

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metrolag 25mg/1ml Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the suspension contains Metronidazole (as benzoate) 25 mg.

3. PHARMACEUTICAL FORM

Oral 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 microorganisms, 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 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) and gynaecological 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.

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.

The usual doses of adults and children are:

What you're taking the medicine for	Number of days you will take the medicine for	How much to take – Adults and children over 12 years of age	How much to take – Children under 12 years of age
Prevention of infections after surgery	1	16ml (400mg) three times during the day before the operation	Your doctor will work out the right dose based on your child's weight.
Bacterial infections	-	A 32ml (800mg) dose followed by 400mg (16ml) three times a day	

Other infections

Adults and children over 10 years of age

What you're taking the medicine for	Number of days you will take the medicine for	How much to take – Adults and children over 10 years of age
Trichomoniasis	1	80ml (2000mg) once a day
	or 5 to 7	16ml (400mg) twice a day
	or 7	8ml (200mg) three times a day
Vaginosis	1	80ml (2000mg) once a day
	or 5 to 7	16ml (400mg) twice a day
Amoebiasis	5 to 10	16ml (400mg) to 32ml (800mg) three times a day
Giardiasis	3	80ml (2000mg) once a day
	or 5	16ml (400mg) three times a day
	or 7 to 10	20ml (500mg) twice a day
Gingivitis	3	8ml (200mg) three times a day
Dental infections	3 to 7	8ml (200mg) three times a day
Leg ulcers and pressure sores	7	16ml (400mg) three times a day

Children under 10 years of age

What you're taking the medicine for	Number of days you will take the medicine for	How much to take – children aged 7-10 years	How much to take – children aged 3-7 years	How much to take - children aged 1-3 years
Trichomoniasis	7	Your doctor will work out the right dose based on your child's weight. This should not exceed 2000mg a day		
Amoebiasis	5 to 10	8ml (200mg) to 16ml (400mg) three times a day	4 ml (100mg) to 8ml (200mg) four times a day	4ml (100mg) to 8ml (200mg) three times a day
		Your doctor will work out the right dose based on your child's weight. This should not exceed 2400mg a day.		
Giardiasis	3	40ml (1000mg) once a day	24ml (600mg) to 32ml (800mg) once a day	20ml (500mg) once a day
		Your doctor will work out the right dose based on your child's weight.		
Gingivitis	3	4ml (100mg) three times a day	4ml (100mg) twice a day	2ml (50mg) three times a day

Children – treatment for a bacterial infection in the stomach (Helicobacter pylori)

Your child will be given Metrolag® with other medicines. Your doctor will work out the right dose based on your child's weight. This should not exceed 500mg twice a day.

Older people and those with liver problems

Your doctor may prescribe a lower dose than that given to adults. This is because you may be more sensitive to the medicine.

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, 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 (see section 5.3), the use of Metronidazole for longer treatment than usually required should be carefully considered.

Excipient Warnings

This medicine contains 100.00 mg liquid sorbitol 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 for oral 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 350 mg of sucrose in each ml. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine may contains methyl and propyl para hydroxybenzoates.

- methyl and propyl parahydroxybenzoates. These may cause an allergic reaction. This allergy may not happen straight away.

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 coadministration is necessary.

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

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 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 adult

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 (see section 4.4).

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, gastrointestinal disturbance and diarrhoea.

The parahydroxybenzoates used in Metronidazole Oral Suspension may cause immediate or delayed hypersensitivity reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 to the company.

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

Carmellose Sodium, Glycerol, Polysorbate, Saccharin Sodium, Methyl Hydroxy benzoate, Propyl Hydroxy benzoate, Ethanol (96%), Liquid Sorbitol (Non Crystallizing), Sucrose , Orange Flavour.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 Months.

6.4. Special precautions for storage

Store at room temperature (15-25°C) in the original packaging.

6.5. Nature and contents of container

Bottle of 100ml.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Lagap SA, UAE
Po. Box 46222
Abu Dhabi, UAE
(A division of Lagap Switzerland)

8. MARKETING AUTHORISATION NUMBER(S)

06024/07859/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Approval : 31-05-2021

10. DATE OF REVISION OF THE TEXT

May 2023