SECTION 2: SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

Metronidazole

5 mg/ml 100 ml Intravenous Infusion

Metronidazole

1. NAME OF THE MEDICINAL PRODUCT

Metronidazole 5 mg/ml 100 ml Intravenous Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 bottle or polymeric container of 100 ml contains 500 mg metronidazole

1 ml contains 5 mg metronidazole.

Excipient with known effect:

Sodium chloride

Water for Injections

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear, almost colourless to pale yellow solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Treatment of anaerobic bacterial infections:

- intra-abdominal infections, including peritonitis, intra-abdominal abscess and liver abscess, caused by *Bacteroides* species including the B. fragilis group (*B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus*), *Clostridium* species, *Eubacterium* species, *Peptococcus* species and *Peptostreptococcus* species
- skin and skin structure infections caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species and *Fusobacterium* species
- gynecologic infections, including endometritis, endomyometritis, tubo-ovarian abscess and postsurgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species and *Fusobacterium* species

- bacterial septicemia caused by *Bacteroide*s species including the *B. fragilis* group and *Clostridium* species
- bone and joint infections, as adjunctive therapy, caused by *Bacteroides* species including the *B. fragilis* group
- central nervous system (CNS) infections, including meningitis and brain abscess, caused by *Bacteroides* species including the *B. fragilis* group
- lower respiratory tract infections, including pneumonia, empyema and lung abscess, caused by *Bacteroides* species including the *B. fragilis* group
- endocarditis caused by *Bacteroides* species including the *B. fragilis* group.

In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to Metronidazole.

- 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.

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

4.2. Posology and method of administration

Treatment of anaerobic bacterial infections

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

Adults: 1000 mg – 1500 mg daily as a single dose or alternatively 500 mg every 8 hours. A maximum of 4 g should not be exceeded during a 24-hour period.

Children > 8 weeks to 12 years of age: The usual daily dose is 20-30 mg/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.

Parenteral therapy may be changed to oral metronidazole when conditions warrant, based upon the severity of the disease and the response of the patient to Metronidazole 5 mg/ml 100 ml Intravenous Infusion. Oral medication should be substituted as soon as feasible at the same dose regimen.

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.

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 infusion of single dose of 1000 mg – 1500 mg, 30-60 minutes preoperatively or alternatively 500mg immediately before, during or after operation, then 500 mg 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.

Amoebiasis

Adults: 1500 mg per day (500 mg every 8 hours) for 5-10 days. In hepatic amoebiasis, at the abscess stage, the abscess must be evacuated concomitantly with metronidazole treatment.

Children: 35 to 50 mg/kg daily in 3 divided doses for 5 to 10 days. A maximum of 2400 mg/day must not be exceeded. In hepatic amoebiasis, at the abscess stage, the abscess must be evacuated concomitantly with metronidazole treatment.

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 hemodialysis, Metronidazole should be re-administered immediately after hemodialysis

Patients with advanced hepatic insufficiency: For patients with severe hepatic impairment (Child-Pugh C), the metronidazole dose should be reduced by 50 %. Serum level monitoring of metronidazole may be required.

Method of administration

Metronidazole 5 mg/ml 100 ml Intravenous Infusion should be infused intravenously at an approximate rate of 5 ml/minute (or one bottle infused over 20 to 60 minutes).

4.3. Contraindications

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

4.4. Special warnings and precautions for use

Liver disease:

Caution is needed in patients with severe hepatic impairment. Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of Metronidazole clearance may occur in the presence of advanced hepatic insufficiency. 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 (CNS) disease

Metronidazole should be used with caution in patients with active disease of CNS. 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 paresthesia and epilepsy. Caution is required in patients with 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 hemodialysis 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 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

As a rule, the usual duration of therapy with intravenous 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 paresthesia, 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:

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: 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

Warfarin and other oral anticoagulants: Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. Patients taking metronidazole and warfarin or other oral coumarins concomitantly should have their prothrombin time and international normalized ratio (INR) monitored more frequently.

Vecuronium (non depolarising curaremimetic): Metronidazole can potentialise the effects of vecuronium.

Combinations to be considered

5 Fluoro-uracile: 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.

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 immobilize 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 fetotoxic effect. However unrestricted administration of 5-nitroimidazole antibiotics 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 (see section 5.3).

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. Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8. Undesirable effects

a. *Summary of the safety profile*

Serious adverse reactions occur rarely with standard recommended regimens. 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.

b. *Tabulated list of adverse reactions*

For estimation of development frequency of side effects the following criteria are used: very common (≥1/10), common (from ≥1/100 to <1/10), uncommon (from ≥1/1,000 to <1/100), rare (from ≥1/10,000 to <1/1,000), very rare (from <1/10,000 including individual case safety report), and "the frequency is not known" (according to the available data, it is not possible to estimate the frequency).

System Organ Class (SOC)	Preferred MedDRA Term	Frequency
Blood and Lymphatic System Disorders	Leukopenia Agranulocytosis Pancytopenia Neutropenia Thrombocytopenia	not known very rare very rare very rare very rare
Immune System Disorder	Anaphylaxis Angiodema Urticaria Fever Anaphylactic shock	rare not known not known not known not known
Metabolism and Nutrition Disorders	Anorexia	not known
Psychiatric Disorders	Psychotic disorders, including confusion and hallucinations Depression Confusional state Insomnia	very rare not known not known not known

Nervous System Disorders	Encephalopathy (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck)	very rare
	Subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug.	very rare
	Drowsiness	very rare
	Dizziness	very rare
	Convulsions	very rare
	Headaches	very rare
	Peripheral sensory neuropathy[§]	not know
	Transient epileptiform seizures	not know
	Aseptic meningitis	not know
Eye Disorders	Diplopia[§§]	very rare
	Myopia[§§]	very rare
	Optic neuropathy/neuritis	not known
Ear and labyrinth disorders	Hearing impaired/hearing loss (including sensorineural)	not known
	Tinnitus	not known
Gastrointestinal Disorders	Taste disorders	not known
	Oral mucositis	not known
	Furred tongue	not known
	Nausea	not known
	Vomiting	not known
	Gastro-intestinal disturbances such as epigastric pain and diarrhea	not known
	Pancreatitis	not known
Hepatobiliary disorders	Cholestatic or mixed hepatitis	very rare
	Hepatocellular liver injury	very rare
	Jaundice	very rare
	Liver failure[&]	not known
Skin and Subcutaneous Disorders	Skin rashes	very rare
	Pustular eruptions	very rare
	Acute generalised exathematous pustulosis	very rare
	Pruritis	very rare
	Flushing	very rare
	Erythema multiforme	not known
	Stevens-johnson syndrome	not known
	Toxic epidermal necrolysis	not known
	Fixed drug eruption	not known
	Urticaria	not known

Musculoskeletal and Connective Tissue Disorders	Myalgia Arthralgia	very rare not known
Renal and urinary disorders	Darkening of urine Dysuria	very rare not known
General and Administration Site Conditions	Asthenia Pyrexia Injection site reaction Malaise Face edema Edema peripheral Chest pain Chills	rare very rare not known not known not known not known not known not known
Investigations	Hepatic enzyme increased (AST, ALT, alkaline phosphatase)	very rare

§ In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.

§§ Vision disorders such as diplopia and myopia, which, in most cases, are transient.

& Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

c. *Reporting of suspected adverse reactions.* Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

To report any side effect(s):

- _____:

- _____

Fax: _____

Call _____ at _____, Exts: _____.

Toll free phone: _____

E-mail____@_____

Website: _____

Please contact the relevant competent authority.

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. PHARMACODYNAMIC 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.

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*.

Mechanism of Action

Metronidazole, a nitroimidazole, exerts antibacterial effects in an anaerobic environment against most obligate anaerobes. Once metronidazole enters the organism by passive diffusion and is activated in the cytoplasm of susceptible anaerobic bacteria, it is reduced; this process includes intra-cellular electron transport proteins such as ferredoxin, transfer of an electron to the nitro group of the metronidazole, and formation of a short-lived nitroso free radical. Because of this alteration of the metronidazole molecule, a concentration gradient is created and maintained which promotes the drug's intracellular transport. The reduced form of metronidazole and free radicals can interact with DNA leading to inhibition of DNA synthesis and DNA degradation leading to death of bacteria. The precise mechanism of action of metronidazole is unclear.

Mechanism of resistance

A potential for development of resistance exists against metronidazole.

Resistance may be due to multiple mechanisms that include decreased uptake of the drug, altered reduction efficiency, overexpression of the efflux pumps, inactivation of the drug, and/or increased DNA damage repair.

Metronidazole does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

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.

SUSCEPTIBLE
Gram negative aerobes
Helicobacter pylori
Anaerobes
Bacteroides fragilis group *(B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B.vulgatus)*
Bifidobacterium (70% strains are resistant)
Bilophila
Clostridium
Clostridium difficile
Clostridium perfringens
Eubacterium
Fusobacterium
Peptococcus
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 approximately 14 – 18 μg/ml are reached at the end of a 20 minute infusion. 2-hydroxy-metabolite peak plasma concentrations of approximately 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 metabolized 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 (approximately 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. Metronidazole is eliminated from plasma with a mean half-life of approximately 8 hours. The half-life of 2-hydroxy-metabolite is approximately 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 hemodialysis, Metronidazole is rapidly excreted and the plasma elimination half-life is decreased to approximately 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 approximately 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 has shown mutagenic activity in in vitro assay systems including the Ames test. Studies in mammals in vivo have failed to demonstrate a potential for genetic damage.

Metronidazole failed to produce any adverse effects on fertility or testicular function in male rats at doses up to 400 mg/kg/day (approximately 2 times the maximum recommended daily dose based on body surface area comparison) for 28 days. Fertility studies have been performed in male mice at doses up to six times the maximum recommended human dose and have revealed no evidence of impaired fertility.

Although metronidazole has been shown to be carcinogenic in certain species of mice following chronic oral administration, 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.

5. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride

Water for Injections

6.2. Incompatibilities

Metronidazole 5 mg/ml solution for Infusion should not be mixed with cefamandole nafate, cefoxitin sodium, penicillin G potassium.

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

In the absence of compatibility studies, 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

Do not store above 30°C/

Keep bottle or polymeric container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Metronidazole 5 mg/ml 100 ml Intravenous Infusion:

Colorless 100 ml glass bottles with a rubber stopper, or 100 mg polymeric container with one or two tubing ports.

The bottle or polymeric container is available in packs of 1 bottle (container) and in multipacks containing 12 bottles(containers).

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Use only if the solution is clear, without visible particles. Do not use if there are any visible particulate matter or if the solution is cloudy. Administer immediately following the insertion of infusion set.

Discard any unused portion. Do not reconnect partially used bottle.

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 5 mg/ml 100 ml Intravenous Infusion may be diluted with appropriate volumes of the following solutions:

- 0.9% sodium chloride Injection
- 5% dextrose Injection
- 5% dextrose and 0.9% sodium chloride Injection
- potassium chloride infusions (20 and 40 mmol/l).

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 solution should be visually inspected prior to use. It must only be used if the solution is clear, almost colorless to pale yellow solution, practically free from particles.

7. Marketing authorization holder

“KRASPHARMA” OJSC

Russia, 660042, 60 let Oktyabrya st. 2, Krasnoyarsk

Tel.: +7 (391) 261-25-90. Fax: +7 (391) 261-17-44

8. Marketing authorization number(s)

Metronidazole 5 mg/ml 100 ml Intravenous Infusion _____

9. Date of first Authorisation/ renewal of the authorisation

_____.

10. Date of revision of the text

_____.