SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Metronidazole 5mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 5mg of Metronidazole

Each 100ml of solution contains 500mg of Metronidazole

This product contains 318mg Sodium per 100ml bag.

For a full list of excipients see 6.1

3 PHARMACEUTICAL FORM

Solution for Infusion

A clear, slightly greenish yellow solution for intravenous infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metronidazole is indicated for the treatment of the following infections caused by metronidazole susceptible anaerobic micro-organisms in adults and children (see sections 4.4 and 5.1)

- The prophylaxis of postoperative infections where anaerobic bacteria are expected to be causative pathogens.
- The treatment of peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, and post-operative wound infections

Treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

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

4.2 Posology and method of administration

Prophylaxis of postoperative infections caused by anaerobic bacteria

Primarily in the context of abdominal (especially colorectal) and gynaecological surgery.

Antibiotic prophylaxis duration should be short and limited to the peri-operative period.

Adults:

500mg 1-2 hours before surgery, repeated after 8 and 16 hours. Oral medication should be substituted as soon as feasible.

Children:

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

Newborn 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.

Adults:

500mg every 8 hours.

Children >8 weeks to 12 years of age:

A single dose of 20 to 30mg/kg/day or alternatively divided into 3 doses of 7.5 mg/kg given every 8 hours. The daily dose may be increased to 40mg/kg. depending on the severity of the infection.

New-borns and Infants less than 8 weeks of age:

A single dose of 15 mg/kg of body weight daily or divided into 2 doses of 7.5 mg/kg every 12 hours.

Pre-Term Newborn Infants with a gestational age less than 40 weeks:

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.

Patients with renal failure (see section 4.4)

Limited data are available in this population. These data do not indicate the need for dose reduction. (see section 5.2.)

In patients undergoing haemodialysis metronidazole and metabolites are efficiently removed during an eight hour period of dialysis. Metronidazole should therefore be re-administered immediately after haemodialysis.

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.

Patients with severe hepatic insufficiency

A reduction of the daily dose in patients with severe hepatic impairment will be necessary. In patients with hepatic encephalopathy the daily dosage should be reduced to one third and may be administered once daily (see section 4.4)

Duration of Treatment (see section 4.3 and 5.3)

Usual treatment duration is 7 days (see sections 4.4 and 5.3).

Method of administration (see section 6.6)

Metronidazole 500mg/100ml Intravenous 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.

Metronidazole 500mg/100ml Intravenous Infusion is for single use only (see section 6.6)

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Metronidazole is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Liver disease:

In patients with severe liver damage, metronida-zole should only be used if its expected benefits clearly outweigh potential hazards.

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of Metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Significant accumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Metronidazole should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

Central Nervous System disease:

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system disease due to the risk of neurological aggravation.

Convulsive seizures, myoclonus and peripheral neuropathy, the latter mainly characterized by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurological signs demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

Renal Disease:

The elimination half-life of metronidazole remains unchanged in the presence of renal failure. Therefore the dosage of metronidazole needs no reduction. Such patients however retain the metabolites of metronidazole. The clinical significance of this is not known at present.

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). See Section 4.5.

Intensive or prolonged Metronidazole therapy:

The duration of therapy with i.v Metronidazole or other imidazole derivatives is usually 7 days and should generally not exceed 10 days. This period may be exceeded in individual cases only after a very careful benefit-risk assessment. Metronidazole and a metabolite have been shown to be mutagenic in some tests with non mammalian cells an increase of certain tumors was noted in animal experiments. Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction.

Regular clinical and laboratory monitoring (including full blood count) 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. Patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures). These effects are normally 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.

General:

Patients should be warned that Metronidazole may darken urine.

Aspartate amino transferase assays may give spuriously low values in patients being treated with metronidzole depending on the method used.

This medicinal product contains 318mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

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 have been reported when metronidazole has been used with the warfarin type of anticouagulants. Prothrombin time should be monitored more frequently and the dose of oral anticoagulants adjusted

5 Fluoro-uracile:

Increase in the toxicity of 5 fluoro-uracile due to a decrease of its clearance.

Busulfan:

Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity. Fatal cases have been reported. Therefore, this combination should be avoided.

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.

Phenytoin

Concomitant administration of phenytoin and Metronidazole may affect the metabolism of Metronidazole.

Cimetidine

Cimetidine may reduce the elimination of metronidazole and subsequently lead to increased metronidazole concentrations in serum.

Ciclosporine:

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.

Carbamazepine

Metronidazole may inhibit the metabolism of carbamazepine and raise the plasma concentrations as a consequence.

Tacrolimus

Concomitant administration with metronidazole leads to increased blood concentrations of tacrolimus. The inhibition of hepatic metabolism of tacrolimus via CYP-450 3A4 is suspected. Frequent monitoring of tacrolimus blood levels and renal function is required particularly at the initiation or the end of the therapy with metronidazole in patients who are stabilized on their tacrolimus regimen.

Amiodarone

Prolongation of the QT-interval and Torsade de pointes has been reported during concomitant treatment with metronidazole and amiodarone. It is recommended to monitor the QT-interval on the ECG in patients receiving this combination therapy. Patients treated on an outpatient basis should be advised to contact immediately the doctor if symptoms of Torsade de pointes occur such as dizziness, palpitations, and syncope.

Mycophenolat mophetil

Substances that alter the gastrointestinal flora (e.g., antibiotics) may reduce the oral bioavailability of mycophenolic acid products. Close clinical and laboratory monitoring for evidence of diminished immunosuppressive effect of mycophenolic acid is recommended during concomitant therapy with anti-infective agents.

Contraceptive drugs

Some antibiotics can, in exceptional cases, decrease the effect of contraceptive pills by interfering with the bacterial hydrolysis of steroid conjugates in the intestine and hereby reduce the re-absorption of unconjugated steroid. Therefore the plasma levels of the active steroid decrease. This unusual interaction can occur in women with a high excretion of steroid conjugates through the bile. About 60 pregnancies have reported in English women using contraceptive pills that concomitantly have taken antibiotics, e.g. ampicillin, amoxicillin and tetracyclines. There are negative studies for trimetoprim-sulpha, roxitromycin and clarithromycin but the amount of data is very small.

Laboratory tests:

Metronidazole may immobilize Treponema and thus may lead to falsely positive Nelson's test. Aspartate amino transferase assays may give spuriously low values in patients being treated with metronidazole depending on the method used.

4.6 Fertility, Pregnancy and lactation

Fertility

Reproduction studies have been performed in rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the fetus following treatment with metronidazole.

However higher doses of metronidazole (about 30 times higher than the maximum oral human dose) caused infertility and marked testicular toxicity in mice and rats.

Pregnancy

Clinical data on a large number of exposed pregnancies and animal data did not show a teratogenic or fetotoxic 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.

Lactation

Metronidazole is excreted in breast milk. Breastfeeding should be stopped if treatment with Metronidazole is necessary.

After the end of the therapy with metronidazole, breastfeeding should not be resumed before another 2 – 3 days because of the prolonged elimination period of metronidazole.

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.

4.8 Undesirable effects

Adverse effects occur mainly at high doses or during prolonged treatment. The most commonly observed adverse effects include nausea, perverted taste and the risk of development of neuropathies during prolonged use.

In assessing side effects, the following convention has been used for classifying frequency:

Very common	:	≥1/10
Common	:	≥1/100 to <1/10
Uncommon	:	≥1/1,000 to <1/100
Rare	:	≥1/10,000 to <1/1,000
Very rare	:	<1/10,000
Not known	:	cannot be estimated from the available data

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

	Rare	Very Rare	Not Known
Blood and lymphatic system disorders:		agranulocytosis, neutropenia, thrombocytopenia, pancytopenia	leucopenia
Immune system disorders:	anaphylaxis		angiodema, urticaria, fever.
Metabolism and nutrition disorders:			anorexia
Psychiatric disorders:		psychotic disorders, including confusion and hallucinations.	depressed mood

Nervous system disorders:		encephalopathy (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug. drowsiness, dizziness, convulsions, headaches	during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced. Aseptic Meningitis
Eye disorders:		vision disorders such as diplopia and myopia, which, in most cases, is transient.	optic neuropathy / neuritis
Gastrointestinal disorders:			taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea.
Hepatobiliary disorders:		abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis which is reversible on drug withdrawal.	
Skin and subcutaneous tissue disorders:		skin rashes, pustular eruptions, pruritis, flushing	erythema multiforme.
Musculoskeletal, connective tissue and bone disorders:		myalgia, arthralgia.	
Renal and urinary		darkening of urine	

disorders:		(due to metronidazole metabolite).	

4.9 Overdose

Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. The clinical symptoms were usually limited to nausea, vomiting, ataxia and slight disorientation

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti bacterials for systemic use: imidazole derivatives

ATC Code: J01XD01

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.

PK/PD relationship

Metronidazole acts in a concentration dependent manner.

Mechanism of action

Metronidazole is taken up into bacterial and human cells. Under anaerobic conditions, metronidazole is converted to reduction products that interact with DNA to cause destruction of helical DNA leading to a protein synthesis inhibition and cell death in susceptible organisms.

Breakpoints

European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints for MIC testing are presented below. EUCAST clinical MIC breakpoints for metronidazole (2011-01-05, v 3.1)

Organism	Susceptible (S) (mg/l)	Resistant (R) (mg/l)
Gram positive anaerobes, except Cl.difficile	≤ 4	>4
Gram negative anaerobes	≤ 4	>4
Clostridium	≤ 1	> 1

difficile		
Non-species related breakpoint	IE	IE

*Insufficient evidence

The prevalence of acquired resistance may vary geographically and with time for selected species and local information is desirable, particularly when treating severe infections.

As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

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 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.

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 evidence of carcinogenicity in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Citric acid monohydrate

Sodium dihydrogen phosphate dihydrate

Sodium hydroxide

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 Years

6.4 Special precautions for storage

Keep container in the outer carton in order to protect from light. Store below 25 ° C. Do not freeze.

6.5 Nature and contents of container

Polycine infusion bags fitted with a polypropylene SFC (Single Function Connection) port. The port is sealed with a synthetic isoprene rubber stopper and a polypropylene snap-cap.

The infusion bags are contained in a clear plastic or aluminium overpouch.

Pack sizes

100 ml bags (500 mg metronidazole) in packs of 5, 10 or 30 bags

6.6 Special precautions for disposal

Use only if the solution is clear, without visible particles and if the container is undamaged. Administer immediately following the insertion of infusion set.

Do not remove unit from overpouch until ready for use.

The inner bag maintains the sterility of the product.

Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of the fluid from the secondary container is completed.

The solution should be administered with sterile equipment using an aseptic technique. The equipment should be primed with the solution in order to prevent air entering the system.

In patients maintained on intravenous fluids, Metronidazole 500mg/100ml Intravenous Infusion may be diluted with appropriate volumes of 0.9% sodium chloride solution, dextrose 5% - 0.9% sodium chloride solution, dextrose 5% w/v or potassium chloride infusions (20 and 40 mmol/litre).

Using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In the case of adverse reaction, infusion must be stopped immediately.

The product should be used immediately after opening.

Discard after single use.

Discard any unused portion.

Do not reconnect partially used bags.

7 MARKETING AUTHORISATION HOLDER

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UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/1466

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