SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

ML-METRO 250 (Metronidazole Tablets BP 250mg)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

Each Tablet contains:

Metronidazole BP 250 mg

Approved colouredused.

Methyl Paraben BP …..0.6 mg

Propyl paraben BP ……0.059 mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Oral Tablets

Yellow coloured, circular flat beveled with break line on one side and other side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metronidazole is 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 Gardnerellavaginalis.

It is also active against Trichomonas, Entamoebahistolytica, Giardia lamblia and Balantidium coli.

Metronidazole 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)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

1. For Anaerobic bacterial infection:

Metronidazole is given orally in an initial dose of 4 tablets or 8 teaspoonful suspension followed by 2 tablets or 4 teaspoonful suspension every 6 hours. A maximum of 4 gm should not be exceeded during 24 hours period. Usual duration of therapy is 7 to 1 days.

2. Treatment of Septicemia, bactaeraemia, peritonitis, brain abscess, necrotising pneumonia, pelvic abscess, pelvic cellulites and postoperative wound infections:

Metronidazole is given orally in a dose of 2 tablets or 4 teaspoonful suspension thrice daily.

3. In ameobiasis:

Metronidazole is given orally in a dose of 3 tablets or 6 teaspoonful suspension thrice daily for 5 to 10 days. Children aged between 1 to 3 years may be given half teaspoonful suspension; those aged between 3 to 7 years may be given 2 teaspoonful suspension and those aged between 7 to 10 years may be given half tablet or 3 teaspoonful suspension.

4. In giardiasis:

The ususal oral dose is 1 tablet or 2 teaspoonful suspension three times daily for 5 to 7 days for adults, children aged between 7 to 10 years; half the adult dose may be given.

5. In trichomoniasis: One day treatment: two grams of Metronidazole, given either as a single dose or in two divided doses of one gm each given in the same day. Seven – day course of treatment : 250 mg three times daily for seven consecutive days.

6. Acute ulcerative gingivitis:

1 tablet or 2 teaspoonful suspension is given three times daily for 3 – 7 days.

Method of administration: Oral administration.

4.3 Contraindications

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

4.4 Special warnings and special precautions for use

Warning

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

Regular clinical and laboratory monitoring (especially leukocyte 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).

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.

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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 (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 of the encephalopathy. Metronidazole should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

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.

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 tests become markedly elevated during treatment, the drug should be discontinued.

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalisedexanthematouspustulosis (AGEP) have been reported with metronidazole. If symptoms or signs of SJS, TEN or AGEP are present, metronidazole treatment must be immediately 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.

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 effects) 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 greater rate 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.

4.6 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, 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.

4.7 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).

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, and pancytopenia

Not known: leucopenia.

Immune system disorders:

Rare: anaphylaxis,

Not known: angioedema, 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:

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, acute generalisedexanthematouspustulosis, pruritis, flushing

Not known: erythema msultiforme, Steven-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).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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

Pharmacotherapeutic group: Antibacterials for systemic use,

ATC code: J01X D01

Metronidazole has antiprotozoal and antibacterial actions and is effective against a wide range of pathogenic microorganisms notably species of Bacteroides, Fusobacteria, Clostridia, Eubacteria, anaerobic cocci and Gardnerellavaginalis. It is also active against Trichomonas vaginalis, Entamoebahistolytica, Giardia lamblia, Balantidium coli 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 excreted in 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 mutagenic effects, while other studies were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch, Micro Crystalline Cellulose, Gelatin, Povidone, ColourTartrazine Yellow Supra, Methyl Paraben, Propyl Paraben, Purified Talc, Sodium Starch Glycolate, Sodium Lauryl Sulfate, Magnesium Stearate, Colloidal Anhydrous Silica.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C in dry place. Protect from light.

6.5 Nature and contents of container

Alu-PVC Blister pack of 10 tablets and such 10 blisters are packed in a carton along with the pack insert.

6.6 Instructions for use and handling

Keep out of reach of children.

7. MARKETING AUTHORISATION HOLDER

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Road No. 9, Opposite MIDC Office,
Wagle Estate, Thane -400604
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8.NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

05587/5686/NMR/2017

9.DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

30-12-2020

10. DATE OF REVISION OF THE TEXT

July 2023