1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed on following page

1.0 Product Name

METROSAM IV [Metronidazole Injection USP (500 mg/ 100 ml)]

2.0 Qualitative and quantitative composition

Each ml of solution for infusion contains 5 mg metronidazole.

Each 100ml of solution for infusion contains 500mg metronidazole.

Excipients having known effect:

Each ml of solution for infusion contains 0.1384 mmol (or 3.2602mg) sodium.

Each 100ml of solution for infusion contains 13.84 mmol (or 326.02 mg) Sodium.

For a full list of excipients, see section 6.1.

3.0 Pharmaceutical Form

Solution for infusion.

A clear and almost colourless to pale yellow solution essentially free form visible particles

4.0 Clinical Data:

4.1 Therapeutic indications

Metronidazole 5mg/ml solution for infusion is indicated when oral medication is not possible in:

- The prophylaxis of pre/postoperative infections due to sensitive anaerobic bacteria particularly species of Bacteroides and anaerobic Streptococci, during abdominal, gynaecological, gastrointestinal or colorectal surgery which carries a high risk of occurrence of this type of infection. The solution may also be used in combination with an antibiotic active against aerobic bacteria.
- The treatment of severe intra-abdominal and gynaecological infections in which sensitive anaerobic bacteria particularly Bacteriodes and anaerobic Streptococci have been identified or are suspected to be the cause.

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

4.2 Dosage and method of administration

Method of administration

Metronidazole 5mg/ml solution for infusion should be infused intravenously at an approximate rate of 5 ml/minute (or one bag infused over 20 to 60 minutes). Oral medication should be substituted as soon as feasible. Prophylaxis of surgical pre/post-operative infection primarily in the context of abdominal (especially colorectal) and gynaecological surgery.

Antibiotic prophylaxis duration should be short, mostly limited to the post-operative period (24 hours but never more than 48 hours). Various schedules are possible.

Adults: Intravenous injection of single dose of 1000mg-1500mg, 30-60 minutes preoperatively or alternatively 500mg immediately before, during or after operation, then 500mg 8-hourly.

Children: Intravenous injection of single dose of 20 to 30 mg/kg, 30-60 minutes preoperatively or alternatively 7.5mg/kg given immediately before, during or after surgery, repeated every 8 hours thereafter. Pre-Term New born Infants with a gestational age less than 40 weeks: A single dose of 10 mg/kg of body weight preoperatively.

The Elderly: Caution is advised in the elderly, particularly at high doses, although there is limited information available on modification of dosage.

Treatment of infections due to anaerobic bacteria.

Intravenous route is to be used initially if patients symptoms preclude oral therapy. Various schedules are possible.

Adults: 1000mg - 1500mg daily as a single dose or alternatively 500mg every 8 hours.

Children: A single dose of 20 to 30mg/kg/day or alternatively divided into 3 doses of 7.5 mg/kg given every 8 hours.

New born Infants less than 8 weeks of age: A lower dose of 15 mg/kg of body weight once daily or 7.5 mg/kg every 12 hours.

Pre-Term New born Infants with a gestational age less than 40 weeks of age: Accumulation of the drug might occur during the first week of life. Serum concentrations should be controlled after a few days of therapy.

The Elderly: Caution is advised in the elderly, particularly at high doses, although there is limited information available on modification of dosage.

Oral medication could be given, at the same dose regimen. Oral medication should be substituted as soon as feasible.

Duration of Treatment

Treatment for seven to ten 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 tract.

Patients with renal failure

Routine adjustments of the dosage of Metronidazole are not considered necessary in the presence of renal failure.

No routine adjustment in the dosage of Metronidazole needs to be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD). However dosage reduction may be necessary when excessive concentrations of metabolites are found.

In patients undergoing haemodialysis, metronidazole should be re administered immediately after haemodialysis.

Patients with advanced hepatic insufficiency

In patients with advanced hepatic insufficiency a dosage reduction with serum level monitoring is necessary.

4.3 Contraindications

Known hypersensitivity to Metronidazole or other imidazole derivatives or any of the excipients (see 6.1 List of excipients).

Metronidazole is contraindicated in the first trimester of pregnancy.

Use of Metronidazole is contraindicated in patients with end stage liver damage, hematopoietic disorders and uncontrolled diseases of the central or peripheral nervous system.

4.4 Special warnings and precautions for use

Liver disease:

Metronidazole is mainly metabolized by hepatic oxidation. Substantial impairment of Metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit ratio of using Metronidazole to treat trichomoniasis in such patients should be carefully considered (for dosage adjustment see section 4.2). Plasma levels of Metronidazole should be closely monitored.

Active Central Nervous System disease:

Metronidazole should be used with caution in patients with active disease of the Central Nervous System. The treatment should be withdrawn in case of ataxia, dizziness, or confusion. The risk of aggravation of the neurological state should be considered in patients suffering from severe central and peripheral neurological diseases, fixed or progressive paraesthesia and epilepsy. Caution is required in patients with active disease of the central nervous system except for brain abscess.

Renal Disease:

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

Sodium restricted patients:

May be harmful to patients on a low sodium diet.

Alcohol:

Patients should be advised not to take alcohol during Metronidazole therapy and at least 48 hours afterwards because of a disulfram-like effect (flushing, vomiting, and tachycardia). See Section 4.5.

Intensive or prolonged Metronidazole therapy:

As a rule, the usual duration of therapy with I.V. Metronidazole or other imidazole derivatives is usually less than 10 days. This period may only be exceeded in individual cases after a very strict benefit-risk assessment. Only in the rarest possible case should the treatment be repeated. Limiting the duration of treatment is necessary because damage to human germ cells cannot be excluded.

Intensive or prolonged Metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction. If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible.

In case of prolonged treatment, occurrence of undesirable effects such as paraesthesia, ataxia, dizziness and convulsive crises should be checked. High dose regimes have been associated with transient epileptiform seizures.

Monitoring:

Regular clinical and laboratory monitoring (including leukocyte formula) are advised in cases of high-dose or prolonged treatment, in case of antecedents of blood dyscrasia, in case of severe infection and in severe hepatic insufficiency. General:

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

4.5 Interactions with other drugs and other forms of interactions

Not recommended concomitant therapy:

Alcohol: Disulfram-like effect (warmth, redness, vomiting, and tachycardia).Alcohol beverage and drugs containing alcohol should be avoided. Patients should be advised not to take alcohol during Metronidazole therapy and at least 48 hours afterwards because of a disulfram-like (Antabuse effect) reaction (flushing, vomiting, and tachycardia).

Concomitant therapy requiring special precautions:

Oral anticoagulants (warfarin): increase of the effects of oral anticoagulants and the risk of haemorrhage (decrease in its liver catabolism). Prothrombin time should be monitored more frequently. The dose of oral anticoagulants should be adjusted during the treatment with Metronidazole and 8 days after withdrawal. A large number of patients have been reported showing an increase in oral anticoagulant activity whilst receiving concomitant antibiotic therapy. The infectious and inflammatory status of the patient, together with their age and general well-being are all risk factors in this context. However, in these circumstances it is not clear as to the part played by the disease itself or its treatment in the occurrence of prothrombin time disorders. Some classes of antibiotics are more likely to result in this interaction, notably fluoroquinolones, macrolides, cyclines, cotrimoxazole and some cephalosporins.

Vecuronium (Non depolarizing curaremimetic): Metronidazole can potentialise the effects of vecuronium.

Combinations to be considered:

5 Fluoro-uracile: increase in the toxicity of 5 fluoro-uracile due to a decrease of its clearance.

Lithium: 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.

Barbiturates - Phenobarbital might induce the metabolism of Metronidazole, which could lead to decreased efficacy of Metronidazole. Cholestyramine may delay or reduce the absorption of Metronidazole. Concomitant administration of phenytoin and Metronidazole may affect the metabolism of Metronidazole.

Cimetidine inhibits the metabolism of Metronidazole.

Cyclosporine - Case reports indicate that concomitant treatment with Metronidazole and Cyclosporine might lead to increased serum levels of cyclosporine. Cyclosporine concentrations and creatinine levels should be monitored.

Laboratory tests:

Metronidazole may immobilize Treponema and thus may lead to falsely positive Nelson's test.

4.6 Pregnancies and breastfeeding

Clinical data on a large number of exposed pregnancies and animal data did not show a teratogenic or foetotoxic effect. However unrestricted administration of nitroimidazolene to the mother may be associated with a carcinogenic or mutagenic risk for the unborn or newborn child.

Therefore Metronidazole should not be given during pregnancy unless clearly necessary. Metronidazole is contraindicated in the first trimester of pregnancy. Metronidazole is excreted in breast milk. During lactation either breastfeeding or Metronidazole should be discontinued.

4.7 Effects on the ability to drive and use machines

No studies have been performed following intravenous treatment with Metronidazole on the ability to drive and use machines. Therefore, it is recommended that patients should not drive or use machines.

4.8 Adverse effects

Common undesirable effects (>1/100 <1/10): gastrointestinal tract: diffuse symptoms of intolerance (like nausea, vomiting), metallic taste, stomatitis and glossitis and dry mouth; myalgia.

Uncommon undesirable effects (>1/1000, <1/100): leucopenia, headaches and weakness.

Rare undesirable effects (>1/10,000, <1/1000):

General: fever, skin rashes, urticaria, erythema multiforme anaphylactic shock, Quincke oedema, pustolosis.

Neurology: drowsiness, dizziness, ataxia, peripheral neuropathy or transient epileptiform seizures, hallucinations.

Blood: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia. Blood dyscrasia is generally reversible but fatal cases have been reported.

Liver: Abnormal function tests, cholestatic hepatitis jaundice, pancreatitis; rare and reversible cases of pancreatitis are reported.

Gastrointestinal: Mucositis, epigastralgia, nausea, vomiting, diarrhoea, anorexia.

Urine: darkening of urine.

Eyes: diplopia, myopia.

Herxheimer reaction.

Changes in the blood picture as well as peripheral neuropathy observed after prolonged treatment or high dosages generally abate after treatment withdrawal.

4.9 Overdose

Symptoms

In cases of overdose in adults, the clinical symptoms are usually limited to nausea, vomiting, ataxia and slight disorientation. In a preterm new-born, no clinical or biological sign of toxicity developed.

Treatment

There is no specific treatment for Metronidazole overdose, Metronidazole infusion should be discontinued. Patients should be treated symptomatically.

5.0 Pharmacological properties

5.1 Pharmacodynamic properties

Metronidazole is an anti-infectious drug belonging to the Pharmacotherapeutic group of nitroimidazole derivatives, which have effect mainly on strict anaerobes. This effect is probably caused by interaction with DNS and different metabolites.

Pharmacotherapeutic group:

Anti bacterials for systemic use: imidazole derivatives ATC code: J01XD01.

And

Pharmacotherapeutic group:

Anti-protozoals: nitroimidazole derivatives. ATC Code: P01AB01.

Metronidazole has anti-bacterial and antiprotozoal actions and is effective against anaerobic bacteria and against Trichomonas vaginalis and other protozoa including Entamoeba histolytica and Giardia lamblia.

Anti-Microbial Spectrum:

The MIC breakpoints separating susceptible from intermediately susceptible and intermediately susceptible from resistant organisms are as following:

S < 4 mg/l and R > 4 mg/l

The prevalence of acquired resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating severe infections. This information gives only approximate guidance on probabilities whether microorganisms will be susceptible to Metronidazole or not.

Categories

SUSCEPTIBLE

Gram negative aerobes Helicobacter pylori

Anaerobes

Bacteroides fragilis

Bifidobacterium>>resistant (70%)

Bilophila

Clostridium

Clostridium difficile

Clostridium perfringens

Eubacterium Fusobacterium

Peptostreptococcus

Prevotella

Porphyromonas

Veillonella

RESISTANT

Gram positive aerobes

Actinomyces

Anaerobes

Mobiluncus

Propionibacterium acnes

ANTIPARASITIC ACTIVITY

Entamoeba histolytica

Giardia intestinalis

Trichomonas vaginalis

Cross-resistance with tindazol occurs.

5.2 Pharmacokinetic properties

Distribution: After administration of a single 500 mg dose, mean Metronidazole peak plasma concentrations of ca. 14-18 μg/ml are reached at the end of a 20 minute infusion. 2-hydroxy-metabolite peak plasma concentrations of ca..3 μg/ml are obtained after a 1 g single I.V. dose. Steady state Metronidazole plasma concentrations of about 17 and 13 -μg/ml are reached after administration of Metronidazole every 8 or 12 hours, respectively.

Plasma protein binding is less than 10%, and the volume of distribution 1.1 ± 0.4 l/kg.

Metabolism: Metronidazole is metabolised in the liver by hydroxylation, oxidation and glucuronidation. The major metabolites are a 2-hydroxy- and an acetic acid metabolite.

Elimination: More than 50% of the administered dose is excreted in the urine, as unchanged Metronidazole (ca. 20% of the dose) and its metabolites. About 20% of the dose is excreted with faeces. Clearance is 1.3 ± 0.3 ml/min/kg, while renal clearance is about 0.15 ml/min/kg. The plasma elimination half-life of Metronidazole is ca. 8 hours, and of the 2-hydroxy-metabolite ca. 10 hours.

Special patient groups: The plasma elimination half-life of Metronidazole is not influenced by renal impairment, however this may be increased for 2- hydroxy- and an acetic acid metabolite. In the case of haemodialysis, Metronidazole is rapidly excreted and the plasma elimination half-life is decreased to ca. 2.5 h. Peritoneal dialysis does not appear to affect the elimination of Metronidazole or its metabolites.

In patients with impaired liver function, the metabolism of Metronidazole is expected to decrease, leading to an increase in the plasma elimination half-life. In patients with severe liver impairment, clearance may be decreased up to ca. 65%, resulting in an accumulation of Metronidazole in the body.

5.3 Preclinical safety data

Metronidazole has been shown to be non-mutagenic in mammalian cells in vitro and in vivo. Metronidazole and a metabolite have been shown to be mutagenic is some tests with non-mammalian cells.

Although Metronidazole has been shown to be carcinogenic in certain species of mice, it was not carcinogenic in either rats or guinea pigs. There is no suspicion of carcinogenicity in man. Further preclinical data on repeated toxicity and toxicity to reproduction add no relevant knowledge for the prescriber.

6.0 Pharmaceutical data

6.1 List of excipients

Citric acid Monohydrate

Di sodium Hydrogen phosphate anhydrous

Sodium Chloride

Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal product except for those mentioned in 6.6.

6.3 Shelf Life

36 months

6.4 Storage Condition

Store below 30°C. Protect from light

Keep medicines out of reach of children.

6.5 Nature and content of the outer packaging

Primary Packing: 100 ml solution packed in Plastic Bottles

Secondary Packing: Bottles overwrapped with polypropylene film roll and packed in carton with leaflet

6.6 Special precautions for disposal and handling

The containers are for single use only. Discard any unused portion. Do not reconnect partially used containers.

Any unused product or waste material should be disposed of in accordance with local requirements.

7.0 Marketing Authorization Holder

SAM PHARMACEUTICAL LIMITED

8/9, Oyadiran Estate, Yaba, Lagos, Nigeria

8.0 Marketing Authorization Number

B4-9113

9.0 Date of first Marketing Authorization / Renewal of Marketing Authorization

31/10/2018

10.0 Date of Revision of The Text

June-2023