BIO METRONIDAZOLE IV

SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
BIO METRONIDAZOLE IV solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 100 mL 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 yellow solution. The solution is sterile and free from particulate matter.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
1. For the treatment of infection 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 BIO METRONIDAZOLE IV is bactericidal, such as *fusobacteria, eubacteria, clostridia* and *anaerobic streptococci*.
BIO METRONIDAZOLE IV is used for anaerobic infections in the following indications:
postoperative wound infections and pelvic inflammatory disease.
Combined therapy is often indicated as these are usually mixed infections.

2. For the prevention of postoperative infections due to anaerobic bacteria:
i. Given before and after gynaecological surgery;
ii. Given before and after appendectomy;
iii. Given before and after colonic surgery.

4.2 Posology and method of administration
Posology
Treatment of anaerobic infections:
Adults and adolescents (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 25 mg per minute (5 mL per minute), but may be administered alone or concurrently (but separately) with other bacteriologically appropriate antibacterial medicines in parental dosage forms. Oral medicine 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 doctor 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 7,5 mg/kg body mass.

Prevention:
Adults and adolescents (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 medicine (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 (7,5 mg BIO METRONIDAZOLE IV)/kg body mass and the oral dose on 7,5 mg/kg body mass.
In infants and other patients maintained on intravenous fluids,
BIO METRONIDAZOLE IV 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).

Method of administration
Intravenous infusion.

4.3 Contraindications
- Hypersensitivity to metronidazole, other imidazoles derivatives, or any of the excipients listed in section 6.1.
- Use of BIO METRONIDAZOLE IV is contraindicated in patients with end stage liver damage, blood dyscrasias and active diseases of the central or peripheral nervous system.
- Pregnancy and lactation.

4.4 Special warnings and precautions for use
Hepatic impairment:
Caution is needed in patients with severe hepatic impairment. The dose of BIO METRONIDAZOLE IV should be reduced as necessary.
BIO METRONIDAZOLE IV is mainly metabolised by hepatic oxidation. Substantial impairment of BIO METRONIDAZOLE IV clearance may occur in the presence of advanced hepatic insufficiency. Doses should be reduced in patients with severe hepatic impairment.
The risk/benefit of using BIO METRONIDAZOLE IV to treat trichomoniasis in such patients should be carefully considered. Plasma levels of BIO METRONIDAZOLE IV 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 central nervous system (CNS) adverse effects. The dose of BIO METRONIDAZOLE IV 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 BIO METRONIDAZOLE IV. In this population, BIO METRONIDAZOLE IV 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, BIO METRONIDAZOLE IV should be discontinued.
Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their doctor and stop using BIO METRONIDAZOLE IV.

Renal disease:
BIO METRONIDAZOLE IV 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.

Patients on a low sodium diet:
BIO METRONIDAZOLE IV contains 13,75 mmol (316 mg) sodium per 100 mL. This may be harmful to patients on a low sodium diet.

Alcohol:
Drinking of alcohol or concomitant administration of medicines formulated with alcohol, including injections, during BIO METRONIDAZOLE IV therapy, and for at least one to three days after cessation of therapy may provoke disulfiram-like reactions such as abdominal cramps, nausea, vomiting, headache or flushing, in some patients. Concomitant use of BIO METRONIDAZOLE IV and disulfiram may increase the side effects (see section 4.5). Acute psychoses and confusional states have been reported when BIO METRONIDAZOLE IV was used concomitantly with disulfiram in alcoholic patients (see section 4.5).

Intensive or prolonged therapy with BIO METRONIDAZOLE IV:
Clinical and laboratory monitoring is advised in patients receiving BIO METRONIDAZOLE IV 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 BIO METRONIDAZOLE IV therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction. Prolonged or intensive treatment with BIO METRONIDAZOLE IV 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.

Monitoring:
BIO METRONIDAZOLE IV may mask the immunological response seen in untreated early syphilis, due to its anti-treponemal activity. Patients suspected of having syphilis while receiving BIO METRONIDAZOLE IV should probably be screened for an additional 4 to 8 weeks.
Regular clinical and laboratory monitoring (including leukocyte formula) are advised in cases of high-dose or prolonged treatment, in case of antecedents of blood dyscrasia, in case of severe infection and in severe hepatic insufficiency.

General:
Patients should be warned that BIO METRONIDAZOLE IV may darken urine due to metronidazole metabolite.
Pseudomembranous colitis has been reported with the use of BIO METRONIDAZOLE IV.
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, as in BIO METRONIDAZOLE IV, to be mutagenic in bacteria and carcinogenic in some animals.
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).

4.5 Interaction with other medicines and other forms of interaction Disulfiram
Acute psychoses or confusion have been associated with the concomitant use of BIO METRONIDAZOLE IV and disulfiram.

Alcohol
When given in conjunction with alcohol, BIO METRONIDAZOLE IV 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 coadministration with warfarin, prothrombin time/INR should be more frequently monitored and warfarin therapy/dose adjusted during treatment with BIO METRONIDAZOLE IV.

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

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 BIO METRONIDAZOLE IV. Plasma concentrations of BIO METRONIDAZOLE IV are decreased by the concomitant administration of phenobarbital, with a consequent reduction in the effectiveness of BIO METRONIDAZOLE IV.

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

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

CYP3A4 substrates
Concomitant use of BIO METRONIDAZOLE IV 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.

Vecuronium (non-depolarising curare mimetic)
BIO METRONIDAZOLE IV can potentialise the effects of vecuronium.

Cholestyramine
Cholestyramine may delay or reduce the absorption of metronidazole.

Busulfan
Plasma concentrations of busulfan may increase during concomitant treatment with BIO METRONIDAZOLE IV, which can result in severe busulfan toxicity and death.

Laboratory tests
BIO METRONIDAZOLE IV may immobilise treponema and thus may lead to falsely positive Nelson's test.
BIO METRONIDAZOLE IV 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
Pregnancy
BIO METRONIDAZOLE IV is contraindicated during pregnancy (see section 4.3).

Breastfeeding
BIO METRONIDAZOLE IV is contraindicated during breastfeeding as metronidazole is excreted in breast milk (see section 4.3). Nursing mothers should either stop breastfeeding or BIO METRONIDAZOLE IV should be discontinued.

Fertility
There are no clinical data relating to the effect of metronidazole on fertility.

4.7 Effects on ability to drive and use machines
BIO METRONIDAZOLE IV 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 machines.

4.8 Undesirable effects
Infections and infestations:
Less frequent: Vaginal candidiasis.

Blood and lymphatic system disorders
Less frequent: Leucopenia, thrombocytopenia, agranulocytosis, neutropenia, pancytopenia.
Frequency not known: Eosinophilia.

Immune system disorders
Less frequent: Hypersensitivity (manifesting as skin rash, fever, angioedema, hives, flushing, urticaria, pruritus), anaphylaxis, anaphylactic shock, Jarisch-Herxheimer reaction.
Frequency not known: Mild erythematous eruptions with fleeting joint pains resembling serum sickness may occur.

Metabolism and nutrition disorders
Frequency not known: Anorexia, decreased appetite.

Psychiatric disorders
Frequency not known: Psychotic disorders including confusion, irritability and hallucinations. Changes in mood or mental state such as depression. Vertigo.

Nervous system disorders
Frequent: Dysgeusia.
Less frequent: Central nervous system (CNS) effects such as weakness, drowsiness, dizziness or light-headedness; headaches. Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and seizures are serious adverse effects associated with high doses or prolonged treatment. CNS toxicity such as ataxia, clumsiness or unsteadiness.
Encephalopathy and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor) which may resolve with discontinuation of the medicine, seizures/convulsions, aseptic meningitis.
Frequency not known: Paraesthesia, hypoaesthesia.

Eye disorders
Less frequent: Transient vision disorders such as diplopia and myopia have been reported. Optic neuropathy.

Vascular disorders
Frequency not known: Thrombophlebitis may follow intravenous administration.

Cardiac disorders
Frequency not known: Tachycardia, palpitations.

Respiratory, thoracic and mediastinal disorders
Frequency not known: Nasal congestion, dyspnoea.

Gastrointestinal disorders
Frequent: Gastrointestinal disturbances, nausea, vomiting, stomatitis, glossitis, oral mucositis. Nausea is sometimes accompanied by headache. Diarrhoea, constipation, dry mouth and furred tongue.
Less frequent: Antibiotic-associated colitis, pancreatitis, upper abdominal pain, tongue discolouration.
Frequency not known: Pseudomembranous colitis, coated tongue and unpleasant taste.

Hepato-biliary disorders
Less frequent: Raised liver enzyme values have occasionally been reported. Cases of reversible abnormal liver function and cholestatic hepatitis, sometimes with jaundice have been reported.

Skin and subcutaneous tissue disorder
Less frequent: Pustular eruptions, mild erythematous eruptions with fleeting joint pains resembling serum sickness, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme.
Frequency not known: Skin rash, flushing, pruritus, face swelling, urticaria, hyperhidrosis.

Musculoskeletal and connective tissue disorders
Frequent: Myalgia.
Frequency not known: Arthralgia, muscle spasms.

Renal and urinary disorders
Less frequent: Urinary tract effects such as dysuria, increased urinary frequency, frequent or painful urination; inability to control urine flow; sense of pelvic pressure, dark urine.

General disorders and administration site conditions
Less frequent: Thrombophlebitis manifesting as pain, tenderness, redness or swelling at site of injection, asthenia, mucosal inflammation, pyrexia.
Frequency not known: Injection site reaction, malaise, face oedema, peripheral oedema, chest pain, chills.

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

4.9 Overdose
Refer to section 4.8.
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 neuropathy. In a preterm newborn, no clinical or biological sign of toxicity developed.

Treatment
BIO METRONIDAZOLE IV infusion should be discontinued. There is no specific antidote, treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES
Category and class: A. 20.2 Other than antibiotics
Pharmacotherapeutic group: Antibacterials for systemic use: imidazole derivatives.
ATC code: J01XD01.

5.1 Pharmacodynamic properties
Metronidazole is a pro-drug; 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 medicines 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
At recommended intravenous doses, peak steady-state serum concentrations are approximately 25 µg/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 medicine is bound to plasma proteins. Therapeutic concentrations also are achieved in cerebrospinal fluid. 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. 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.
In patients with impaired liver function, the metabolism of metronidazole is expected to decrease, leading to an increase in the plasma elimination half-life. In patients with severe liver impairment, clearance may be decreased up to approximately 65 %, resulting in an accumulation of metronidazole in the body.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Citric acid monohydrate
Dibasic sodium phosphate (anhydrous)
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
24 months.

6.4 Special precautions for storage
Store at or below 30 °C. Do not refrigerate.
For single use only. Discard any remaining contents after use.
Protect from light.

6.5 Nature and contents of container
BIO METRONIDAZOLE IV is packed in a 100 mL transparent white LDPE bottle. Each bottle is wrapped with a transparent clear polypropylene wrapper.

6.6 Special precautions for disposal and other handling
BIO METRONIDAZOLE IV injection is compatible with the following injections:
Sodium chloride injection 0,9 % m/v (normal saline injection)
Dextrose 5 % m/v injection
Bacteriostatic water for injection
Bacteriostatic sodium chloride 0,9 %
Ringer's injection, lactated.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Biotech Laboratories (Pty) Ltd
Ground Floor, Block K West, Central Park
400 16th Road, Randjespark
Halfway House
Midrand 1685

8. REGISTRATION NUMBER
42/20.2/0567

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14 September 2012

10. DATE OF REVISION OF THE TEXT
05 May 2023

BIO METRONIDAZOLE IV

SKEDULERINGSTATUS
S4

1. NAAM VAN DIE MEDISYNE
BIO METRONIDAZOLE IV oplossing vir infusie

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING
Elke 100 mL oplossing bevat 500 mg metronidasool.
Suikervry.
Vir die volle lys van die hulpstowwe, sien afdeling 6.1.

3. FARMASEUTIESE VORM
Oplossing vir infusie.
'n Helder, kleurlose tot liggeel oplossing. Die oplossing is steriel en vry van enige deeltjies.

4. KLINIESE BESONDERHEDE
4.1 Terapeutiese indikasies
1. Vir die behandeling van infeksie waar anaërobiese bakterieë as patogene geïdentifiseer is of vermoed word, veral *Bacteroides fragilis* en ander bakteroïede spesies, insluitend ander spesies waarvoor BIO METRONIDAZOLE IV bakterisidies is, soos bv. *fusobakterieë, eubakterieë, clostridia* en *anaërobiese streptococci*.
BIO METRONIDAZOLE IV word gebruik vir anaerobiese infeksies in die volgende gevalle:
Postoperatiewe wondinfeksies en buik inflammatoriese siekte.
Gekombineerde terapie word gereeld aangedui aangesien hierdie gewoonlik gemengde infeksies is.

2. Vir die voorkoming van post-operatiewe infeksies as gevolg van anaërobiese bakterieë:
i. Gegee voor en na ginekologiese chirurgie;
ii. Gegee voor en na blindedermoperasie;
iii. Gegee voor en na kolonchirurgie.

4.2 Posologie en metode van toediening
Posologie
Behandeling van anaerobiese infeksies:
Dosering vir volwassenes en adolessente (ouer as 12 jaar):
100 mL (500 mg/100 mL) deur binneaarse infusie elke 8 ure. Die inspuiting moet binneaars toegedien word teen 'n dosis van 25 mg per minuut (5 mL per minuut), maar kan ook alleen of gelyktydig toegedien word (as aparte inspuiting) saam met ander bakteriologies toepaslike antibakteriële medisyne in parenterale doseervorme.
Sodra dit moontlik/ herhaalbaar is moet orale medisyne die binneaarse roete vervang teen 'n dosis van 40 mg elke 8 ure. Behandeling vir sewe dae behoort bevredigend te wees vir meeste pasiënte, maar, afhangende van die kliniese en bakteriologiese assesserings mag die dokter dalk besluit om die behandeling te verleng, bv. vir die uitwissing van infeksie van areas wat nie gedreineer kan word nie of wat aanspreeklik is vir endogene herbesmetting deur anaërobiese patogene vanuit die derm, orofarynks of genitale kanaal.

Kinders jonger as 12 jaar:
Soos in dosering vir volwassenes, maar die eenmalige binneaarse dosis is gebaseer op 1,5 mL/kg liggaamsgewig (7,5 mg metronidasool/kg liggaamsgewig) en die orale dosis van 7,5 mg/kg liggaamsgewig.

Voorkomende gebruik:
Dosering vir volwassenes en adolessente (12 jaar en ouer):
100 mL (500 mg/100 mL) deur binneaarse infusie dadelik voor, gedurende of na die operasie gevolg deur dieselfde dosis 8-uurliks totdat orale medisyne (200 - 400 mg 8-uurliks) gegee kan word.

Kinders jonger as 12 jaar:
Soos in dosering vir volwassenes, maar die eenmalige binneaarse dosis is gebaseer op 1,5 mL (7,5 mg BIO METRONIDAZOLE IV)/kg liggaamsgewig en die orale dosis op 7,5 mg/kg liggaamsgewig.
In babas en ander pasiënte wat gehandhaaf word op bineaarse vloeistof, mag BIO METRONIDAZOLE IV verdun word met toepaslike volumes van normale soutoplossing, dekstrose soutoplossing, dekstrose 5 % m/v of kaliumchlooried inspuitings (20 mmol en 40 mmol/liter).

Metode van toediening
Binneaarse infusie.

4.3 Kontraindikasies
- Hipersensitiwiteit vir metronidasool, ander imidasoolderivate of enige van die hulpstowwe gelys in afdeling 6.1.
- Die gebruik van BIO METRONIDAZOLE IV is teenaangedui in pasiënte met eindstadium lewerbeskadiging, bloeddiskrasieë en aktiewe siektes van die sentrale of perifere senustelsel.
- Swangerskap en borsvoeding.

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik
Lewerimperking:
Versigtigheid is nodig in pasiënte met ernstige lewerinkorting. Die dosis van BIO METRONIDAZOLE IV moet verlaag word soos nodig.
BIO METRONIDAZOLE IV word hoofsaaklik gemetaboliseer deur leweroksidasie. Aansienlike verswakking van BIO METRONIDAZOLE IV opruiming mag voorkom in die teenwoordigheid van gevorderde lewerontoereikendheid. Dosisse moet verlaag word in pasiënte met ernstige lewerinkorting.
Die risiko/ voordeel van BIO METRONIDAZOLE IV gebruik om trichomoniasis te behandel in sulke pasiënte moet versigtig oorweeg word. Plasmavlakke van BIO METRONIDAZOLE IV moet versigtig gemonitor word.
Versigtigheid is nodig in pasiënte met hepatiese enkefalopatie. Pasiënte met ernstige hepatiese enkefalopatie metaboliseer metronidasool stadig, wat lei tot die opeenhoping van metronidasool. Dit mag 'n verergering van die sentralesenuweestelsel (SSS) nadelige effekte hê. Die dosis van BIO METRONIDAZOLE IV moet verlaag word soos nodig.
Gevalle van ernstige hepatotoksisiteit/ akute lewerversaking insluitende gevalle met 'n noodlottige uitkoms met 'n baie vinnige aanvang na behandeling begin is in pasiënte met Cockayne se sindroom is gerapporteer vir produkte wat metronidasool vir sistemiese gebruik bevat, soos BIO METRONIDAZOLE IV. In hierdie populasie moet BIO METRONIDAZOLE IV daarom na versigtige voordeel-risiko oorweging gebruik word en slegs as geen ander alternatiewe behandeling beskikbaar is nie. Lewerfuksietoetse moet gedoen word voordat die terapie begin word, gedurende terapie en na die einde van die terapie totdat lewerfuksie binne normale perke is of totdat die basislynwaardes bereik is. Indien die lewerfunksietoetse merkbaar verhoog is gedurende behandeling, moet BIO METRONIDAZOLE IV gestaak word.
Pasiënte met Cockayne se sindroom moet aangeraai word om onmiddelik enige simptome van potensiële lewerbeskadiging aan hul dokter te rapporteer en moet BIO METRONIDAZOLE IV staak.

Niersiekte:
BIO METRONIDAZOLE IV word gedurende hemodialise verwyder en moet toegedien word na die prosedure voltooi is.
Pasiënte met nierinkorting, insluitende pasiënte wat peritonale dialise ontvang moet gemonitor word vir tekens van toksisiteit as gevolg van die moontlike opeenhoping van toksiese metronidasoolmetaboliete.

Pasiënte op 'n lae natriumdieet:
BIO METRONIDAZOLE IV bevat 13,75 mmol (316 mg) natrium per 100 mL. Dit mag skadelik wees vir pasiënte op 'n lae natriumdieet.

Alkohol:
Die drink van alkohol or gelyktydige toediening van medisyne wat met alkohol geformuleer is, insluitende inspuitings, gedurende terapie met BIO METRONIDAZOLE IV en vir ten minste een tot drie dae na die staking van terapie mag disulfiram-agtige reaksies soos maagkrampe, naarheid, braking, hoofpyn of blosing veroorsaak in sommige pasiënte. Gelyktydige gebruik van BIO METRONIDAZOLE IV en disulfiram mag die newe-effekte verhoog (sien afdeling 4.5). Akute psigose en verwarde toestande is gerapporteer wanneer BIO METRONIDAZOLE IV gelyktydig met disulfiram gebruik is in alkoholiese pasiënte (sien afdeling 4.5).

Intensiewe of langdurige terapie met BIO METRONIDAZOLE IV:
Kliniese en laboratoriummonitering word aanbeveel in pasiënte wat BIO METRONIDAZOLE IV vir meer as 10 dae ontvang. Hierdie periode mag slegs oorskry word in individuele gevalle na 'n baie streng voordeel-risiko assessering. Slegs in die skaarste moontlike gevalle moet die behandeling herhaal word. Die beperking van die duur van behandeling is nodig omdat beskadiging van die menslike kiemselle nie uitgesluit kan word nie.
Intensiewe of verlengde BIO METRONIDAZOLE IV-terapie moet slegs onder noukeurige toesig vir kliniese en biologiese effekte onder spesialisaanwysing gedoen word. Verlenge of intensiewe behandeling met BIO METRONIDAZOLE IV is geassosieer met perifere neuropatie, verbygaande epileptiforme aanvalle en leukopenie.
In die geval van verlengde behandeling, moet die voorkoms van nadelige effekte soos parestesie, ataksia, duiseligheid en konvulsiewe krisisse nagegaan word.

Monitering:
BIO METRONIDAZOLE IV mag die immunologiese reaksie wat gesien word in vroeë sifilis masker as gevolg van sy anti-treponemale aktiwiteit. Pasiënte wat vermoedelik sifilis het terwyl hulle BIO METRONIDAZOLE IV ontvang moet waarskynlik getoets word vir 'n addisionele 4 tot 8 weke.
Gereelde kliniese en laboratoriummonitering (insluitend leukosietformule) word aanbeveel in gevalle van hoë-dosis of verlengde behandeling, in die geval van antesedente van bloeddyskrasie, in geval van ernstige infeksie en in ernstige lewerontoereikendheid.

Algemeen:
Pasiënte moet gewaarsku word dat BIO METRONIDAZOLE IV hul uriene mag donkerder maak as gevolg van die metronidasool metaboliet.
Pseudomembraneuse kolitis is aangemeld met die gebruik van BIO METRONIDAZOLE IV.
Gelyktydige toediening van busulfan: aangesien die plasmavlakke van busulfan aansienlik verhoog mag word mag dit lei tot busulfan toksisiteit en dood.
Studies het getoon dat metronidasool, soos bevat in BIO METRONIDAZOLE IV, mutageniteit in bakterieë getoon het en is kankerverwekkend in sommige diere. Dit is gevind dat die halfleeftyd van metronidasool langer is babas en in pasiënte met ernstige lewerinperking. Die hidroksi-metaboliet halfleeftyd word verleng in pasiënte met aansienlike nierinkorting (sien afdeling 5.2).

4.5 Interaksie met ander medisyne en ander vorms van interaksie
Disulfiraam
Akute psigose of verwarring is geassosieer met die gelyktydige gebruik van BIO METRONIDAZOLE IV en disulfiraam.

Alkohol
Wanneer dit saam met alkohol gegee word, mag BIO METRONIDAZOLE IV 'n disulfiram-tipe reaksie uitlok in sommige individue (effekte sluit intense vasodilatasie en blosing op die gesig en nek, rusteloosheid, angstigheid, tagikardie, tagipnee, hoofpyn, naarheid, braking, hiperpnee, borspyn, sweet, bleekheid en hipotensie). Reaksies het voorgekom na die toediening van medisyne wat met alkohol geformuleer word, insluitende inspuitings sowel as na alkohol gedrink word. Alkoholiese drankies en medisyne wat alkohol bevat moet nie gebruik word gedurende terapie en vir ten minste 1 - 3 dae na behandeling nie (sien afdeling 4.4).

Orale teenstolmiddel terapie (warfarien-tipe)
Potensiasie van die teenstoleffek en verhoogde hemorragiese risiko moet gemonitor word. In die geval van gelyktydige toediening met warfarien moet protrombien tyd/ INR meer gereeld gemonitor word en die warfarienterapie/ dosis moet aangepas word gedurende behandeling met BIO METRONIDAZOLE IV.

Litium
Plasmavlakke van litium mag verhoog word deur BIO METRONIDAZOLE IV. Plasmakonsentrasies van litium, kreatinien en elektroliete moet gemonitor word in pasiënte wat behandel word met litium terwyl hulle BIO METRONIDAZOLE IV ontvang.

Siklosporien
Risiko van verhoging van siklosporien serumvlakke. Serum siklosporien en serum kreatinien moet deeglik gemonitor word wanneer gelyktydige toediening nodig is.

Fenitoïen of fenobarbitaal
Daar is bewyse dat fenitoïen die metabolisme van BIO METRONIDAZOLE IV verhoog. Plasmakonsentrasies van BIO METRONIDAZOLE IV word verlaag deur die gelyktydige toediening van fenobarbitaal met 'n gevolglike verlaging in die effektiwiteit van BIO METRONIDAZOLE IV.

5-Fluorourasiel
Verlaagde opruiming van 5-flourourasiel mag lei tot verhoogde toksisiteit van 5-fluorourasiel.

Simetidien
Hepatiese metabolisme mag verlaag wanneer BIO METRONIDAZOLE IV en simetidien gelyktydig gebruik word, wat moontlik lei tot vertraagde uitskeiding en verhoogde serum metronidasool konsentrasies met 'n verhoogde risiko vir neurologiese newe-effekte.

CYP3A4 substrate
Gelyktydige gebruik van BIO METRONIDAZOLE IV en CYP3A4 substrate (bv. amiodaroon, takrolimus, siklosporien, karbamasepien en kinidien) mag die onderskeie CYP3A4-substraat plasmavlakke verhoog. Monitering van plasmakonsentrasies van CYP3A4 substrate mag nodig wees.

Vekuronium (nie-depolariserende kurare mimetikum)
BIO METRONIDAZOLE IV kan die effkte van Vekuronium potensiëer.

Cholestyramien
Cholestyramien mag die absorpsie van metronidasool vertraag of verminder.

Busulfan
Plasmakonsentrasies van busulfan mag verhoog gedurende gelyktydige behandeling met BIO METRONIDAZOLE IV, wat kan lei tot ernstige busulfan toksisiteit en die dood.

Laboratoriumtoetse
BIO METRONIDAZOLE IV mag treponema onbeweeglik maak en dus lei tot 'n fals-positiewe Nelson se toets.
BIO METRONIDAZOLE IV mag inmeng met serumaspartaattransaminase (AST), alanientransaminase (ALT), laktaatdehidrogenase (LDH), trigliseriede en glukoseheksokinase bepalings. Metronidasool veroorsaak 'n verhoging in ultravioletabsorpsie teen 340 nm, wat lei tot vals verlaagde waardes.

4.6 Vrugbaarheid, swangerskap en borsvoeding
Swangerskap
BIO METRONIDAZOLE IV is teenaangedui gedurende swangerskap (sien afdeling 4.3).

Borsvoeding
BIO METRONIDAZOLE IV is teenaangedui gedurende borsvoeding omdat metronidasool in borsmelk uitgeskei word (sien afdeling 4.3). Moeders wat borsvoed moet of ophou borsvoed of behandeling met BIO METRONIDAZOLE IV staak.

Vrugbaarheid
Daar is geen kliniese data met betrekking tot die effek van metronidasool op vrugbaarheid nie.

4.7 Effekte op die vermoë om te bestuur en om masjiene te gebruik
BIO METRONIDAZOLE IV het die potensiaal om verwarring, duiseligheid, onbestendigheid, aanvalle of visuele afwykings te veroorsaak. Wanneer hierdie simptome voorkom moet pasiënte aangeraai word om nie te bestuur of masjinerie te hanteer nie.

4.8 Ongewensde effekte
Infeksies en infestasies:
Minder gereeld: Vaginale candidiasis.

Bloed en lymfatiese sisteem versteurings
Minder gereeld: Leukopenie, trombositopenie, agranulositose, neutropenie, pansitopenie.
Frekwensie onbekend: Eosinofilie.

Immuunsisteem versteurings
Minder gereeld: Hipersensitiwiteit (wat maifesteer as veluitslag, koors, angioedeem, korwe, blosing, urtikarie, pruritus), anafilakse, anafilaktiese skok, Jarisch-Herxheimer reaksie.
Frekwensie onbekend: Matige eritemateuse uitbarstings met vlugtige gewrigspyn wat lyk soos serumsiekte mag voorkom.

Metabolisme en voedingsversteurings
Frekwensie onbekend: Anoreksie, verlaagde aptyt.

Psigiatriese versteurings
Frekwensie onbekend: Psigotiese versteurings insluitende verwarring, prikkelbaarheid en hallusinasies. Veranderinge in bui of geestestoestand soos byvoorbeeld depressie. Vertigo.

Senuweestelsel versteurings
Gereeld: Dysgeusie.
Minder gereeld: Sentrale senuweestelsel (SSS) effekte soos swakheid, slaperigheid, duiseligheid of lighoofdigheid; hoofpyne. Perifere neuropatie wat gewoonlik voorkom as gevoelloosheid of prikkeling in die ledemate en aanvalle is ernstige nadelige effekte wat met hoë dosisse of langdurige behandeling kan voorkom. SSS soos ataksie, lompheid of onbestendigheid. Enkefalopatie en subakute serebellêre sindroom (bv. ataksie, disartrie, ingekorte loop, nystagmus en bewing) wat kan verbygaan met die staking van die medisyne, aanvalle/ stuiptrekkings, aseptiese meningitis.
Frekwensie onbekend: Parestesie, hipoastesie.

Oogversteurings
Minder gereeld: Verbygaande sigversteurings soos dubbel visie (diplopie) en miopie is gerapporteer. Optiese neuropatie.

Vaskulêre versteurings
Frekwensie onbekend: Tromboflebitis mag voorkom na binneaarse toediening.

Hartversteurings
Frekwensie onbekend: Tagikardie, hartkloppings.

Respiratoriese, torakale en mediastinale versteurings
Frekwensie onbekend: Geblokte neus, dyspnee.

Gastroïntestinale versteurings
Gereeld: Gastroïntestinale versteurings, naarheid, braking, stomatitis, glossitis, orale mukositis. Naarheid gaan patykeer gepaard met hoofpyn. Diarree, hardlywigheid, droë mond en harige tong.
Minder gereeld: Antibiotika-geassosieerde kolitis, pankreatitis, boonste maagpyn, verkleuring van die tong.
Frekwesie onbekend: Pseudomembraneuse kolitis, bedekte tong en onaangename smaak.

Hepatobiliêre versteurings
Minder gereeld: Verhoogde lewerensiemwaardes is af en toe gerapporteer. Gevalle van omkeerbare abnormale lewerfunksie en cholestatiese hepatitis, soms met geelsug, is ook gerapporteer.

Vel en onderhuidse weefsel versteurings
Minder gereeld: Pustulêre uitbarstings, matige eritemateuse uitbarstings met vlugtige gewrigspyn wat soos serumsiekte lyk, Stevens-Johnson se sindroom, toksiese epidermale nekrolise, erythema multiforme.
Frekwensie onbekend: Veluitslag, blosing, pruritus, swelling van die gesig, urtikaria, hiperhidrose.

Muskuloskeletale en bindweefsel versteurings
Gereeld: Myalgie.
Frekwensie onbekend: Artralgie, spierspasmas.

Renale en urinêre versteurings
Minder gereeld: Urienweg effekte soos disurie, verhoogde urinêre frekwensie, gereelde of pynvolle urinering, onvermoë om urienvloei te beheer, gevoel van bekkendruk, donker uriene.

Algemene versteurings en toedieningsplektoestande
Minder gereeld: Tromboflebitis wat maifesteer as pyn, gevoelligheid, rooiheid of swelling by die plek van toediening, astenie, slymvliesinflammasie, pireksie.
Frekwensie onbekend: Reaksie by die plek van toediening, malaise, gesigsedeem, perifere edeem, borspyn, rillings.

Aanmelding van vermoedelike nadelige reaksies
Die aanmelding van vermoedelike nadelige reaksies na die magtiging van BIO-METRONIDAZOLE IV is belangrik. Dit laat voordurende monitering van die voordeel/ risiko balaans van BIO-METRONIDAZOLE IV toe. Gesondheidsorgverskaffers word gevra om enige vermoedelike nadelige reaksie aan SAHPRA te rapporteer deur die **Adverse Drug Reactions Reporting Form**, wat aanlyn onder SAHPRA se publikasies gevind kan word. SAHPRA se publikasies: https://www.sahpra.org.za/Publications/Index/8.

4.9 Oordosis
Verwys na afdeling 4.8.
Simptome
In gevalle van oordosis in volwassenes is die kliniese simptome gewoonlik beperk tot naarheid, braking en neurotoksiese effekte insluitend ataksie, effense disoriëntasie, verwarring, aanvalle, en perifere neuropatie. In 'n vroeggebore baba het geen kliniese of biologiese teken van vergiftiging ontwikkel nie.

Behandeling
BIO METRONIDAZOLE IV infusie moet gestaak word. Daar is geen spesifieke teenmiddel nie, behandeling is simptomaties en ondersteunend.

5. FARMAKOLOGIESE EIENSKAPPE
Kategorie en klas: A. 20.2 Ander antibiotikum
Farmakoterapeutiese groep: Antibakteriële middels vir sistemiese gebruik: imidasoolderivate.
ATC kode: J01XD01.

5.1 Farmakodinamiese eienskappe
Metronidasool is 'n voorlopergeneesmiddel; dit vereis reduktiewe aktivering van die stikstof-groep deur vatbare organismes. Die moederverbinding deurdring die selmembraan onveranderd, maar sodra dit binne die sel is, word die stikstof-groep onder die redokstoestande wat in die anaerobe sel teenwoordig is, verminder. Gereduseerde metronidasool wat sitotoksies is, maar wel 'n kortstondige leeftyd het, het 'n interaksie met DNS wat 'n verlies veroorsaak van die heliksstruktuur, dit verbreek die string en het gevolglike inhibering van nukleïensuur sintese. Dit veroorsaak uiteindelik seldood. Metronidasool besit baktericidiese aktiwiteit teen aërobiese bakterieë.
Metronidasool toon antiprotosale aktiwiteit teenoor *Trichomonas vaginalis* en ander protosoë, insluitende *Entamoeba histolytica* en *Giardia lamblia*.
Metronidasool het geen uitwerking op Candida spesies nie end it affekteer nie die asidofiliese flora van die vagina nie. Metronidasool belemmer nie die aktiwiteit van ander antibakteriese medisyne wat aktief is teen 'n verskeidenheid van anaërobe en fakultatiewe anaerobe nie. Metronidasool manifesteer antibakteriese aktiwiteit teenoor alle anaërobiese kokki en beide anaerobe gram-negatiewe bacilli, insluitende die Bacteroides spesies en anaërobiese spoorvormende gram-positiewe bacilli.

5.2 Farmakokinetiese eienskappe
Teen aanbevole binneaarse dosisse is piek geykvlak serumkonsentrasies ongeveer 25 µg/mL. Metronidasool word versprei na die been, lewer en lewerabsesse, longe, vaginale afskeidings, seminale vloeistowwe, gal, speeksel en borsmelk. Dit kruis ook die plasenta en die bloedbreinskans.
Die halfleeftyd is ongeveer 8 ure in plasma en die verspreidingsvolume daarvan is ongeveer dit van die totale liggaamswater. Minder as 20 % van die medisyne is aan plasmaproteïene gebind. Terapeutiese konsentrasies word bereik in die serebrospinale vloeistof. Die lewer is die belangrikste area waar metabolisme plaasvind, met meer as 50 % van die sistemiese opruiming van metronidasool wat hier plaasvind. Die hydroski-metaboliet het 'n halfleeftyd van 12 ure. Ongeveer 60 - 80 % word deur die niere in uriene uitgeskei (20 % van hierdie hoeveelheid word onveranderd uitgeskei)en ongeveer 6 - 15 % is onaktiewe metaboliete in die stoelgang.
Metronidasool en sy metaboliete word beduidend deur hemodialise verwyder, maar nie beduidend deur peritonale dialise nie.
In pasiënte met ingeperkte lewerfunksie word daar verwag dat die metabolisme van metronidasool sal verlaag wat lei tot 'n verhoogde plasma-uitskeidingshalfleeftyd. In pasiënte met ernstige lewerinkorting mag uitskeiding verlaag word met ongeveer tot 65 % wat lei tot 'n opeenhoping van metronidasool in die liggaam.

6. FARMASEUTIESE BESONDERHEDE
6.1 Lys van hulpstowwe
Sitroensuur monohidraat
Watervrye dibasiese natriumfosfaat
Natriumchlooried
Water for inspuiting.

6.2 Onverenigbaarhede
Hierdie medisyne moet nie met ander medisyne gemeng word behalwe die wat in afdeling 6.6 genoem word nie.

6.3 Rakleeftyd
24 maande.

6.4 Spesiale voorsorgmaatreëls vir bewaring
Bewaar teen of benede 30 °C. Moenie in die yskas verkoel nie.
Vir eenmalige gebruik alleenlik. Gooi enige oorblywende inhoud weg na gebruik.
Beskerm teen lig.

6.5 Aard en inhoud van die houer
BIO METRONIDAZOLE IV word verpak in 'n wit, deurskynende 100 mL LDPE bottel. Elke bottel is toegedraai met 'n deurskynende polipropileen omhulsel.

6.6 Spesiale voorsorgmaatreëls vir wegdoening en ander hantering
BIO METRONIDAZOLE IV inspuiting is verenigbaar met die volgende inspuitings:
Natriumchlooried inspuiting 0,9 % m/v (normale soutoplossing inspuiting)
Dekstrose 5 % m/v inspuiting
Bakteriostatiese water vir inspuiting
Bakteriostatiese Natriumchlooried 0,9 %
Ringer's laktaat inspuiting.

7. HOUER VAN DIE SERTIFIKAAT VAN REGISTRASIE
Biotech Laboratories (Edms.) Bpk
Grondvloer, Blok K Wes, Central Park
16de Weg 400, Randjespark
Halfway House
Midrand 1685

8. REGISTRASIENOMMER
42/20.2/0567

9. DATUM VAN EERSTE MAGTIGING/ HERNUWING VAN DIE MAGTIGING
14 September 2012

10. DATUM VAN DIE HERSIENING VAN DIE TEKS
05 Mei 2023

PI 420567/4