SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Metronidazole B.Braun 500 MG / 100 ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 5 mg of metronidazole

100 ml of solution contain 500 mg of metronidazole

Excipient with known effect :

1 ml solution contains

Sodium chloride	7.4 mg
Disodium phosphate dodecahydrate	1.5 mg

Electrolyte content (per 100 ml):

Sodium	14 mmol
Chloride	13 mmol

This medicinal product contains 14 mmol (or 322 mg) sodium per 100 ml.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless up to faintly, straw- coloured solution, practically free from particles

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. necrotizing 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, caesarian 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).

4.2. Posology and method of administration

Posology

Unless otherwise directed the following dosage guidelines are recommended:

Adults and children over 12 years:

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 (approximately 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

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.

Administration can also be performed in a diluted form by adding the product to an I.V. carrier solution such as 0.9 % sodium chloride or 5 % dextrose injection.

Simultaneously prescribed antibiotics are to be administered separately.

Open bottles with unused portions shall not be stored but discarded.

Do not use equipment containing aluminum that would come in contact with the drug solution.

Duration of therapy

The duration of therapy 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

Hypersensitivity to metronidazole or other nitroimidazole derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

Patients with hepatic impairment

In patients with severe liver damage metronidazole 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 cumulation 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. (see section 4.2).

Due to the risk of aggravation, metronidazole should also be used in patients with active or chronic severe peripheral and central nervous system diseases only if its

expected benefits clearly outweigh potential hazards.
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.
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).
In the case of severe hypersensitivity reactions (e.g. anaphylactic shock), treatment with Metronidazole B.Braun 500 MG / 100 ML must be discontinued immediately and established emergency treatment must be initiated by qualified healthcare professionals.
Severe persistent diarrhoea occurring during treatment or during the subsequent weeks may be due to pseudomembranous colitis (in most cases caused by clostridium difficile), see section 4.8. This intestinal disease, precipitated by the antibiotic treatment, may be life-threatening and requires immediate appropriate treatment.
Anti-peristaltic medicinal products must not be given.
The duration of therapy with metronidazole or drugs containing other nitroimidazoles
should not exceed 10 days. Only in specific elective cases and if definitely needed, the treatment period may be extended, accompanied by appropriate clinical and laboratory monitoring. Repeat therapy should be restricted as much as possible and to specific elective cases only. These restrictions must be observed strictly because the possibility of metronidazole developing mutagenic activity cannot be safely excluded
and because in animal experiments an increase of the incidence of certain tumours has been noted.
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 benefitrisk 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.

Prolonged therapy with metronidazole may be associated with bone marrow depression, leading to an impairment of haematopoiesis. Manifestations see section 4.8. Blood cell counts should be carefully monitored during prolonged therapy.

This medicinal product contains 14 mmol (or 322 mg) sodium per 100 ml. This is to be taken into consideration for patients on a controlled sodium diet.

Interference with laboratory tests

Metronidazole interferes with the enzymatic-spectrophotometric determination of aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), triglycerides and glucose hexokinase resulting in decreased values (possibly down to zero).

Metronidazole has a high absorbance at the wavelength at which nicotinamideadenine dinucleotide (NADH) is determined. Therefore elevated liver enzyme concentrations may be masked by metronidazole when measured by continuous-flow methods based on endpoint decrease in reduced NADH. Unusually low liver enzyme concentrations, including zero values, have been reported.

Patients should be warned that Metronidazole may darken urine.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions

Interactions with other medicinal products

Amiodarone

QT interval prolongation and torsade de pointes have been reported with the coadministration of metronidazole and amiodarone. It may be appropriate to monitor QT interval on the ECG if amiodarone is used in combination with metronidazole.

Patients treated on an outpatient basis should be advised to seek medical attention if they experience symptoms that could indicate the occurrence of torsade de pointes such as dizziness, palpitations, or syncope.

Barbiturates

Phenobarbital may increase the hepatic metabolism of metronidazole, reducing its plasma half life to 3 hours.

Busulfan

Coadministration with metronidazole may significantly increase the plasma concentrations of busulfan. The mechanism of interaction has not been described. Due to the potential for severe toxicity and mortality associated with elevated busulfan plasma levels, concomitant use with metronidazole should be avoided.

Carbamazepine

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

Cimetidine

Concurrently administered cimetidine may reduce the elimination of metronidazole in isolated cases and subsequently lead to increased metronidazole concentrations in serum.

Contraceptive drugs

Some antibiotics can, in some 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. There are case reports of oral contraceptive failure in association with different antibiotics, e.g. ampicillin, amoxicillin, tetracyclines and also metronidazole.

Coumarin derivatives

Concomitant treatment with metronidazole may potentiate the anticoagulant effect of these and increase the risk for bleeding as a consequence of decreased hepatic degradation. Dose adjustment of the anticoagulant can be necessary.

Ciclosporine

During simultaneous therapy with cyclosporine and metronidazole there is a risk for increased serum concentrations of cyclosporine. Frequent monitoring of cyclosporine and creatinine is required.

Disulfiram

Simultaneous administration of disulfiram may cause states of confusion or even psychotic reactions. Combination of both agents must be avoided.

Fluorouracil

Metronidazole inhibits the metabolism of concurrently administered fluorouracil, i.e. the plasma concentration of fluorouracil is increased.

Lithium

Caution is to be exercised when metronidazole is administered simultaneously with lithium salts, because under metronidazole therapy raised serum concentrations of lithium have been observed. 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.

Mycophenolat mofetil

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.

Phenytoin

Metronidazole inhibits the metabolism of concurrently administered phenytoin, i.e. the plasma concentration of phenytoin is increased. On the other hand, the efficacy of metronidazole is reduced when phenytoin is administered concurrently.

Tacrolimus

Coadministration with metronidazole may increase the blood concentrations of tacrolimus. The proposed mechanism is inhibition of hepatic tacrolimus metabolism via CYP 3A4. Tacrolimus blood levels and renal function should be checked frequently and the dosage adjusted accordingly, particularly following initiation or discontinuation of metronidazole therapy in patients who are stabilized on their tacrolimus regimen.

Other forms of interaction

Alcohol

Disulfiram-like effect. Alcoholic beverages and drugs containing alcohol should be avoided.

4.6 Fertility, pregnancy and lactation

Pregnancy and Lactation

Fertility

Animal studies only indicate a potential negative influence of metronidazole on the male reproductive system if high doses lying well above the maximum recommended dose for humans were administered.

Contraception in males and females

– See section 4.5 ‘contraceptive drugs’

Pregnancy

The safety of the use of metronidazole during pregnancy has not sufficiently been demonstrated. In particular, reports on the use during early pregnancy are contradictory. Some studies indicated an increased rate of malformations. In animal studies with metronidazole no teratogenicity was observed (see section 5.3).

During the first trimester, Metronidazole B.Braun 500 MG / 100 ML should only be used to treat severe life-threatening infections, if there is no safer alternative.

During the second and third trimester, Metronidazole B.Braun 500 MG / 100 ML may also be used to treat other infections if its expected benefits clearly outweigh any possible risk.

Breast-feeding

Since metronidazole is secreted into breast milk, nursing should be stopped during therapy. Also after the end of the therapy with metronidazole, nursing should not be resumed before another 2 – 3 days because of the prolonged half-life 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

Undesirable effects are mainly associated with prolonged use or high doses. The most commonly observed effects include nausea, abnormal taste sensations and the risk of neuropathy in case of long term treatment.
In the following listing, for the description of the frequencies of undesirable effects the following terms are used:

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

Common: Superinfections with candida (e.g. genital infections)

Rare: Pseudomembranous colitis

Details regarding emergency treatment see section 4.4.

Blood and lymphatic system disorders

Very rare: granulocytopenia, agranulocytosis, pancytopenia and thrombocytopenia

Not known: Leucopenia, aplastic anaemia

Immune system disorders

Rare: Severe acute systemic hypersensitivity reactions: anaphylaxis, up to anaphylactic shock.

Not known: Angioedema.

Metabolism and nutrition disorders

Not known: Anorexia

Psychiatric disorders

Very rare: Psychotic disorders, including states of confusion, hallucination

Not known: Depression

Nervous system disorders

Very rare:	Encephalopathy, headache, fever, drowsiness, dizziness, disturbances in sight and movement, vertigo, ataxia, dysarthria, convulsions.
Not known:	Somnolence or insomnia, myoclonuis, seizures, peripheral neuropathy manifesting as paraesthesia, pain, furry sensation, and tingling in the extremities. Aseptic meningitis.
Eye disorders	
Very rare:	Disturbance of vision, e.g. diplopia, myopia.
Not known:	Oculogyric crisis, optic neuropathy/neuritis (isolated cases)
Cardiac disorders	
Rare:	ECG changes like flattening of T-wave
Gastro-intestinal disorders	
Very rare:	Pancreatitis
Not Known:	Vomiting, nausea, diarrhoea, glossitis and stomatitis, eructation with bitter taste, epigastric pressure, metallic taste, furred tongue Dysphagia (caused by central nervous effects of metronidazole)
Hepatobiliary disorders	
Very rare:	Abnormal values of hepatic enzymes and bilirubin Hepatitis, jaundice
Skin and subcutaneous tissue disorders	
Very rare:	Allergic skin reactions, e. g. pruritus, urticaria, STEVENS-JOHNSON syndrome, toxic epidermal necrolysis
Not known:	Erythema multiforme
Musculoskeletal and connective tissue disorders	
Very rare:	Arthralgia, myalgia
Renal and urinary disorders	
Uncommon:	Dark coloured urine (due to a metabolite of metronidazole)
General disorders and administration site conditions	

Not known:	Vein irritations (up to thrombophlebitis) after intravenous administration. States of weakness, fever

Paediatric population

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

Reporting 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/

4.9. Overdose

As signs and symptoms of overdose the undesirable effects described under section 4.8 may appear. Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation.

Treatment

There is no specific treatment or antidote that can be applied in the case of gross overdose of metronidazole. If required, metronidazole can be effectively eliminated by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmaco-therapeutic group: Anti-infectives for systemic use – imidazole derivatives

ATC Code: J01X D01

Mechanism of action

Metronidazole itself is ineffective. It is a stable compound able to penetrate

into microorganisms.
Under anaerobic conditions nitroso radicals acting on DNA are formed from metronidazole by the microbial pyruvate-ferredoxin-oxidoreductase, with oxidation of ferredoxin and flavodoxin. Nitroso radicals form adducts with base pairs of the DNA, thus leading to breaking of the DNA chain and consecutively to cell death.

PK/PD relationship
Metronidazole acts in a concentration dependent manner. The efficacy of metronidazole mainly depends on the quotient of the maximum serum concentration (cmax) and the minimum inhibitory concentration (MIC) relevant for the microorganism concerned.

Breakpoints
For the testing of metronidazole usual dilution series are applied. The following minimum inhibitory concentration have been established to distinguish susceptible from resistant microorganisms:
EUCAST (European Committee on Antimicrobial Susceptibility Testing, Version 1.3, January 5, 2011) breakpoints separating susceptible (S) from resistant organisms (R) are as follows:

Gram-positive anaerobes (S: ≤ 4 mg/l R > 4 mg/l)

Gram-negative anaerobes (S: ≤ 4 mg/l R > 4 mg/l)

List of susceptible and resistant organisms.

Commonly susceptible species
Anaerobes
Bacteroides fragilis
Clostridium difficile°
Clostridium perfringens°Δ
Eubacterium
Fusobacterium spp.°
Peptoniphilus spp.°
Peptostreptococcus spp.°

Porphyromonas spp.°
Prevotella spp.
Veillonella spp.°
Other micro-organisms
Entamoeba histolytica°
Gardnerella vaginalis°
Giardia lamblia°
Trichomonas vaginalis°

Inherently resistant organisms
All obligate aerobes
Gram-positive micro-organisms
Actinomyces spp.
Enterococcus spp.
Propionibacterium acnes
Staphylococcus spp.
Streptococcus spp.
Gram-negative micro-organisms
Enterobacteriaceae
Haemophilus spp.
Mobiluncus

° At the time of publication of these tables, no up-to-date data were available. In primary literature, standard reference books and therapy recommendations susceptibility of the respective strains is assumed.

$^{\Delta}$ Only to be used in patients with allergy to penicillin

Mechanisms of resistance to metronidazole

The mechanisms of metronidazole resistance are still understood only ipart. Strains of Bacteroides being resistant to metronidazole possess genes encoding nitroimidazole reductases converting nitroimidazoles to aminoimidazoles. Therefore the formation of the antibacterially effective nitroso radicals is inhibited.

There is full cross resistance between metronidazole and the other nitroimidazole derivatives (tinidazole, ornidazole, nimorazole).

The palence of acquired resistance of individual species may vary, depending on region and time. Therefore especially for the adequate treatment of severe infections specific local information regarding resistance should be available. If there is doubt about the efficacy of metronidazole due to the local resistance situation, expert advice should be sought. Especially in the case of severe infections or failure of treatment, microbiological diagnosis including determination of species of the microorganism and its susceptibility to metronidazole is required.

5.2. Pharmacokinetic properties

Absorption:

Metronidazole is readily absorbed from the gastrointestinal tract and the oral bioavailability is > 90%. Consequently, the same mg dose will result in similar exposure (AUC) when switching between intravenous and oral dosing.

Distribution:

Metronidazole is widely distributed in body tissues after injection. It also diffuses across the placenta, and is found in breast milk of nursing mothers in concentrations equivalent to those in serum. Protein binding is less than 20 %, the apparent volume of distribution is 36 litres.

Biotransformation:

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide formation. Its metabolites include an acid oxidation product, a hydroxy derivative and glucuronide. The major metabolite in the serum is the hydroxylated metabolite, the major metabolite in the urine is the acid metabolite.

Elimination:

Approximately 80% of the substance is excreted in urine with less than 10% in the form of the unchanged drug substance . Small quantities are excreted via the liver. Elimination half-life is 8 (6-10) hours.

Characteristics in special patient groups:

Renal insufficiency delays excretion only to an unimportant degree. The elimination half-life of metronidazole remains unchanged in the presence of renal failure, however such patients retain the metabolites of metronidazole. The clinical significance of this is not known at present.

Delayed plasma clearance and prolonged serum half-life (up to 30 h) is to b expected in severe liver disease.

5.3 Preclinical safety data

Repeated dose toxicity

Following repeated administration ataxia and tremor were observed in the dog and a dose-dependent increase in hepatocellular degeneration was observed in the monkey during a 12 month study.

Mutagenic and tumorigenic potential

Metronidazole was mutagenic in bacteria after nitroreduction, however it was not mutagenic in mammalian cells in vitro and in vivo. In addition, DNA damage was not observed in the lymphocytes of patients treated with metronidazole.

There is evidence to suggest that metronidazole is tumorigenic in the mouse and rat. There was an increase in the incidence of lung tumours in mice (after the oral administration of 3.1-fold the maximum recommended human dose of metronidazole of 1,500 mg/d), however, this does not seem to be due to a genotoxic mechanism as no changes in the mutation rates were observed in various organs of transgenic mice following high doses of metronidazole.

Reproduction toxicity

No teratogenicity or embryotoxicity was observed in the rat or rabbit. Following repeated administration for 26-80 weeks to rats, testicular and prostatic dystrophy were observed at high doses (14.2 to 28.5-fold the maximum recommended human dose of metronidazole of 1,500 mg/d).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,

Disodium phosphate dodecahydrate,

Citric acid monohydrate,

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened

The expiry date of the product is indicated on the packaging materials.

After first opening:

From a microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ° C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Pack sizes :

Plastic container: 10 x 100 ml

Plastic container: 20 x 100 ml

Not all pack sizes may be marketed.

7 MANUFACTURER

B. Braun Melsungen, AG,
Carl- Braun Str. 1, D-34212, Melsungen, Germany

8 MARKETING AUTHORISATION HOLDER

Lapidot Medical Import and Marketing Ltd.
Hashita 8, Industrial Zone, Caesarea 3088900.

9 MARKETING AUTHORISATION NUMBER

120-33-30082-00

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