SmPC

(SUMMARY OF PRODUCT CHARACTERSTICS)

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1.0 NAME OF THE MEDICINAL PRODUCT

Metronidazole Injection USP 5mg/mL

2.0 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100mL contains:

Metronidazole USP..... 500 mg

In isotonic solution.....qs

For excipients, see 6.1

3.0 PHARMACEUTICAL FORM

Solution for infusion

An almost colourless to pale yellow solution

4.0 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metronidazole Injection USP is indicated in adults and children when oral medication is not possible for the following indications:

- The prophylaxis of 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 intraabdominal 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 Posology and method of administration

Method of Administration

Metronidazole Injection USP should be infused intravenously at an approximate rate of 5 ml/minute. Oral medication should be substituted as soon as feasible.

Prophylaxis against postoperative infections caused by anaerobic bacteria:

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: Intra-venous 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 < 12 years: 20-30 mg/kg as a single dose given 1-2 hours before surgery.

Newborns with a gestation age <40 weeks: 10 mg/kg body weight as a single dose before operation.

Anaerobic infections

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

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

Children > 8 weeks to 12 years of age: The usual daily dose is 20-30mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.

Children < 8 weeks of age: 15 mg/kg as a single dose daily or divided into 7.5 mg/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 preferably be monitored after a few days of therapy.

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.

Bacterial vaginosis

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

Urogenital trichomoniasis

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

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

Giardiasis

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

Children 7 to 10 years: 1000 mg once daily for 3 days
Children 3 to 7 years: 600 to 800 mg once daily for 3 days
Children 1 to 3 years: 500 mg once daily for 3 days

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

Amoebiasis

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

Children 7 to 10 years: 200 to 400 mg 3 times daily for 5-10 days
Children 3 to 7 years: 100 to 200 mg 4 times daily for 5-10 days
Children 1 to 3 years: 100 to 200 mg 3 times daily for 5-10 days

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

Eradication of Helicobacter pylori in paediatric patients

As a part of a combination therapy, 20 mg/kg/day not to exceed 500 mg twice daily for 7-14 days.

Official guidelines should be consulted before initiating therapy

Elderly Population

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

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

Metronidazole is contraindicated in the first trimester of pregnancy.

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

4.4 Special warnings and precautions for use

Liver disease:

Metronidazole is mainly metabolised 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. Plasma levels of Metronidazole should be closely monitored.

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.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole.

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, tachycardia).

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 Interaction with other medicinal products and other forms of interaction

Not recommended concomitant therapy

Alcohol

Disulfram-like effect (warmth, redness, vomiting, 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, 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 depolarising 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.

Busulfan

Plasma concentrations of busulfan may increase during concomitant treatment with metronidazole, which can result in serious busulfan toxicity.

Laboratory tests

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

4.6 Fertility, pregnancy and lactation

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 breast-feeding or Metronidazole should be discontinued.

4.7 Effects on 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 Undesirable 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, Stevens Johnson Syndrome and Toxic Epidermal Necrolysis.

Neurology

drowsiness, dizziness, ataxia, peripheral neuropathy or transient epileptiform seizures, hallucinations, Encephalopathy, optic neuropathy and aseptic meningitis.

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.

Frequency, type and severity of adverse reactions in children are the same as in adults.

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 newborn, 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: Antibacterials for systemic use: imidazole derivatives

ATC Code: J01XD01

Pharmacotherapeutic group: Antiprotozoals: nitroimidazole derivatives

ATC Code: P01AB01.

Metronidazole has antibacterial 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:

$S \leq 4$ 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

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 PARTICULARS

6.1 List of excipient

Sodium Chloride

Water for Injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal product

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C. Protect from light. Do not freeze.
Keep the medicines out of reach of children.

6.5 Nature and contents of container

100mL Solution in LDPE bottles

6.6 Special precautions for disposal and other handling

Use only if the solution is clear, without visible particles and if the container is undamaged.

The product should be used immediately after opening.

Discard after single use.

Discard any unused portion.

7.0 MARKETING AUTHORISATION HOLDER

Mark Pharmaceuticals Limited

Lagos, Nigeria.

8.0 MARKETING AUTHORISATION NUMBER(S)

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9.0 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10.0 DATE OF REVISION OF THE TEXT

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