Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flagyl 400mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 400 mg of metronidazole.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.
White to off-white biconvex, capsule-shaped film-coated tablet imprinted 'Flagyl 400', plain reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metronidazole is indicated in adults and children for the following indications:

- In the treatment of urogenital trichomoniasis
- In the treatment of acute ulcerative gingivitis.
- In the treatment of infections due to E. histolytica (including carrier states).
- In the treatment of infections due to G. Lamblia (including carrier states).
- In the prevention and treatment of infections due to anaerobic bacteria, particularly species of Bacteroides, anaerobic streptococci, fusobacteria, clostridia, etc.
- In the treatment of acute dental infections.
- In the treatment of non-specific vaginitis.

Metronidazole is indicated in adults only for the following indications:

- In the treatment of chronic pressure sores and ulcers with possible infection due to anaerobes.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Oral

Recommended Dosages:

Urogential trichomoniasis

Adults and children over 10 years:
2000 mg as a single dose or 200 mg 3 times daily for 7 days or 400 mg twice daily for 5 – 7 days

Children <10 years:
40 mg/kg orally as a single dose or 15 – 30 mg/kg/day divided in 2 – 3 doses for 7 days; not to exceed 2000 mg/dose

Acute ulcerative gingivitis

Adults and children over 10 years:
600 mg daily in 3 divided doses for 3 days.

Paediatric population:

Aged 7 to 10 years: 300 mg daily in 3 divided doses for 3 days.
Aged 3 to 7 years: 200 mg daily in 2 divided doses for 3 days.
Aged 1 to 3 years: 150 mg in 3 divided doses for 3 days.

Amoebiasis

Adults and children over 10 years:
400 – 800 mg 3 times daily for 5 – 10 days.

Paediatric population:
Aged 7 to 10 years: 200 – 400 mg 3 times daily for 5 – 10 days
Aged 3 to 7 years: 100 – 200 mg 4 times daily for 5 – 10 days
*Aged 1 to 3 years:*100 – 200 mg 3 times daily for 5 – 10 days

Alternatively, doses may be expressed by body weight: 35 – 50 mg/kg daily in 3 divided doses for 5 – 10 days, not to exceed 2400 mg/day

Giardiasis

Adults and children over 10 years:
2000 mg once daily for 3 days, or 400mg three times daily for 5 days

Paediatric population:
Aged 7 to 10 years: 1000 mg once daily for 3 days.
Aged 3 to 7 years: 600 mg – 800 mg once daily for 3 days.
Aged 1 to 3 years: 500 mg once daily for 3 days.

Alternatively, as expressed in mg per kg of body weight: 15 – 40 mg/kg/day divided in 2 – 3 doses.

Anaerobic infections

Treatment

Adults:
800 mg followed by 400 mg 8 hourly.

Paediatric population:
Children >8 weeks to 12 years of age: The usual daily dose is 20 – 30 mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.

Children <8 weeks of age: 15mg/kg as a single dose daily or divided into 7.5mg/kg every 12 hours.

In newborns with a gestation age <40 weeks: accumulation of metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferably be monitored after a few days therapy.

Prophylaxis against postoperative infections caused by anaerobic bacteria

Adults:
400 mg at 8 hourly intervals during the 24 hours immediately preceding operation, followed post operatively by intravenous or rectal administration until oral dosing can be resumed.

Paeditric population:
Children <12 years: 20 – 30 mg/kg as a single dose given 1 – 2 hours before surgery
Newborns with a gestation age <40 weeks: 10 mg/kg body weight as a single dose before operation

Eradication of helicobacter pylori in paediatric patients:
As part of a combination therapy, 20 mg/kg/day not to exceed 500 mg twice daily for 7 – 14 days. Official guidelines should be consulted before initiating therapy.

Dental Infections
The usual total daily dose is 600 – 800 mg in divided doses. Treatment should generally be continued for 3 – 7 days.

Chronic pressure sores and ulcers

Adults:
1200 mg daily in 3 divided doses.

Bacterial Vaginitis

Adults and Adolescents:
A single dose of 2000 mg may be used or 400 mg twice daily for 5 – 7 days.

Adjustment of dosage does not appear necessary in patients with renal impairment.

In the case of children whose weights are below those usual for their age, or of infants below 10 kg in weight, dosage of metronidazole should be reduced proportionately.

Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

Elderly
Caution is advised particularly at high doses. No information is available on modification of dosage.

Hepatic Encephalopathy
Daily dosage should be reduced to one third and may be given once daily (see section 4.4).

4.3 Contraindications

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological aggravation.
Use in patients with known hypersensitivity to metronidazole.

4.4 Special warnings and precautions for use

The use of Flagyl for prolonged treatment duration should be carefully weighed. If prolonged therapy is required, the physician should bear in mind the possibility of peripheral neuropathy or leucopenia. Both effects are usually reversible. It is recommended that haematological tests be carried out regularly and that patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, vertigo, convulsive seizures) (see section 4.8).

High dosage regimens have been associated with transient epileptiform seizures. Caution is required in patients with active disease of the central nervous system except for brain abscess.

Metronidazole and a metabolite have been shown to be mutagenic in some tests with non mammalian cells.

Intensive or prolonged metronidazole therapy should be conducted only under conditions of close surveillance for clinical and biological effects and under specialist direction.

Metronidazole is removed during haemodialysis and should be administered after the procedure is finished.

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.

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

Cases of severe bullous skin reactions, sometimes fatal, 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). The majority of cases of SJS reported occurred within 7 weeks of starting treatment with metronidazole. Patients should be advised

of the signs and symptoms and monitored closely for skin reactions. If symptoms of SJS, TEN or AGEP (e.g. flu-like symptoms, progressive skin rash often with blisters or mucosal lesions) are present, treatment must be immediately discontinued (see section 4.8).

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

Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards (see section 4.5).

Hepatotoxicity in patients with Cockayne Syndrome

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 products containing metronidazole for systemic use. In this population, metronidazole should not be used unless the benefit is considered to outweigh the risk and if no alternative treatment is available. Liver function 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, the drug should be discontinued. Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole (see section 4.8).

Metronidazole 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 oxidized 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.

4.5 Interaction with other medicinal products and other forms of interaction

Potentiation of the anticoagulant effect and increased hemorrhagic risk caused by decreased hepatic catabolism. In case of coadministration, prothrombin time should be more frequently monitored and anticoagulant therapy adjusted during treatment with metronidazole.

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. Plasma levels of lithium may be increased by 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.

Phenytoin or Phenobarbital: increased elimination of metronidazole resulting in reduced plasma levels.A similar effect may occur with other drugs which induces hepatic enzymes.

Patients should be advised not to take alcohol, (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).

Disulfiram: psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.

Cyclosporin: risk of elevation of the cyclosporin serum levels. Serum cyclosporine and serum creatinine should be closely monitored when coadministration is necessary.

5-Fluorouracil: reduced clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil.

Busulfan: Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

Drugs that prolong QT interval: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

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. Its effects on foetal organogenesis are not known. If used, high dosage regimens should be avoided. The drug

crosses the placenta and is excreted in breast milk in which concentrations 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, 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

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

- epigastric pain, nausea, vomiting, malaise, diarrhoea.
- oral mucositis, taste disorders, dry mouth, anorexia.
- reversible cases of pancreatitis.
- tongue discolouration/furry tongue.

Immune system disorders

- angioedema, anaphylactic shock.

Nervous system disorders

- peripheral sensory neuropathy, paraesthesia
- 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, vertigo

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.

Ear and labyrinth disorders

- hearing impaired/hearing loss (including sensorineural)
- tinnitus

Blood and lymphatic system disorders

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

Hepatobiliary disorders

- increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported.
- cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole mostly when used in combination with other antibiotic drugs.

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (see section 4.4).

Skin and subcutaneous tissue disorders

- rash, pruritus, flushing, urticaria
- pustalar eruptions, acute generalised exanthematous pustulosis
- fixed drug eruption
- Stevens-Johnson syndrome, toxic epidermal necrolysis.

General disorders and administration site conditions

- fever

Cardiac disorders

- Frequency not known: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

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 treatment for gross overdosage of Flagyl. In cases of suspected massive overdosage, a symptomatic and supportive treatment should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic properties

A nitroimidazole derivative is 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 T½ of about 6 - 10 hours. Metronidazole is excreted in milk but the intake of a suckling infant of a mother receiving normal dosage would be considerablyless than the therapeutic dosage for infants.

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 effect of metronidazole, with some studies reporting mutagenic effects, while other studies were negative.

Therefore, the use of Flagyl for prolonged treatment duration should be carefully weighed (see section 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate Dihydrate
Maize Starch

Povidone
Magnesium Stearate
Hypromellose
Macrogol 400
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30^{o}C in the original packaging in order to protect from light.

6.5 Nature and contents of container

Flagyl Tablets are available in PVDC coated uPVC/aluminium foil blister packs (opaque white film) containing 14 Flagyl 400 mg tablets and securitainers containing 100 x 400 mg tablets.

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 Limited T/A SANOFI
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0540/100/008

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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