METRIS

Metronidazole Injection USP (0.5% w/v)

1. COMPOSITION

Active Ingredient:

Each 100 ml contains:

Metronidazole USP……500 mg

Excipients:

Sodium Chloride BP, Citric Acid Monohydrate BP, Anhydrous Disodium Hydrogen Phosphate BP and Water for Injections BP

2. PRODUCT DESCRIPTION

Metris is available as 100 mL Nipple Head Plastic Bottle & Eurohead Plastic Bottle.

It is an almost colourless to pale yellow solution, free from visible particles.

3. INDICATION

Metronidazole Injection USP (0.5 % w/v) is indicated in adults and children when oral medication is not possible for the following indications:

- For anaerobic bacteria infection especially Bacteroides fragilis and other species of bacteroides, Fusobacteria, Eubacteria, Clostridia and anaerobic cocci
- For the treatment of septicaemia, bacteremia, brain abscess, necrotizing pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulites, peritonitis and postoperative anaerobic infection
- Prevention of postoperative infections due to anaerobic bacteria particularly species of bacteroides and anaerobic streptococcus

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

4. RECOMMENDED DOSE AND ROUTE OF ADMINISTRATION

General Dosage Recommendations

Adults and Children (>12 years)

- Intravenous infusion of metronidazole 500 mg every 8 hours (infusion rate: 5 mL/min)
- Metronidazole can be administered alone or in combination with other antibacterial agents (given separately)
- It should be substituted by oral metronidazole 400 mg 3 times daily for 7 days as soon as feasible

Children (<12 years)

- Intravenous infusion of metronidazole 7.5 mg/kg body weight (1.5 mL) or by oral 7.5 mg/kg body weight every 8 hours

Prophylaxis

Adults and Children (>12 years)

- Intravenous infusion of metronidazole 500 mg before operation and continued every 8 hours until oral dose is obtainable. The oral dose of metronidazole is 200 - 400 mg 3 times daily for 7 days

Children (<12 years)

- Intravenous infusion of metronidazole 7.5 mg/kg body weight (1.5 mL) or by oral 3.7 - 7.5 mg/kg body weight every 8 hours

Special Populations
Elderly

- Dosage adjustment may be necessary
- Plasma metronidazole levels should be monitored

Hepatic Impairment

- Reduce doses below those usually recommended
- Monitor plasma metronidazole levels and observe for toxicity

Renal Impairment

- Dose adjustment is no necessary in patients with mild to moderate renal function impairment.
- Do not specifically reduce the dose in anuric patients, since accumulated metabolites may be rapidly removed by dialysis
- Unchanged drug and its metabolites are removed during haemodialysis and a further dose of metronidazole should be given after haemodialysis to replace the loss

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

Route of Administration
Metronidazole Injection USP (0.5 % w/v) 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

5. CONTRAINDICATIONS

Hypersensitivity to the active substance, to other imidazole derivatives or to any of the excipients.

6. WARNINGS AND PRECAUTIONS

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. 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

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 14.19 mmol (325 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 72hours after taking metronidazole because of a disulfram-like effect (abdominal cramps, nausea, headaches, flushing, vomiting and 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:
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).

7. PREGNANT AND LACTATION

Pregnancy
Metronidazole crosses the placental barrier.
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.

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.

8. EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

No studies have been performed following intravenous treatment with Metronidazole on the ability to drive and use machines. Some adverse reactions to metronidazole such as seizure, dizziness, optic neuropathy, may impair the ability to drive or operate machines.
Therefore it is recommended that patients should not drive or use machines.

9. INTERACTIONS WITH OTHER MEDICAMENTS

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 disulfram-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.

10. SIDE EFFECTS

The following adverse reactions have been reported with Metronidazole, listed by MedDRA System Organ Class (SOC), Preferred Term and frequency.

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

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

11. SYMPTOMS AND TREATMENT OF 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 neurophathy.

Treatment

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

12. PHARMACODYNAMIC PROPERTIES (INCLUDING ATC):

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: J01XD0

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.

13. 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 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.

14. INSTRUCTIONS FOR USE

1. Do not use if leaks are found and return for replacement.
2. Bring the injection bottle to room temperature or preferably to 37° C just before use.
3. Clean the spout of injection bottle with surgical spirit.
4. Keep the bottle on a table or on a hard surface and insert the cannula of the sterile infusion set into the spout of injection bottle (please note that the cannula of the infusion set should be inserted fully and not half way into the spout of the Metris bottle to avoid leakage.)
5. For administration hold the bottle upside down.
6. Inject intravenously slowly at a rate of about 5 ml/minute.
7. To admit air, insert a sterile injection cannula on the top of the inverted bottle anywhere above the level of the liquid.
8. Admixture of 10.0% Glucose, Penicillin G. Potassium and Ringer Lactate Solution to Metris is contraindicated because of chemical incompatibility.

15. PACKAGING SIZE

100 mL in Nipplehead Plastic Bottle & Eurohead Plastic Bottle.

16. STORAGE CONDITION

Store below 30^0C, protected from light. Do not freeze.

For Single use only.

17. DATE OF REVISION OF TEXT

17th June 2020

18. MANUFACTURER

Otsuka Pharmaceutical India Private Limited
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