SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

FLAGYL 200 (Tablets)

FLAGYL 400 (Tablets)

FLAGYL SUSPENSION

COMPOSITION:

FLAGYL 200

Each tablet contains:	Metronidazole	200 mg
Preservative:	Methyl hydroxybenzoate	0,1 % *m/m*

Excipients:

Maize starch, calcium carbonate, methyl hydroxybenzoate, sodium lauryl sulphate, stearic acid and microcrystalline cellulose.

FLAGYL 400

Each tablet contains:	Metronidazole	400 mg
Preservative:	Methyl hydroxybenzoate	0,1 % *m/m*

Contains tartrazine.

Excipients:

Methyl hydroxybenzoate, maize starch, calcium carbonate, microcrystalline cellulose, potassium dihydrogen phosphate, sodium hydroxide, sodium lauryl sulphate, stearic acid and yellow dye (CI 19140).

FLAGYL SUSPENSION

Each 5 ml contains:	Benzoyl metronidazole equivalent to metronidazole		200 mg
Preservatives:	Methyl hydroxybenzoate	0,08 % *m/v*	
	Propyl hydroxybenzoate	0,02 % *m/v*	

Contains sugar (sucrose).

Excipients:

Sodium dihydrogen phosphate, methyl hydroxybenzoate, propyl hydroxybenzoate, ethanol, sucrose, veegum h.v., lemon flavouring, oil of orange and water.

PHARMACOLOGICAL CLASSIFICATION:

A 20.2.6 Antimicrobial (chemotherapeutic) agents: Medicines against protozoa

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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. Metronidazole has bactericidal activity against obligate anaerobic bacteria, whether they are Gram-positive or -negative and bacilli or cocci. It has no antibacterial activity against aerobic and facultative anaerobic bacteria. Metronidazole does not interfere with the activity of antibacterial agents which are active against a variety of aerobes and facultative anaerobes.

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 conditions prevalent in the anaerobic cell.

The reduced product is known to damage DNA causing eventual death of the organism.

Pharmacokinetic properties:

Metronidazole is absorbed from the gastrointestinal tract and widely distributed in body tissues. Approximately 30-40 % of a dose is metabolised in the liver and excreted in the urine, together with the unchanged compound. 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, breast milk and in abscess cavities.

INDICATIONS:

a) In the oral treatment of:

- urogenital trichomoniasis
- non-specific vaginitis
- all forms of amoebiasis
- giardiasis
- acute ulcerative gingivitis (Vincent's)
- acute pericoronitis

b) 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, clostridia, eubacteria and anaerobic streptococci.

FLAGYL has been used successfully for anaerobic infections in the following conditions: pelvic inflammatory disease and postoperative wound infections. Combined therapy is often indicated as there are usually mixed infections.

c) 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

d) Treatment of *Helicobacter pylori*-associated gastritis and duodenal ulcer. FLAGYL is used in combination with bismuth subsalicylate or colloidal bismuth subcitrate and appropriate antibiotic therapy.

CONTRAINDICATIONS:

Hypersensitivity to metronidazole and other imidazoles.

Co-administration with busulfan (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS:

Patients should be advised not to take alcohol during FLAGYL therapy and for at least one to three days afterwards because of the possibility of a disulfiram-like reaction (see INTERACTIONS).

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

Pseudomembranous colitis has been reported with the use of FLAGYL.

Studies have shown FLAGYL to be mutagenic in bacteria and carcinogenic in some animals.

FLAGYL should be administered with caution to patients with hepatic encephalopathy.

FLAGYL should be used with great care in patients with blood dyscrasias or with active or chronic disease of the central and peripheral nervous system.

All patients receiving FLAGYL for more than 10 days should be monitored and treatment discontinued if signs of peripheral neuropathy or central nervous system toxicity develop. Doses should be reduced in patients with severe liver disease.

FLAGYL has anti-treponemal activity and may mask the immunological response seen in untreated early syphilis; contacts of syphilis receiving FLAGYL should probably be screened for an additional 4 to 8 weeks.

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

Driving a vehicle or performing hazardous tasks:

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

FLAGYL SUSPENSION contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take Flagyl suspension.

FLAGYL 400 tablets contain tartrazine which may cause allergic-type reactions (including bronchial asthma) in certain individuals. Although the overall incidence of tartrazine sensitivity in the general population is currently thought to be low, it is frequently seen in patients who also have aspirin sensitivity.

INTERACTIONS:

Disulfiram:

Acute psychoses or confusion have been associated with the concomitant use of FLAGYL and disulfiram.

Alcohol:

When given in conjunction with alcohol, FLAGYL may provoke a disulfiram-like reaction in some individuals (effects include intense vasodilation and flushing of the face and neck, restlessness, anxiety, tachycardia, tachypnoea, headache, nausea, vomiting, hyperpnoea, chest pains, sweating, pallour and hypotension); reactions have occurred after the administration of pharmaceutical preparations formulated with alcohol, including injections, as well as after drinking alcohol.

Alcoholic beverages and medicine containing alcohol should not be consumed during therapy and for at least 1 to 3 days afterwards (see WARNINGS AND SPECIAL PRECAUTIONS).

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 FLAGYL.

Lithium:

Plasma levels of lithium may be increased by FLAGYL. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive FLAGYL.

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

5-Fluorouracil:

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

Busulfan:

Plasma levels of busulfan may be increased by FLAGYL, which may lead to severe busulfan toxicity and death (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

Cimetidine:

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

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

FLAGYL crosses the placental barrier and is excreted in breast milk. Women using Flagyl should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE:

The tablets should be taken with or after food.

FLAGYL SUSPENSION is administered orally. It is recommended that it be taken at least 1 hour before food.

Immature children and babies weighing less than 10 kg should receive proportionally smaller doses, as advised by the medical practitioner. Children over 10 years may be given a suitable proportion of the adult dosage according to body mass.

	DURATION OF DOSAGE IN DAYS	ADULTS	CHILDREN		
			7 TO 10 YEARS	3 TO 7 YEARS	1 TO 3 YEARS
UROGENITAL TRICHO-MONIASIS. Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently.	1	2 g as a single dose			
	7	200 mg three times daily or 400 mg twice daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
	2	800 mg in the morning and 1,2 g in the evening			
NON-SPECIFIC VAGINITIS	7	400 mg twice daily			
	OR 1	2 g as a single dose			
AMOEBIASIS a) Invasive intestinal disease in susceptible subjects.	5	800 mg three times daily	400 mg three times daily	200 mg four times daily	200 mg three times daily
AMOEBIASIS b) Intestinal disease in less susceptible subjects and “chronic amoebic hepatitis”.	5 to 10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily

	DURATION OF DOSAGE IN DAYS	ADULTS	CHILDREN		
			7 TO 10 YEARS	3 TO 7 YEARS	1 TO 3 YEARS
AMOEBIASIS c) Amoebic liver abscess, also other forms of extra-intestinal amoebiasis.	5	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
AMOEBIASIS (d) Symptomless cyst passers.	5 to 10	400 to 800 mg three times daily	200 to 400 mg three times daily	100 to 200 mg four times daily	100 to 200 mg three times daily
GIARDIASIS A second course of treatment may be necessary for some patients two weeks after the end of the first course.	3	2 g once daily	1 g once daily	600 to 800 mg once daily	500 mg once daily
ACUTE ULCERATIVE GINGIVITIS	3	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
ACUTE PERICORONITIS	3 to 7	200 mg three times daily			

Anaerobic infections

a) Treatment:

FLAGYL may be given alone or concurrently with other bacteriologically-appropriate antibacterial agents. They should be given for 7 days or longer depending on clinical and bacteriological assessments of the patient's condition.

Adults: Initially, 800 mg followed by 400 mg by mouth every 8 hours.

Children: 7,5 mg/kg body mass by mouth every 8 hours.

b) Prevention:

Adults: Administered in doses similar to those used for the treatment of established infection. 400 mg may be given every 8 hours in the 24 hours before surgery followed postoperatively by intravenous or rectal administration until oral therapy is possible.

Children: as for treatment (a).

Treatment of *Helicobacter pylori*-associated gastritis and duodenal ulcer

The following regimens have been used:

a) FLAGYL 200-250 mg – 4-5 times a day for 14 days in combination with other medicines. To obtain a dosage of 250 mg FLAGYL (metronidazole), 6,25 ml of the FLAGYL SUSPENSION should be administered.

SIDE EFFECTS:

The adverse effects of FLAGYL are generally dose related. The following side effects have been reported:

Blood and the lymphatic system disorders:

Less frequent: Agranulocytosis, neutropenia and thrombocytopenia

Frequency unknown: Leucopenia

Immune system disorders:

Less frequent: Anaphylaxis

Frequency unknown: Angioedema, urticaria

Metabolism and nutrition disorders:

Frequency unknown: Anorexia

Psychiatric disorders:

Less frequent: Psychotic disorders including confusion, irritability and hallucinations, changes in mood or mental state such as depression or confusion

Nervous system disorders:

Less frequent: Weakness, dizziness, drowsiness, insomnia, cases of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia dysathria, gait impairment, nystagmus and tremor), which may resolve with discontinuation of the medicine

Frequency unknown: Peripheral neuropathy, usually presenting as numbness or tingling in the extremities, and epileptiform seizures are serious adverse effects on the nervous system that have been associated especially with high doses of FLAGYL or prolonged treatment

Eye disorders:

Less frequent: The occurrence of transient vision disorders such as diplopia and myopia may follow the use of FLAGYL.

Respiratory, thoracic and mediastinal disorders:

Frequency unknown: Nasal congestion

Gastrointestinal disorders:

Frequent: Gastrointestinal disturbances, especially nausea and taste disorders; nausea is sometimes accompanied by headache, and vomiting. Diarrhoea, dry mouth, a furred tongue, oral mucositis and stomatitis

Less frequent: Pseudomembranous colitis

Hepato-biliary disorders:

Less frequent: Increase in liver enzymes (AST, ALT, alkaline phosphatase) and cholestatic hepatitis sometimes with jaundice

Frequency unknown: Pancreatitis and raised liver enzyme values

Skin and subcutaneous tissue disorders:

Less frequent: Pustular eruptions, mild erythematous eruptions with fleeting joint pains resembling serum sickness

Frequency unknown: Skin rashes, flushing, and pruritus

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Myalgia and arthralgia

Renal and urinary disorders:

Less frequent: Urethral discomfort and darkening of the urine

General disorders and administration site conditions:

Frequency unknown: Fever

Post marketing experience:

The adverse effects listed below are based on data from post-marketing experience:

Nervous system disorders:

- Headache, aseptic meningitis

Eye disorders:

- Transient vision disorders such as blurred vision, decreased visual acuity, changes in colour vision
- Optic neuropathy/neuritis

Gastrointestinal disorders:

- Epigastric pain

Hepato-biliary disorders

- Mixed hepatitis and hepatocellular liver injury
- Cases of liver failure requiring liver transplant have been reported in patients treated with FLAGYL in combination with other antibiotic medication

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

See SIDE EFFECTS above.

Treatment is symptomatic and supportive.

IDENTIFICATION:

FLAGYL 200: Circular, off-white to cream biconvex tablets, impressed "FLAGYL 200" on the one side.

FLAGYL 400: Circular, yellow, biconvex tablets, impressed "FLAGYL 400" on the one side, breakline on the reverse.

FLAGYL SUSPENSION: Off-white, coarse, suspension with an orange and lemon odour.

PRESENTATION:

FLAGYL 200 – White opaque polypropylene securitainers in pack sizes of 21 and 250 tablets

FLAGYL 400 – White opaque polypropylene securitainers in pack sizes of 10 and 100 tablets

FLAGYL SUSPENSION – Amber glass bottles in pack sizes of 50 ml and 100 ml suspension

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Protect from light.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

FLAGYL 200 - A370 (Act 101/1965)

FLAGYL 400 - D/20.2.6/228

FLAGYL SUSPENSION - F/20.2.6/50

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

sanofi-aventis south africa (pty) ltd

2 Bond Street

Midrand

South Africa

1685

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

Date registered:

FLAGYL 400: 03 October 1973

FLAGYL SUSPENSION: 14 February 1975

Date revised: 20 March 2018

NAMIBIA

Scheduling status: NS2

Registration numbers:

FLAGYL 200: 03 1001884

FLAGYL 400: 90/20.2/00308

FLAGYL SUSPENSION: 90/20.2.6/00311

BOTSWANA

Scheduling status: S2

Registration numbers:

FLAGYL 200: B9305190

FLAGYL 400: B9305195

FLAGYL SUSPENSION: B9305200