

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flagyl Suppositories 0.5g

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 500 mg of Metronidazole.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository.

Cream-coloured, torpedo-shaped suppositories.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In the prevention and treatment of infections due to anaerobic bacteria, particularly species of *Bacteroides*, anaerobic *Streptococci*, *Fusobacteria*, *Clostridia*, etc.

4.2 Posology and method of administration

Rectal.

Recommended Dosage:

Adults:

1g 8 hourly. Substitute oral medication as early as possible. If rectal administration is prolonged beyond 3 days reduce dose to 1g 12 hourly for remainder of course.

Children:

7.5 mg/kg 8 hourly.

Prophylaxis against anaerobic infection-chiefly in the context of abdominal (especially colorectal) and gynaecological surgery:

Adults:

1g 8 hourly.

Children one half or a quarter of a 500mg suppository 8 hourly.

4.3 Contraindications

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. Use in patients known to be hypersensitive to metronidazole.

4.4 Special warnings and precautions for use

The use of Flagyl for prolonged treatment duration should be carefully weighed

1. If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible. High dosage regimes have been associated with transient epileptiform seizures. Caution is required in patients with active disease of the central nervous system except for brain abscess.
2. Metronidazole and a metabolite have been shown to be mutagenic in some tests with non-mammalian cells.
3. Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction.
4. Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.
5. Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. The risk/benefit using metronidazole to treat trichomoniasis in such patients should be carefully considered.
6. Flagyl should be administered with caution to patients with hepatic encephalopathy.
7. Patients should be warned that metronidazole may darken urine (due to metronidazole metabolite).
8. Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.5 Interaction with other medicinal products and other forms of interaction

1. Potentiation of coumarin anticoagulant effects may occur with metronidazole and anticoagulant activity should be carefully monitored during concurrent therapy.
2. Patients should be advised not to take alcohol during, (or drugs containing alcohol) during metronidazole therapy and for at least 48 hours afterwards because of a disulfiram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).
3. Disulfiram: psychotic reaction have been reported in patients who were using metronidazole and disulfiram concurrently.
4. Lithium retention observed by increased plasma lithium levels, 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 concentration of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.
5. Cyclosporin: risk of elevation of the cyclosporin serum levels. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.
6. 5-Fluorouracil: reduced clearance of 5 fluorouracil resulting in increased toxicity of 5-fluorouracil.
7. Phenytoin or Phenobarbital: increased elimination of metronidazole resulting in reduced plasma levels.
8. Busulfan: plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

4.6 Fertility, pregnancy and lactation

Metronidazole should only be used during pregnancy or lactation following careful evaluation and only if considered essential by the physician. If used, high dosage regimes should be avoided. The drug crosses the placenta and is excreted in breast milk in which concentration equal those in serum. Unnecessary exposure to the drug should be avoided.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Frequency, type and severity of adverse reactions in children are the same as in adults.

Gastrointestinal Disorders

- epigastric pain, nausea, vomiting, diarrhoea.
- oral mucositis, taste disorders, dry mouth, anorexia.
- reversible cases of pancreatitis.

Immune system disorders

- angioedema, anaphylactic shocks.

Nervous system disorders

- peripheral sensory neuropathy.
- headache, convulsions, dizziness.
- reports 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 drug.
- aseptic meningitis

Psychiatric disorders

- psychotic disorders including confusion, hallucinations.
- depressed mood

Eye disorders

- transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity. Changes in color vision.
- Optic neuropathy/neuritis.

Blood and lymphatic system disorders

- cases of agranulocytosis, neutropenia and thrombocytopenia have been reported.

Hepatobiliary disorders

- cases of reversible abnormal liver function tests and cholestatic hepatitis sometimes with jaundice have been reported.

Skin and subcutaneous tissue disorders

- rash, pruritus, flushing, urticaria
- pustular eruptions

General disorders and administration site conditions

- fever

4.9 Overdose

Single oral doses of metronidazole, up to 12 g 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 overdosage, a symptomatic and supportive treatment should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Flagyl - the drug has antiprotozoal and antibacterial actions including activity against anaerobic bacteria, entamoeba histolytica.

5.2 Pharmacokinetic properties

A nitroimidazole derivative well absorbed and widely distributed in the body. It is metabolised by acid oxidation, hydroxylation and glucuronidation and excreted in urine and faeces with a T_{1/2} of about 7-8 hours.

5.3 Preclinical safety data

Metronidazole has been shown to be carcinogenic in the mouse and in the rat. However, similar studies in the hamster have given negative results and epidemiological studies in humans have provided no 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 and in humans in vivo, there was inadequate evidence of mutagenic effects.

Therefore, the use of Flagyl for prolonged treatment duration should be carefully weighed. (See Section 4.4 “Warnings and Precautions”).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Suppository Base E75

Suppository Base W35

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container

Performed PVC/polyethylene laminates.

Moulded plaquettes of cellulose acetate, plasticized with approximately 22% diethylphthalate/triphenylphosphate sealed with heat using glycerol triacetate adhesive.

Pack size: boxes 10 x 500 mg suppositories.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

sanofi-aventis Ireland Ltd.
Citywest Business Campus
Dublin 24.

8 MARKETING AUTHORISATION NUMBER

PA 540/100/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30th September 1977

Date of last renewal: 30th September 2007

10 DATE OF REVISION OF THE TEXT

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