SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
METRONIDAZOLE 500 mg/100 mL FRESENIUS solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 100 mL of the solution contains:
500 mg metronidazole

Sugar free.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for infusion.
A clear, colourless to pale straw-coloured, sterile solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
1. 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 is bactericidal, such as fusobacteria, eubacteria, *Clostridia* and anaerobic *Streptococci*.
   METRONIDAZOLE FRESENIUS has been used successfully for anaerobic infections in the following indication: pelvic inflammatory disease and postoperative wound infections. Combined therapy is often indicated as there are usually mixed infections.

2. For the prevention of postoperative abdominal and pelvic infections due to anaerobic bacteria:
   i. given before and after gynaecological surgery;
   ii. given before and after appendicectomy;
   iii. given before and after colonic surgery.

4.2 Posology and method of administration
A. TREATMENT
Adults and children over 12 years:
100 mL (500 mg) by intravenous infusion eight hourly. The injection should be infused intravenously at the rate of 25 mg per minute (5 mL per minute) but may be administered alone or concurrently (but separately), with other bacteriologically appropriate antibacterial medicines in parenteral dosage forms.
Oral medication with 400 mg 8 hourly should be substituted as soon as this becomes feasible. Treatment for seven days should be satisfactory for most patients but, depending upon clinical and bacteriological assessments, the physician might decide to prolong 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/kg body mass (7,5 mg metronidazole/kg body mass) and the oral dose of 7 mg/kg body mass.

B. PREVENTION

Adults and children over 12 years:

100 mL (500 mg) by intravenous infusion immediately before, during or after an operation, followed by the same dose eight hourly until oral medication (200 – 400 mg 8 hourly) can be given.

Children under 12 years:

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

In infants and other patients maintained on intravenous fluids, METRONIDAZOLE FRESENIUS may be diluted with appropriate volumes of normal saline, dextrose saline, dextrose 5 % *m/v* or potassium chloride injections (20 mmol and 40 mmol/litre).

4.3 Contraindications

- Hypersensitivity to metronidazole or any other ingredient of METRONIDAZOLE FRESENIUS (see section 6.1).
- METRONIDAZOLE FRESENIUS should not be used in patients with blood dyscrasias or with active disease of the central nervous system.
- METRONIDAZOLE FRESENIUS use should be avoided during pregnancy and lactation.

4.4 Special warnings and precautions for use

Intensive or prolonged treatment

Clinical and laboratory monitoring is advised in patients receiving METRONIDAZOLE FRESENIUS for more than 10 days. This period may only be exceeded in individual cases after a very strict benefit-risk assessment. Only in the rarest possible case should the treatment be repeated. Limiting the duration of treatment is necessary because damage to human germ cells cannot be excluded.

Intensive or prolonged METRONIDAZOLE FRESENIUS therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction. Prolonged or intensive treatment with METRONIDAZOLE FRESENIUS has been associated with peripheral neuropathy, transient epileptiform seizures and leukopenia.

In case of prolonged treatment, occurrence of undesirable effects such as paraesthesia, ataxia, dizziness and convulsive crises should be checked. High dose regimes have been associated with transient epileptiform seizures.

Pseudomembranous colitis has been reported following the use of METRONIDAZOLE FRESENIUS.

The half-life of metronidazole is reported to be longer in neonates and in patients with severe hepatic impairment; that of the hydroxyl metabolite is prolonged in patients with substantial renal impairment (see section 5.2).

Hepatic impairment

Caution is needed in patients with severe hepatic impairment. The dose of METRONIDAZOLE FRESENIUS should be reduced as necessary. METRONIDAZOLE FRESENIUS is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit ratio of using METRONIDAZOLE FRESENIUS to treat trichomoniasis in such patients should be carefully considered. Plasma levels of metronidazole should be closely

monitored. Caution is needed in patients with hepatic encephalopathy. Patients with severe hepatic encephalopathy metabolise metronidazole slowly, with resultant accumulation of metronidazole. This may cause exacerbation of CNS adverse effects. The dose of METRONIDAZOLE FRESENIUS should be reduced as necessary.

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, such as METRONIDAZOLE FRESENIUS. In this population, METRONIDAZOLE FRESENIUS 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, METRONIDAZOLE FRESENIUS should be discontinued.
Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop using METRONIDAZOLE FRESENIUS.

Renal disease
METRONIDAZOLE FRESENIUS 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.

Alcohol
Patients should be advised not to drink alcohol before, during METRONIDAZOLE FRESENIUS therapy and for at least one day and up to 3 days afterwards because of the possibility of a disulfiram-like reaction (see section 4.5).

General
Co-administration with busulfan: as plasma level of busulfan may be increased significantly, it may lead to severe busulfan toxicity and death.

Studies have shown METRONIDAZOLE FRESENIUS to be mutagenic in bacteria and carcinogenic in some animals. METRONIDAZOLE FRESENIUS should be administered with caution to patients with hepatic encephalopathy.
METRONIDAZOLE FRESENIUS has anti-treponemal activity and may mask the immunological response seen in untreated early syphilis; contacts of patients with syphilis receiving METRONIDAZOLE FRESENIUS should probably be screened for an additional 4 – 8 weeks.

Patients should be warned that METRONIDAZOLE FRESENIUS may darken the urine (due to metronidazole metabolite).

Due to increased risk for adverse reactions, regular clinical and laboratory monitoring (including blood count) are advised in cases of high-dose, prolonged or repeated treatment, in

case of antecedents of blood dyscrasia, in case of severe infection and in severe hepatic insufficiency.

Patients on low sodium diet
METRONIDAZOLE FRESENIUS contains sodium. This may be harmful to patients on a low sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Disulfiram:
Acute psychoses or confusion have been associated with the concomitant use of METRONIDAZOLE FRESENIUS and disulfiram.

Alcohol:
When given in conjunction with alcohol, METRONIDAZOLE FRESENIUS 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).

Oral anticoagulant therapy (warfarin type):
Potentiation of the anticoagulant effect and increased haemorrhagic risk. In case of co-administration with warfarin, prothrombin time/INR should be more frequently monitored, and warfarin therapy/dose adjusted during treatment with METRONIDAZOLE FRESENIUS.

Lithium:
Plasma levels of lithium may be increased by METRONIDAZOLE FRESENIUS. Plasma concentration of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive METRONIDAZOLE FRESENIUS.

Ciclosporin:
Risk of elevation of ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when co-administration is necessary.

Phenytoin or phenobarbital:
There is evidence that phenytoin might accelerate the metabolism of METRONIDAZOLE FRESENIUS. Plasma concentrations of METRONIDAZOLE FRESENIUS are decreased by the concomitant administration of phenobarbital, with a consequent reduction in the effectiveness of METRONIDAZOLE FRESENIUS.

5-Fluorouracil:
Reduced clearance of 5-flourouracil resulting in increased toxicity of 5-fluorouracil may occur.

Busulfan:

Plasma levels of busulfan may be increased by METRONIDAZOLE FRESENIUS, which may lead to severe busulfan toxicity and death (see section 4.3, and section 4.4).

Cimetidine:
Hepatic metabolism may be decreased when METRONIDAZOLE FRESENIUS and cimetidine are used concurrently, possibly resulting in delayed elimination and increased serum metronidazole concentrations with an increased risk of neurological side effects.

Vecuronium (non-depolarising curaremimetic):
METRONIDAZOLE FRESENIUS can potentialise the effects of vecuronium.

Cholestyramine:
Cholestyramine may delay or reduce the absorption of METRONIDAZOLE FRESENIUS.

CYP3A4 substrates:
Concomitant use of METRONIDAZOLE FRESENIUS and CYP3A4 substrates (e.g., amiodarone, tacrolimus, cyclosporine, carbamazepine, and quinidine) may increase respective CYP3A4-substrate plasma levels. Monitoring of plasma concentrations of CYP3A4 substrates may be necessary.

Laboratory tests:
METRONIDAZOLE FRESENIUS may immobilise treponema and thus may lead to falsely positive Nelson's test. METRONIDAZOLE FRESENIUS may interfere with serum aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase determinations. Metronidazole causes an increase in ultraviolet absorbance at 340 nm resulting in falsely decreased values.

4.6 Fertility, pregnancy and lactation
Safety and efficacy in pregnancy and lactation have not been established.
METRONIDAZOLE FRESENIUS crosses the placenta barrier and is excreted in breastmilk.
METRONIDAZOLE FRESENIUS should not be used during pregnancy and women breastfeeding their infants.

4.7 Effects on ability to drive and use machines
Patients should be warned about the potential for confusion, dizziness, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects
The following side effects have been reported.

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: Weakness, dizziness, drowsiness, insomnia, headache. 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, aseptic meningitis, ataxia, dysarthria. 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 FRESENIUS or prolonged treatment.
Frequency unknown: Paraesthesia, hypoaesthesia.

Eye disorders
Less frequent: The occurrence of transient vision disorder such as diplopia and myopia may follow the use of METRONIDAZOLE FRESENIUS, optic neuropathy.

Vascular disorders
Thrombophlebitis may follow intravenous administration of METRONIDAZOLE FRESENIUS.

Cardiac disorders:
Frequency unknown: Tachycardia, palpitations.

Respiratory, thoracic and mediastinal disorders
Frequency unknown: Nasal congestion, dyspnoea.

Gastrointestinal disorders
Frequent: Gastrointestinal discomfort, especially nausea and taste disorders; nausea is sometimes accompanied by headache and vomiting. Diarrhoea, dry mouth, a furred tongue, oral mucositis, stomatitis, glossitis and constipation.
Less frequent: Antibiotic-associated colitis, pancreatitis, upper abdominal pain, tongue discolouration.
Frequency unknown: Pseudomembranous colitis, coated tongue and unpleasant taste.

Hepatobilary 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.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of METRONIDAZOLE FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of METRONIDAZOLE FRESENIUS. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms
In cases of overdose in adults, the clinical symptoms are usually limited to nausea, vomiting and neurotoxic effects, including ataxia, slight disorientation, confusion, seizures and peripheral neurophathy.

Treatment
There is no specific treatment for gross overdosage. METRONIDAZOLE FRESENIUS infusion should be discontinued. The treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2 Antimicrobial agents.
Pharmacotherapeutic group: Antibacterials for systemic use: imidazole derivatives
ATC code: J01XD01

Metronidazole is active against a variety of anaerobic bacteria, particularly *Bacteroides fragilis*. Metronidazole has antiprotozoal activity against *Trichomonas vaginalis* and other protozoa, including *Entamoeba histolytica* and *Giardia lamblia*. It does not affect the acidophilic flora of the vagina and it has no effect on *Candida* species. Its mechanism of action is reflected in a selective toxicity to anaerobic or microaerophilic micro-organisms and for other anoxic or hypoxic cells. In susceptible

cells the nitro group of metronidazole is reduced by electron transport proteins with low redox potentials (such as ferredoxin in *Clostridia*); these proteins play a much more important role in the metabolism of such cells than they do in aerobes. Metronidazole thus acts as an electron sink and deprives the cell of required reducing equivalents.

The following has been proposed as the mode of action of metronidazole: the parent compound penetrates the cell membrane unchanged, but once inside the cell the nitro group is reduced in the redox condition prevalent in the anaerobic cell.
The reduced product is known to damage deoxyribonucleic acid (DNA) causing eventual death of the organism.

5.2 Pharmacokinetic properties
The elimination half-life of metronidazole is about 8 hours; that of the hydroxyl metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates and in patients with severe hepatic impairment; that of the hydroxyl metabolite is prolonged in patients with substantial renal impairment (see section 4.4). Metronidazole is absorbed from the gastrointestinal tract and widely distributed in body tissue. Approximately 30 – 40 % of a dose is metabolised in the liver; the majority of a dose of metronidazole is extracted in the urine, mainly as metabolites; a small amount appears in the faeces.
Metronidazole is able to pass the blood-brain barrier. It reaches therapeutic concentrations in most other body fluids, i.e. saliva, bile, urine, amniotic fluid, breastmilk and in abscess cavities.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Citric acid (for pH-adjustment),
disodium phosphate (E339ii) (for pH-adjustment),
sodium chloride,
water for injection.

6.2 Incompatibilities
This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life
PVC bags: 36 months.
free*flex*® bags: 24 months.

6.4 Special precautions for storage
Protect from light.
PVC bags: Store at or below 25°C.
free*flex*® bags: Store at or below 30°C.

6.5 Nature and contents of container
100 mL **free***flex*® or PVC bags. Pack size: 1, 40 or 50.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

METRONIDAZOLE FRESENIUS injection compatibilities
METRONIDAZOLE FRESENIUS is compatible with the following injection:
Sodium chloride injection 0,9 % *m/v* (normal saline injection)
Dextrose 5 % *m/v* injection
Sodium chloride 0,18 % and dextrose 4 % *m/v* injection
Potassium chloride injection 20 mmol/litre
Potassium chloride injection 40 mmol/litre.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd
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8. REGISTRATION NUMBER

Q/20.2/92

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 June 1982

10. DATE OF REVISION OF THE TEXT

15 February 2021

Kenya: H2004/150, POM
Namibia: NS2 90/20.2/00425
Zambia: 254/012, POM
Zimbabwe: 7.2.5 Other Antibacterials
2006/7.2.5/4438, PP