For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

SUMMARY OF PRODUCT

CHARACTERISTICSMETROGYL-200

(Metronidazole Tablets BP 200 mg)

1. NAME OF THE MEDICINAL PRODUCT

METROGYL-200
(Metronidazole Tablets BP 200 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg metronidazole
Each tablet contains Sodium Methyl hydroxy Benzoate 0.5 mg

3. PHARMACEUTICAL FORM

Film-coated tablets

PHYSICAL DESCRIPTION

Pink round biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1.Therapeutic indications

Metronidazole tablets are indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Metronidazole is active against a wide range of pathogenic micro-organisms notably species of *Bacteroides, Fusobacteria, Clostridia, Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.

It is also active against *Trichomonas, Entamoeba histolytica, Giardia lamblia* and *Balantidium coli*.

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

1. The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci.
2. The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated.
3. Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male.
4. Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis).

5. All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers).
6. Giardiasis.
7. Acute ulcerative gingivitis.
8. Anaerobically-infected leg ulcers and pressure sores.
9. Acute dental infections (e.g. acute pericoronitis and acute apical infections).

Considerations should be given to official guidance on the appropriate use of antibacterialagents.

4.2.Posology and method of administration

Oral route of administration.

Metronidazole tablets should be swallowed with water (not chewed). It is recommended that the tablets be taken during or after a meal.
Prophylaxis against anaerobic infection: Chiefly in the context of abdominal (especiallycolorectal) and gynaecological surgery.

Adults
400mg 8 hourly during 24 hours immediately preceding operation followed by postoperative intravenous or rectal administration until the patient is able to take tablets.

Children
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 beforeoperation.

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.

Treatment of established anaerobic infection:
Adults
800mg followed by 400mg 8 hourly.

Children
Children > 8 weeks to 12 years of age: The usual daily dose is 20-30mg/kg/day as asingle dose or divided into 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, therefore the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.

Protozoal and other infections:

<table>
<tr><td colspan="6">Dosage is given in terms of metronidazole or metronidazole equivalent</td></tr>
<tr><td></td><td>Duration of dosage indays</td><td>Adults and children over 10 years</td><td colspan="3">Children</td></tr>
<tr><td></td><td></td><td></td><td>7 to 10</td><td>3 to 7 years</td><td>1 to 3 years</td></tr>
<tr><td></td><td></td><td></td><td>years</td><td></td><td></td></tr>
<tr><td rowspan="2">Urogenital trichomoniasis

Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently</td><td>7

Or</td><td>2000mg as single dose or 200mg three times daily or</td><td colspan="3">40mg/kg orally as a single dose or 15-30mg/kg/day divided in 2-3 doses; not to exceed 2000mg/dose</td></tr>
<tr><td>5-7</td><td>400mg twice daily</td><td></td><td></td><td></td></tr>
<tr><td>Bacterial vaginosis</td><td>5-7
Or</td><td>400mg twice daily</td><td></td><td></td><td></td></tr>
</table>

	1	2000mg asa single dose			
Amoebiasis (a) Invasive intestinal disease insusceptible subjects	5	800mg three times daily	400mg three times daily	200mg fourtimes daily	200mg three times daily
(b) Intestinal disease in less susceptible subjects andchronic amoebic hepatitis	5-10	400mg three times daily	200mg three times daily	100mg fourtimes daily	100mg three times daily
(c) Amoebic liver abscess also other forms ofextra-intestinal amoebiasis	5	400mg three times daily	200mg three times daily	100mg fourtimes daily	100mg three times daily
(d) Symptomless cyst passers	5-10	400-800mg three timesdaily	200-400mg three times daily	100-200mg four timesdaily	100-200mg three timesdaily
	Alternatively, dosses may be expressed by body weight 35 to 50 mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed2400mg/day.				
Giardiasis	3	2000mg once dailyor	1000mg once daily	600-800mg once daily	500mg once daily

	5	400mg three times daily or			
	7-10	500mg twice daily			
	Alternatively, as expressed in mg per kg of body weight: 15-40mg/kg/day divided in 2-3 doses.				
	Duration of dosage indays	**Adults and children over 10 years**	**Children**		
			7 to 10 years	**3 to 7 years**	**1 to 3 years**
Acute ulcerative gingivitis	3	200mg three timesdaily	100mg three times daily	100mg twice daily	50mg threetimes daily
Acute dental infections	3-7	200mg three times daily			
Leg ulcers andpressure sores	7	400mg three times daily			
Children and infants weighing less than 10kg should receive proportionally smallerdosages. Elderly: Metronidazole tablet is well tolerated by the elderly but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.					

Eradication of Helicobacter pylori in paediatric patients:

As a part of a combination therapy, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy.Contraindications

Known hypersensitivity to nitroimidazoles, metronidazole or any of the excipients.

4.3. Special warnings and precautions for use

Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of Metronidazole tablets 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).

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.

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 testsbecome 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.

There is a 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 howeverretain 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 tablets need be made 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 and the resulting high plasma concentrations of metronidazole may contribute to the symptoms

ofthe encephalopathy. Metronidazole should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one thirdand may be administered once daily.

Patients should be warned that metronidazole may darken urine.

Due to inadequate evidence on the mutagenicity risk in humans, the use of Metronidazole tablets for longer treatment than usually required should be carefully considered.

"The product contains Sodium Methyl Hydroxy Benzoate which may cause allergicreactions (possibly delayed)."

4.4.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 anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.

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 concentrations 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 greaterrate than normally, reducing the half-life to approximately 3 hours.
Metronidazole reduces the clearance of 5 fluorouracil and can therefore result in increased toxicity of 5 fluorouracil.

Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin 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.

4.5.Fertility, pregnancy and lactation

There is inadequate evidence of the safety of metronidazole in pregnancy but it has been in wide use for many years without apparent ill consequence. Nevertheless Metronidazole tablets, like other medicines, should not be given during pregnancy or during lactation unless the physician considers it essential; in these circumstances the short, high-dosage regimens are not recommended.

4.6.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.

4.7.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.

<u>Blood and lymphatic system disorders:</u>
Very rare: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
Not known: leucopenia.

<u>Immune system disorders:</u>
Rare: anaphylaxis
Not known: angiodema, urticaria, fever.

<u>Metabolism and nutrition disorders:</u>
Not known: anorexia.

<u>Psychiatric disorders:</u>
Very rare: psychotic disorders, including confusion and hallucinations.
Not known: depressed mood

<u>Nervous system disorders:</u>
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) which may resolve on discontinuation of the drug.
- drowsiness, dizziness, convulsions, headaches

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.
- aseptic meningitis

Eye disorders:
Very rare: vision disorders such as diplopia and myopia, which, in most cases, is transient.
Not known: optic neuropathy/neuritis

Ear and labyrinth disorders:
Not known: hearing impaired/hearing loss (including sensorineural), tinnitus

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

Hepatobiliary disorders:
Very rare:
- increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, jaundice and pancreatitis which is reversible on drug withdrawal.
- cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders:
Very rare: skin rashes, pustular eruptions, pruritis, flushing
Not known: erythema multiforme, 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 urine (due to metronidazole metabolite).

4.8. 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

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

Metronidazole has antiprotozoal and antibacterial actions 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 rapidly and almost completely absorbed on administration of Metronidazole tablets; peak plasma concentrations occur after 20 min to 3 hours.
The half-life of metronidazole is 8.5 ± 2.9 hours. Metronidazole can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis. Metronidazole is excretedin milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants.

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 mutageniceffects, while others studies were negative.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sr. no.	Name of excipient	Specification
1.	Maize Starch	BP
2.	Sodium Methyl Hydroxy Benzoate	BP
3.	Colloidal Anhydrous Silica	BP
4.	Hydrogenated Castor oil	NF
5.	Magnesium Stearate	BP
6.	Opadry Pink II 85G 54815 (Qualitative Composition)	IH
	POLYVINYL ALCOHOL-PART. HYDROLYZED (USP,FCC,PhEur, JPE)	
	TALC (USP,FCC, PhEur, JP,JECFA)	
	TITANIUM DIOXIDE (USP, FCC, Ph.Eur, JP)	
	MACROGOL/PEG (NF, FCC, PhEur, JECFA, JP)	
	LECITHIN (SOYA) (NF,JPE,FCC,JSFA)	
	PONCEAU 4R ALUMINUM LAKE (JECFA, JP MO)	
7.	Purified Water	BP

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

3 years

6.4. Special precautions for storage

Do not store above 30°C, in a dry place. Protect from light.

6.5. Nature and contents of container

Alu-PVC blister pack of 10 tablets. 10 such blister is packed in a carton along withleaflet and

Alu-PVC blister of 2 x 10 tablets. 5 such blister packed in a carton along with leaflet(combipack)

6.6. Instructions for use and handling

"Any unused product or waste material should be disposed of in accordance withlocal requirements."

7. MARKETING AUTHORISATION HOLDER

Unique Pharmaceutical Laboratories(A Div. of J. B. Chemicals & Pharmaceuticals Ltd.) Plot No.4, Phase IV, G.I.D.C. Industrial Estate, City – Panoli, Dist. – Bharuch – 394 116, I **India.**

8. MARKETING AUTHORISATION NUMBER

TAN 21 HM 0293

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20th August, 2021

10. DATE OF REVISION OF THE TEXT

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