LAPIDOT MEDICAL

24.11.2020

רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא

Metronidazole B. Braun, solution for injection

חומר פעיל :

Metronidazole B. Braun 500 MG / 100 ML

להלן עדכונים בעלון לרופא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן צהוב משמעותו החמרה, ~~טקסט~~ משמעותו מחיקה):

4.3 Contraindications

~~In patients with prior history of hypersensitivity to Metronidazole or other nitroimidazole derivatives.~~

~~During the first trimester of pregnancy in patients with trichomoniasis.~~

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

~~Convulsive Seizures and Peripheral Neuropathy:~~

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

~~*Precautions*~~

~~In case of organic diseases of the C.N.S. and blood dyscrasia such as granulocytopenia, metronidazole should be used with necessary caution.~~

~~Metronidazole interferes with the spectrophotometric determination of SGOT, SGPT, LDH resulting in decreased values.~~

~~In patients with severe hepatic disease, who metabolize metronidazole slowly, doses below those usually recommended should be administered cautiously~~

~~*Side effects*~~

~~A serious adverse reaction: convulsive seizures.~~

~~Very seldom may occur:~~

~~G.I. upset (nausea, vomiting, epigastric distress, diarrhea). Burning sensation in the tongue, metallic taste, overgrowth of Candida, rash, urticaria.~~

~~Central disorders (headache, dizziness, somnolence, in coordination, depressions).~~

~~Drug fever.~~

~~Thrombophlebitis.~~

~~Darkened urine.~~

~~Mild leucopenia may occur. Thus regular blood count is required.~~

~~Peripheral neuropathy has been observed, similarly myalgia and paresthesia.~~

~~In inflammatory diseases of meninges metronidazole diffuses well into the cerebrospinal fluid and may eventually lead to peripheral neuropathy.~~

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 500mg/100ml Solution for Infusion 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~~*Carcinogenesis, Mutagenesis*~~

~~Metronidazole has been shown to be carcinogenic in mice and rats. Also, it has been shown to have mutagenic, activity in in-vitro assay systems, but not in mammals studies~~

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

~~Alcoholic beverages are to be avoided during metronidazole therapy, Since side-effects such as dizziness and vomiting may be the consequence. Psychotic reactions may occur with the concurrent use of disulfiram, therapy with the latter should be discontinued 2 weeks before starting metronidazole.~~

~~Drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, cause reduced metronidazole plasma levels.~~

~~Drugs that decrease microsomal liver enzymes activity, as cimetidine, decrease plasma clearance of metronidazole.~~

~~Metronidazole potentiates the anticoagulant effect of oral anticoagulants. If administered concomitantly, the~~

~~Quick's time may have to be rechecked and the prothrombin time monitored regularly.~~

~~No interactions or adverse reactions in case of separate administration of metronidazole and sulfonamides or antibiotics have been observed to date.~~

~~In Vitro tests on the effects of a combined therapy of antibiotics and metronidazole have revealed the following results:~~

~~Moderate synergic effect for:~~

~~Acylureido-penicillins, Spiramycin, Rifampicin, Clindamycin,~~

~~Tetracycline.~~

~~Marked synergic effect for:~~

~~Nalidixic acid.~~

~~No interaction with:~~

~~Ampicillin, streptomycin, gentamicin and fusidic acid.~~

~~In animal tests (effective dose 50%) no antagonism between mertonidazole and ampicillin, chloramphenicol, rifampicin, nalidixic acid and cotrimoxazole could be ascertained (tested against E. coli).~~

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

~~After the first trimester of pregnancy metronidazole should only be administered in vital situations.~~

~~Since metronidazole is secreted in breast milk, therapy is either to be discontinued during the lactation period or the nursing to be interrupted. Also after cessation of therapy with metronidazole nursing should not be resumed before another 2–3 days because of the prolonged half-life period of metronidazole~~.

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 500 mg/100 ml Solution for Infusion should only be used to treat severe life-threatening infections, if there is no safer alternative.
During the second and third trimester, Metronidazole 500 mg/100 ml Solution for Infusion 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.

^ 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.

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