AUSCEL LABORATORIES LTD.

Product Name: AUSGYL TABLETS

Generic Name: Metronidazole Tablets B.P. 400 mg

1.3 Product Information

1.3.1 Summary of product characteristics

1. Name of the medicinal product

Ausgyl Tablets

2. Qualitative and quantitative composition

Each tablet contains 400 mg metronidazole.

For a full list of excipients, see section 6.1

3. Pharmaceutical form

Uncoated tablets

White to off-white, circular biconcave, uncoated tablets impressed 'AUSGYL 200' on one face & a breakline on other side.

4. Clinical particulars

4.1 Therapeutic indications

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

Ausgyl 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*.

Ausgyl 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.

7. Acute ulcerative gingivitis.

8. Anaerobically-infected leg ulcers and pressure sores.

9. Acute dental infections (e.g. acute pericoronitis and acute apical infections).

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Oral route of administration.

Ausgyl 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.

Adults

400 mg 8 hourly during 24 hours immediately preceding operation followed by postoperative intravenous or rectal administration until the patient is able to take tablets.

Children

Children < 12 years: 20-30mg/kg as a single dose given 1-2 hours before surgery Newborns with a

gestation age < 40 weeks: 10mg/kg body weight as a single dose before operation

Anaerobic infections: The duration of a course of Ausgyl treatment is about 7 days but it will depend upon the seriousness of the patient's condition as assessed clinically and bacteriologically.
Treatment of established anaerobic infection:

Adults

800 mg followed by 400 mg 8 hourly.

Children

Children > 8 weeks to 12 years of age: The usual daily dose is 20-30mg/kg/day as a single dose or divided into 7.5mg/kg every 8 hours. The daily dose may be increased to 40mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.

Children < 8 weeks of age: 15mg/kg as a single dose daily or divided into 7.5mg/kg every 12 hours. In newborns with a gestation age < 40 weeks, accumulation of metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.

Protozoal and other infections:

AUSCEL LABORATORIES LTD.

Product Name: AUSGYL TABLETS

Generic Name: Metronidazole Tablets B.P. 400 mg

Dosage is given in terms of metronidazole or metronidazole equivalent					
	Duration of dosage in days	Adults and children over 10 years	Children		
			7 to 10 years	3 to 7 years	1 to 3 years
Urogenital trichomoniasis Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently	7 Or 5- 7	2000mg as a single dose or 400 mg three times daily or *400mg twice daily*	40mg/kg orally as a single dose or mg/kg/day divided in 2-3 doses; not to exceed 2000mg/dose		15-30
Bacterial vaginosis	5-7 Or	400 mg twice daily			

	1	2000mg as a single dose			
Amoebiasis (a) Invasive intestinal disease in susceptible subjects	5	800 mg three times daily	400 mg three times daily	400 mg four times daily	400 mg three times daily
(b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis	5-10	400 mg three times daily	400 mg three times daily	100 mg four times daily	100 mg three times daily

(c) Amoebic liver abscess also other forms of extra-intestinal amoebiasis	5	400 mg three times daily	400 mg three times daily	100 mg four times daily	100 mg three times daily
(d) Symptomless cyst passers	5-10	400-800 mg three times daily	200-400 mg three times daily	100-400 mg four times daily	100-400 mg three times daily
	Alternatively, doses may be expressed by body weight 35 to 50mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400mg/day				
Giardiasis	3	2000mg once daily or	1000mg once daily	600-800 mg once daily	500 mg once daily
	5	400mg three times daily or			
	7-10	500mg twice daily			

	Alternatively, as expressed in mg per kg of body weight: 15-40mg/kg/day divided in 2-3 doses.

Dosage is given in terms of metronidazole or metronidazole equivalent

	Duration of dosage in days	Adults and children over 10 years	Children		
			7 to 10 years	3 to 7 years	1 to 3 years
Acute ulcerative gingivitis	3	400 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
Acute dental infections	3-7	400 mg three times daily			

Leg ulcers and pressure sores	7	400 mg three times daily			

Children and infants weighing less than 10 kg should receive proportionally smaller dosages.
Elderly: Ausgyl is well tolerated by the elderly but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.

Eradication of Helicobacter pylori in paediatric patients:

As a part of a combination therapy, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days.

Official guidelines should be consulted before initiating therapy.

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 Ausgyl 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, Ausgyl 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 Ausgyl 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. Ausgyl 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 ausgyl 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 metabolise 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 Ausgyl, 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 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: angiodema, 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 (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, 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 exathematous pustulosis, pruritis, flushing

Not known: erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders: Very rare: myalgia, arthralgia.

Renal and urinary disorders:

Very rare: darkening of urine (due to metronidazole metabolite). Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 overdosage. 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
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.

5.2 Pharmacokinetic properties

Metronidazole is rapidly and almost completely absorbed on administration of Ausgyl 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 others studies were negative.

6. Pharmaceutical particulars

6.1 List of excipients

Calcium hydrogen phosphate (E341),

Starch maize,

Povidone K30 (E1201),

Magnesium stearate (E572),

Tablet coat

Pharmacoat 615 (E464),

Macrogol 400 Ph. Eur.

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

Ausgyl tablets 400 mg are available in aluminium/plastic blisters of 21 tablets and HDPE bottles of 100 and 250 tablets.

Not all pack sizes may be marketed

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing authorization

holder Auscel Laboratories Ltd.,

Plot 40799 Shinco Rd,

Rayfield,

Jos, Plateau state.

8. Marketing authorization number(s)

Not available

9. Date of first authorization/renewal of the authorization

Not available

10. Date of revision of the text

Not available