Anegyn®

Metronidazole

0,5% W/V (100 ml)

ANEGYN INJECTION 0.5% W/V

1. Description

1.1 Active Ingredient

Metronidazole

1.2 Pharmaceutical Form

A clean, bright, pale yellow sterile isotonic solution for intravenous infusion.

1.3 Composition

Active ingredient: Metronidazole

Excipients: Sodium phosphate, Citric acid anhydrous, Sodium chloride, Water for injections.

1.4 Nature and Contents of Container

Anegyn Injection 0.5% w/v (100 ml) is available in Viaflex minibags.

2. Indications

Anegyn is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.

Anegyn is active against a wide range of pathogenic microorganisms notably species of *Bacteroides, Fusobacteria, Clostridia, Eubacteria,* anaerobic cocci and *Gardnerella vaginalis.*

It is indicated in:

The prevention of postoperative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic Streptococci.

The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and

postoperative wound infections from which pathogenic anaerobes have been isolated.

3. Dosage and Administration

Slow intravenous infusion of one 100 ml plastic bag (500 mg) over a period of 30 to 60 minutes. Oral medication should be substituted as soon as feasible.

Anaerobic Infections*:* 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.

Prophylaxis against anaerobic infection:

Adults

Usually, 500mg infused over 30 to 60 minutes immediately before surgery, followed by 2 infusions of 500mg at 8 hours and 16 hours after the initial dose.

Children

20 to 30 mg/kg per day using the same protocol.

Treatment of established anaerobic infections: Intravenous route is to be used initially if patient's symptoms preclude oral therapy.

Adults

1 to 1.5g per day in 2 to 3 intravenous infusions.

Children

20 to 30 mg/kg per day in 2 to 3 intravenous infusions.

Elderly

Caution is advised in the elderly. Particularly at high doses although there is limited information available on modification of dosage.

4. Contra-indications

Known hypersensitivity to metronidazole.

5. Special Warnings

Metronidazole should be used with caution in patient with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological aggravation.

Patients should be advised not to take alcohol during metronidazole therapy and for at least one day afterward because of the possibility of a disulfiram-like (Antabuse effect) reaction.

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 functions tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.

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

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalized exanthematous pustulosis (AGEP) have been reported with metronidazole (see Section 11). If symptoms or signs of SJS, TEN or AGEP are present, Anegyn Injection treatment must be immediately discontinued.

6. Precautions

The use of Anegyn for prolonged treatment duration should be carefully weighed.

If for compelling reasons, metronidazole must be administered longer than the usually recommended duration, it is recommended that hematological tests, especially leucocyte count should be carried out regularly and that patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paresthesia, ataxia, dizziness, convulsive seizures).

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

Metronidazole has no direct activity against aerobic or facultative anaerobic bacteria.

There is a possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might persist.
The elimination half-life of metronidazole remains unchanged in the presence of renal failure. Therefore the dosage of metronidazole needs no reduction. Such patients
however retain the metabolites of metronidazole. The clinical significance of this is not known at present.
In patients undergoing haemodialysis metronidazole and metabolites are efficiently removed during an eight hour period of dialysis. Metronidazole should therefore be re-administered immediately after haemodialysis.
No routine adjustment in the dosage of Anegyn need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).
Metronidazole is mainly metabolized by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency.
Significant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Anegyn should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.
Aspartate amino transferase assays may give spuriously low values in patients being treated with metronidazole depending on the method used.
Cefuroxime sodium is physically and chemically compatible with Anegyn. The following drugs have been shown to be physically compatible in terms of pH and appearance with Anegyn injection over the normal period of administration, although there is no evidence of chemical stability: amikacin sulphate, ampicillin sodium, carbenicillin sodium, cephazolin sodium, cefotaxime sodium, cephalothin sodium, chloramphenicol sodium succinate, clindamycin phosphate, gentamicin sulphate, hydrocortisone sodium succinate, latamoxef disodium, netilmicin sulphate and tobramycin sulphate. In patients maintained on intravenous fluids, Anegyn injection may be diluted with appropriate volumes of normal saline, dextrose-saline, dextrose 5% w/v or potassium chloride infusions(20 and 40 mmol/liter). Apart from the above, Anegyn should on no account be mixed with any other substance.

7. Interactions

Disulfiram: psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.
Alcohol: alcoholic beverages and drugs containing alcohol should not be consumed during therapy and for at least one day afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).
Oral anticoagulant therapy (warfarin type): potentiation of the anticoagulant effect and increased hemorrhagic risk caused by decreased hepatic catabolism. In case of coadministration, prothrombin time should be more frequently monitored and anticoagulant therapy adjusted during treatment with metronidazole.
Lithium: Plasma levels of lithium may be increased by metronidazole. Plasma concentration of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive

metronidazole.

Cyclosporin: risk of elevation of cyclosporine serum levels. Serum cyclosporine and serum creatinine should be closely monitored when coadministartion is necessary.

Phenytoin or phenobarbital:increased elimination of metronidazole resulting in reduced plasma levels.

5 Fluorouracil: reduced clearance of 5 fluorouracil resulting in increased toxicity of 5 fluorouracil.

Busulfan: Plasma level of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

8. Pregnancy

As metronidazole crosses the placental barrier and as its effects on human fetal organogenesis are not known, its use in pregnancy should be carefully evaluated.

There is inadequate evidence of the safety of metronidazole in pregnancy. Anegyn should not therefore be given during pregnancy or during lactation unless the physician considers it essential; in these circumstances the short, high-dosage regimens are not recommended.

9. Lactation

As metronidazole is excreted in human milk, unnecessary exposure to the drug should be avoided.

10. Driving a Vehicle or Performing Other Hazardous Tasks

Patients should be warned about the potential for confusion, dizziness, hallucinations, convulsions or eye disorders, and advised not to drive or operate machinery if these symptoms occur.

11. Adverse Reactions

Gastrointestinal disorders

- epigastric pain, nausea, vomiting, diarrhea.
- oral mucositis, taste disorders, anorexia.
- reversible cases of pancreatitis.
- Tongue discoloration/furry tongue (e.g. due to fungal overgrowth).

Immune system disorders

- angioedema, anaphylactic shock.

Nervous system disorders

- peripheral sensory neuropathy.
- headache, convulsions, dizziness.
- 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 drug.
- aseptic meningitis.

Psychiatric disorders

- psychotic disorders including confusion, hallucinations.
- depressed mood.

Eye disorders

- transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision.

- optic neuropathy/neuritis.

Ear and labyrinth disorders

- hearing impaired/hearing loss (including sensorineural)
- tinnitus

Blood and lymphatic system disorders

- cases of agranulocytosis, neutropenia and thrombocytopenia have been reported.

Hepatobiliary disorders

- increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported.
- case of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders

- rash, pruritus, flushing, urticaria.
- Pustular eruptions , acute generalized exanthematous pustulosis
- Fixed drug eruption
- Stevens-Johnson syndrome, toxic epidermal necrolysis.

General disorders and administration site conditions

- fever

Agranulocytosis, neutropenia, thrombocytopenia and pancytopenia, often reversible on drug withdrawal, have very rarely been reported, although fatalities have occurred.

12. Overdose

Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdose.

12.1 Signs and Symptoms

Symptoms were limited to vomiting, ataxia and slight disorientation.

12.2 Management

There is no specific antidote for metronidazole overdosages. In case of suspected massive overdosages, a symptomatic and supportive treatment should be institute.

13. Pharmacodynamic

Metronidazole has antiprotozoal and antibacterial actions and is effective against *Trichomonas vaginalis* and other protozoa including *Entamoeba histolytica* and *Giardla lamblia* and against anaerobic bacteria.

14. Pharmacokinetic

Metronidazole is widely distributed in body tissues after injection. At least half the dose is excreted in the urine as metronidazole and its metabolites, including an acid oxidation product, a hydroxy derivative and glucuronide. Metronidazole diffuses

across the placenta, and is found in breast milk of nursing mothers in concentrations equivalent to those in serum.

10% of the dose is bound in plasma.

Clearance: 1.3 ± 0.3 ml/min/kg.

Volume of distribution: 1.1 ± 0.4 litres/kg.

Half-life: 8.5 ± 2.9 hours.

Effective concentration: 3-6 micrograms/ml.

15. Non-Clinical Safety Data

15.1 Carcinogenicity

Metronidazole has been shown to be carcinogenic in the mouse and in the rat. However similar studies in the hamster have given negative results and epidemiological studies in humans have provided no evidence of an increased carcinogenic risk in humans. Therefore, the use of Anegyn for prolonged treatment duration should be carefully weighed.

15.2 Mutagenicity

Metronidazole has been shown to be mutagenic in bacteria *in vitro.* In studies conducted in mammalian cells *in vivo*, there was inadequate evidence of a mutagenic effect of metronidazole, with some studies reporting mutagenic effects, while other studies were negative.

Therefore, the use of Anegyn for prolonged treatment duration should be carefully weighed.

16. Incompatibilities

Anegyn injection should not be mixed with cefamandole nafate, cefoxitin sodium, dextrose 10% w/v, compound sodium lactate injection, penicillin G potassium.

17. Shelf-Life

24 months.

18. Storage Conditions

Store below 25°C, protect from light.

19. Preparation and Handling

The Viaflex containers are for single use only. Discard any unused portion. Do not reconnect partially used containers.

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