SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BUCOGYL ®, film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Spiramycin..... 1.5 MIU
Metronidazole..... 250 mg

For a film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL PARTICULARS

Film-coated tablet.

4. CLINICAL DATA

4.1. Therapeutic indications

BUCOGYL, film-coated tablet is indicated for the curative treatment of odonto-stomatological infections such as dental abscesses, in adults and children, after assessing the benefit-risk ratio of treatment with this fixed combination based on spiramycin-metronidazole and when no other antibiotic treatment can be used (see sections 4.2, 4.4 and 5.1).
Official recommendations regarding the appropriate use of antibacterial agents should be taken into account.

4.2. Posology and method of administration

Posology

Children over 15 years old and adults:

- 2 to 3 tablets per day in 2 or 3 doses (i.e.: 3 to 4.5 MIU of spiramycin and 500 to 750 mg of metronidazole).
- In severe cases, the dosage may be increased to 4 tablets per day.
- There is some uncertainty about the optimal dose of this fixed combination (see section 5.1).

Method of administration

Oral route.
The tablets should be swallowed with a large glass of water.
The tablets should be taken with meals.

4.3. Contraindications

- Hypersensitivity to spiramycin and/or metronidazole and/or any other antibiotic of the imidazole family or to any of the excipients mentioned in section 6.1.
- Child under 15 years old.

4.4. Special warnings and precautions for use

Scope of use of this specialty

Since antibiotic monotherapy is expected to be suitable for treating most oral and dental infections, the necessity of using a fixed-dose combination of spiramycin and metronidazole should be carefully considered, given the possibility of

taking each antibiotic separately. It is recommended that first-line treatment for oral and dental infections use the antibiotic therapy offering the best benefit-risk ratio.

Hypersensitivity / skin and skin appendages

- 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 initiated.

- Cases of severe skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), have been reported with spiramycin-metronidazole. Patients should be informed of the signs and symptoms, and close monitoring of the skin is necessary.

- The occurrence of signs or symptoms of Stevens-Johnson syndrome, Lyell's syndrome (e.g., progressive rash often accompanied by blisters or mucosal lesions) or AGEP (Acute Generalized Exanthematous Pustulosis) (see section 4.8) requires discontinuation of treatment and contraindicates any further administration of spiramycin or metronidazole alone or in combination.

Central nervous system

- If symptoms suggestive of encephalopathy or cerebellar syndrome appear, the patient's management should be immediately reassessed and treatment with metronidazole should be stopped.

- Cases of encephalopathy have been reported with metronidazole during post-marketing surveillance. Cases of MRI changes associated with encephalopathy have also been observed (see section 4.8). The lesions observed are most frequently 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 upon discontinuation of treatment. Rare cases of fatal outcome have been reported.

- Monitor for the appearance of signs suggestive of encephalopathy or in case of worsening in patients with central neurological disease.

- In the event of aseptic meningitis under metronidazole, reintroduction of the treatment is not recommended or should be subject to a benefit-risk assessment in the event of serious infection.

Peripheral nervous system

- Monitor for signs suggestive of peripheral neuropathies, particularly in cases of prolonged treatment or in patients with severe, chronic or progressive peripheral neurological conditions.

Psychiatric disorders

- Psychotic reactions, with possible risky behavior for the patient, can occur from the first doses of treatment, particularly in patients with a history of psychiatric illness (see section 4.8). Metronidazole should then be discontinued, the physician informed, and the necessary therapeutic measures taken immediately.

Bloodline

- In cases of a history of hematological disorders, high-dose treatment and/or prolonged treatment, it is recommended to have regular blood tests, particularly monitoring of the leukocyte differential.

- In cases of leukopenia, the opportunity to continue treatment depends on the severity of the infection.

QT interval prolongation

- Cases of QT interval prolongation have been reported in patients taking macrolides, including spiramycin.

- Caution is advised when treating with spiramycin in patients with known risk factors for QT interval prolongation, such as:

○ an uncorrected electrolyte imbalance (e.g., hypokalemia, hypomagnesemia),

○ congenital long QT syndrome,

○ Cardiac conditions (e.g., heart failure, myocardial infarction, bradycardia). Concomitant treatment with drugs known to prolong the QT interval (e.g., class IA and III antiarrhythmics, tricyclic antidepressants, certain antibiotics, certain antipsychotics). The elderly, newborns, and women may be more susceptible to QT prolongation.

(See sections 4.2, 4.5, 4.8 and 4.9)

Liver disorders

- Cases of severe hepatotoxicity/acute liver failure, including fatal cases with a very rapid onset after initiation of treatment in patients with Cockayne syndrome, have been reported with metronidazole-containing products intended for systemic use. Therefore, in this population, metronidazole should only be used after a thorough benefit-risk assessment and only if no alternative treatment is available. Liver function tests should be performed immediately before starting treatment, throughout treatment, and after treatment completion until liver function is within normal limits or until baseline values are achieved. If 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 damage to their doctor and to stop taking metronidazole.

G6PD enzyme deficiency

- In patients with G6PD deficiency, cases of acute hemolysis have been reported with spiramycin administered orally or by injection. Its prescription should therefore be avoided, and the use of an alternative treatment, if available, is strongly recommended.

- In the absence of an alternative, the decision must take into account, for each patient, the risk of hemolysis and the potential benefit expected from the treatment. If this medication is prescribed, the occurrence of any hemolysis must be monitored.

Drug interactions

- The 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).

Interactions with paraclinical examinations

- Metronidazole can immobilize treponemes and therefore cause a false positive Nelson test.

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

RELATED TO SPIRAMYCIN

Associations requiring precautions for use

+ Drugs that can cause torsades de pointes: class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide), class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide), sultopride (benzamide neuroleptic), other torsadogenic agents (arsenic trioxide, bepridil, cisapride, diphemanil, IV dolasetron, IV erythromycin, levofloxacin, mizolastine, moxifloxacin, prucalopride, toremifene, IV vincamine)
Increased risk of ventricular arrhythmias, particularly torsades de pointes
+ Levodopa
When combined with carbidopa: inhibition of carbidopa absorption with a decrease in levodopa plasma concentrations. Clinical monitoring and possible adjustment of the levodopa dosage.

RELATED TO METRONIDAZOLE

Antabuse reaction

Many medications cause an antabuse-like reaction with alcohol, and their combination with alcohol is not recommended.

Associations not recommended

+ Alcohol (beverage or excipient)
Antabuse-like reaction (flushing, redness, vomiting, tachycardia). Avoid consuming alcoholic beverages and medications containing alcohol. Ensure complete elimination of the medication by referring to its half-life before resuming consumption of alcoholic beverages or medications containing alcohol.
+ Busulfan
With high doses of busulfan: doubling of busulfan concentrations by metronidazole.
+ Disulfiram
Risk of episodes of acute psychosis or confusional state, reversible upon discontinuation of the combination.

Associations requiring precautions for use

+ Enzyme-inducing anticonvulsants
Decreased plasma concentrations of metronidazole due to increased hepatic metabolism by the inducer.
Clinical monitoring and possible adjustment of metronidazole dosage during treatment with the inducer and after its discontinuation.
+ Rifampicin
Decreased plasma concentrations of metronidazole due to increased hepatic metabolism by rifampicin.
Clinical monitoring and possible adjustment of metronidazole dosage during rifampicin treatment and after its discontinuation.
+ Lithium
Increased lithium levels, potentially reaching toxic values, with signs of lithium overdose.
Strict monitoring of lithium levels and possible adjustment of lithium dosage.

Associations to consider

+ Fluorouracil (and by extrapolation, tegafur and capecitabine):
Increased toxicity of fluorouracil due to decreased clearance.

Specific problems related to INR imbalance

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotics. A significant infectious or inflammatory context, age, and the patient's general condition appear to be risk factors. In these circumstances, it is difficult to distinguish between the infectious disease and its treatment as the cause of the INR imbalance. However, certain classes of antibiotics are more frequently implicated: these include fluoroquinolones, macrolides, tetracyclines, cotrimoxazole, and some cephalosporins.

Interactions with paraclinical examinations

Metronidazole can immobilize treponemes and therefore cause a false positive Nelson test.

4.6. Fertility, pregnancy and breastfeeding

Pregnancy

The use of this medication may be considered during pregnancy if needed, regardless of the stage of pregnancy.
METRONIDAZOLE
Clinically, analysis of a large number of exposed pregnancies has apparently revealed no particular malformative or fetotoxic effects of metronidazole. However, only epidemiological studies could confirm the absence of risk.
Animal studies have not shown any teratogenic effects of metronidazole.
SPIRAMYCIN
The use of spiramycin can be considered during pregnancy if needed. Indeed, widespread use of spiramycin during pregnancy has not, to date, revealed any malformative or fetotoxic effects of this molecule.

Breastfeeding

Metronidazole and spiramycin pass into breast milk; therefore, avoid administering this medication during breastfeeding.

4.7. Effects on the ability to drive vehicles and use machinery

Patients should be warned of the potential risk of dizziness, confusion, hallucinations, seizures or visual disturbances and advised not to drive vehicles or operate machinery if such disturbances occur.

4.8. Undesirable effects

RELATED TO SPIRAMYCIN

Heart conditions

- Frequency not known: QT interval prolongation, ventricular arrhythmia, ventricular tachycardia, torsades de pointes which may lead to cardiac arrest (see section 4.4).

Immune system disorders

- Frequency not known: vasculitis including Henoch-Schönlein purpura or rheumatoid purpura, anaphylactic shock (see section 4.4).

Gastrointestinal disorders

- Common: abdominal pain, nausea, vomiting, stomach pain, diarrhea, pseudomembranous colitis.

Skin and subcutaneous tissue disorders

- Frequent: eruptions.

- Frequency not known: urticaria, pruritus, Quincke's edema, Stevens-Johnson syndrome, Lyell's syndrome, acute generalized exanthematous pustulosis (AGEP) (see section 4.4).

Disorders of the nervous system

- Very common: occasional and transient paresthesias.

- Common: transient dysgeusia.

Hepatobiliary disorders

- Very rare: abnormalities in liver function tests.

- Frequency not known: cases of cholestatic, mixed or, more rarely, cytolytic hepatitis.

Hematological and lymphatic system disorders

- Frequency not known: leukopenia, neutropenia, hemolytic anemia (see section 4.4).

RELATED TO METRONIDAZOLE

Hematological and lymphatic system disorders

- Neutropenia, agranulocytosis and thrombocytopenia.

Psychiatric disorders

- Hallucinations;

- Psychotic reactions with paranoia and/or delusions which may be accompanied in isolation by suicidal thoughts or acts (see section 4.4);

- Depressed mood.

Disorders of the nervous system

- Peripheral sensory neuropathies;

- Headaches;

- Dizziness;

- Confusion ;

- Convulsions;

- Encephalopathies may be associated with MRI changes that are generally reversible upon discontinuation of treatment. Exceptional cases of fatal outcome have been reported (see section 4.4);

- Subacute cerebellar syndrome (ataxia, dysarthria, gait disturbances, nystagmus, tremors (see section 4.4);

- Aseptic meningitis (see section 4.4).

Eye conditions

- Transient visual disturbances such as blurred vision, diplopia, myopia, decreased visual acuity and changes in color vision;

- Optic neuropathies/neuritis.

Gastrointestinal disorders

- Minor digestive problems (epigastric pain, nausea, vomiting, diarrhea);

- Glossitis with a sensation of dry mouth, stomatitis, taste disturbances, anorexia;

- Pancreatitis reversible upon discontinuation of treatment;

- Discoloration or change in the appearance of the tongue (fungal infection).

Hepatobiliary disorders

- Elevated liver enzymes (ALT, AST, alkaline phosphatase), very rare cases of acute liver injury of a cytolytic (sometimes jaundiced), cholestatic, or mixed nature. Isolated cases of hepatocellular failure requiring liver transplantation have been reported.

Skin and subcutaneous tissue disorders

- Hot flashes, itching, skin rash, sometimes fever;

- Urticaria, Quincke's edema, anaphylactic shock (see section 4.4);

- Very rare cases of acute generalized exanthematous pustulosis (see section 4.4);

- Lyell's syndrome;

- Stevens-Johnson syndrome;

- Fixed pigmented erythema.

Miscellaneous

- Appearance of a reddish-brown color in the urine due to the presence of water-soluble pigments from the metabolism of the product.

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. Healthcare professionals should report any suspected adverse reactions using the FRILAB reporting form available under the pharmacovigilance tab of the website: www.frilab.ch

4.9. Overdose

There is no specific antidote for spiramycin or metronidazole.
In case of overdose, treatment is symptomatic.
SPIRAMYCIN-RELATED DISORDERS
There is no known toxic dose for spiramycin.
The expected signs at high doses are digestive: nausea, vomiting, diarrhea.
Cases of QT interval prolongation that resolved upon discontinuation of treatment have been observed in newborns treated with high doses of spiramycin and after intravenous administration of spiramycin in subjects at risk of QT interval prolongation. In cases of spiramycin overdose, an ECG is therefore recommended to measure the QT interval, especially when other associated risk factors are present (hypokalemia, congenital long QT syndrome, concomitant use of drugs that prolong the QT interval and/or cause torsades de pointes).
METRONIDAZOLE-RELATED DISORDERS
Cases of single doses of up to 12 g have been reported in suicide attempts and accidental overdoses. Symptoms were limited to vomiting, ataxia, and mild disorientation.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic class: combinations of antibacterial agents Spiramycin and Metronidazole
ATC Code: J01RA04
This medication is a combination of spiramycin, an antibiotic from the macrolide family, and metronidazole, an antibiotic from the nitroimidazole family, reserved for oral and dental infectious pathology.
SPECTRUM OF ANTIMICROBIAL ACTIVITY
SPIRAMYCIN
The critical concentrations separate susceptible strains from strains with intermediate susceptibility, and the latter from resistant strains:
S ≤ 1 mg/l and R > 4 mg/l
The prevalence of acquired resistance can vary geographically and over time for certain species. Therefore, it is useful to have information on local resistance prevalence, especially when treating severe infections. If necessary, expert advice should be sought, particularly when the drug's effectiveness in certain infections may be compromised by the level of local resistance.

Classes
SPECIES THAT ARE USUALLY SENSITIVE
Gram-positive aerobes
Corynebacterium diphtheriae
Rhodococcus equi
Gram-negative aerobes
Bordetella pertussis
Campylobacter
Legionella ($)
Moraxella
Moraxella catarrhalis (Branhamella catarrhalis)
Neisseria gonorrhoeae ($)
Anaerobes
Actinomyces
Clostridium perfringens ($)
Eubacterium
Mobiluncus
Porphyromonas
Prevotella
Propionibacterium acnes
Others
Borrelia burgdorferi
Chlamydia trachomatis
Chlamydophila pneumoniae
Coxiella
Leptospires
Mycoplasma pneumoniae
Treponema pallidum
Ureaplasma urealyticum ($)
SPECIES THAT ARE VARIABLY SENSITIVE
(acquired resistance ≥ 10%)
Gram-positive aerobes
Enterococcus spp . (+)
Methicillin-susceptible *Staphylococcus*
Staphylococcus (+) (1)
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus viridans
Anaerobes
Peptostreptococcus
NATURALLY RESISTANT SPECIES
Gram-positive aerobes
Corynebacterium jeikeium
Nocardia asteroides
Gram-negative aerobes
Acinetobacter
Enterobacteriaceae
Haemophilus

Pseudomonas **Anaerobes** *Fusobacterium* **Others** *Mycoplasma hominis*

($) Species naturally intermediate in the absence of a resistance mechanism.
(+) The prevalence of bacterial resistance is > 50% in France.
(1) The frequency of methicillin resistance is approximately 20 to 50% of all staphylococci and is found mainly in hospital settings.

Antiparasitic activity

Spiramycin has *in vitro* and *in vivo activity* against *Toxoplasma gondii* .

METRONIDAZOLE
The critical concentrations separate susceptible strains from strains with intermediate susceptibility, and the latter from resistant strains:

EUCAST clinical breakpoints for metronidazole		
Organisms	Sensitive (S) (mg/l)	Resistant (R) (mg/l)
Gram-positive anaerobes except *Clostridium difficile*	≤ 4	> 4
Clostridium difficile	≤ 2	> 2
Gram-negative anaerobes	≤ 4	> 4
Helicobacter pylori	≤ 8	> 8

The prevalence of acquired resistance can vary geographically and over time for certain species. Therefore, it is useful to have information on local resistance prevalence, especially when treating severe infections. If necessary, expert advice should be sought, particularly when the drug's effectiveness in certain infections may be compromised by the level of local resistance.

Classes
SPECIES THAT ARE USUALLY SENSITIVE **Anaerobes** *Bacteroides fragilis* *Bilophila wadsworthia* *Clostridium* spp. including *Clostridium difficile* and *Clostridium perfringens* *Fusobacterium* *Peptostreptococcus* *Porphyromonas* *Prevotella* *Veillonella*
SPECIES WITH VARYING SENSITIVITY **(acquired resistance ≥ 10%)** **Gram-negative aerobes** *Helicobacter pylori* **Anaerobes** *Bifidobacterium* (+) *Eubacterium*
NATURALLY RESISTANT SPECIES **Anaerobes** *Actinomyces* *Mobiluncus* *Propionibacterium acnes*

(+) The prevalence of bacterial resistance is ≥ 50% in France.
Antiparasitic activity

Sensitive species

Entamoeba histolytica
Giardia intestinalis
Trichomonas vaginalis
Synergy: the average MIC of the two products isolated and combined shows that there is a synergy to inhibit certain sensitive bacterial strains.
Against *Bacteroides fragilis* , approximately 16 times less spiramycin and 4 times less metronidazole are required.

MIC in µg/ml		
***Bacteroides* strains**	**melanogenic**	***Bacteroides fragilis***
Metronidazole alone	0.25	0.5
Metronidazole + spiramycin 0.125 µg/ml	0.062	0.125
Spiramycin alone	2	32
Spiramycin + metronidazole 0.125 µg/ml	0.125	2

This data concerning the synergy between the two antibiotic components (spiramycin and metronidazole) of this fixed combination is old.
Their relevance and contribution to the use of this fixed combination need to be considered with caution, particularly regarding the determination of the optimal dose of this fixed combination.

5.2. Pharmacokinetic properties

SPIRAMYCIN

Absorption

Spiramycin is absorbed rapidly, but incompletely. It is not affected by food intake.

Distribution

After oral administration of 6 MIU, the maximum serum concentration is 3.3 µg/ml.
The plasma half-life is approximately 8 hours.
Spiramycin does not penetrate the cerebrospinal fluid (CSF). It passes into breast milk.
Plasma protein binding is low (10%).
There is excellent salivary and tissue diffusion (lungs: 20-60 µg/g, tonsils: 20-80 µg/g, infected sinuses: 75-110 µg/g, bones: 5-100 µg/g).
Ten days after stopping treatment, 5 to 7 µg/g of active ingredient remains in the spleen, liver, kidneys.
Macrolides penetrate and accumulate in phagocytes (neutrophils, monocytes, peritoneal and alveolar macrophages).
Intraphagocytic concentrations are high in humans.
These properties explain the activity of macrolides on intracellular bacteria.

Biotransformation

Spiramycin is metabolized in the liver, with the formation of chemically unknown but active metabolites.

Elimination

- Urine: 10% of the ingested dose.

- Very significant biliary elimination: concentrations 15 to 40 times higher than serum concentrations.

- Spiramycin is present in significant quantities in feces.

METRONIDAZOLE

Absorption

After oral administration, metronidazole is rapidly absorbed, at least 80 percent within one hour. Peak serum levels obtained after oral administration are similar to those obtained after intravenous administration of equivalent doses.
Oral bioavailability is 100 percent. It is not significantly altered by the simultaneous ingestion of food.

Distribution

Approximately 1 hour after a single 500 mg dose, the maximum serum concentration reached is, on average, 10 micrograms/ml. After 3 hours, the average serum concentration is 13.5 micrograms/ml.
The plasma half-life is 8 to 10 hours.
Binding to blood proteins is low: less than 20 percent
The apparent distribution volume is significant at around 40 l (i.e. 0.65 l/kg).
Diffusion is rapid and significant, with concentrations close to serum levels, in: the lungs, kidneys, liver, skin, bile, CSF, saliva, seminal fluid, vaginal secretions.
Metronidazole crosses the placental barrier and passes into breast milk.

Biotransformation

The metabolism is primarily hepatic. Through oxidation, two main compounds are formed:

- The "alcohol" metabolite, the main metabolite, has a bactericidal activity on anaerobic bacteria of about 30 percent of that of metronidazole, and an elimination half-life of about 11 hours;

- The "acidic" metabolite, in small quantities, has a bactericidal activity of about 5 percent of that of metronidazole.

Elimination

High hepatic and biliary concentration. Low colonic concentration. Low fecal elimination. Excretion is mainly urinary since metronidazole and oxidized metabolites excreted in the urine represent approximately 35 to 65 percent of the administered dose.

DIFFUSION IN THE ORAL SPHERE

The two components of this drug are concentrated in saliva, gingival tissue and alveolar bone.
The concentrations of spiramycin and metronidazole were measured in human serum and these different media 2 hours after administration of two RODOGYL tablets; the results obtained, expressed in micrograms/ml or micrograms/g, are as follows:

Concentrations	Serum	Saliva	Gum	alveolar bone
Spiramycin	0.68 ± 0.22	1.54 ± 0.41	26.63 ± 9.65	113.9 ± 41.16
Metronidazole	35.03 ± 12.35	15.32 ± 3.16	7.43 ± 6.34	5.73 ± 2.72

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Core : sodium starch glycolate (type A), mannitol, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose.
Film coating : SEPIFILM white [hypromellose (E464), macrogol 6000, titanium dioxide (E171)].

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store at a temperature below 25°C.

6.5. Nature and contents of container

30 tablets in thermoformed blisters (PVC/Aluminium).

6.6. Special precautions for disposal and handling

No special requirements.

7. OPERATOR

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SWISS

8. MANUFACTURER

INPHARMASCI
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PROUVY, 59121
France

9. DATE OF REVISION OF THE TEXT

04.12.2025

10. DOSIMETRY

Not applicable.

11. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

CONDITIONS FOR PRESCRIPTION AND DISPENSING

List I.