

**Final approved PI (clean copy) dated 24.10.2021**

**SCHEDULING STATUS:** **S4**

**1. NAME OF THE MEDICINE:**

**FLAGYL SUSPENSION**

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION:**

Each 5 ml of suspensions contains: benzoyl metronidazole equivalent to metronidazole 200 mg

Contains sugar: sucrose 3 g/5 mL

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

For excipients, see section 6.1.

**3. PHARMACEUTICAL FORM:**

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

**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.

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- 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.

**4.2 Posology and method of administration:**

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.

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INDICATION	DURATION OF DOSAGE IN DAYS	ADULTS	CHILDREN		
			7 TO 10 YEARS	3 TO 7 YEARS	1 TO 3 YEARS
<b>UROGENITAL TRICHOMONIASIS.</b>  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	--	--	--
<b>NON-SPECIFIC VAGINITIS</b>	7	400 mg twice daily	--	--	--
	OR 1	2 g as a single dose	--	--	--
<b>AMOEBIASIS</b> 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
<b>AMOEBIASIS</b> 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
<b>AMOEBIASIS</b> c) Amoebic liver abscess, also other	5	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily

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forms of extra-intestinal amoebiasis.					
<b>AMOEBIASIS</b> (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
<b>GIARDIASIS</b> 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
<b>ACUTE ULCERATIVE GINGIVITIS</b>	3	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
<b>ACUTE PERICORONITIS</b>	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.

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*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.

**4.3 Contraindications:**

Hypersensitivity to metronidazole, other imidazoles and any of the excipients of Flagyl.

Co-administration with busulfan (see section 4.4 and 4.5).

**4.4 Special warnings and precautions for use:**

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).

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

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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. 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 generalized 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.

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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).

**Information on excipients:**

- *Sucrose*: 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 (see section 2).
- *Preservatives*: Methyl hydroxybenzoate (E218) and propyl hydroxybenzoate (E216) can cause an allergic reaction in some people (possibly delayed).

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- *Alcohol:* Flagyl suspension contains 0,8 % alcohol (ethanol) by volume.

**4.5 Interactions with other medicines and other forms of interaction:**

**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 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.

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**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.

**4.6 Fertility, pregnancy and lactation:**

Safety in pregnancy and lactation has not been established.

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

**4.7 Effects on the 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:**

**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

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**Nervous system disorders:**

*Less frequent:* 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 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

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*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, 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

**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 generalized exanthematous pustulosis, fixed drug eruption, Stevens Johnson syndrome, toxic epidermal necrolysis (see section 4.4).

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***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:

- The Pharmacovigilance Unit at Sanofi: Email: [za.drugsafety@sanofi.com](mailto:za.drugsafety@sanofi.com) or Tel: 011 256-3700, or

SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form” found online under SAHPRA’s publications: <https://www.sahpra.org.za/Publications/Index/8>.

**4.9 Overdose:**

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.

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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

Methyl hydroxybenzoate E 218 (see section 2 and 4.4)

Oil of orange

Propyl hydroxybenzoate E 216 (see section 2 and 4.4)

Sodium dihydrogen phosphate

Sucrose (see section 2 and 4.4)

Veegum H.V.

Water.

**6.2 Incompatibilities:**

Not applicable.

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**6.3 Shelf life:**

3 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 SUSPENSION is packed in amber glass bottles in pack sizes of 50 ml and 100 ml suspension.**

**7. HOLDER OF CERTIFICATE OF REGISTRATION:**

sanofi-aventis south africa (pty) ltd.

2 Bond Street,

Midrand

South Africa,

1685

**8. REGISTRATION NUMBERS:**

**FLAGYL SUSPENSION: F/20.2.6/50**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:**

FLAGYL SUSPENSION: 14 February 1975

**10. DATE OF REVISION OF THE TEXT:**

24.10.2021

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**NAMIBIA**

Scheduling status: NS2

Registration number:

FLAGYL SUSPENSION: 90/20.2.6/00311

**BOTSWANA**

Scheduling status: S2

Registration numbers:

FLAGYL SUSPENSION: B9305200