancy or lactation unless the physician considers it essential, should this be the case then short, high-dosage regimens are not recommended.

## 4.7 Effects on ability to drive and use machines

Patients should be warned that drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders could occur, and advised them not to drive or operate machinery if they get the se symptoms.

## 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).

Serious adverse reactions occur rarely with standard recommended regimens. 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, pancytopenia,
Not known: leucopenia.

Immune system disorders:

Rare: anaphylaxis
Not known: angiodema, urticaria, 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:

Uncommon: drowsiness, dizziness, convulsions, headaches

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) which may resolve on discontinuation of the drug.

Not known: during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.

Eye disorders:

Very rare: vision disorders such as diplopia and myopia, which in most cases, is transient.

Gastrointestinal disorders:

Not known: taste disorders, oral mucositis, furry tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea.

Hepatobiliary disorders:

Very rare: abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis reversible on drug withdrawal.

Skin and subcutaneous tissue disorders:

Very rare: skin rashes, pustular eruptions, pruritis, flushing
Not known: erythema multiforme.

Musculoskeletal, connective tissue and bone disorders:

Uncommon: asthenia
Very rare: myalgia, arthralgia.

Renal and urinary disorders:

Very rare: darkening of urine (due to metronidazole metabolite).

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 (see section 4.4).

### 4.9 Overdose

After single doses up to 12 g metronidazole have been reported in suicidal attempts and accidental overdoses, vomiting, nausea, ataxia and disorientation were observed.

There is no specific antidote for metronidazole overdose. symptomatic and supportive treatment should be instituted.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic code: Antibacterials for systemic use, ATC code J01X D01.

Metronidazole has antiprotozoal and antibacterial properties and is effective against *Trichomonas vaginalis* and other protozoa including *Entamoeba histolytica* and *Giardia lamblia*, and against anaerobic bacteria.

### 5.2 Pharmacokinetic properties

Metronidazole is readily absorbed from the rectal mucosa and widely distributed in body, maximum concentrations occur in the serum after about 1 hour and traces can be detected after 24 hours.

At least half the dose is excreted in the urine as metronidazole and its metabolites, including an acid oxidation product, a hydroxy derivative and

glucoronide. Metronidazole diffuses across the placenta and is found in breast milk in concentrations equivalent to those in serum.

### 5.3 Preclinical safety data

Metronidazole has been shown to be carcinogenic in mice and rats following chronic oral administration, however, similar studies in the hamster have given negative results. Epidemiological studies have not provided clear evidence of a 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 other studies were negative.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of Excipients

Hard fat (Witepsol E75 and W35).

### 6.2. Incompatibilities

Not known.

### 6.3. Shelf-Life

36 months.

### 6.4. Special Precautions for Storage

Do not store above 25°C. Protect from light.

### 6.5. Nature and Content of Container

Sealed PVC moulds containing the suppositories inside a cardboard carton.

Pack size: 10

### 6.6. Instructions for Use, Handling and Disposal

Not applicable.

## 7 MARKETING AUTHORISATION HOLDER

Sandoz Limited
Frimley Business Park,
Frimley,
Camberley,
Surrey,
GU16 7SR,
United Kingdom.

### 8. MARKETING AUTHORISATION NUMBER(S)

PL 4416/0053

### 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

25 May 1982/30 April 1997

## 10 DATE OF REVISION OF THE TEXT

24/07/2023