SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flagyl 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole ..... 250.00 mg

For one film-coated tablet.
Excipient(s) with known effect: wheat starch (containing gluten) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Trichomonias, acute intestinal amebiasis.

Infections due to anaerobic bacteria, lambliasis.

4.2. Posology and method of administration

Posology

- Amebiosis
  - Adults
    1.50 g/day in 3 intakes.
  - Children
    30 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:
    - 0.50 g/day in 2 oral intakes,
    - 1 pessary/day.

If PHARMACEUTICAL FORM of pessary is not optional, the physician should consider alternative therapies for these patients.

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):
    0.50 g/day in 2 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
    0.750 g to 1 g/day for 5 consecutive days.
  - Children:
    6 to 10 years: 375 mg/day

10 to 15 years: 500 mg/day

- Nonspecific vaginitis
  500 mg (2X250mg) twice daily for 7 days

The partner should be treated concomitantly.

- Treatment of infections caused by susceptible anaerobic micro-organisms (first-line treatment or replacement treatment)
  - Adults:
    1 g to 1.5 g/day.
  - Children:
    20 mg to 30 mg/kg/day.

4.3. Contraindications

- Hypersensitivity to the active substance metronidazole or to imidazoles or to any of the excipients listed in section 6.1.
- Wheat allergy (except in patients with coeliac disease) (see section 4.4).
- Children under 6 years of age because of the pharmaceutical form (see section 4.4).

4.4. Special warnings and precautions for use

Hypersensitivity / Skin and appendages

Allergic reactions, including anaphylactic shock, can occur and be life-threatening (see section 4.8). In this case, treatment with metronidazole must be discontinued and appropriate medical treatment initiated.

If, at the start of treatment, patients experience generalised erythema with fever and pustules, acute generalised exanthematous pustulosis should be suspected (see section 4.8). If this occurs, treatment must be discontinued and any further administration of metronidazole alone or in combination with other agents is contraindicated.

Severe skin reactions have been reported with metronidazole, such as Stevens-Johnson syndrome, toxic epidermal necrolysis (or Lyell's syndrome), and acute generalised exanthematous pustulosis (AGEP). Patients must be informed of the signs and symptoms of these conditions and the skin should be closely monitored.

If any signs or symptoms of Stevens-Johnson syndrome, toxic epidermal necrolysis (e.g., progressive skin rash often with blisters or mucosal lesions) or AGEP (generalised erythema with fever and pustules) (see section 4.8) occur, treatment must be discontinued and any further administration of metronidazole alone or in combination with other agents is contraindicated.

Central nervous system

If symptoms suggestiveof encephalopathy or cerebellar syndrome occur (for example, ataxia, dysarthria, gait disturbance, nystagmus, tremor, vertigo, confusion, convulsions, peripheral sensory neuropathy, headache (see section 4.8)), the patient's treatment must be immediately reassessed, and therapy with metronidazole treatment must be discontinued.

Cases of encephalopathy have been reported as part of post-marketing surveillance of the drug. Cases of MRI changes associated with encephalopathy have also been observed (see section 4.8). Damage is most often located in the cerebellum (particularly in the dentate nucleus) and in the splenium of the corpus callosum. Most cases of encephalopathy and MRI changes are reversible on treatment discontinuation. Very rare cases of fatal outcome have been reported.

Patients should be monitored for warning signs of encephalopathy, and exacerbation of symptoms in patients with CNS disorders. If aseptic meningitis occurs during treatment, rechallenge with metronidazole is not recommended, and an assessment of the benefit/risk ratio should be done for patients with serious infection.

Peripheral nervous system

Patients should be monitored for warning signs of peripheral neuropathy, particularly in long-term treatment or in patients with severe, chronic or progressive peripheral neurological disorders.

Psychiatric disorders

From administration of the first doses, patients may experience psychotic reactions, including self-endangering behaviour, particularly if they have a history of psychiatric disorders (see section 4.8). If this happens, metronidazole must be discontinued, the physician informed, and appropriate therapeutic

measures instituted immediately.

Haematological effects

In patients who have a history of haematological disorders or who are receiving high-dose and/or long-term treatment, regular blood tests, and particularly leukocyte counts, should be performed.

In patients with leukopenia, continued treatment will depend on how serious the infection is.

Excipient with known effect

Wheat starch (containing gluten)

This medicine contains trace amounts of gluten (from wheat starch) and is therefore unlikely to cause problems for patients with coeliac disease.
One tablet contains no more 8.215 micrograms of gluten.

Patients with an allergy to wheat (different from coeliac disease) should not take this medicinal product (see section 4.3).

Paediatric population

Tablets are contraindicated in children under 6 years of age because of the risk of pulmonary aspiration. Other presentations of metronidazole-based medicinal products are available for young children.

Interaction with other medicinal products

Concomitant use of metronidazole and alcohol is not recommended (see section 4.5).

Concomitant use of metronidazole and busulfan is not recommended (see section 4.5).

Concomitant use of metronidazole and disulfiram is not recommended (see section 4.5).

Interference with paraclinical examinations and laboratory tests

Metronidazole may immobilise treponemes, and thus lead to false positive results for the Nelson test.

Metronidazole may interfere with certain types of blood tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], triglycerides, glucose), which may lead to a false negative or an abnormally low result. These analytical methods are based on a decrease in ultraviolet absorbance, which occurs when hydrogenated nicotinamide adenine dinucleotide (NADH) is oxidised to nicotinamide adenine dinucleotide (NAD). This interference is due to the similarity of the absorption peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Patients with Cockayne Syndrome Cases of severe hepatotoxicity/acute liver failure of very rapid onset after treatment initiation, including cases with fatal outcome, have occurred in patients with Cockayne syndrome who were administered medicinal products containing metronidazole intended for systemic use. In this population, metronidazole must therefore be used after thorough evaluation of the benefit/risk ratio and only if no alternative treatment is available. Liver function tests must be performed just before treatment initiation, during treatment and after treatment discontinuation, until liver function values are within the normal range, or until baseline values are reached. If the liver function test values markedly increase during treatment, the medicinal product should be discontinued.

Patients with Cockayne syndrome must be instructed to immediately report any symptoms of potential liver damage to their doctor and to stop taking metronidazole.

4.5. Interaction with other medicinal products and other forms of interaction

Antabuse reaction

Many medicinal products trigger an antabuse effect with alcohol and their concomitant use with alcohol is not advisable.

Inadvisable combinations

+ Alcohol (beverage or excipient)

An antabuse effect (hot flushes, erythema, vomiting, tachycardia) may occur. Patients should not consume alcoholic beverages or medicinal products containing alcohol. Alcoholic beverages or medicinal products containing alcohol should not be ingested again until medicinal products have been completely eliminated from the body. The half-life should be used as a reference.

+ Busulfan

When co-administered with high busulfan doses, metronidazole causes a two-fold increase in plasma busulfan concentrations.

+ Disulfiram

There is a risk of acute psychotic episodes or confusion, reversible on discontinuation of the drug combination.

+ Drugs causing QT interval prolongation

Cases of QT interval prolongation have been reported, particularly when metronidazole is administered with medicinal products that may prolong the QT interval.

Combinations requiring precautions for use

+ Enzyme-inducing anticonvulsants

Decreased plasma concentrations of metronidazole can occur due to increased liver metabolism by the inducer.

Clinical monitoring is required, and the metronidazole dose may need to be adjusted during and after treatment with the inducer.

+ Rifampicin

Decreased plasma concentrations of metronidazole can occur due to increased liver metabolism by rifampicin.

Clinical monitoring is required, and the metronidazole dose may need to be adjusted during and after treatment with rifampicin.

+ Lithium

Increased blood lithium levels can occur, which can reach toxic levels with signs of lithium overdose.

Strict monitoring of blood lithium levels should be performed, and the lithium dose adjusted if necessary.

Combinations to be taken into consideration

Fluorouracil (and by extrapolation, tegafur and capecitabine)

Increased fluorouracil toxicity can occur due to decreased clearance.

Specific issue: INR imbalance

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotics. The severity of the infection or inflammation, age and general health status of the patient appear to be risk factors. Under these circumstances, it seems difficult to determine to what extent the infection itself or its treatment play a role in the INR imbalance. However, certain classes of antibiotics are more involved, particularly fluoroquinolones, macrolides, cyclines, cotrimoxazole and certain cephalosporins.

4.6. Fertility, pregnancy and lactation

Pregnancy

There is no evidence from animal studies that metronidazole is teratogenic. Therefore, no malformative effect is expected in humans. To date, substances causing malformations in humans have been shown to be teratogenic in animals during well-conducted studies in two species.

In man, analysis of a large number of exposed pregnancies did not seem to show any particular teratogenic or foetotoxic effects of metronidazole.

However, only epidemiological studies would make it possible to rule out any risk. Therefore, metronidazole may be prescribed during pregnancy if necessary.

Breast-feeding

Since metronidazole is excreted in breast milk, administration should be avoided in breast-feeding women.

4.7. Effects on ability to drive and use machines

Patients should be warned of the potential risk of dizziness, confusion, hallucinations and seizures or vision disorders, and should be advised not to drive or operate machines if they experience such symptoms.

4.8. Undesirable effects

Blood and lymphatic system disorders

- Neutropenia, agranulocytosis, thrombocytopenia.

Cardiac disorders

- Not known: Cases of QT interval prolongation have been reported, particularly when metronidazole is administered with medicinal products that may prolong the QT interval.

Psychiatric disorders

- Hallucinations,
- Psychotic reactions with paranoia and/or delirium possibly accompanied by suicidal ideation or suicide attempts in some isolated cases (see section 4.4),
- Depressed mood.

Nervous system disorders

- Peripheral sensory neuropathy,
- Headache,
- Dizziness,
- Confusion,
- Seizures,
- Encephalopathy that may be associated with MRI changes, generally reversible upon treatment discontinuation. Very rare cases of fatal outcome have been reported (see section 4.4),
- Sub-acute cerebellar syndrome (ataxia, dysarthria, gait disorders, nystagmus, tremor) (see section 4.4),
- Aseptic meningitis (see section 4.4).
- Frequency not known: posterior reversible encephalopathy syndrome (PRES)*

*the ADR is applicable only for systemic formulations

Eye disorders

- Transient vision disorders such as blurred vision, diplopia, myopia, reduced visual acuity, impaired colour vision,
- Neuropathy / optic neuritis.

Gastrointestinal disorders

- Minor gastrointestinal disorders (epigastric pain, nausea, vomiting, diarrhoea),
- Glossitis with dry mouth, stomatitis, taste disorders, anorexia,
- Pancreatitis, reversible on treatment discontinuation,
- Discolouration or change in the appearance of the tongue (mycosis).

Hepatobiliary disorders

- Elevated liver enzyme levels (AST, ALT, alkaline phosphatase), very rare cases of acute cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice, have been reported. Isolated cases of hepatocellular insufficiency possibly requiring liver transplantation have been reported.

Skin and subcutaneous tissue disorders

- Hot flushes, pruritus, skin rash occasionally with fever,
- Urticaria, angioedema, anaphylactic shock (see section 4.4),
- Very rare cases of acute generalised exanthematous pustulosis (see section 4.4),
- Toxic epidermal necrolysis,
- Stevens-Johnson syndrome,
- Fixed drug eruption.

Other effects

- Urine can appear reddish-brown as water-soluble pigments may be found due to metabolism of the drug.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at https://sideeffects.health.gov.il/.

Overdose

Administration of up to 12 g as a single dose has been reported in cases of attempted suicide and accidental overdose.

The symptoms were limited to vomiting, ataxia and mild disorientation. There is no specific antidote to metronidazole overdose. If massive overdose occurs, symptomatic treatment should be instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antibacterial antibiotics belonging to the 5-nitroimidazole group, ATC code: J01XD01 — P01AB01 (J: Anti-infectives for systemic use, other antibacterials - imidazole derivatives - P: Anti-protozoals, agents against amoebiasis and other protozoal diseases - nitroimidazole derivatives).

The MIC breakpoints differentiating susceptible from intermediate strains, and intermediate from resistant strains are as follows: S ≤ 4 mg/L and R > 4 mg/L

The prevalence of acquired resistance in certain species can vary geographically and over time. It is therefore useful to have local information on the prevalence of resistance, especially in treating severe infections. These data are only guidelines indicating the probability of susceptibility of a bacterial strain to this antibiotic.

When the variability of prevalence of resistance of a bacterial species is known in France, it is indicated in the table below:

Category	**Prevalence of acquired resistance in France (>10%) (range)**
Susceptible species	
Gram-negative aerobes	
Helicobacter pylori	*30%*
Anaerobes	
Bacteroides fragilis	
Bifidobacterium	*60-70%*
Bilophila	
Clostridium	
Clostridium difficile	
Clostridium perfringens	
Eubacterium	*20-30%*
Fusobacterium	
Peptostreptococcus	
Porphyromonas	
Prevotella	
Veillonella	
Resistant species	
Gram-positive aerobes	
Actinomyces	
Anaerobes	
Moibluncus	

Propionibacterium acnes	
Antiparasitic activity	
Entamoeba histolytica	
Giardia intestinalis	
Trichomonas vaginalis	

5.2. Pharmacokinetic properties

Absorption

Following oral administration, metronidazole is rapidly absorbed (at least 80% within one hour). Peak plasma concentrations obtained after oral administration are similar to those obtained after IV administration of equivalent doses.

Oral bioavailability is 100%. It is not significantly affected by concomitant intake of food.

Distribution

- Approximately one hour after a single 500 mg dose, the mean peak plasma concentration is 10 micrograms/mL. After 3 hours, the mean plasma concentration is 13.5 micrograms/mL.
- The plasma half-life is from 8 to 10 hours.
- The drug is poorly bound to plasma protein, i.e., below 20%.
- The apparent volume of distribution is high (approximately 40 L, i.e., 0.65 L/kg).
- The drug is rapidly and widely distributed, with concentrations close to plasma concentrations, in the lungs, kidneys, liver, skin, bile, CSF, saliva, semen and vaginal secretions.

Metronidazole crosses the placental barrier and is excreted in breast milk.

Biotransformation

Metabolism is mainly hepatic. Two main compounds are formed by oxidation:

- The 'alcohol' metabolite (major metabolite) with antibacterial activity against anaerobes that is approximately 30% that of metronidazole, and an elimination half-life of approximately 11 hours;
- The 'acid' metabolite, in small amounts, with a bactericidal activity of approximately 5% that of metronidazole.

Elimination

High concentrations of metronidazole can be found in the liver and bile. Low concentrations of the drug are found in the colon. Metronidazole is poorly excreted in the faeces. It is mainly eliminated in the urine since metronidazole and its oxidised metabolites, eliminated in the urine, account for approximately 35 to 65% of the administered dose.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Wheat starch, povidone K30, magnesium stearate, hypromellose, macrogol 20 000.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Do not store above 30ºC. Protect from light.

6.5. Nature and contents of container

(PVC/Aluminium) blisters.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi Israel ltd.

Greenwork Park, P.O box 47, Yakum, ISRAEL

8. MARKETING AUTHORISATION NUMBER

- 106 97 21742

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