Date of approval: 17 September 2023

Professional Information for FLAGYL SUSPENSION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

FLAGYL SUSPENSION 200 mg/5 mL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL of suspension contains: metronidazole benzoate equivalent to 200 mg metronidazole.

Contains sugar: sucrose 3 g/5 mL.

Preservatives: methyl parahydroxybenzoate 0,08 % *m/v* and propyl parahydroxybenzoate 0,02 % *m/v*.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Off-white, coarse, oral suspension with an orange and lemon flavour.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 post-operative wound infections. Combined therapy is often indicated as there are usually mixed infections.

c) Prevention of post-operative 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.

4.2 Posology and method of administration

Posology

FLAGYL 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.

INDICATION	DURATION OF DOSAGE IN DAYS	ADULTS	CHILDREN		
			7 TO 10 YEARS	3 TO 7 YEARS	1 TO 3 YEARS
UROGENITAL TRICHOMONIASIS	1	2 g as a single dose	--	--	--
Where re-infection is likely, in adults the		200 mg three times daily or	100 mg three times daily	100 mg twice daily	50 mg three times daily

consort should receive a similar course of treatment concurrently	7	400 mg twice 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
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	3	2 g once daily	1 g once daily	600 to 800 mg once daily	500 mg once daily

after the end of the first course.					
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 post-operatively 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 should be administered.

Special populations

Patients with hepatic impairment:

Metronidazole, as in FLAGYL, is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency.
Significant accumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Therefore, FLAGYL should 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 with renal impairment:

The elimination half-life of metronidazole remains unchanged in the presence of renal failure. Therefore, the dosage of metronidazole, as in FLAGYL, needs no reduction. However, such patients 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. Therefore, FLAGYL should be re-administered immediately after haemodialysis.
No routine adjustment in the dosage of FLAGYL need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

Method of administration

Oral administration.

4.3 Contraindications

- Hypersensitivity to metronidazole, other imidazoles and any of the excipients of FLAGYL listed in section 6.1.
- Co-administration with busulfan (see sections 4.4 and 4.5).
- Co-administration with disulfiram (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

QT prolongation has been reported, particularly when metronidazole, as in FLAGYL, was administered with medicines with the potential for prolonging the QT interval (see section 4.5).
Avoid the use of FLAGYL in patients who have a history of congenital long QT syndrome, torsades de pointes, cardiac arrhythmias including ventricular tachycardia or family history of sudden death.

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 section 4.5).
Psychotic reactions have been reported in patients who were using metronidazole, as in FLAGYL and disulfiram concurrently (see sections 4.3 and 4.5).

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.

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 medicines containing metronidazole (the active ingredient of FLAGYL) for systemic use. In this population, FLAGYL 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 (see section 4.5). If the liver function tests become markedly elevated during treatment, FLAGYL should be discontinued.

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

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 (see section 4.8). If symptoms or signs of SJS, TEN or AGEP are present, FLAGYL treatment must be immediately discontinued.

Cases of suicidal ideation with or without depression have been reported during treatment with FLAGYL. Patients should be advised to discontinue treatment and contact their healthcare provider immediately if they experience psychiatric symptoms during treatment (see section 4.8).

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).

For information on renal and hepatic insufficiency, please see section 4.2. Monitoring for metronidazole associated adverse events is recommended (see sections 4.8 and 5.2).

Information on excipients:

- *Sucrose***:** FLAGYL 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 (see section 2).
- *Preservatives:* Methyl hydroxybenzoate (E218) and propyl hydroxybenzoate (E216) can cause an allergic reaction in some people (possibly delayed).
- *Alcohol:* FLAGYL contains 0,8 % alcohol (ethanol) by volume.

4.5 Interaction with other medicines and other forms of interaction

Disulfiram:

Acute psychoses or confusion have been associated with the concomitant use of FLAGYL and disulfiram (see sections 4.3 and 4.4).

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, pallor 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 section 4.4).

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 sections 4.3 and 4.4).

Medicines that prolong QT interval:

QT prolongation has been reported, particularly when FLAGYL was administered with medicines with the potential for prolonging the QT interval.

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.

Interferences with laboratory and diagnostic test:

Metronidazole, as in FLAGYL, may interfere with certain types of blood test determinations in blood (aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], triglycerides, glucose), which may lead to false negative or an abnormally low result. These analytical determinations are based on a decrease in ultraviolet absorbance, a fact that occurs when nicotinamide adenine dinucleotide hydrogen (NADH) is oxidised to nicotinamide adenine dinucleotide (NAD). The interference is due to the similarity in the absorption peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

FLAGYL crosses the placental barrier.

Breastfeeding

FLAGYL is excreted in breast milk. Women using FLAGYL should not breastfeed their infants.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for confusion, dizziness, vertigo, hallucinations, convulsions or eye disorders (see section 4.8), and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

a. Summary of the safety profile

Serious adverse reactions occur rarely with standard recommended regimens. Medical practitioners 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.

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).

The adverse effects of FLAGYL are generally dose related.

The following side effects have been reported:

System organ class	Common (≥ 1/100 to < 1/10)	Rare (≥ 1/10 000 to < 1/1 000)	Very rare (< 1/10 000)	Not known
Blood and lymphatic system			agranulocytosis, neutropenia,	leucopenia

disorders			thrombocytopenia	
Immune system disorders		anaphylaxis		angioedema, urticaria
Metabolism and nutrition disorders				anorexia
Psychiatric disorders			psychotic disorders including confusion, irritability and hallucinations, changes in mood or mental state such as depression	
Nervous system disorders			weakness, dizziness, drowsiness, insomnia, cases of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus and tremor), which may resolve with discontinuation of FLAGYL	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			transient vision disorders such as diplopia and myopia	
Respiratory, thoracic and mediastinal disorders				nasal congestion
Gastro-intestinal disorders	gastro-intestinal disturbances,	pseudo-membranous colitis		

	nausea (accompanied by headache) taste disorders, vomiting, diarrhoea, dry mouth, furred tongue, oral mucositis, stomatitis			
Hepatobiliary disorders			increase in liver enzymes (AST, ALT, alkaline phosphatase) and cholestatic hepatitis sometimes with jaundice	pancreatitis and raised liver enzyme values
Skin and subcutaneous tissue disorders			pustular eruptions, mild erythematous eruptions with fleeting joint pains resembling serum sickness	skin rashes, flushing and pruritus
Musculo-skeletal, connective tissue and bone disorders			myalgia and arthralgia	
Renal and urinary disorders			urethral discomfort and darkening of the urine	
General disorders and administration site conditions				fever

Post-marketing experience

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

Nervous system disorders: headache, aseptic meningitis, vertigo

Eye disorders: transient vision disorders such as blurred vision, decreased visual acuity, changes in colour vision, optic neuropathy/neuritis

Ear and labyrinth disorders: hearing impaired/hearing loss (including sensorineural), tinnitus

Cardiac disorders: QT prolongation has been reported, particularly when FLAGYL was administered with medicines with the potential for prolonging the QT interval, ventricular tachycardia (including torsades de pointes)

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

Skin and subcutaneous tissue disorders: acute generalised exanthematous pustulosis, fixed drug eruption, Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form" found online under SAHPRA's publications:**

https://www.sahpra.org.za/Publications/Index/8 or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity.

See section 4.8 above.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

A 20.2.6 Antimicrobial (chemotherapeutic) agents: Medicines against protozoa.

Pharmacotherapeutic group: Anti-bacterials for systemic use, ATC code: J01X D01

5.1 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.

5.2 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol (see section 4.4)

Lemon flavouring

Magnesium aluminium silicate (Type IC)

Methyl parahydroxybenzoate E 218 (see sections 2 and 4.4)

Oil of orange

Propyl parahydroxybenzoate E 216 (see sections 2 and 4.4)

Sodium dihydrogen phosphate dihydrate

Sucrose (see sections 2 and 4.4)

Water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light. Keep in the original container until required for use.

6.5 Nature and contents of container

FLAGYL is packed in amber glass bottles in a pack size of 100 mL suspension.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBER

F/20.2.6/50

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 February 1975.

10. DATE OF REVISION OF THE TEXT

17 September 2023

NAMIBIA

Scheduling status: NS2

Registration number:

90/20.2.6/00311

BOTSWANA

Scheduling status: S2

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