

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Metronidazole injection 500mg/100ml

2. Qualitative and quantitative composition

Each 100ml contains: Metronidazole 500mg.

3. Pharmaceutical form

Injection

A clear, colourless or almost colourless liquid.

4. Clinical particulars

4.1 Therapeutic indications

Metronidazole 500mg/100ml Intravenous Injection 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 500mg/100ml Intravenous Injection 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 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

Hypersensitivity to the active substance, to other imidazole derivatives

4.4 Special warnings and precautions for use

Liver disease:

Caution is needed in patients with severe hepatic impairment. The dose of metronidazole should be reduced as necessary. 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 (for dosage adjustment see section 4.2). Plasma levels of Metronidazole should be closely monitored.

Caution is needed in patients with hepatic encephalopathy. Patients with severe hepatic encephalopathy metabolize metronidazole slowly, with resultant accumulation of metronidazole. This may cause exacerbation of CNS adverse effects. The dose of metronidazole should be reduced as necessary.

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 Peripheral and Central Nervous System. Severe neurological disturbances (including seizures and peripheral and optic neuropathies) have been reported in patients treated with metronidazole. Stop metronidazole treatment if any abnormal neurologic symptoms occur such as ataxia, dizziness, confusion or any other CNS adverse reaction. The risk of aggravation of the neurological state should be considered in patients with fixed or progressive paraesthesia, epilepsy and active disease of the

central nervous system except for brain abscess.

Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, dysarthria, and accompanied by CNS lesions seen on magnetic resonance imaging (MRI). CNS symptoms and CNS lesions, are generally reversible within days to weeks upon discontinuation of metronidazole.

Aseptic meningitis can occur with metronidazole. Symptoms can start within hours of dose administration and generally resolve after metronidazole therapy is discontinued (see section 4.8).

Blood Dyscrasias

Metronidazole should be used with caution in patients with evidence or history of blood dyscrasia as agranulocytosis, leukopenia and neutropenia have been observed following metronidazole administration.

Renal Disease:

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

Patients with renal impairment, including patients receiving peritoneal dialysis, should be monitored for signs of toxicity due to the potential accumulation of toxic metronidazole metabolites.

Sodium restricted patients:

This medicinal product contains 13.5 mmol (310 mg) sodium per 100 mL. To be taken into consideration by patients on a controlled sodium diet.

Alcohol:

Patients should be advised to discontinue consumption of alcoholic beverages or alcohol-containing products before, during, and up to 72 hours after taking metronidazole because of a disulfiram-like effect (abdominal cramps, nausea, headaches, 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:

Due to increased risk for adverse reactions, regular clinical and laboratory monitoring (including blood count) are advised in cases of high-dose, prolonged or repeated 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:

Disulfiram: Concurrent use of metronidazole and disulfiram may result in psychotic reactions and confusion. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

Alcohol: Disulfiram-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 72 hours afterwards because of a disulfiram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).

Concomitant therapy requiring special precautions:

Oral anticoagulants (warfarin): metronidazole may increase the anticoagulant effects of warfarin and other oral anticoagulants, resulting in a prolongation of the prothrombin time and increased risk of haemorrhage (decrease in its liver catabolism). Patients taking metronidazole and warfarin or other oral coumarins concomitantly should have their prothrombin time and international normalized ratio (INR)

monitored more frequently. Patients should be monitored for signs and symptoms of bleeding.

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.

Cholestyramine may delay or reduce the absorption of Metronidazole.

Phenytoin, barbiturates (phenobarbital): concomitant administration of drugs that induce microsomal liver enzyme activity, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole and therefore decrease its efficacy.

Cimetidine : concomitant administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may cause decreased metabolism and reduced plasma clearance of metronidazole which may result in metronidazole toxicity.

Concomitant use of metronidazole and CYP3A4 substrates (e.g., amiodarone, tacrolimus, cyclosporine, carbamazepine, and quinidine) may increase respective CYP3A4-substrate plasma levels. Monitoring of plasma concentrations of CYP3A4 substrates may be necessary.

Busulfan: Plasma concentrations of busulfan may increase during concomitant treatment with metronidazole, which can result in serious busulfan toxicity such as sinusoidal obstruction syndrome, gastrointestinal mucositis, and hepatic veno-occlusive disease.

Laboratory tests:

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

Metronidazole may interfere with serum aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase determinations. Metronidazole causes an increase in ultraviolet absorbance at 340 nm resulting in falsely decreased values.

4.6 Fertility, pregnancy and lactation

Pregnancy

Metronidazole crosses the placental barrier.

Clinical data on a large number of exposed pregnancies and animal data did not show a teratogenic or foetotoxic effect. However unrestricted administration of nitroimidazolenone 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.

Lactation

Metronidazole is excreted in breast milk. During lactation either breast-feeding or Metronidazole should be discontinued.

Fertility

There are no clinical data relating to the effect of metronidazole on fertility.

Animal studies demonstrated adverse effects on the male reproductive system that are wholly or partially reversible after treatment withdrawal.

4.7 Undesirable effects

There are no data available on adverse reactions from Baxter-sponsored clinical trials conducted with Metronidazole. The following adverse reactions have been reported with Metronidazole, listed by MedDRA System Organ Class (SOC), Preferred Term and frequency. The following frequency groupings are used: very common ($\geq 1/10$); common ($\geq 1/100$ and $< 1/10$); uncommon ($\geq 1/1,000$ and $< 1/100$); rare ($\geq 1/10,000$ and $< 1/1,000$); very rare ($< 1/10,000$) and not known (cannot be estimated from the available data).

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

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
Blood and Lymphatic System Disorders	Leukopenia	uncommon
	Agranulocytosis	rare
	Pancytopenia	rare
	Neutropenia	rare

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	Thrombocytopenia Eosinophilia	rare not known
Immune System Disorder	Anaphylactic shock Jarisch-Herxheimer reaction Hypersensitivity	rare rare not known
Metabolism and Nutrition Disorders	Decreased appetite	not known
Psychiatric Disorders	Hallucinations Depression Confusional state Insomnia	rare not known not known not known
Nervous System Disorders	Dysgeusia Headache Encephalopathy Meningitis aseptic Seizure Somnolence Neuropathy peripheral Ataxia Dizziness Dysarthria Hypoaesthesia Paraesthesia	common uncommon rare rare rare rare rare rare rare rare not known not known not known
Eye Disorders	Optic neuropathy Diplopia Myopia	rare rare rare
Cardiac Disorders	Tachycardia Palpitations	not known not known
Respiratory, Thoracic and Mediastinal Disorders	Dyspnoea	not known
Gastrointestinal Disorders	Glossitis Stomatitis Dry mouth Pancreatitis Abdominal pain upper Diarrhoea Nausea Vomiting Constipation Tongue discoloration	common common common rare rare rare rare rare rare not known not known
Hepatobiliary disorders	Jaundice cholestatic	rare

Skin and Subcutaneous Disorders	Stevens-Johnson syndrome	rare
	Toxic epidermal necrolysis	rare
	Angioedema	rare
	Erythema multiforme	rare
	Pruritus	not known
	Swelling face	not known
	Urticaria	not known
	Hyperhidrosis	not known
Rash	not known	
Musculoskeletal and Connective Tissue Disorders	Myalgia	common
	Muscle spasms	not known
	Arthralgia	not known
Renal and urinary disorders	Chromaturia	rare
	Dysuria	not known
General and Administration Site Conditions	Asthenia	uncommon
	Mucosal inflammation	rare
	Pyrexia	rare
	Injection site reaction	not known
	Malaise	not known
	Face oedema	not known
	Oedema peripheral	not known
	Chest pain	not known
Chills	not known	
Investigations	Hepatic enzyme increased	not known

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme.

4.8 Overdose

Symptoms

In cases of overdose in adults, the clinical symptoms are usually limited to nausea, vomiting and neurotoxic effects, including ataxia, slight disorientation, confusion, seizures and peripheral neuropathy.

Treatment

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

5. Pharmacological properties

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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

and

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:

$S \leq 4 \text{ mg/l}$ and $R > 4 \text{ mg/l}$

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.

<i>Categories</i>
<u>SUSCEPTIBLE</u>
<i>Gram negative aerobes</i>
<i>Helicobacter pylori</i>
<i>Anaerobes</i>
<i>Bacteroides fragilis</i>
<i>Bifidobacterium</i> >> resistant (70%)
<i>Bilophila</i>
<i>Clostridium</i>
<i>Clostridium difficile</i>
<i>Clostridium perfringens</i>
<i>Eubacterium</i>
<i>Fusobacterium</i>
<i>Peptostreptococcus</i>

<i>Prevotella</i>
<i>Porphyromonas</i>
<i>Veillonella</i>
<u>RESISTANT</u>
<i>Gram positive aerobes</i>
<i>Actinomyces</i>
<i>Anaerobes</i>
<i>Mobiluncus</i>
<i>Propionibacterium acnes</i>
<u>ANTIPARASITIC ACTIVITY</u>
<i>Entamoeba histolytica</i>
<i>Giardia intestinalis</i>
<i>Trichomonas vaginalis</i>

Cross-resistance with tinidazole 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 injection. 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 compared to patients with renal impairment.

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 in 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.

Daily peroral metronidazole at 5-times the maximum human daily dose for greater than 4 weeks caused testicular toxicity and infertility in male rats. Fertility was restored in most subjects by 8 weeks after cessation of treatment, whereas the lower testicular and epididymal weights and sperm counts had improved but were still observed.

Daily peroral metronidazole at approximately 6-times the maximum human daily dose for ≥ 2 weeks caused testicular toxicity in male mice. Most indices of testicular toxicity were restored within 2 months after cessation of treatment, whereas the lower testicular and epididymal weights had improved but were still observed.

These studies demonstrate that the adverse effects of metronidazole on the male reproductive system are wholly or partially reversible after treatment withdrawal.

6. Pharmaceutical particulars

6.1 Incompatibilities

Do not use equipment containing aluminum (e.g., needles, cannulae) that would come in contact with the drug solution as precipitates may form.

Metronidazole is incompatible with (includes but is not limited to):

- Aztreonam
- Cefamandole nafate
- Cefoxitin
- Penicillin G

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

100ml LDPE bottle

7. APPLICANT/MANUFACTURER

Applicant name: TEKA PHARMACEUTICAL COMPANY LIMITED

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