PROFESSIONAL INFORMATION FOR METRONIDAZOLE 500 mg/100 mL LAMAR

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

METRONIDAZOLE 500 mg/100 mL LAMAR solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 5 mg metronidazole.

Each 100 mL bottle contains 500 mg of metronidazole.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear and colourless or pale yellowish aqueous solution, free of visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of infections in which anaerobic bacteria have been identified or are suspected as pathogens, particularly *Bacteroides fragilis* and other species of *Bacteroides*, and including other species for which METRONIDAZOLE 500 mg/100 mL LAMAR is bactericidal, such as anaerobic S*treptococci spp.*, *Fusobacteria spp*., *Eubacteria spp.* and *Clostridia spp*.

a) METRONIDAZOLE 500 mg/100 mL LAMAR is used for anaerobic infections in the following indications:

- Postoperative wound infections and pelvic inflammatory disease.

- As there are usually mixed infections, combination therapy is often indicated.

b) METRONIDAZOLE 500 mg/100 mL LAMAR is also used for the prevention of postoperative infections due to anaerobic bacteria.

Given before and after:

- Appendicectomy,
- Gynaecological surgery, and
- Colonic surgery.

4.2 Posology and method of administration

Posology:

Treatment of anaerobic infections

Adults and adolescent (over 12 years) dose:

100 mL (500 mg/100 mL) by intravenous infusion every 8 hours. The injection should be infused intravenously at the rate of 5 mL per minute but may be administered alone or concurrently (but separately) with other bacteriologically appropriate antibacterial agents in parenteral dosage forms.

400 mg oral medication should be substituted three times daily as soon as this becomes feasible. Treatment for seven days should be satisfactory for most but, depending upon clinical and bacteriological assessments, the medical practitioner might decide to prolong the treatment, e.g., for the eradication of infection from sites which cannot be drained or are liable to endogenous recontamination by anaerobic pathogens from the gut, oropharynx, or genital tract.

Children under 12 years:

As for adults, but the single intravenous dose is based on 1,5 mL (7,5 mg METRONIDAZOLE 500 mg/100 mL LAMAR) / kg body mass and the oral dose on

7,5 mg/kg body mass.

Prevention

Adults and adolescent (over 12 years) dose:

100 mL (500 mg/100 mL) by intravenous infusion immediately before, during or after operation, followed by the same dose 8 hourly until oral medication.

Children under 12 years:

As for adults but the single intravenous dose is based on 1,5 mL (7,5 mg METRONIDAZOLE 500 mg/100 mL LAMAR) /kg body mass and the oral dose on 7,5 mg/kg body mass.

Method of administration:

Intravenous infusion.

4.3 Contraindications

- Hypersensitivity to metronidazole or other nitroimidazoles and to any of the excipients listed in section 6.1.
- METRONIDAZOLE 500 mg/100 mL LAMAR should be avoided in pregnancy and lactation (see section 4.6).
- METRONIDAZOLE 500 mg/100 mL LAMAR should not be used in patients with blood dyscrasias or with active disease of the central nervous system.

4.4 Special warnings and precautions for use

Neurological and haematological effects

Convulsive seizures, myoclonus, leukopenia and peripheral neuropathy, the latter mainly characterized by numbness or paraesthesia of an extremity, 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.

Hypersensitivity

In the case of severe hypersensitivity reactions (e.g., anaphylactic shock), treatment with METRONIDAZOLE 500 mg/100 mL LAMAR must be discontinued immediately and established emergency treatment must be initiated by qualified health care professionals.

Diarrhoea

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.

Nitroimidazoles

The duration of therapy with metronidazole or medicines containing other nitroimidazoles should not exceed 10 days. Only in specific elective cases and if 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.

Nervous system diseases

Due to the risk of aggravation, metronidazole should be avoided in patients with active or chronic severe peripheral and central nervous system diseases. Treatment should be discontinued if signs of peripheral neuropathy or nervous

system toxicity develop.

Hepatic impairment

Doses should be reduced in patients with severe hepatic impairment.

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 medicine should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their medical practitioner and stop taking metronidazole.

Haematopoiesis

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

Alcohol

Intake of alcoholic beverages must be avoided during metronidazole therapy since adverse reactions such as dizziness and vomiting may occur (disulfiram-like effect).

Ingestion of alcohol during METRONIDAZOLE 500 mg/100 mL LAMAR therapy,

and for at least one day after cessation of therapy may provoke disulfiram-like reactions such as abdominal cramps, nausea, vomiting, headache or flushing, in some patients. Acute psychoses and confused state have been reported when METRONIDAZOLE 500 mg/100 mL LAMAR is taken concomitantly with disulfiram in alcoholic patients.

The administration of pharmaceutical preparations formulated with alcohol, including injections, drinking alcohol or the concomitant use of METRONIDAZOLE 500 mg/100 mL LAMAR and disulfiram may increase the side effects.

General

METRONIDAZOLE 500 mg/100 mL LAMAR may mask the immunological response seen in untreated early syphilis, due to its anti-treponemal activity. Patients suspected of having syphilis while receiving METRONIDAZOLE 500 mg/100 mL LAMAR should be screened for an additional 4 to 8 weeks.

Renal disease

METRONIDAZOLE 500 mg/100 mL LAMAR is removed during haemodialysis and should be administered after the procedure is finished. Patients with renal impairment, including patients receiving peritoneal dialysis, should be monitored for signs of toxicity due to the potential accumulation of toxic metronidazole metabolites.

Special warnings/precautions regarding excipients

METRONIDAZOLE 500 mg/100 mL LAMAR contains 310 mg sodium per solution for infusion equivalent to 16% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interference with laboratory tests

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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 nicotinamide-adenine 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.

4.5 Interaction with other medicines and other forms of interaction

METRONIDAZOLE 500 mg/100 mL LAMAR is reported to impair the metabolism or excretion of several medicines including warfarin, phenytoin, lithium, and fluorouracil, with the consequent potential for an increased incidence of adverse effects.

Phenytoin

There is some evidence that phenytoin might accelerate the metabolism of metronidazole, thereby reducing the efficacy of METRONIDAZOLE 500 mg/100 mL LAMAR when phenytoin is administered concurrently. On the other hand, metronidazole, as in METRONIDAZOLE 500 mg/100 mL LAMAR, inhibits the metabolism of concurrently administered phenytoin, i.e., the plasma concentration of phenytoin is increased.

Amiodarone

QT interval prolongation and torsades 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 torsades de pointes such as dizziness, palpitations, or syncope.

Barbiturates

Plasma concentrations of metronidazole, as in METRONIDAZOLE 500 mg/100 mL LAMAR is decreased by the concomitant administration of phenobarbital, with a consequent reduction in the effectiveness of METRONIDAZOLE 500 mg/100 mL LAMAR.

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

Cimetidine has increased plasma concentrations of metronidazole and might increase the risk of neurological side effects.

Contraceptive medicines

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 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.

Cyclosporine

Metronidazole might increase the risk of elevation of the serum levels 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 medicines must be avoided.

Alcohol

When given in conjunction with alcohol, METRONIDAZOLE 500 mg/100 mL LAMAR may provoke a disulfiram-like reaction in some individuals (effects including intense vasodilation and flushing on the face and neck, restlessness, anxiety, tachycardia, tachypnoea, headache, nausea, vomiting, hyperpnoea, chest pains, sweating, pallor and hypotension). Reactions have occurred after the administration of medicines formulated with alcohol, including injections as well as after drinking alcohol. Alcoholic beverages and medicines containing alcohol should not be consumed during therapy and for at least 1 – 3 days afterwards (see section 4.4).

Fluorouracil

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

Lithium

Lithium concentrations may increase (when therapy is introduced) and thus serum lithium and serum creatinine levels should be monitored several days after beginning treatment to detect lithium intoxication.

Mycophenolate 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 medicines.

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.

Vecuronium (non-depolarising curaremimetic)

METRONIDAZOLE 500 mg/100 mL LAMAR can potentialise the effects of vecuronium.

Cholestyramine

Cholestyramine may delay or reduce the absorption of METRONIDAZOLE 500 mg/100 mL LAMAR.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Contraception in male and females (see section 4.5).

Pregnancy

METRONIDAZOLE 500 mg/100 mL LAMAR should not be used during pregnancy.

Breastfeeding

Since metronidazole is secreted into breastmilk, nursing is to be interrupted 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 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.

4.7 Effects on ability to drive and use machines:

Effects on ability to drive and use machines even when used as directed, metronidazole may alter reactivity so far that the ability to drive or to use machinery is impaired. This holds true to still a higher degree at the beginning of treatment or in combination with alcohol intake.

METRONIDAZOLE 500 mg/100 mL LAMAR has the potential to cause confusion, dizziness, unsteadiness, convulsions, or visual disorders. When these symptoms occur patients should be advised not to drive or operate machinery.

4.8 Undesirable effects

Undesirable effects are mainly associated with prolonged use or high doses. The

most frequently observed effects include nausea, abnormal taste sensations and the risk of neuropathy in case of long-term treatment.

System Organ Class	Frequency	Adverse drug reactions
Blood and lymphatic system disorders	Less Frequent	Leukopenia, agranulocytosis, pancytopenia, neutropenia, thrombocytopenia
	Frequency unknown	Eosinophilia
Immune system disorders	Less Frequent	Anaphylaxis, anaphylactic shock, Jarisch-Herxheimer reaction, angioedema
	Frequency unknown	Hypersensitivity
Metabolism and nutrition disorders	Frequency unknown	Anorexia, decreased appetite
Psychiatric disorders	Less frequent	Psychotic disorders including confusion, irritability and hallucinations, changes in mood or mental state such as depression or confusion
	Frequency unknown	Vertigo
Nervous system disorders	Frequent	Dysgeusia

	Less frequent Frequency unknown	Weakness, dizziness, drowsiness, insomnia, headache, encephalopathy (e.g. confusion) and subacute cerebellar, aseptic meningitis, ataxia, dysarthria, peripheral neuropathy Paraesthesia, hypoaesthesia
Eye disorders	Less frequent	The occurrence of transient vision disorder such as diplopia and myopia, optic neuropathy
Vascular disorders	Frequency unknown	Thrombophlebitis
Cardiac disorders	Frequency unknown	Tachycardia, palpitations
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Nasal congestion, dyspnoea
Gastrointestinal disorders	Frequent Less frequent	Gastrointestinal discomfort, nausea, vomiting, diarrhoea, dry mouth, furred tongue, constipation Antibiotic-associated colitis, pancreatitis, upper abdominal

		pain, tongue discolouration
	Frequency unknown	Pseudomembranous colitis, coated tongue and unpleasant taste
Hepatobiliary disorders	Less frequent	Reversible abnormal liver function and cholestatic hepatitis, sometimes with jaundice
	Frequency unknown	Raised liver enzyme values
Skin and subcutaneous tissue disorders	Less frequent	Pustular eruptions, mild erythematous eruptions with fleeting joint pains resembling serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
	Frequency unknown	Skin rash, fever, flushing, pruritus, face swelling, urticaria, hyperhidrosis
Musculoskeletal and connective tissue disorders	Frequent	Myalgia
	Frequency unknown	Muscle spasms, arthralgia
Renal and urinary disorders	Less frequent	Urethral discomfort and darkening of the urine may occur

	Frequency unknown	Dysuria
General and administration site conditions	Less frequent	Asthenia, mucosal inflammation, pyrexia
	Frequency unknown	Injection site reaction, malaise, facial oedema, peripheral oedema, chest pain, chills

Description of selected adverse reactions

Nervous system disorders:

Reports of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor), which may resolve with discontinuation of the medicine.

Peripheral neuropathy usually presenting as numbness or tingling in the extremities, and epileptic form seizures are serious adverse effects on the nervous system that have been associated especially with high doses of METRONIDAZOLE 500 mg/100 mL LAMAR or prolonged treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA's website.

4.9 Overdose

Symptoms:

As signs and symptoms of overdose the undesirable effects described under section 4.8 may appear.

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.

In cases where haemodialysis is not required, patients should receive appropriate supportive care, including close monitoring and symptomatic management, to ensure adequate recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A.20.2 Other than antibiotics.

ATC Code: J01X D01.

Mechanism of action

- Metronidazole is a prodrug; it requires reductive activation of the nitro group by susceptible organisms. The parent compound penetrates the cell membrane unchanged, but once inside the cell the nitro group is reduced by the reduction oxidation conditions prevalent in the anaerobic cell. Reduced metronidazole, which is cytotoxic but short-lived, interacts with DNA to cause a loss of helical structure, strand breakage, and resultant inhibition of nucleic acid synthesis and cell death.
- Metronidazole has bactericidal activity against anaerobic bacteria. Metronidazole has antiprotozoal activity against *Trichomonas vaginalis* and other protozoa, including *Entamoeba histolytica* and *Giardia lamblia*. Metronidazole has no effect on *Candida species*, and it does not affect the

acidophilic flora of the vagina.

- Metronidazole does not impede the activity of antibacterial agents which are active against a variety of aerobes and facultative anaerobes. Metronidazole manifests antibacterial activity against all anaerobic cocci and both anaerobic gram-negative bacilli, including *Bacteroides* species, and anaerobic spore-forming gram-positive bacilli.

5.2. Pharmacokinetic properties

Distribution

At recommended intravenous doses, peak steady-state serum concentrations are approximately 25 mcg/mL. Metronidazole is distributed to the bone, liver and liver abscesses, lungs, vaginal secretions, seminal fluids, bile, saliva, and breast milk. It also crosses the placenta and the blood brain barrier. The half-life in plasma is about 8 hours, and its volume of distribution is approximately that of total body water. Less than 20 % of the drug is bound to plasma proteins. Therapeutic concentrations also are achieved in cerebrospinal fluid.

Metabolism

The liver is the main site of metabolism, and this accounts for over 50 % of the systemic clearance of metronidazole. The hydroxy metabolite has a half-life of 12 hours.

Elimination

About 60 – 80 % is excreted in urine via the kidneys (20 % of this amount is excreted unchanged), and about 6 – 15 % as inactive metabolites in faeces. Metronidazole and its metabolites are significantly removed by haemodialysis, but insignificantly by peritoneal dialysis.

6. PHARMACEUTICAL PARTICULARS

PROFESSIONAL INFORMATION FOR METRONIDAZOLE 500 mg/100 mL LAMAR

6.1 List of excipients

Citric acid monohydrate

Disodium phosphate dihydrate

Sodium chloride

Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for

those mentioned in section 6.6.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

Polypropylene bottle containing 100 mL of solution for infusion.

Pack size: packages with 1, 4, 10, 25, 50 or 100 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

METRONIDAZOLE 500 mg/100 mL LAMAR can be diluted with glucose 5%,

Ringer's lactate, glucose-sodium chloride and sodium chloride 0,9%.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Lamar International (Pty) Ltd

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8. REGISTRATION NUMBERS

60/20.2/0072

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 July 2026