1. Name of the medicinal product

Metronidazole 0.5%w/v Solution for Infusion.

2. Qualitative and quantitative composition

Each ml of solution for infusion contains 5mg metronidazole.

Excipients:

Each ml of solution for infusion contains 8 mg sodium chloride.

3. Pharmaceutical form

Solution for infusion

4. Clinical particulars

4.1 Therapeutic indications

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

In the treatment of severe infections due to anaerobic bacteria, particularly species of Bacteroides, anaerobic Streptococci, etc., and for prophylaxis against such infections, in patients for whom oral medication is not practical.

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

4.2 Posology and method of administration

Metronidazole infusion should be infused intravenously at an approximate rate of 5 ml/min.

Oral medication should be substituted as soon as feasible.

Prophylaxis against anaerobic infection: *Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.*

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Adults

500mg shortly before operation, repeated 8 hourly. Oral doses of 200 mg or 400 mg 8 hourly to be started as soon as feasible.

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 before operation

Anaerobic Infections: Treatment for seven days should be satisfactory for most patients but, depending upon clinical and bacteriological assessments, the physician might decide to prolong treatment e.g. for the eradication of infection from sites which cannot be drained or are liable to endogenous recontamination by anaerobic pathogens from the gut, oropharynx or genital

Treatment of established anaerobic infections: Intravenous route is to be used initially if patient's symptoms preclude oral therapy.

Adults

500 mg 8 hourly.

Children

Children > 8 weeks to 12 years of age: The usual daily dose is 20-30mg/kg/day as a single 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.

Bacterial vaginosis:

Adolescents: 400mg twice daily for 5-7 days or 2000mg as a single dose.

Urogenital trichomoniasis:

Adults and adolescents: 2000mg as a single dose or 200mg 3 times daily for 7 days or 400mg twice daily for 5-7 days

Children < 10 years: 40mg/kg orally as a single dose or 15-30 mg/kg/day divided in 2-3 doses for 7 days; not to exceed 2000mg/dose

Giardiasis:

> 10 years: 2000mg once daily for 3 days, or 400mg three times daily for 5 days, or 500mg twice daily for 7 to 10 days

Children 7 to 10 years: 1000mg once daily for 3 days

Children 3 to 7 years: 600 to 800mg once daily for 3 days

Children 1 to 3 years: 500mg once daily for 3 days

Alternatively, as expressed in mg per kg of body weight: 15-40mg/kg/day divided in 2-3 doses.

Amoebiasis:

> 10 years: 400 to 800mg 3 times daily for 5-10 days

Children 7 to 10 years: 200 to 400mg 3 times daily for 5-10 days

Children 3 to 7 years: 100 to 200mg 4 times daily for 5-10 days

Children 1 to 3 years: 100 to 200mg 3 times daily for 5-10 days

Alternatively, doses may be expressed by body weight: 35 to 50mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400mg/day

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

Elderly

Caution is advised in the elderly. Particularly at high doses although there is limited information available on modification of dosage.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

The use of Metronidazole for prolonged treatment duration should be carefully weighed

If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible. High dosage regimes have been associated with transient epileptiform seizures. Caution is required in patients with active disease of the central nervous system except for brain abscess.

Metronidazole and a metabolite have been shown to be mutagenic in some tests with non mammalian cells.

Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction.

Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

Metronidazole is mainly metabolized by hepatic oxidation. Substantial impairment of Metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit using Metronidazole to treat trichomoniasis in such patients should be carefully considered.

Flagyl should be administered in caution to people with hepatic encephalopathy.

Cases of severe bullous skin reactions, sometimes fatal, such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Metronidazole The majority of cases of SJS reported occurred within 7 weeks of starting treatment with Metronidazole. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If symptoms of SJS or TEN (e.g. flu-like symptoms, progressive skin rash often with blisters or mucosal lesions) are present, treatment should be discontinued .

Patients should be warned that Metronidazole may darken urine (due to Metronidazole metabolite).

Patients should be advised not to take alcohol during Metronidazole therapy and for at least 48 hours afterwards .

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 disulfiramlike (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 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 Pregnancy and lactation

There is inadequate evidence of the safety of metronidazole in pregnancy. Flagyl should not therefore 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 are advised not to drive or operate machinery if these symptoms occur.

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4.8 Undesirable effects

Gastrointestinal Disorders

- epigastric pain, nausea, vomiting, diarrhoea.
- oral mucositis, taste disorders, dry mouth, anorexia.
- reversible cases of pancreatitis.
- tongue discolouration/furry tongue

mmune system disorders

- angioedema, anaphylactic shock.

Nervous system disorders

- peripheral sensory neuropathy.
- headache, convulsions, dizziness.
- reports of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve with discontinuation of the drug.
- aseptic meningitis

Psychiatric disorders

- psychotic disorders including confusion, hallucinations.
- depressed mood

Eye disorders

- transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity. Changes in color vision.
- Optic neuropathy/neuritis.

Blood and lymphatic system disorders

- cases of agranulocytosis, neutropenia and thrombocytopenia have been reported.

Hepatobiliary disorders

- increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported.
- cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole, mostly when used in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders

- rash, pruritus, flushing, urticaria
- pustular eruptions
- Stevens-Johnson syndrome, toxic epidermal necrolysis.

General disorders and administration site conditions

- fever

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 over dosage.

In cases of suspected massive over dosage, a 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 widely distributed in body tissues after injection. At least half the dose is excreted in the urine as metronidazole and its metabolites, including an acid oxidation product, a hydroxy derivative and glucuronide.

Metronidazole diffuses across the placenta, and is found in breast milk of nursing mothers in concentrations equivalent to those in serum.

10% of the dose is bound in plasma.

Clearance: 1.3 ± 0.3 ml/min/kg, volume of distribution: 1.1 ± 0.4 litres/kg.

Half-life: 8.5 ± 2.9 hours.

Effective concentration 3-6 micrograms/ml.

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

Sodium chloride

Water for Injections B.P.

6.2 Incompatibilities

Flagyl infusion should not be mixed with cefamandole nafate, cefoxitin sodium, dextrose 10% w/v, compound sodium lactate injection, penicillin G potassium.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C, but do not freeze.

6.5 Nature and contents of container

Pack sizes: 100 mL

The bottles Low Density Polyethylene plastic are overwrapped with a protective plastic pouch.

6.6 Special precautions for disposal and other handling

Metronidazole containers are for single use only. Discard any unused portion.

Do not reconnect partially used containers.

7. Marketing authorisation holder

Abacus Parenteral Drugs Ltd. Uganda

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P.O.Box 31376, Kampala, Uganda.

8. Marketing authorisation number(s):

7544/06/11

9. Date of first authorisation/renewal of the authorisation:

June 2011

10. Date of revision of the text

05/04/2016

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