

1. Name of the medicinal product

Trogyl plus Tablets

2. Qualitative and quantitative composition

Each Tablet contains Metronidazole BP 200mg and Diloxanide Furoate BP 250mg

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Oral Tablet

Round, flat-faced, bevel-edged, yellow Tablets, scored on one side and plain on the other side

4. Clinical particulars

4.1 Therapeutic indications

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

Trogyl plus Tablets is active against a wide range of pathogenic micro-organisms notably species of *Bacteroides*, *Fusobacteria*, *Clostridia*, *Eubacteria*, anaerobic cocci and *Gardnerella vaginalis*.

It is also active against *Trichomonas*, *Entamoeba histolytica*, *Giardia lamblia* and *Balantidium coli*.

Trogyl plus Tablet is indicated in adults and children for the following indications:

1. The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci.
2. The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated.
3. Urogenital trichomoniasis in the female (trichomonal vaginitis) and in the male.
4. Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or Gardnerella vaginitis).
5. All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers).
6. Giardiasis.

4.2 Posology and method of administration

Oral route of administration.

Trogyl plus Tablets should be swallowed with water (not chewed). It is recommended that the Tablets be taken during or after a meal.

Prophylaxis against anaerobic infection: Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.

4.3 Contraindications

Known hypersensitivity to nitroimidazoles, metronidazole or any of the excipients.

4.4 Special warnings and precautions for use

Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of Trogyl Plus Tablets for more than 10 days is considered to be necessary and patients should be monitored for adverse reactions, such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures).

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

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 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 generalised exanthematous pustulosis (AGEP) have been reported with metronidazole. If symptoms or signs of SJS, TEN or AGEP are present, Trogyl Plus Tablets treatment must be immediately discontinued.

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. The dosage of metronidazole therefore 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 Trofyl plus Tablets need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

Metronidazole is mainly metabolised 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. Trofyl plus Tablets 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.

Patients should be warned that metronidazole may darken urine.

Due to inadequate evidence on the mutagenicity risk in humans (see section 5.3), the use of Trofyl plus Tablets for longer treatment than usually required should be carefully considered.

4.5 Interaction with other medicinal products and other forms of interaction

Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction. Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.

Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.

Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole. Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Patients receiving phenobarbital or phenytoin metabolize metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.

Metronidazole reduces the clearance of 5 fluorouracil and can therefore result in increased toxicity of 5 fluorouracil.

Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

4.6 Pregnancy and lactation

There is inadequate evidence of the safety of metronidazole in pregnancy but it has been in wide use for many years without apparent ill consequence. Nevertheless, Trofyl Plus Tablets, like other medicines, should not be given during pregnancy or during lactation unless the physician considers it essential; in these circumstances the short, high-dosage regimens are not recommended.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The frequency of adverse events listed below is defined using the following convention:

very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Serious adverse reactions occur rarely with standard recommended regimens. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

Blood and lymphatic system disorders:

Very rare: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia

Not known: leucopenia.

Immune system disorders:

Rare: anaphylaxis

Not known: angioedema, urticaria, fever.

Metabolism and nutrition disorders:

Not known: anorexia.

Psychiatric disorders:

Very rare: psychotic disorders, including confusion and hallucinations. Not known: depressed mood

Nervous system disorders:

Very rare:

- encephalopathy (e.g. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysarthria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug.

- drowsiness, dizziness, convulsions, headaches

Not known:

- during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.

- aseptic meningitis

Eye disorders:

Very rare: vision disorders such as diplopia and myopia, which, in most cases, is transient.

Not Known: optic neuropathy/neuritis

Ear and labyrinth disorders

Not known: hearing impaired/hearing loss (including sensorineural), tinnitus

Gastrointestinal disorders:

Not known: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea.

Hepatobiliary disorders:

Very rare:

- increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, jaundice and pancreatitis which is reversible on drug withdrawal.

- cases 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:

Very rare: skin rashes, pustular eruptions, acute generalised exanthematous pustulosis, pruritis, flushing

Side effects include flatulence, itchiness, and hives. In general, the use of Diloxanide is well tolerated with minimal toxicity. Although there is no clear risk of harm when used during pregnancy, Diloxanide should be avoided in the first trimester if possible.

Diloxanide Furoate is not recommended in women who are breast feeding, and in children <2 years of age

4.9 Overdose

Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation. There is no specific antidote for metronidazole overdose. In cases of suspected massive overdose, symptomatic and supportive treatment should be instituted.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ATC code: J01X D01

Agents Against Amoebiasis and Other Protozoal Diseases, ATC code: P01AC01

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

Diloxanide Furoate destroys trophozoites of *E. histolytica* and prevents amoebic cyst formation. The exact mechanism of Diloxanide is unknown. Diloxanide is structurally related to chloramphenicol and may act in a similar fashion by blocking protein synthesis.

The prodrug, Diloxanide Furoate, is metabolized in the gastrointestinal tract to release the active drug, Diloxanide. 90% of each dose is excreted in the urine and the other 10% is excreted in the feces.

5.2 Pharmacokinetic properties

Metronidazole is rapidly and almost completely absorbed on administration of Trofyl Plus Tablets; peak plasma concentrations occur after 20 min to 3 hours.

The half-life of metronidazole is 8.5 ± 2.9 hours. Metronidazole can be used in chronic renal failure; it is rapidly removed from the plasma by dialysis. Metronidazole is excreted in milk but the intake of a suckling infant of a mother receiving normal dosage would be considerably less than the therapeutic dosage for infants.

5.3 Preclinical safety data

Metronidazole has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in the hamster have given negative results.

Epidemiological studies have provided no clear evidence of an increased carcinogenic risk in humans.

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

6. Pharmaceutical particulars

6.1 List of excipients

Dicalcium Phosphate

Maize Starch

Gelatin

Sodium Methyl Paraben

Sodium Propyl Paraben

Tartrazine Colour

Talc

Sodium Lauryl Sulphate

Magnesium Stearate

Cross Carmelose Sodium

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C in the original packaging (protect from light).

6.5 Nature and contents of container

Trogyl (10x10) Unit Boxes, Trogyl literatures (100x1000's) Shippers, PVC 206mm clear Aluminium foil 203mm

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing authorization holder

Name: Biodeal Laboratories Ltd

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Country: Kenya

Telephone: +254 720 333829

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8. Marketing authorization number(s)

PPB KENYA- H2008/14605.482

9. Date of first authorization/renewal of the authorization

07/04/2009