1. NAME OF THE MEDICINAL PRODUCT

Metrodine® (Metronidazole 200mg) tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lactose hydrous, Corn starch, Sodium starch glycolate, Polyvinyl pyrrolidone, Yellow iron oxide, Sodium starch glycolate, Magnesium stearate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solid- (tablet)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metrodine® tablet is indicated for the treatment of susceptible anaerobic and protozoal infections in the following conditions:
Amebiasis, symptomatic and asymptomatic trichomoniasis, skin and skin structure infections; intra-abdominal infectrion (as part of combination regimen) systemic anaerobic infections, trearment of antihiotic-association pseudomembranou colitis (AAPC), bacterial vaginosis, as part of a multi-drug regimen for Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence; also used in Crohn's disease and hepatic encephalopathy.

4.2 Posology and method of administration

Posology

Children (6-12 years): 1- $1^1/_2$ tablets three times daily
Adults (over 12 years): 2 tablets three times daily

Method of administration

4.3 Contraindications

Chronic alcohol dependence to metronidazole or any component of the formulation; first trimester of pregnancy since found to be carcinogic in rats.

4.4 Special warnings and precautions for use

Patients with hepatic impairment metabolize metronidazole slowly, with resultant accumulation of metronidazole in the plasma. Metrodine tablets should not be administered to patients with severe (Child-Pugh C) hepatic impairment unless it is deemed that the benefits outweigh the risks in these patients. For patients with mild to moderate hepatic impairment, no dosage adjustment is needed. Patients with hepatic impairment who receive the usual recommended dose of Metrodine tablets should be monitored for metronidazole associated adverse events

4.5 Interaction with other medicinal products and other forms of interaction

Ethanol may cause a disulfiram-like reaction. Warfarin and metronidazole may increase bleeding times which may result in bleeding. Cimetidine may increase Metronidazole levels. Metronidazole may inhibit metabolism of cisapride causing potential arrhymias; avoid concurrent use.
Metronidazole may increase lithium levels/toxicity.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies of Metrodine® in pregnant women. There are published data from case-control studies, cohort studies, and 2-meta-analyses that include more than 5000 pregnant women who used metronidazole during pregnancy. Many studies included first trimester exposures. One study showed an increased risk of cleft lip, with or without cleft palate, in infants exposed to metronidazole in-utero; however, these finding were not confirmed. In addition, more than ten randomized placebo-controlled clinical trials enrolled more than 5000 pregnant women to assess the use of antibiotic treatment (including metronidazole) for bacterial vaginosis on the incidence of preterm delivery.

Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy. Three studies conducted to assess the risk of infant cancer following metronidazole exposure during pregnancy did not show an increased risk; however, the ability of these studies to detect such a signal was limited. Metronidazole crosses the placental barrier and its effects on the human fetal organogenesis are not known. Reproduction studies have been performed in rats, rabbits, and mice at doses about four times the recommended human dose based on body surface area comparisons. There was no evidence of harm to the fetus due to metronidazole.

Nursing mothers: Metronidazole is present in human milk at concentrations similar to maternal serum levels, and infant serum levels can be close to or comparable to infant therapeutic levels. Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Alternatively, a nursing mother may choose to pump and discard human milk for the duration of metronidazole therapy, and for 24 hours after therapy ends and feed her infant stored human milk or formula.

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.

<u>Blood and lymphatic system disorders:</u>

Very rare: agranulocytosis, neutropenia, thrombocytopenia, and pancytopenia

Not known: leucopenia.

<u>Immune system disorders:</u>

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.

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 generalised exanthematous pustulosis, pruritis, flushing

Not known: erythema multiforme, Steven-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption.

Musculoskeletal, connective tissue and bone disorders:

Very rare: myalgia, arthralgia.

Renal and urinary disorders: darkening of 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. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Metronidazole has antibacterial and antiprotozoal actions and is effective 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 vaginalis, Entamoeba histolytica, 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

Lactose hydrous 200
Corn starch
Sodium starch glycolate
Polyvinyl pyrrolidone
Tartrazine yellow
Yellow iron oxide
Sodium starch glycolate
Magnesium stearate

6.2 Incompatibilities

None

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 30^0C. Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

A blister pack of 10 x 10 tablets in a folded hard board carton

6.6 Special precautions for disposal

None

7. APPLICANT/MANUFACTURER

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8. MARKETING AUTHORISATION NUMBER

04-7950

9. DATE OF FIRST AUTHORIZATION

03/11/2006

10. DATE OF REVISION OF THE TEXT

05/2023