SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flagyl 1g Suppositories.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 1.0 g metronidazole.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository

A cream coloured, smooth, torpedo-shaped suppository.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. 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, Eubacteria, Clostridia and anaerobic cocci.

Flagyl has been used successfully in: septicaemia, bacteraemia, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, peritonitis and post-operative wound infection from which one or more of these anaerobes have been isolated.

2. Prevention of post-operative infections due to anaerobic bacteria, particularly species of Bacteroides and anaerobic Streptococci.

4.2 Posology and method of administration

Posology

1. Treatment of Anaerobic Infections:

Adults and children over 10 years: 1 g suppository inserted into the rectum eight hourly for three days. Oral medication with 400 mg three times daily should be substituted as soon as this becomes feasible. If rectal medication must be continued for more than three days, the suppositories should be inserted at 12 hourly intervals.

Children (5 – 10 years): As for adults but with 500 mg suppositories and oral medication with 7.5 mg/kg bodyweight three times daily.

Infants and children under 5 years: As for children of 5 – 10 years but with appropriate reduction in dosage of suppositories (one half of a 500 mg suppository for 1 – 5 years and one quarter of a 500 mg suppository for under 1 year).

2. Prevention of Anaerobic Infections:

In appendectomy and post-operative medication for elective colonic surgery.

Adults and children over 10 years: 1 g suppository inserted into the rectum two hours before surgery and repeated at eight hourly intervals until oral medication (200 – 400 mg three times daily) can be given to complete a seven day course.

If rectal medication is necessary after the third post-operative day, the frequency of administration should be reduced to 12 hourly.

Children (5 – 10 years): 500 mg suppositories administered as for adults until oral medication (3.7 – 7.5 mg/kg bodyweight three times daily) becomes possible.

Method of administration

Rectal

4.3 Contraindications

Known hypersensitivity to nitroimidazoles, metronidazole or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

There is a possibility that after *Trichomonas vaginalis* has been eliminated a gonococcal infection might persist.

Patients should be warned that metronidazole may darken urine. For information on renal and hepatic insufficiency, please see section 4.2.

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.

Neuropathy (central and peripheral)
Metronidazole has no direct activity against aerobic or facultative anaerobic bacteria. 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, vertigo, 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.

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).

Skin and subcutaneous tissue disorders
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. If symptoms or

signs of SJS, TEN or AGEP are present, Flagyl treatment must be immediately discontinued.

Interference with laboratory tests
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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Alcohol: 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.

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

Oral anticoagulant therapy (warfarin type): 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: 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.

Phenytoin and phenobarbital: Patients receiving phenobarbital or phenytoin metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.

5-fluorouracil: Metronidazole reduces the clearance of 5-fluorouracil and can therefore result in increased toxicity of 5-fluorouracil.

Ciclosporin: Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

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

There is inadequate evidence of the safety of metronidazole in pregnancy, but it has been in wide use for many years without apparent ill consequence.

Nevertheless Flagyl, like other medicines, 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, vertigo, 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: angioedema, 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 (e.g. confusion, vertigo, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (e.g. 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
- vertigo
- posterior reversible encephalopathy syndrome (PRES)

Eye disorders:
Very rare: vision disorders such as diplopia and myopia, which in most cases, is transient
Not known: optic neuropathy/neuritis

Ear and labyrinth disorders:
Not known: hearing impaired/hearing loss (including sensorineural), tinnitus

Cardiac disorders:
Not known: QT prolongation has been reported particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval

Gastrointestinal disorders:
Not known: taste disorders, oral mucositis, furred tongue, 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

Cases of severe irreversible hepatotoxicity/acute live 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:
Very rare: skin rashes, pustular eruptions, acute generalised exanthematous pustulosis (AGEP), pruritis, flushing
Not known: erythema multiforme, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), fixed drug eruption

Musculoskeletal, connective tissue and bone disorders:
Very rare: myalgia, arthralgia

Renal and urinary disorders:
Very rare: darkening of urine (due to metronidazole metabolite)

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 group: Anti-bacterials 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

Metronidazole is readily absorbed from the rectal mucosa and widely distributed in body tissues. Maximum concentrations occur in the serum after about 1 hour and traces are detected after 24 hours.

At least half the dose is excreted in the urine as metronidazole and its metabolites, including an acid oxidation product, a hydroxy derivative and glucoronide. Metronidazole diffuses across the placenta, and is found in breast milk of nursing mothers in concentrations equivalent to those in serum.

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 suppository also contain the following excipients:

Suppository base E75 and suppository base W35

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 20°C.

Store in the original package in order to protect from light

6.5 Nature and contents of container

Flagyl suppositories are available PVC/polyethylene bandoliers containing 10 suppositories.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Fidia Pharma UK Ltd
170 Edmund Street,
Ground Floor
Birmingham,
B3 2HB,
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 56485/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 September 1991

Date of latest renewal: 03 January 2007

10 DATE OF REVISION OF THE TEXT

21/11/2025