PACKAGE LEAFLET

Package leaflet: Information for the patient

Metronidazole 5 mg/ml solution for infusion

Metronidazole

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

The name of your medicine is Metronidazole5 mg/mL solution for infusion
In the rest of this leaflet the name of the medicine will be Metronidazole.

What is in this leaflet

1. What Metronidazole is and what it is used for

Metronidazole belongs to a group of medicines known as antibiotics and is used to treat severe infections caused by bacteria that can be killed by the active substance metronidazole.

You may be given Metronidazole for the treatment of any of the following diseases:

- Infections of the blood, brain, lung, bones, genital tract, pelvic area, liver, intestines and stomach

If required, your treatment may be supplemented by other antibiotics. Metronidazole may be given as a preventive measure prior to operations associated with a higher risk of infection with what are known as anaerobic bacteria, mainly in gynaecology or surgery on stomach and gut.

2. What you need to know before you are given Metronidazole

Do not take Metronidazole
- if you are allergic to metronidazole, other similar substances or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor, pharmacist or nurse before being given Metronidazole if you have:
- severe liver damage
- a blood formation disorder or
- a disease of brain, spinal cord or nerves

Therefore, your doctor will very carefully determine whether you should be treated with Metronidazole.

If convulsive fits or any other nerve affections (e.g. numbness in limbs) become apparent during therapy, your treatment will promptly be revised.
Treatment must be stopped or revised immediately if you get severe diarrhea which may be due to a severe large bowel disease called “pseudomembranous colitis” (see also section 4). As prolonged use of metronidazole may impair blood formation (see section “Possible side effects”), your blood counts will be monitored during treatment.

If you received this medicine your urine may be darkened.

Cases of severe liver toxicity/acute liver failure, including cases with a fatal outcome, in patients with Cockayne syndrome have been reported with product containing metronidazole.

If you are affected by Cockayne syndrome, your doctor should also monitor your liver function frequently while you are being treated with metronidazole and afterwards.

Tell your doctor immediately and stop taking metronidazole if you develop:
- Stomach pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine, putty or mastic coloured stools or itching.

Treatment with Metronidazole should not usually be continued for longer than 10 days; the treatment period will only be extended in exceptional circumstances and if absolutely necessary. Repeat therapy with metronidazole will be restricted to cases where this is absolutely necessary. In such a case, you will be monitored particularly carefully.

Other medicines and Metronidazole

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Amiodarone (used to treat irregular heartbeat)
When you receive this medicine, your heart function should be monitored. You should see your doctor if you notice any heart function abnormalities, dizziness or fainting.

Barbiturates (the active substance in sleeping pills)
The duration of action of metronidazole is reduced by phenobarbital; your metronidazole dose may therefore have to be increased.

Birth control pills
Your birth control pill may be less reliable while you are being given metronidazole.

Busulfan
Metronidazole should not be given to patients receiving busulfan because in that case toxic effects are more likely to occur.

Carbamazepine (a drug for the treatment of epilepsy)
This combination also warrants caution because metronidazole may increase the duration of action of carbamazepine.

Cimetidine (a drug for the treatment of stomach disorders)
Cimetidine may reduce the elimination of metronidazole in isolated cases and subsequently leads to increased serum metronidazole concentrations.

Coumarin derivatives (drugs that inhibit blood clotting)
Metronidazole may enhance the blood clotting inhibition brought about by coumarins. So if you are taking a medicine that inhibits blood clotting (for example warfarin), you may need less of it during treatment with metronidazole.

Cyclosporin (a drug used to suppress undesirable immune responses)
When cyclosporin is given together with metronidazole, the blood levels of cyclosporin may increase; your doctor will therefore have to adjust your cyclosporin dose as appropriate.

Disulfiram (used in alcohol withdrawal therapy)
If you are taking disulfiram, you must not be given metronidazole, or disulfiram must be stopped. Combined use of these two drugs may lead to states of confusion up to the point of a serious mental disorder (psychosis).

Drugs containing alcohol
Please refer to section "Metronidazole with food, drink and alcohol".

Fluorouracil (an anticancer drug)
The daily dose of fluorouracil may have to be reduced when giving it together with metronidazole because metronidazole may lead to an increase of the blood level of fluorouracil.

Lithium (used to treat mental illness)
Treatment with lithium preparations requires particularly careful monitoring during treatment with metronidazole, and the dose of the lithium preparation may need to be re-adjusted. Lithium treatment should be tapered or withdrawn before administration of metronidazole.

Mycophenolate mofetil (used for the prevention of rejection reactions after organ transplant)
Its effect may be weakened by metronidazole, so careful monitoring of the effect of the medicine is recommended.

Phenytoin (a drug for the treatment of epilepsy)
If you are taking phenytoin, your doctor will treat you with metronidazole only with caution because metronidazole may increase the duration of action of phenytoin. On the other hand, phenytoin may reduce the effect of metronidazole.

Tacrolimus (used to suppress unwanted immune reactions)
The blood levels of this agent and your kidney function should be checked when starting and stopping treatment with metronidazole.

Metronidazole with food, drink and alcohol

Alcohol
You must not drink any alcoholic beverages or drugs containing alcohol while you are being given metronidazole and up to 48 hours afterwards because this may cause intolerance reactions such as dizziness and vomiting.

Pregnancy, breast-feeding and fertility

If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

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
If you are taking a birth-control pill, please refer to section "Other medicines and Metronidazole.

Pregnancy
If you are pregnant, your doctor will not treat you with metronidazole unless she/he considers this absolutely necessary.

Breast-feeding
You should not breast-feed during treatment with metronidazole and not resume nursing for another 2–3 days thereafter because metronidazole passes into breast milk.

Driving and using machines

While taking Metronidazole you may feel sleepy, dizzy, confused, see or hear things that are not there (hallucinations), have fits (convulsions) or temporary eyesight problems (such as blurred or double vision). If this happens, do not drive or use any machinery or tools.

Metronidazole contains sodium

This medicine contains 310.58 mg sodium (main component of cooking/table salt) in each 100 mL. This is equivalent to 15.5% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Metronidazole is given

Dosage
Dosage depends on the nature and severity of your illness, your age and body weight, and your individual response to treatment.

The following dosages are usually prescribed:

Adults and adolescents
Treatment of amoebiasis

1.50 g per day (500 mg three times daily, intravenous infusions).

Treatment of infections
Adults
You will be given 100 mL of the medicine (500 mg of metronidazole) every 8 hours.

In most cases treatment will take 7 days. Only exceptionally treatment may be continued beyond this time, although a duration of 10 days should not normally be exceeded.

The dose will be the same for patients with kidney diseases.
For patients with liver diseases, lower doses may be required.
If you were treated by artificial kidney your doctor will schedule your infusion after dialysis has been finished. No routine dose adjustment is necessary.

Prevention of infections that might occur after operations
When used for prevention of infection in surgery, you may be given 500 mg of the medicine before the operation. The dose will be repeated 8 and 16 hours after the operation.

Elderly

Your doctor will give you this medicine only with special caution.

Use in children
Dosing in children is based on body weight (BW).

Treatment of amoebiasis
35 to 50 mg/kg/day intravenously, divided into 3 doses for 5 to10 days. A maximum of 2400 mg/day must not be exceeded.

Treatment of infections

Age	**Dosage**
8 weeks to 12 years	20 – 30 mg of metronidazole per kg BW per day as a single dose or divided into 7.5 mg of metronidazole per kg BW every 8 hours. The daily dose may be increased to 40 mg of metronidazole per kg BW if infection is severe.
Under 8 weeks	15 mg of metronidazole per kg BW as a single dose daily or divided into 7.5 mg per kg BW every 12 hours.
Newborns of less than 40 weeks gestational age	As metronidazole may accumulate in these patients during the first week of life, the concentration of metronidazole in the blood will be checked after a few days of treatment.

Usually treatment will take 7 days.

Prevention of infections that might occur after operations:

Age	**Dosage**
Less than 12 years	20 – 30 mg of metronidazole per kg BW as a single dose given 1 – 2 hours before surgery
Newborns of less than 40 weeks gestational age	10 mg of metronidazole per kg BW as a single dose before surgery

Method of administration and duration of treatment

Metronidazole is administered through a drip directly into a vein (intravenous infusion).
The infusion of one bottle usually takes 60 minutes, but it should not be done within less than 20 minutes.

The entire metronidazole treatment period is usually 7 days and must not exceed 10 days unless this is absolutely necessary (see also section "Warnings and precautions"). If you are concurrently receiving other antibiotics your doctor will give you those medicines separately.

If you are given more Metronidazole than you should:

Undesirable effects, as described in the next section, may occur as signs or symptoms of an overdose. Single oral doses of metronidazole, up to 12 g have been reported in suicide attempts and accidental overdoses.
Symptoms were limited to vomiting, ataxia and slight disorientation.
There is no known specific antidote or specific treatment of a massive overdose, but metronidazole can be removed by dialysis (that is treatment with artificial kidney) from the body.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects occur mostly at high doses or with prolonged use.
Talk to your doctor straight away if you notice any of the following side effects:

Rare (may affect up to 1 in 1,000 people):
- Severe persistent diarrhoea (possibly a symptom of a severe bowel infection called pseudomembranous colitis, see paragraph "*Emergency management of pseudomembranous enterocolitis"*)
- Severe acute hypersensitivity reactions up to allergic shock

Very rare (may affect up to 1 in 10,000 people):
- White blood cell and platelet counts may decrease during treatment (granulocytopenia, agranulocytosis, pancytopenia, thrombocytopenia)
- Hepatitis (liver inflammation), jaundice, inflammation of the pancreas
- Brain disorders, lack of coordination
- Brain fever not caused by bacterials (aseptic meningitis)
- Severe inflammatory rash on mucous membranes and the skin with fever, redness and blistering, in extremely rare cases up to skin detachment over extended areas (Stevens-Johnson Syndrome)

Not known (frequency cannot be estimated from the available data):
- Mild to moderate hypersensitivity reactions, swelling of your face, mouth, throat and/or tongue (angioedema)
- Gaze spasm, damage or inflammation of the nerves of your eyes
- Reduced white blood cell, count (leucopenia), severe anaemia (aplastic anaemia)
- Seizures, nervous disorders such as numbness, pain, furry sensation or tingling in the arms or legs
- Toxic epidermal necrolysis
- Acute liver failure in patients with Cockayne Syndrome (see section 2 "Warnings and precautions")

Other side effects include

Common (may affect up to 1 in 10 people):
- Infections with yeasts (e.g. genital infections)

Uncommon (may affect up to 1 in 100 people):
- Darkened urine (due to a metabolite of metronidazole)

Rare (may affect up to 1 in 1,000 people):
- Changes in ECG

Very rare (may affect up to 1 in 10,000 people):
- Psychotic disorders, including states of confusion, hallucination
- Headache, dizziness, drowsiness, fever, disturbance of sight and movement, giddiness, speech defects, convulsions
- Visual disturbances, e.g. double vision, short-sightedness
- Liver function disorders (such as elevated serum levels of certain enzymes and bilirubin)
- Allergic skin reactions like itching, hives

- Joint and muscle pain

Not known (frequency cannot be estimated from the available data):
- Sickness, feeling sick, diarrhoea, inflammation of tongue or mouth, belching and bitter taste, metallic taste, pressure above the stomach, furry tongue
- Difficulty swallowing
- Anorexia
- Sad (depressed) mood
- Sleepiness or sleeplessness, muscle twitching
- Reddening and itching of the skin (erythema multiforme)
- Vein wall irritation (to the point of inflamed veins and thrombosis) after intravenous administration, states of weakness, fever

Emergency management of pseudomembranous enterocolitis.
In the event of severe persistent diarrhoea, you must promptly inform your doctor because this may be due to pseudomembranous colitis, a serious condition that must be treated immediately. Your doctor will stop metronidazole and provide appropriate treatment.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

Reporting side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www. hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Metronidazole

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of the month.
- This medicine does not require any special storage conditions.

After first opening the medicinal product should be used immediately. For single use only.
Do not use this medicine if container is found leaking or solution is not clear.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Metronidazole contains
- The active substance is metronidazole. Each bottle of solution for infusion contains 500 mg metronidazole.
  Each mL of solution for infusion contains 5 mg metronidazole.
- The other ingredients are disodium phosphate dodecahydrate, citric acid monohydrate, sodium chloride, and water for injections.

What Metronidazole looks like and contents of the pack

This medicine is presented in the form of an injectable almost colourless to pale yellow solution for infusion in a blow-fill-sealed 100 mL polypropylene bottle over-sealed with a molded plastic cap with a rubber gasket and a pull ring or with a plastic cap and twin ports.

Metronidazole is available in packs containing 10, 20 or 24 bottles.

Not all pack sizes may be marketed.

Marketing Authorization Holder
Noridem Enterprises Ltd.
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This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Netherlands:	Metronidazol Noridem 5 mg/ml, oplossing voor infusie
United Kingdom (Northern Ireland):	Metronidazole 500 mg/100 mL Solution for infusion
Austria:	Metronidazol BRADEX 5 mg/ml Infusionslösung
Belgium:	Metronidazole Noridem 500mg/100ml, oplossing voor infusie / solution pour perfusion / Infusionslösung
France:	METRONIDAZOLE NORIDEM 500 mg/100 ml, solution pour perfusion
Hungary:	Metronidazol Noridem 5 mg / ml oldatos infúzió
Slovakia:	Metronidazole Noridem 5 mg/ml infúzny roztok
Czech Republic:	Metronidazole Noridem
Luxemburg:	METRONIDAZOLE NORIDEM 500 mg/100 ml, solution pour perfusion
Croatia:	Metronidazol Noridem 5 mg/ml otopina za infuziju
Slovenia:	Metronidazol Noridem Enterprises 5 mg/ml raztopina za infundiranje
Denmark:	Metronidazole Noridem
Spain:	Metronidazol Noridem 5 mg/ml solución para perfusión EFG
Finland:	Metronidazole Noridem 5 mg/ml infuusioneste, liuos
Ireland:	Metronidazole 5 mg/ml solution for infusion
Italy:	Metronidazolo Noridem
Norway:	Metronidazole Noridem
Poland:	Metronidazol Noridem
Portugal:	Metronidazol Noridem
Romania:	Metronidazol Noridem 5 mg/ml soluţie perfuzabilă
Sweden:	Metronidazole Noridem

This leaflet was last revised in {MM/YYYY}.

The following information is intended for healthcare professionals only:

Posology and method of administration

Posology

The dosage is adjusted according to the patient's individual response to therapy, her/his age and body weight and according to nature and severity of the disease.

The following dosage guidelines should be followed:

Adults and adolescents:

Amoebiasis
1.50 g per day (500 mg three times daily, intravenous infusions).
In hepatic amoebiasis, at the abscess stage, the abscess must be evacuated concomitantly with metronidazole treatment. Duration of treatment: 5-10 days

Treatment of anaerobic infections
500 mg (100 mL) every 8 hours. Alternatively 1000 mg – 1500 mg may be given daily as a single dose.
The duration of therapy is dependent on the effect of the treatment. In most cases a treatment course of 7 days will be sufficient. If clinically indicated, treatment may be continued beyond this time although a duration of 10 days should not normally be exceeded.

Prophylaxis against post-operative infection caused by anaerobic bacteria
500 mg, with administration completed approximately one hour before surgery. The dose is repeated after 8 and 16 hours.

The Elderly:
Caution is advised in the elderly, particularly at high doses, although there is limited information available on modification of dosage.

Paediatric population

Amoebiasis
35 to 50 mg/kg/day intravenously, divided into 3 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.

Treatment of anaerobic infections
Children > 8 weeks to 12 years of age:
The usual daily dose is 20 – 30 mg per kg BW per day as a single dose or divided into 7.5 mg per kg BW every 8 hours. The daily dose may be increased to 40 mg per kg BW, depending on the severity of the infection.

Neonates and infants < 8 weeks of age:
15 mg per kg BW as a single dose daily or divided into 7.5 mg per kg BW every 12 hours.
In newborns with a gestational 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 therapy.

Duration of treatment is usually 7 days.

Prophylaxis against postoperative infections caused by anaerobic bacteria:
Children < 12 years:
20 – 30 mg/kg BW as a single dose given 1 – 2 hours before surgery
Newborns with a gestation age < 40 weeks:
10 mg/kg BW as a single dose before surgery

Patients with renal insufficiency
Limited data are available in this population. These data do not indicate the need for dose reduction.

In patients undergoing haemodialysis the conventional dose of metronidazole should be scheduled after haemodialysis on dialysis days to compensate the removal of metronidazole during the procedure.
No routine dose adjustment is necessary in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

Patients with hepatic insufficiency
As serum half-life is prolonged and plasma clearance is delayed in severe hepatic insufficiency, patients with severe liver disease will require lower doses.
In patients with hepatic encephalopathy, the daily dosage should be reduced to one third and may be administered once daily.

Method of administration

Intravenous use.
The contents of one bottle are to be infused slowly i.v., i.e. 100 mL max. over not less than 20 minutes, but normally over one hour.
Concurrently prescribed antibiotics are to be administered separately.