SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLAGYL oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Metronidazole benzoate .....40 mg/ml

Corresponding to Metronidazole……25 mg/ml

1 measuring spoon (5 ml) contains 125 mg of metronidazole.

Excipients with known effect: ethanol (96 per cent), sucrose, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections caused by anaerobic bacterias, amebiosis, lambliasis and trichomonas.

4.2 Posology and method of administration

Posology

- Amoebiasis
  - Adults
    1.50 g Metronidazole / daily as three divided doses.
  - Paediatric population

    30 to 40 mg Metronidazole / kg / day in three divided doses.

In patients with hepatic amoebiasis, in the abscess, stage, abscess drainage should be performed in conjunction with metronidazole therapy.

Treatment duration is 7 consecutive days.

- Trichomoniasis
  - In women (urethritis and vaginitis due to Trichomonas), preferably, ten-day treatment combining the following:
    - 0.50 g Metronidazole / day by oral route as two divided doses.
    - 1 pessary/day.

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

    It is important that the partner be treated concomitantly, regardless of whether there are clinical signs of Trichomonas vaginalis infestation, even without a positive laboratory test result.
  - In men (Urethritis trichomonal):
    0.50 g Metronidazole / day by oral route as 2 divided doses for 10 days.

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

- Lambliasis
  - Adults
    0.750 g to 1 g Metronidazole / day for five consecutive days.
  - Children:
    from 2 to 5 years of age: 250 mg Metronidazole / day.
    from 5 to 10 years of age: 375 mg Metronidazole / day.
    from 10 to 15 years of age: 500 mg Metronidazole / day.
- Non-specific vaginitis
  500 mg Metronidazole twice daily for 7 days.

The patient's partner should be treated at the same time.

- Treatment of infections caused by anaerobes
  (as first-line or replacement treatment).
  - Adults:
    1 to 1.5 g Metronidazole / day.
  - Children:
    20 to 30 mg Metronidazole / kg / day.

Method of administration

For oral use.

For oral administration use the measuring spoon provided with the bottle in the carton (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or the class of imidazoles, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity/skin and appendices

Allergic reactions, including anaphylactic shock, can occur and may be life-threatening (see section 4.8). In these cases, metronidazole should be discontinued and appropriate medical treatment should be implemented.

The onset of a pyrexial generalised erythema associated with pustules at the beginning of treatment should lead to the suspicion of acute generalised exanthematous pustulosis (see section 4.8); this requires therapy cessation and contraindicates any new administration of metronidazole, alone or combined.

Cases of severe skin reaction including Stevens-Johnson syndrome, Lyell's Syndrome and acute generalised exanthematous pustulosis (AGEP) have been reported with metronidazole. Patients must be informed of the signs and symptoms and the skin should be closely monitored.

The occurrence of signs or symptoms of Stevens-Johnson syndrome, Lyell's Syndrome (e.g., progressive rash often with blisters or mucous membrane injuries) or AGEP (pyrexial generalised erythema with pustules) (see section 4.8) requires therapy cessation and contraindicates any new administration of metronidazole, alone or combined.

Central nervous system

If symptoms suggestive of 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 management must be immediately reassessed, and the metronidazole treatment must be discontinued.

Cases of encephalopathy have been reported during post-marketing monitoring of this medicine. Cases of MRI changes associated with encephalopathy have also been observed (see section 4.8). The observed lesions are localised more frequently in the cerebellum (particularly in the dentate nucleus) and in the splenium of the corpus callosum. Most encephalopathy cases and MRI changes are reversible upon treatment discontinuation. Rare cases with fatal outcomes have been reported.

Signs suggestive of encephalopathy or deterioration in patients with central neurological conditions should be monitored.

In the event of aseptic meningitis while being treated with metronidazole, reinitiating treatment is not recommended or must be subject to an assessment of the benefit/risk ratio in the case of a severe infection.

Peripheral nervous system

Signs suggestive of peripheral neuropathy, especially in the case of prolonged treatment or in patients with severe, chronic or progressive peripheral neurological conditions, should be monitored.

Psychiatric disorders

Psychotic reactions with possible risky behaviour for the patient can occur starting from the first doses of the treatment, particularly in patients with psychiatric history (see section 4.8). Metronidazole should therefore be discontinued, the doctor informed and the necessary therapeutic measures taken immediately.

Blood disorders

In the case of history of haematological disorders, with a high-dose treatment and/or prolonged treatment, it is recommended to perform regular blood tests, especially differential white blood cell count.

In the case of leucopoenia, treatment continuation depends on the severity of the infection.

Hepatotoxicity in patients with Cockayne Syndrome

Cases of severe hepatotoxicity/acute hepatic failure, including cases resulting in a fatal outcome with a very fast onset after initiation of the treatment 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 no alternative treatment is available. Hepatic function tests must be performed before the start of treatment, throughout the treatment and after the end of treatment, until the hepatic function is within a normal range or until the initial values are obtained. If the hepatic function tests become significantly increased during the treatment, the medicinal product should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report all symptoms of potential hepatic lesions to their doctor and to stop taking metronidazole (see section 4.8).

Excipient with known effect

This medicinal product contains sucrose. Its use is not recommended in patients with fructose intolerance, glucose-galactose malabsorption syndrome or sucrase-isomaltase deficiency.

This medicinal product contains 3 g of sucrose per measuring spoon, which should be taken into account in the daily allowance in the case of a low-sugar diet or diabetes.

This medicinal product contains 1% by vol of ethanol (alcohol), i.e., up to 40 mg of alcohol per measuring-spoon which is equivalent to 12 ml of beer, 5 ml of wine per dose. The use of this medicinal product is dangerous in alcoholic subjects and must be taken into account in pregnant or breast-feeding women, children and high-risk groups, such as those with liver failure or epilepsy.

This medicinal product contains less than 1 mmol (23 mg) of sodium per dose; that is, it is essentially “sodium-free”.

This medicinal product contains “parahydroxybenzoate” and may cause allergic reactions (possibly delayed reactions).

Interaction with other medicinal products

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

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

The 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 Nelson test results.

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.

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. Consuming alcoholic beverages and other medicinal products containing alcohol should be avoided. 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 medicinal product combination.

+ Medicinal products 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 account

+ Fluorouracil (and via extrapolation, tegafur and capecitabine)

Increased fluorouracil toxicity can occur due to decreased clearance.

Specific issues related to 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 is difficult to distinguish between the role of the

infectious disease and that of its treatment in the onset of changes in the INR. However, certain classes of antibiotics are more commonly involved: these particularly include the fluoroquinolones, macrolides, tetracyclines, co-trimoxazole and some cephalosporins.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies do not indicate any teratogenic effect. As there is no teratogenic effect in animals, no malformative effect is expected in humans. To date, substances which cause malformations in humans have been found to be teratogenic in animals during well-conducted studies on two species.

In clinical practice, the analysis of a high number of exposed pregnancies did not clearly reveal any teratogenic or particular foetotoxic effect of metronidazole. However, only epidemiological studies would make it possible to rule out a risk. Therefore, metronidazole can be prescribed during pregnancy if needed.

Breast-feeding

Metronidazole is excreted in human milk and should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

It is necessary to warn patients about the potential risk of vertigo, confusion, hallucinations, seizures, or vision disorders and advise them not to drive or use machines if this type of disorder occurs.

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 that, in isolated cases, can be accompanied by suicidal ideation or suicide attempts (see section 4.4),
- Depressed mood.

Nervous system disorders

- Peripheral sensory neuropathy,
- Headaches,
- Dizziness,
- Confusion,
- Seizures,
- Encephalopathy that may be associated with MRI changes are usually reversible upon therapy cessation. Rare cases with fatal outcomes have been reported (see section 4.4),
- Subacute cerebellar syndrome (ataxia, dysarthria, gait disorder, nystagmus, tremors) (see section 4.4),
- Aseptic meningitis (see section 4.4).

Eye disorders

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

Gastrointestinal disorders

- Mild gastrointestinal disorders (epigastric pain, nausea, vomiting, diarrhoea),
- Glossitis with the feeling of a dry mouth, stomatitis, taste disorders, anorexia,
- Pancreatitis reversible upon therapy cessation,

- Discolouration or change in the tongue's appearance (mycosis).

Hepatobiliary disorders

- Raised liver enzyme levels (AST, ALT, alkaline phosphatase), very rare cases of acute cholestatic or mixed hepatitis and hepatic damage (sometimes with jaundice), have been reported. Isolated cases of hepatocellular insufficiency possibly requiring liver transplant have been reported.
- Cases of severe irreversible hepatotoxicity/acute hepatic failure, including cases resulting in a fatal outcome with a very fast onset after initiation of the treatment in patients with Cockayne syndrome, have been reported with products containing metronidazole for systemic use (see section 4.4).

Skin and subcutaneous tissue disorders

- Flushing, pruritus, skin eruption, occasionally accompanied with fever,
- Urticaria, angiooedema, anaphylactic shock (see section 4.4),
- Very rare cases of acute generalised exanthematous pustulosis (see section 4.4),
- Lyell's syndrome,
- Stevens-Johnson syndrome,
- Fixed drug eruption.

Other effects

- Reddish-brown coloured urine due to the water-soluble pigments from metabolism of the medicinal product.

Reporting of suspected adverse reactions

Reporting of 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/.

4.9 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: anti-parasitic antibacterial antibiotics of the nitro-5-imidazoles family, ATC code: J01XD01 – P01AB01 (J: Anti-infectives, other antibacterial-derived imidazoles - P: antiprotozoals, drugs against amoebiasis and other metronidazole-derived protozooses)

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:

Categories	**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	
Mobiluncus	
Propionibacterium acnes	
Antiparasitic activity	
Entamoeba histolytica	
Giardia intestinalis	
Trichomonas vaginalis	

5.2 Pharmacokinetic properties

Absorption

Metronidazole benzoate is gradually hydrolysed as it passes through the gastrointestinal tract. The absorption of metronidazole benzoate is 30% less (area under the curve) than that of metronidazole.

Peak plasma concentrations are obtained after 4 hours following oral administration of the product.

At identical doses, metronidazole and metronidazole benzoate do not have significantly different therapeutic results.

The plasma half-life is 6.9 hours by HPLC.

Distribution

- Plasma protein binding is below 10%.
- The medicinal product is rapidly and widely distributed in the lungs, kidneys, liver, skin, bile, CSF, saliva, semen and vaginal discharge.
  Metronidazole crosses the placental barrier and is excreted in breast milk.

Biotransformation

Two unconjugated metabolites with antibacterial activity are formed (10%).

Elimination

High concentrations of metronidazole can be found in the liver and bile. Low concentrations of the medicinal product are found in the colon. Metronidazole is poorly excreted in the faeces. It is mainly excreted in the urine (40 to 70%, with approximately 20% in unchanged form) causing reddish or brown colouration of the urine.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ready to use sucrose solution / sucrose powder, Ph. Eur., Ethanol 96%, aluminum magnesium silicate, saccharin sodium, Sodium dihydrogen phosphate dihydrate, methyl parahydroxybenzoate, concentrated lemon essence, deterpenated orange essence, propyl parahydroxybenzoate, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

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

After opening the bottle, this medicinal product can be stored for 8 days maximum when stored at a temperature not higher than 30°C.

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

120 ml in a (glass) bottle sealed with a child safety cap made of polypropylene/polyethylene with a polyethylene film, with a 5 ml measuring spoon.

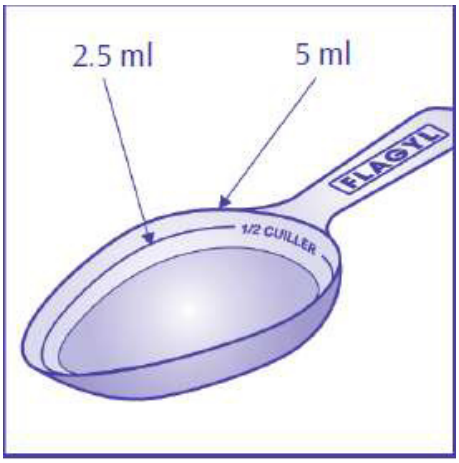
6.6 Special precautions for disposal and other handling

1.To open the bottle, turn the child-resistant cap by pressing it down, as shown in the diagram below:

2. This medicine is administered using a measuring spoon for oral administration provided with the bottle in the box. The use of this measuring spoon is strictly for oral administration of FLAGYL suspension.

The total volume of the measuring spoon filled to the brim corresponds to a volume of 5 ml, i.e., a 125 mg dose of metronidazole.

A volume of 2.5 ml, equivalent to a 62.5 mg dose of metronidazole, can be administered using the measuring spoon filled at the “½ spoon” ("1/2 CUILLER") mark.



One measuring spoon filled to the top (5 mL) contains 125 mg of metronidazole. One half measuring spoon filled to the "1/2 spoon" ("1/2 CUILLER") (2.5 mL) mark contains 62.5 mg of metronidazole.

3. After each use, close the bottle of the oral suspension, rinse the measuring spoon for oral administration well with water and dry. Then immediately store the measuring spoon for oral administration in its box somewhere inaccessible to children. Never separate the measuring spoon for oral administration from the medicinal product's other items of packaging (bottle, box, package leaflet).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Once the treatment is complete, it must be returned to the pharmacist (open boxes including the measuring spoon as well as the bottle) for correct and appropriate destruction of this medicinal product.

7. MARKETING AUTHORISATION HOLDER

Sanofi-aventis Israel ltd. 10 Beni Gaon, POB 8090, Netanya.

8. MARKETING AUTHORISATION NUMBER(S)

104-56-22129

Revised in June 2023 according to MoH guidelines.