1. NAME OF THE MEDICINAL PRODUCT

FLAGYL 250mg Tablets

FLAGYL SUSPENSION 125mg/5ml

FLAGYL 500mg Vaginal Pessary

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FLAGYL 250mg Tablets

Each film coated tablet contains 250mg metronidazole.

For a full list of excipients, see section 6.1

FLAGYL SUSPENSION 125mg/5ml

Each ml contains metronidazole benzoate 40mg corresponding to metronidazole 25mg

Excipients:

The product contains 0.8% alcohol, the content in the suspension is 8mg alcohol per ml.

The product contains 60.0% Sucrose, the content in the suspension is 0.6g sucrose per ml.

For a full list of excipients, see section 6.1

FLAGYL 500mg Vaginal Pessary

Each pessary contains 500mg metronidazole.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

FLAGYL 250mg Tablets

Oral tablet
4. CLINICAL PARTICULARS

4.1 Therapeutic indications

The indications are based on the antiparasitic and antibacterial activity and the pharmacokinetic characteristics of metronidazole, taking into consideration both the clinical studies carried out with the medicinal product and its place in the range of anti-infectious drugs currently available.

It is important to take into account official recommendations concerning the appropriate use of antibacterial.

FLAGYL 250mg Tablets and FLAGYL SUSPENSION 125mg/5ml

It is indicated in the treatment of infections caused by anaerobic micro-organisms, amebiosis, lambliasis and trichomoniasis.

FLAGYL 500mg Vaginal Pessary

Topical treatment of Trichomonas vaginitis and nonspecific vaginitis.

4.2 Posology and method of administration

Amebiosis

Adults

1.50g/day in 3 intakes

Children

30mg to 40 mg/kg/day in 3 intakes

In the event of amebic liver abscess, drainage or aspiration of pus should be performed in conjunction with metronidazole therapy.

Treatment duration is 7 consecutive days.

Trichomoniasis

- in women (trichomonas urethritis and vaginitis), a 10-day treatment period associating:
  - 0.50g/day in two oral intakes
• 1 pessary/day

The sexual partner should be treated concomitantly, whether presenting with clinical signs of trichomonas vaginalis infection or not, even if laboratory test results are negative.

- in men (trichomonas urethritis):
  - 0.50g/day in two oral intakes for 10 days

In very rare cases, it may be necessary to increase the daily dose to 0.750 g or 1 g.

**Lambliasis**

**Adults**

0.750g to 1 g/day for 5 consecutive days

**Children**

Tablets:

- 6 to 10 years: 375 mg/day
- 10 to 15 years: 500 mg/day

Suspension:

- 2 to 5 years: 250 mg/day
- 5 to 10 years: 375 mg/day
- 10 to 15 years: 500 mg/day

**Non-specific vaginitis**

500mg (2X250mg) oral tablets or suspension twice daily for 7 days or

1 pessary daily per vaginal route during 7 days in combination with oral treatment, if required.

The partner should be treated concomitantly.

**Treatment of infections caused by susceptible anaerobic micro-organisms**

(first line treatment or replacement treatment)

**Adults**

1g to 1.5g/day

**Children**

20 mg to 30 mg/kg/day
4.3 Contraindications

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

4.4 Special warnings and precautions for use

For all presentations

Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of Flagyl 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.

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 Flagyl 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. Flagyl 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 flagyl for longer treatment than usually required should be carefully considered.

In addition:

For Flagyl Tabs

Flagyl tablets contains wheat starch (gluten) which may cause allergic reactions

For Flagyl Suspension

Flagyl suspension contains methylhydroxybenzoate and propylhydroxybenzoate which may cause allergic reactions (possibly delayed).

Flagyl suspension contains small amounts of ethanol (alcohol), less than 100mg per 5ml.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

**For Flagyl vaginal pessary**

The simultaneous use of Flagyl pessary with condoms or diaphragms may increase the risk of rupture of the latex.

**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. Flagyl 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, 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

**Gastrointestinal disorders:**

Not known: taste disorders, oral mucositis, tongue discoloration/ furred tongue (e.g. due to fungal overgrowth), 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, pruritis, flushing

Not known: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders:

Very rare: myalgia, arthralgia.

Renal and urinary disorders:

Very rare: darkening of urine (due to metronidazole metabolite).

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 code: 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

For Flagyl Tablets

Absorption

After oral administration, metronidazole is rapidly absorbed, at least 80 % in one hour. The plasma peaks obtained
after oral administration are the same than those obtained after intravenous administration of similar doses.

Bioavailability via oral route is 100%. It is not significantly decreased by simultaneous ingestion of food.

**Diffusion**

- About 1 hour after single dose of 500 mg, the mean maximal plasma concentration is 10 microgrammes/ml. After 3 hours, the mean plasma concentration is 13.5 microgrammes/ml.
- Plasma half-life is 8 to 10 hours.
- Blood protein-binding is less than 20%.
- The apparent distribution volume is important about 40 l (i.e. 0.65 l/kg).
- It is rapidly and extensively distributed with concentrations close to serum levels, in the lungs, kidneys, liver, skin, bile, C.S.F., saliva, seminal fluid, vaginal secretions. It passes through the placenta and into the mother's milk.

**Biotransformation**

The product is metabolized principally in the liver by oxidation. Two metabolites are formed:

- The principal "alcohol" metabolite, that has about 30% of the antibacterial activity of metronidazole against anaerobic bacteria, and an elimination half-life of about 11 hours;
- The "acid" metabolite, present in lower quantities, that has about 5% of the antibacterial activity of metronidazole.

**Excretion**

Strong hepatic and biliary concentration; weak colic concentration; weak faecal elimination.

Excretion is chiefly of urine as metronidazole and oxidized metabolites excreted in urine represent about 35 to 65 per cent of the administered dose.

**For Flagyl Suspension**

**Absorption**

Benzoylmetronidazole is hydrolysed gradually during its transit through the alimentary canal. The absorption of benzoylmetronidazole is 30% less (area under the curve) than that of metronidazole.

The plasma peak appears 4 h after the oral administration of the product.

At the same dose regimen, metronidazole and benzoylmetronidazole do not indicate significantly different therapeutic results.

The plasma half-life is 6.9 h according to H.P.L.C.

**Diffusion**

- Blood protein-binding is less than 10%.
- There is rapid and considerable diffusion in the lungs, kidneys, liver, skin, bile, C.S.F., saliva, seminal fluid, vaginal
secretions. It passes through the placenta and into the mother’s milk.

**Biotransformation.**

It produces two non-conjugated metabolites which exhibit antibacterial activity (10%)

**Excretion.**

Strong hepatic and biliary concentration; weak colic concentration; weak faecal elimination.

Excretion is chiefly of urine (40—70 %, about 20 % of which remains unchanged), causing a brown or reddish colouration of the urine

**FLAGYL Vaginal Pessary**

Systemic penetration is minimal following vaginal administration.

Plasma half-life is 8 to 10 hours.

Plasma protein binding is slight, less than 20%.

Diffusion is fast and marked in the lungs, kidneys, liver, bile, CSF, skin, saliva and vaginal secretions. It crosses the placenta barrier and is excreted into breast milk.

Metabolism is essentially hepatic: two non-conjugated oxidated active metabolites (5 to 30% activity) are formed.

Excretion is chiefly urinary: metronidazole and oxidated metabolites, excreted in urine, account for about 35 to 65% of the dose administered.

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**

**FLAGYL 250mg Tablets**

Wheat starch, Povidone K30, Hypromellose, Macrogol 20000, Magnesium stearate

**FLAGYL SUSPENSION 125mg/5ml**

Sucrose, Ethanol 96%, magnesium silico aluminate, Sodium saccharine, Sodium dihydrogen phosphate dihydrate, Methylparahydroxybenzoate, Concentrated lemon essence, Deterpenated orange essence, Propylparahydroxybenzoate, Purified water.
FLAGYL  500mg Vaginal Pessary

Hard fat

6.2 Special precautions for storage
Flagyl 250 mg tablets – Do not store above 25°C.

Flagyl suspension - Do not store above 30°C.
Shelf life after first opening- 8 days.

Flagyl 500 mg vaginal pessary – Do not store above 25°C.

7. MANUFACTURER
Flagyl 250 mg tablets –Sanofi Aventis, S.P.A., Spain.

Flagyl suspension – Unither Liquid Manufacturing, France.

Flagyl 500 mg vaginal pessary – Unither Liquid Manufacturing France.

8. MARKETING AUTHORISATION NUMBER(S)
Sanofi-aventis Israel Ltd.

10 Beni Gaon, POB 8090, Netanya

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in October 2013.