Rovamycin - SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

ROVAMYCIN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Spiramycin 1.5 MIU for one film-coated tablet.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Respiratory tract infections, infections caused by clamydia, cryptosporidiosis pregnancy toxoplasmosis.

4.2. Posology and Method of Administration

Posology

Patients with normal renal function:

Usually:
- Adults: 6 to 9 million IU/24 hours, i.e. 4 to 6 tablets per day, taken as 2 or 3 divided doses.
- Children: 1.5 to 3 million IU per 10 kg of body weight per day, taken as 2 or 3 divided doses.

Sore throats should be treated for 10 days.

Prophylaxis of meningococcal meningitis
- Adults: 3 million IU/12 hours.
- Children: 75 000 IU/kg/12 hours.

for the duration of treatment for meningococcal meningitis is 5 days.

In patients with renal insufficiency:
No dose adjustment is necessary.

Method of Administration

The tablets should be swallowed whole with a glass of water.

4.3. Contraindications

- Hypersensitivity to the active substance, other macrolids or to any of the excipients listed in section 6.1.
- Children under 6 years of age, due to the risk of pulmonary aspiration resulting from the tablet form.

4.4. Special warnings and precautions for use

Cases of severe skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalised exanthematous pustulosis (AGEP) have been reported with Rovamycine. 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 eruption often with blisters or mucosal lesions) or AGEP (generalised febrile erythema associated with pustules) (see section 4.8) occur, treatment must be discontinued and any further administration of spiramycin alone or in combination with other agents is contraindicated.
As the active substance is not eliminated via the renal route, there is no need to adjust the dose in patients with kidney failure.
Very rare cases of haemolytic anaemia have been reported in patients with glucose-6-phosphate-dehydrogenase deficiency. Use of spiramycin in these patients is therefore not recommended.

Prolongation of the QT interval

Cases of prolonged QT interval have been reported in patients taking macrolides, including spiramycin.
Caution should be exercised when using spiramycin, in patients with known risk factors for prolongation of the QT interval such as:

- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia),
- congenital long QT syndrome,
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).
- concomitant use of medicinal products that are known to prolong the QT interval (e.g. class IA and III antiarrhythmics, tricyclic antidepressants, some antibiotics, some antipsychotics, hydroxychloroquine and chloroquine),
- elderly subjects, neonates and women may be more susceptible to QT prolongation. (See sections 4.2, 4.5, 4.8 and 4.9)

This medicinal product contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially 'sodium-free'.

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

Combinations requiring precautions for use

+ Torsades de pointes-inducing medicinal products: class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide), class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide), sultopride (benzamide neuroleptic), and other torsadogens (arsenic compounds, bepridil, cisapride, diphemanil, dolasetron IV, erythromycin IV, levofloxacin, mizolastine, moxifloxacin, prucalopride, toremifene, vincamine IV)

Increased risk of ventricular arrhythmias, particularly torsades de pointes.

+ Levodopa

In combination with carbidopa: carbidopa absorption is inhibited, and levodopa plasma concentrations decreased.
Clinical parameters should be monitored, and the levodopa dosage levels adjusted if necessary.

+ Hydroxychloroquine or chloroquine

Spiramycin should be used with caution in patients receiving these medicines known to prolong the QT interval due to the potential to induce serious adverse cardiovascular events (including QT prolongation, cardiac arrythmias and Torsade de Pointes) and to increase the risk of cardiovascular mortality.

Special INR imbalance-related issues

Numerous cases of increased activity of oral anticoagulants in patients receiving antibiotic therapy have been reported. The severity of the infection or inflammation, patient age and general state 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 groups of antibiotics are more involved, particularly fluoroquinolones, macrolides, cyclines, co-trimoxazole and certain cephalosporins.

4.6. Fertility, pregnancy and lactation

Pregnancy

Use of spiramycin can be considered during pregnancy if necessary. To date widespread use of spiramycin during pregnancy has shown no teratogenic or foetotoxic effects related to this medicinal product.

Breast-feeding

Significant amounts of the medicinal product are excreted in human breast milk. Gastrointestinal disorders have been reported in neonates. Breast-feeding is therefore not recommended in women being treated with this medicinal product.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Adverse reactions are presented by system organ class and in order of frequency. Frequency is defined as follows: very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Cardiac disorders

Not known: Prolonged QT interval, ventricular arrhythmia, ventricular tachycardia, torsades de pointes possibly leading to cardiac arrest (see section 4.4).

Immune system disorders

Not known: vasculitis including Henoch-Schönlein purpura or purpura rheumatica, anaphylactic shock (see section 4.4).

Gastrointestinal disorders

Common: abdominal pain, nausea, vomiting, gastric pain, diarrhoea, pseudomembranous colitis.

Skin and subcutaneous tissue disorders

Common: eruption.

Not known: urticaria, pruritus, angioedema, Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP) (see section 4.4).

Nervous system disorders

Very common: occasional, transient paraesthesia.

Common: transient dysgeusia.

Hepatobiliary disorders

Very rare: liver function test abnormalities.

Not known: mixed or, more rarely, cytolytic cholestatic hepatitis.

Blood and lymphatic system disorders

Not known: leukopenia, neutropenia, haemolytic anaemia (see section 4.4).

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.
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

The toxic dose of spiramycin is unknown.
Gastrointestinal disorders can be expected after high dose, i.e. nausea, vomiting and diarrhoea.
Cases of prolonged QT interval that abated on treatment discontinuation were observed in neonates treated with high doses of spiramycin, and after IV administration of spiramycin in patients at risk for prolonged QT-interval. If spiramycin overdose occurs, an ECG should be performed to measure the QT interval, especially if there are other risk factors (hypokalaemia, congenital prolongation of the QTc interval, medicinal product combinations that prolong QT interval and/or induce torsades de pointes).
There is no specific antidote.
Symptomatic treatment is recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, ATC code: J01FA02

Spiramycin is an antibacterial antibiotic of the macrolide group.

ANTIBACTERIAL SUSCEPTIBILITY TESTING

The MIC breakpoints differentiating susceptible strains from intermediate strains, and intermediate strains from resistant strains are as follows:
S $\leq$1 mg/L and R >4 mg/L

The prevalence of acquired resistance in certain species may vary geographically and over time. It is therefore useful to have information on the prevalence of local resistance, especially when 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 is known for a given bacterial species in France, it is indicated in the following table:

Category	Incidence of acquired resistance in France (> 10%) (range)
SUSCEPTIBLE SPECIES	
Gram positive aerobes	
Bacillus cereus	
Corynebacterium diphtheriae	
Enterococci	50% – 70%
Rhodococcus equi	
Methicillin-sensitive staphylococcus	
*Methicillin-resistant staphylococcus**	70 – 80%
Streptococcus B	
Unclassified Streptococcus	30 – 40%
Streptococcus pneumoniae	35 – 70%
Streptococcus pyogenes	16 - 31%
Gram negative aerobes	
Bordetella pertussis	
Branhamella catarrhalis	
Campylobacter	
Legionella	
Moraxella	
Anaerobes	
Actinomyces	
Bacteroides	30 – 60%
Eubacterium	
Mobilincus	
Peptostreptococcus	30 – 40%
Porphyromonas	
Prevotella	
Propionibacterium acnes	
Other	
Borrelia burgdorferi	
Chlamydia	
Coxiella	
Leptospires	
Mycoplasma pneumoniae	
Treponema pallidum	

MODERATELY SUSCEPTIBLE SPECIES (in vitro intermediate susceptibility) **Gram negative aerobes** *Neisseria gonorrhoeae* **Anaerobes** *Clostridium perfringens* **Others** *Ureaplasma urealyticum*	
RESISTANT STRAINS **Gram positive aerobes** *Corynebacterium jeikeium* *Nocardia asteroides* **Gram negative aerobes** *Acinetobacter* Enterobacteria *Haemophilus* *Pseudomonas* **Anaerobes** *Fusobacterium* **Others** Mycoplasma hominis	

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

* The incidence of methicillin resistance is approximately 30 to 50% for all staphylococci and is mainly found in the hospital setting.

5.2. Pharmacokinetic properties

Absorption
Absorption of spiramycin is rapid but incomplete. Food has no effect on absorption.

Distribution
After oral administration of 6 MIU of spiramycin, the peak serum concentration is 3.3 microgram/mL.
The plasma half-life is close to 8 hours.

Spiramycin does not pass into the CSF. It is excreted in breast milk.
The medicinal product is poorly bound to plasma protein (10%).

Spiramycin is very well distributed in saliva and tissue (lungs: 20 - 60 microgram/g; tonsils: 20 - 80 microgram/g; infected sinuses: 75-110 microgram/g; bone: 5-100 microgram/g).

Ten days after treatment discontinuation, 5 to 7 microgram/g of active substance remains in the spleen, liver and kidneys.

Macrolides penetrate and accumulate in phagocytes (neutrophils, monocytes, peritoneal and alveolar macrophages).
Intraphagocyte concentrations are high in humans.
These properties account for the effect of macrolides on intracellular bacteria.

Biotransformation

Spiramycin is metabolised in the liver, resulting in the formation of chemically unknown though active metabolites.

Elimination
- Urine: 10% of the ingested dose.
- Biliary excretion is very high, i.e., 15 to 40 times higher than serum concentrations.
- Appreciable amounts of spiramycin can be found in the faeces.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Microcrystalline cellulose, pregelatinized maize starch, hydroxypropylcellulose, croscarmellose sodium, hypromellose, magnesium stearate, macrogol 6000, titanium dioxide, anhydrous colloidal silica

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 25°C

6.5 Nature and contents of container

16 film coated tablets in (PVC/Aluminium) blisters.

7. MARKETING AUTHORISATION HOLDER AND IMPORTER AND ITS ADDRESS

Sanofi-aventis Israel ltd P.O.B. 8090 Netanya

8. REGISTRATION NUMBER
465923868

Revised in January 2024 according to MoH guidelines.