SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metronidazole Fresenius 500 mg/100 ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 5 mg metronidazole.
Each 100 ml vial contains 500 mg metronidazole.

Excipients:
Each ml contains 0.135 mmol (3.10 mg) of sodium.
100 ml contains 13.5 mmol (310 mg) of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion
Clear solution
The solution is iso-osmotic and its pH is between 4.8 and 5.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of infection which are or may be due to anerobic bacteria, especially Bacteriodes species, including Bacteriodes fragilis, Fusobacterium, Eurobacterium and Clostridium species.

The treatment is effective in cases of:

- Infections of the C.N.S (e.g. brain abscess, meningitis),
- Infections of the lung and pleura (e.g. necrotising pneumonia, aspiration pneumonia, lung abscess),
- Endocarditis,
- After operations (e.g. recto-colonic surgery) and infections of the G.I. tract,
- Suppurating diseases in the abdominal and pelvic area (peritonitis, liver abscess, endometritis),
- Gynaecologic infections (e.g. hysterectomy, caesarean section, childbed fever, septic abortus),
- Osteomyelitis,
- Septicaemia in thrombophlebitis,
- Severe form of intestinal and hepatic amoebiasis.
- A prophylactic use is always indicated in operations with a high risk of anaerobic infections (gynaecologic and intra-abdominal operations).

Consideration should be given to official guidance on the appropriate use of antibacterial agents in the application of Metronidazole Fresenius.

4.2 Posology and method of administration

The dose of metronidazole is dependent on the type and the severity of the infection, the age and the body weight of the patient, and the clinical response.

Unless prescribed otherwise, the following dose recommendations are applicable:

Adults and adolescents over 12 years of age

Maintenance dose:
Approximately 7.5 mg Metronidazole/kg body weight over one hour every 8 hours, corresponding to 100 ml
(500 mg) Metronidazole injection for a 70 Kg adult.
Loading dose: 15 mg/kg infused over one hour (appro- ximately 1 g for 70 kg adult): A maximum of 1.4 g should not be exceeded during 24 hours.

Safety and effectiveness in children have not been established.

In renal insufficiency the dose interval is to be extended to 12 hours.

In severe hepatic disease plasma metronidazole levels have to be monitored. The usually recommended dose may eventually have to be reduced.

Method of administration

Intravenous use.

The contents of 1 bottle are to be infused slowly I. V., i.e. 100 ml max. in 20 minutes but usually in 60 minutes.
For preventive therapy prior to operations it is recommended to administer the single dose unit of 500 mg shortly before starting operation.

A concomitant intravenous administration of suitable antibiotics which have to be administered separately is possible.

Duration of administration

Treatment with Metronidazole Fresenius should not exceed 10 days.
However, in special, well-founded cases the treatment may be extended.
Repeat therapy should be restricted as much as possible and to specific elective cases only. This limitation must be strictly observed because the possibility of metronidazole developing mutagenic and carcinogenic activity cannot be safely excluded.
Prophylactic use should be discontinued within 12 hours after surgery. If there are signs of infection, obtain specimens for cultures to identify the causative organisms.

4.3 Contraindications

Metronidazole Fresenius must not be used in patients with hypersensitivity to metronidazole or other nitroimidazole derivatives or any of the excipients of the medicinal product.

4.4 Special warnings and precautions for use

Metronidazole has no direct activity against aerobic or facultative anaerobic bacteria.

Regular clinical and laboratory monitoring are advised if administration of Metronidazole Fresenius for more than 10 days is considered to be necessary.

There is a possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might persist.

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

In patients undergoing haemodialysis metronidazole and metabolites are efficiently removed during an 8 hour period of dialysis. Therefore, Metronidazole Fresenius should be re-administered immediately after haemodialysis. No routine adjustment in the dosage of Metronidazole Fresenius needs to be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Significant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Therefore, Metronidazole Fresenius should be administered with caution to patients with hepatic impairment (see section 4.2).

In case of severe hepatic failure and impairment of the haematopoiesis, e.g. granulozytopenia, Metronidazole Fresenius should be used only in case of a positive benefit-risk assessment.

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.

During the treatment with metronidazole occasionally leucopenia, granulocytopenia, and in very rare cases agranulocytosis and thrombocytosis can occur. Therefore, regular controls of blood count are advised in case of a longer treatment with metronidazole.

Metronidazole Fresenius should be used with caution in patients with active or severe chronic disease of the PNS and CNS. There are isolated reports about the occurrence of seizures and peripheral neuropathies, mainly numbness and paraesthesia of the limbs, during the treatment with metronidazole. In very rare cases, especially in long-term therapy with metronidazole in high dosages, structural cerebellar lesions with respective symptoms (see section 4.8) could be seen in MRI; cessation of metronidazole treatment usually results in relief of the symptoms and resolution of the structural lesions. In the evidence of neurological disorders, the benefit-risk ratio has to be reassessed immediately with respect to the continuation of the metronidazole therapy.

In case of severe hypersensitivity reactions, e.g. anaphylactic shock, the administration of Metronidazole Fresenius has to be stopped immediately and the usual emergency measures have to be initiated by appropriate qualified personnel.

Severe and persistent persistent diarrhoea occurring during the treatment with Metronidazole Fresenius or in the subsequent weeks can be caused by pseudomembranous enterocolitis (in

most cases by *Clostridium difficile*) which can be life-threatening (see section 4.8). In this case the treatment with Metronidazole Fresenius has to be abandoned immediately and an adequate treatment has to be initiated. Medicinal products inhibiting peristalsis have to be avoided

This medicinal product contains 13.5 mmol (310 mg) of sodium per 100 ml of solution. This should be taken into account in patients on a controlled sodium diet and in cases where fluid restriction is required.

4.5 Interaction with other medicinal products and other forms of interaction

Cumarin derivates

In patients receiving anticoagulants of the warfarin type, the dosage of the anticoagulants has to be adjusted accordingly as metronidazole intensify the inhibition of blood coagulation. There is no interaction with heparin.

Alcohol

Alcohol beverages should not be consumed during metronidazole therapy because hypersensitivity reactions like erythema on the head and neck, nausea, vomiting, headaches and giddiness (disulfiram-like reactions) may occur.

Disulfiram

Administration of disulfiram and metronidazole has been associated with psychoses and confusion.

Lithium

Caution is advisable in case of administration of lithium containing medicinal products because an increase of serum lithium concentrations has been reported resulting in signs of lithium toxicity (tremor, convulsions). Lithium retention is accompanied by evidence of possible renal damage. Therefore, 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

Concomitant administration of barbiturates (hexobarbital or phenobarbital) containing medicinal products induces a reduction in the effectiveness of metronidazole by shortening the elimination half-life to approximately 3 hours.

Phenytoin

Metronidazole inhibits the metabolism of concomitantly administered phenytoin whereby the plasma concentration of phenytoin is increased. Simultaneously, phenytoin is decreasing the effectiveness of metronidazole.

Cimetidin

In single cases cimetidine containing medicinal products may impair the elimination of metronidazole with an increase in the blood levels of metronidazole.

Fluorouracil

Metronidazole reduces the clearance of 5 fluorouracil and can therefore result in increased toxicity of 5 fluorouracil.

Ciclosporin

Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Busulfan
Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

Carbamazepine
Metronidazole inhibits the metabolism of carbamazepine which leads to an increase of the plasma concentration of carbamazepine.

Tacrolimus
Simultaneous administration of metronidazole results in an increase of the tacrolimus plasma level which has to be controlled frequently as well as the renal function, especially at the beginning and at the end of a metronidazole treatment in patients who are adjusted to a definite tacrolimus medication.

Amiodarone
Prolongation of QT-intervals and torsade de pointes have been reported when metronidazole and amiodarone were administered concomitantly. Regular ECG controls are recommended. Out-patients are advised to consult their physicians in case of symptoms of torsade de pointes like drowsiness, palpitations, and sycope occur.

Mycophenolate mofetil
Substances like antibiotics which alter the intestinal flora may decrease the oral bioavailability of mycophenol acids. Close monitoring concerning a decrease of the immunosuppressive effects of mycophenol acids is advised when anti-infectives are administered concomitantly.

Other antibiotics
Moderate synergistic response of metronidazole to antibiotics like tetracycline, spiramycin, clindamycin, acylureido-penicillins and rifampicin has been reported.
Nalidixic acid and metronidazole show clear synergistic influence.
Antagonistic effects were not reported. In animal studies (50% effective dose) an antagonism of metronidazole and novobiocin, cephalexin, chloramphenicol, rifampicin, nalidixic acid and cotrimoxazole could not be detected.

Laboratory tests
Metronidazole may interfere with certain types of determinations of serum chemistry values, such as GOT, resulting in decreased values.
Laboratory test interferences (in vitro) have not been reported in case of simultaneous administration of metronidazole and ampicillin, streptomycin, gentamicin or fusidic acid.
AST, ALT, LDH, triglycerides, and glucose assays may give spuriously low values in patients being treated with metronidzole depending on the method used.

4.6 Fertility, pregnancy and lactation

Pregnancy
Although there is no revealed evidence of embryotoxicity or foetotoxicity, Metronidazole Fresenius should only be used during the first trimester of pregnancy in cases of severe life-threatening infections. During the second and third trimester of pregnancy, Metronidazole Fresenius should only be used after careful benefit/risk evaluation.

Lactation
Breast-feeding should be interrupted or treatment with metronidazole should be discontinued.

4.7 Effects on ability to drive and use machines

Metronidazole can alter reactions to such an extent that the ability to drive and operate machines can be impaired. These potential effects like drowsiness, dizziness, confusion, hallucinations, convulsions, or transient visual disorders are increased at the beginning of treatment and in conjunction with alcohol consumption.

4.8 Undesirable effects

Serious adverse reactions occur rarely with standard recommended regimens, rather at high dosages. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.The most frequent undesirable effects are nausea, taste disorders, and the risk of the development of neuropathies in case of long-term treatment. Frequency, type and severity of adverse reactions in children are the same as in adults.
The evaluation of undesirable effects is based on the following definition of 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	Frequency cannot be estimated from the available data

Infections and infestations
Rare: Candida superinfection in the genital area

Blood and lymphatic system disorders
Uncommon: Leukopenia and granulocytopenia, thrombocytopenia
Very rare: Agranulocytosis, aplastic anaemia (in isolated cases)
Blood counts are advised in case of prolonged administration

Immune system disorders
Uncommon: Mild to moderate hypersensitivity reactions like pruritus, urticaria, erythema multiforme, angio-edema, and drug fever
Very rare: Severe acute systemic hypersensitivity reactions: anaphylactic reactions up to anaphylactic shock in extreme cases
Not known: Stevens-Johnson Syndrome, toxic epidermal necrolysis

Metabolism and nutrition disorders
Not known: Anorexia

Psychiatric disorders
Uncommon: Psychotic disorders, including hallucinations, agitation, depression

Nervous system disorders
Uncommon: Headache, dizziness, somnolence, insomnia.
During intensive and/or prolonged metronidazole therapy peripheral sensory neuropathy (e.g. numbness, pain, furriness and tingling sensation in the limbs) and transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.
Very rare: Aseptic meningitis, encephalopathy (e.g. confusion, fever, headache, paralysis, light sensitivity, visual disturbances, movement disturbances, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus, and tremor) which usually resolve after dose reduction or discontinuation of the drug (see section 4.4).

Eye disorders
Uncommon: Visual disturbances, diplopia, myopia
Not known: Oculomotor spasm, optic neuropathy

Gastrointestinal disorders
Uncommon: Nausea, vomiting, diarrhoea, glossitis, stomatitis, bitter eructation, metallic taste, gastrointestinal disturbances, coated tongue.
Very rare: severe and persistent diarrhoea during or after the therapy can be caused by pseudomembranous enterocolitis (in most cases by *Clostridium difficile*) which can be life-threatening (see section 4.4).
Not known: Pancreatitis which is reversible on drug withdrawal.

Hepatobiliary disorders
Uncommon: Hepatic disorders e.g. increased transaminases and bilirubin in serum.
Very rare: Cholestatic hepatitis, jaundice which is reversible on drug withdrawl

Musculoskeletal, connective tissue disorders
Uncommon: Myalgia, arthralgia

Renal and urinary disorders
Uncommon: Darkening of urine (due to metronidazole metabolite)
Rare: Dysuria, cystitis, urinary incontinence.

General disorders and administration site conditions
Common: Phlebitis up to thrombophlebitis.
Uncommon: Sensation of weakness.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/ and emailed to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com.

4.9 Overdose

The risk of overdosage can be excluded in case of proper intravenous infusion and when used in accordance with the recommended dosage instructions. If needed, Metronidazole Fresenius can be effectively eliminated by haemodialysis.
In case of adverse reactions prompt evaluation should be made of the benefit/risk ratio for the continuation of the therapy. If necessary, the treatment with metronidazole should be stopped. Therapy may be continued using another appropriate antibiotic/chemotherapeutic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antibiotics – imidazole derivates

Metronidazole belongs to the group of nitroimidazoles.

ATC Code: J01XD01

Mechanism of action
Metronidazole itself is antimicrobially ineffective. It represents the stable starting compound capable of penetration, from which, under anaerobic conditions, microbial pyruvate-ferrodoxin oxidoreductase forms nitroso-radicals by oxidation of ferredoxin and flavodoxin that then attack the DNA. Nitroso-radicals form adducts with base pairs in the DNA, which leads to DNA strand breaks and consequently to cell death.

Correlation between pharmacokinetics and pharmacodynamics
The efficacy mainly depends on the ratio of maximum serum concentration (Cmax) to minimal inhibitory concentration (MIC) of the pathogen.

Mechanism(s) of resistance
The resistance mechanisms of anaerobic bacteria against metronidazole have only been partially elucidated to date:

- Metronidazole resistant *Bacteroides* strains possess resistance determinants which encode the nitroimidazole reductases that transform nitroimidazoles to aminoimidazoles. This leads to inhibition of the formation of the nitroso-radicals that are responsible for the antibacterial effects.
- The resistance of *Helicobacter pylori* to metronidazole is attributable to mutations in a NADPH nitroreductase encoding gene. These mutations lead to an exchange of amino acids and thus to a loss of function of the enzyme. The activation step from metronidazole to the reactive nitroso-radical is thus omitted.
  There is total cross-resistance between metronidazole and the other nitroimidazole derivates (tinidazole, ornidazole, nimorazole).

Limit values
Testing of metronidazole is conducted using the standard dilution series method. The following minimum inhibitory concentrations have been determined for susceptible and resistant pathogens:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) Version 6.0, valid from 2016-01-01) breakpoints

Organism	Susceptible	Resistant
Clostridium difficile	≤ 2 mg/l	> 2 mg/l
Other Gram-positive anaerobes	≤ 4 mg/l	> 4 mg/l
Helicobacter pylori	≤ 8 mg/l	> 8 mg/l
Gram-negative anaerobes	≤ 4 mg/l	> 4 mg/l

5.2 Pharmacokinetic properties

Metronidazole Fresenius is administered by intravenous infusion. Therefore, the bioavailability is 100%.

Following usual intravenous dosage regimen metronidazole achieves plasma concentrations between 10 µg/ml and 30 µg/ml. These concentrations appear to be sufficient for the antimicrobial effect of the drug.

After intravenous infusion of 600 mg metronidazole over 20 minutes serum concentrations of about 35.2 µg/ml after 1 hour, 33.9 µg/ml after 4 hours and 23.7 µg/ml after 8 hours were achieved.

In human organism different metabolites are formed. The major metabolites are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole (the “hydroxy” metabolite) and 2-methyl-5-nitroimidazole-1-acetic acid (the “acid” metabolite).

Metronidazole is bound to plasma proteins at 10-20%. The elimination half-life of metronidazole is about 8 hours. The apparent distribution volume is about 36 l.

Approximately 80% of metronidazole is excreted in urine. The unchanged metronidazole accounts for less than 10%. Small amounts of about 6% are excreted via the liver. Elimination is only slightly prolonged in patients with impaired renal function. Elimination may be delayed in patients with severe hepatic insufficiency. Half-life may be prolonged in patients with severe hepatic insufficiency (up to 30 hours).

5.3 Preclinical safety data

Acute toxicity

The acute toxicity in mice has been checked foolowing two routes of administration. The oral LD_{50} of metronidazole exceeds 3800 mg/kg body weight. The intraperitoneal LD_{50} of metronidazole exceeds 3950 mg/kg body weight. Therefore, the acute toxicity is very low. The intravenous LD_{50} exceeds 1200 - 1500 mg/kg body weight.

Chronic/Sub-chronic toxicity

Chronic toxicity studies in rats over 26 - 80 weeks did not reveal any adverse reactions. After daily doses of about 300 to 600 mg/kg body weight testis dystrophy and prostatic atrophy were reported. Toxic effects in dogs following a daily dose of 75 mg/kg body weight were ataxia and tremor. In studies in monkeys after a daily dose of 45, 100 or 225 mg/kg body weight over one year, a dose-dependent increase of liver cell degeneration could be observed.

A daily dose of 18 mg/kg body weight is regarded as lowest toxic dose in man after continuous oral administration over 8 weeks. Rare adverse effects are cholestatic hepatosis and peripheral neuropathy.

Genotoxicity and Carcinogenicity

Studies in different rodents revealed a low carcinogenic potential of metronidazole.

Although follow-up studies in humans showed no evidence of an increased carcinogenic risk after administration of metronidazole, there is a theoretical risk caused by the reduced metabolite which is formed by the intestinal flora and detected in very small amounts in urine.

Metronidazole has shown mutagenic activity in several studies in bacteria using different activating systems. Further in vitro and in vivo studies failed to demonstrate a potential for genetic damage.

Increased rates of chromosomal aberrations were observed in lymphocytes in patients receiving metronidazole therapy for a long period.

Reproductive toxicity studies

There was no evidence of teratogenic effects or other fetotoxic effects when metronidazole was administered at a daily dosage of 200 mg/kg body weight to rats or at a daily dosage of 150 mg/kg body weight to rabbits.

Metronidazole is widely distributed into body tissues and readily crosses the placenta. Metronidazole is also distributed into the milk in concentrations of more than 50% of the concurrent serum concentration of the drug.

Safety of treatment with metronidazole in pregnancy is not sufficiently proven. Especially for the use during the first trimester the available data are controversial.

Evidence from some studies suggests that metronidazole is associated with impaired rate of abortion. Up to now, the risk of possible late symptoms including the risk of carcinogenicity is not fully determined.

In case of unlimited use of nitroimidazoles by the mother, a carcinogenic or teratogenic risk exists for the foetus or the neonate. Evidence of embryotoxicity or foetotoxicity is not yet available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Disodium Phosphate 12 H_2O
Citric acid monohydrate

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

3 years

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.
Keep the vials in the outer carton in order to protect from light.

6.5 Nature and contents of container

100 ml colourless glass vial (type II glass) with halobutyl rubber stopper and aluminium cap.
Packs of 10 vials of 100 ml solution for infusion

6.6 Special precautions for disposal and other handling

Metronidazole Fresenius can be administered by intravenous infusion combined with 0.9% sodium chloride solution, glucose/sodium chloride solutions, 5% glucose solution, potassium chloride solutions (20 mmol, 40 mmol) and Ringer's solution.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Neopharm (Israel) 1996 Ltd
Hashiloach 6 , POB 7063 Petach Tikva 4917001

8. MANUFACTURER

Fresenius Kabi Deutschland GmbH, Friedberg, Germany

9. MARKETING AUTHORISATION NUMBER

158 82 34430 00

Revised in June 2022 according to MOH guidelines