RULID TABLETS

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RULID 150 mg, film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Roxithromycin 150 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of infections caused by microorganisms sensitive to roxithromycin e.g: ENT bronchopulmonary, genital and skin manifestations.

4.2 Posology and method of administration

Posology

Adults: 300 mg per day, i.e. 1 x 150 mg tablet in the morning and evening, preferably before meals.

Treatment duration

Treatment duration for throat infections is 10 days.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Allergy to Macrolides
- Coadministration with:
  - vasoconstrictive ergot alkaloids: dihydroergotamine, ergotamine (see section 4.5).
  - Colchicine (see section 4.5).
- Concomitant therapy with medicines having a narrow therapeutic window and being substrates of CYP3A4 (such as, astemizole, terfenadine, cisapride or pimozide (see section 4.5).
- Women breast-feeding an infant who is treated with cisapride (see section 4.6).
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4.4 Special Warnings and Precautions for use

Special Warnings

Excipient with known effect

This medicinal product contains glucose. It should therefore not be used in patients with glucose-galactose malabsorption syndrome.

Liver failure

Administration of roxithromycin is not recommended in patients with severe liver failure. In patients with mild to moderate liver failure, roxithromycin should be used with caution. If it must be administered in these subjects, regular liver function tests are required and if necessary, the dose should be reduced.

Renal ifailure

The amount of active substance and its metabolites eliminated by the renal route is small (10% of the oral dose). No dose adjustment is therefore required in patients with kidney failure.

Elderly subjects

In elderly subjects, the elimination half-life is prolonged. However, after repeated administration of 150 mg every 12 hours, peak plasma concentrations, and the AUC at steady state between two doses of roxithromycindid not differ compared to younger subjects.
No dose adjustment is therefore required in elderly patients.

Co-administration with ergot alkaloids

Severe vasoconstriction (ergotism), potentially leading to peripheral necrosis, has been reported when macrolides are co-admonistered with vasoconstrictive ergot alkaloids. Before prescribing roxithromycin (see sections 4.3 and 4.5), the physician should make sure that the patient is not receiving treatment with these alkaloids.

Coadministration of roxithromycin with dopaminergic ergot alkaloids is not recommended (see section 4.5).

Serious bullous reactions

Cases of serious bullous skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) have been reported with roxithromycin (see Section 4.8).
If the patient experiences symptoms or signs of AGEP, SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions), Rulid treatment should be discontinued.

Precautions for use

Prolongation of the QT interval

Under certain conditions, macrolides, including roxithromycin, have the potential to prolong the QT interval. Roxithromycin should therefore be used with caution in patients with congenital prolonged QT syndrome and proarrhythmic conditions (e.g. uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia), and in patients receiving treatments which may prolong the QT interval such as Class IA and class III

antiarrhythmic agents and drugs such as astemizole, cisapride or pimozide (see sections 4.5 and 4.8).

Myasthenia

As with other macrolides, roxithromycin may aggravate myasthenia.

Clinical monitoring in long-term treatment

Monitoring of liver function, renal function and blood count is particularly recommended in long-term treatment (e.g. treatment duration exceeding 2 weeks) (See Section 4.8).

Clostridium difficile infection

Cases of Clostridium difficile-associated diarrhea (CDAD) have been reported with the use of almost all antibiotics, including roxithromycin (see Section 4.8). Severity of the disorder can vary from mild diarrhea to life-threatening pseudomembranous enterocolitis. Antibiotic treatment modifies colon flora, thus leading to an excessive proliferation of C. difficile.

C. difficile produces A and B toxins which contribute to the development of CDAD. These toxin-producing strains increase morbidity and mortality since these infections may be refractory to the antibiotic treatment and the patient may require a colectomy. The possibility of CDAD should be considered in all patients who develop diarrhea following the use of antibiotics and treatment with roxithromycin should be stopped immediately. It is important that CDAD be considered as a possible diagnosis in patients who have diarrhea during or following antibiotic treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations (see section 4.3 Contraindications)

+ Colchicine
Colchicine-induced adverse effects are potentiated, which may be fatal.

+ Cisapride
There is an increased risk of ventricular arrhythmias, especially torsades de pointes.

+ Ergotamine/Dihydroergotamine
Ergotism may occur, potentially leading to peripheral necrosis (due to decreased hepatic elimination of ergotamine and inhibition of hepatic elimination of dihydroergotamine).

Inadvisable combinations (see Special warnings, Section 4.4)

+ Dopaminergic ergot alkaloids (bromocriptine, cabergoline, lisuride, pergolide) (see section 4.4).
Plasma concentrations of the dopaminergic agent are increased along with a potential increase in activity or occurrence of signs of overdose.

+ Drugs likely to induce torsades de pointes (see Section 4.4)
(amiodarone, amisulpride, arsenic compounds, bepridil, chlorpromazine, citalopram, cyamemazine, diphemanil, disopyramide, dofetilide, dolasetron, domperidone,

dronedarone, droperidol, erythromycin, escitalopram, flupentixol, fluphenazine, halofantrine, haloperidol, hydroquinidine, ibutilide, levofloxacin, levomepromazine, lumefantrine, mequitazine, methadone, mizolastine, moxifloxacin, pentamidine, pimozide, pipamperone, pipotiazine, prucalopride, quinidine, sertindole, sotalol, spiramycin, sulpiride, sultopride, tiapride, toremifene, vandetanib, vincamine, zuclopenthixol).

This serious cardiac rhythm disorder can be caused by a number of antiarrhythmic and non-antiarrhythmic drugs. Hypokalemia (especially induced by potassium-depleting agents) is a promoting factor, as is bradycardia (especially induced by bradycardia-inducing agents) or pre-existing congenital or acquired QT interval prolongation. The medicinal products which cause this adverse effect include class la and III antiarrhythmic agents, and certain neuroleptics. Other agents not belonging to these classes are also involved.

There is an increased risk of ventricular arrhythmias, especially torsades de pointes.

When co-administering these agents, clinical and ECG monitoring are required.

Terfenadine

Certain macrolides are capable of a pharmacokinetic interaction with terfenadine leading to increased serum concentrations of the latter. This may result in severe ventricular arrhythmia, typically torsades de pointes. Although such a reaction has not been demonstrated with roxithromycin and studies in a limited number of healthy volunteers have not shown any pharmacokinetic interaction or relevant ECG changes, the concomitant use of roxithromycin and terfenadine cannot be recommended.

Astemizole and Pimozide

Other drugs, such as astemizole, cisaprid or pimozide, which are metabolized by hepatic CYP3A4 isozyme have been associated with QT interval prolongation and/or cardiac arrhythmias (typically torsades de pointes) as a result of an increased serum concentration subsequent to interaction with significant inhibitors of this isozyme, including some macrolide antibiotics. Roxithromycin has no or limited ability to form a complex with CYP3A4 and therefore to inhibit the metabolism of other drugs that are metabolized by this isozyme. A potential for clinical interaction of roxithromycin with the above mentioned drugs cannot be either ascertained or ruled out in confidence; therefore, simultaneous use of roxithromycin with such drugs is not recommended (see Section 4.4).**Class IA and III antiarrhytmic agents**

Roxithromycin, like other macrolides, should be used with caution in patients receiving Class IA and III antiarrhythmic agents (see section 4.4).

<u>Combinations requiring precautions for use</u>

\+ **Bradycardia-inducing agents**

There is an increased risk of ventricular arrhythmias, especially torsades de pointes. Clinical and ECG monitoring are required.

\+ **Vitamin K antagonists** (acenocoumarol, fluindione, phenindione, warfarin)

The vitamin K antagonist effect and the risk of haemorrhage are increased. INR should be monitored more frequently. Dose adjustment of the vitamin K antagonist during treatment with the macrolide and after treatment discontinuation may be necessary.

<u>Special INR imbalance-related issues</u>

Numerous cases of increased oral anticoagulant activity have been reported

in patients receiving antibiotic therapy. The severity of the infection or inflammation, patient's age and general health status appear to be predisposing 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, cyclins, cotrimoxazole, and certain cephalosporins.

\+ **Atorvastatin, simvastatin**
There is an increased risk of adverse (concentration-dependent) effects such as rhabdomyolosis.
Lower doses of the cholesterol-lowering drug should be used.

+ Ciclosporin
There is a risk of increased blood ciclosporin and creatinine concentrations.
Blood ciclosporin concentrations should be assayed, kidney function tests carried out and dosage adjustments made during coadministration and after discontinuation of treatment with the macrolide.

+ Disopyramide
An in vitro study has shown that roxithromycin can displace protein-bound disopyramide. Such an effect in vivo may result in increased serum levels of free disopyramide. Consequently, ECG and, if possible, the disopyramide serum levels should be monitored.

+ Digoxin and other digitalis glycosides

Blood digoxin levelsare increased due to increased absorption.

Clinical monitoring (symptoms and ECG) should be performed and, possibly, monitoring of blood digoxin levels during and after treatment with azithromycin.

This clinical monitoring is mandatory if symptoms occur that are suggestive of digitalis glycoside overdose. Cardiac toxicity of digitalis glycosides may cause the following symptomps: nausea, vomiting, diarrhea, headache or vertigo, arrhythmia or heart conduction disorders.

<u>Combinations to be taken into account</u>

+ Midazolam
There is a slight increase in the sedative effects of midazolam.

+ Theophylline (and, by extrapolation, aminophylline)
There is a risk of increased blood theophylline levels, especially in children. However, this generally does not require any adjustment of the usual dose.

\+ **Roxithromycin is a weak CYP3A inhibitor.**
The effect of roxithromycin on exposure to drugs predominantly cleared by CYP3A metabolism would be expected to be 2-fold or less. Caution should be exercised when roxithromycin is concomitantly prescribed with a drug metabolized by CYP3A (such as rifabutin and bromocriptine).

4.6 Fertility, Pregnancy and lactation

Pregnancy

As a precaution, roxithromycin should preferably not be used during pregnancy. Although there is no evidence of teratogenic or fetotoxic effects from animal studies at doses higher than 200 mg/kg/day or 40 times the therapeutic dose in humans, the clinical data are insufficient.

Lactation

Most macrolides have been found to be excreted in breast milk, at concentrations equal to or higher than plasma concentrations. However, the amounts ingested by the breast-fed newborns are low compared to pediatric doses. The highest risk for the infant is intestinal flora imbalance. Breast-feeding during treatment is therefore possible. If the breast-fed infant develops gastrointestinal disorders (intestinal candidiasis, diarrhea), breast-feeding must be stopped (or treatment with the drug discontinued).

If the breast-fed newborn or infant is being treated with cisapride, use of macrolides in the mother is contraindicated as a precaution due to the potential risk of interaction (torsades de pointes) in the infant.

4.7 Effects on the ability to drive and use machines

Visual disturbances and blurred vision may affect the ability to drive or use machines (see Section 4.8). Patients, particularly those who drive or use machines, should be warned that there is a risk of dizziness when using this medicinal product.

4.8 Undesirable effects:

The table below summarizes the undesirable effects reported during clinical trials and recorded in the pharmacovigilance database, categorized by system organ class and by frequency. The categories of frequency are defined by applying the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); and Frequency Unknown (cannot be estimated from the available data).

System Organ Class	Very common >1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Frequency Unknown (cannot be estimated from the available data)
Infections and infestations				Superinfection (in long-term use): colitis due to Clostridium difficile (Pseudomembranous enterocolitis (see section 4.4).
Blood and lymphatic system disorders			Eosinophilia	Thrombocytopenia, neutropenia, agranulocytosis (see section 4.4).
Immune system disorders				Hypersensitivity reactions such as urticaria, angioedema, bronchospasm, anaphylactoid reactions or anaphylactic shock

Psychiatric disorders				Hallucinations, Confusion
Nervous system disorders		Headache, dizziness,		Paresthesia, ageusia, dysgeusia, parosmia, anosmia.
Gastrointestinal disorders		Nausea, vomiting, Dyspepsia (gastric pain), diarrhea		Bloody diarrhea pancreatitis.
Hepatobiliary disorders				Jaundice, cholestatic hepatitis or acute cytolytic hepatitis (see section 4.4)
Skin and subcutaneous tissue disorders		Rash	Bollous skin reactions including erythema multiforme, Urticaria	Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (see section 4.4), Purpura, Angioedema, Acute generalized exanthematous pustulosis (AGEP)
Investigations				Elevation in AST, ALT transaminases. Elevation in serum alkaline phosphatase
Ear and labyrinth disorders				Transient deafness, Hypoacusia, Vertigo, tinnitus
Eye disorders				Visual disturbances, blurred vision
Cardiovascular disorders				Prolongation of the QT interval. Ventricular arrhythmia such as torsades de pointe or ventricular tachycardia which may cause ventricular fibrillation or cardiac arrest (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 https://sideeffects.health.gov.il/.

4.9 Overdose:

Action to be taken in the event of overdose: gastric lavage and symptomatic treatment.
There is no specific antidote.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIBACTERIALS FOR SYSTEMIC USE
ATC code: J01FA06 (J: anti-infectives)
Roxithromycin is an antibiotic of the macrolide group.

SPECTRUM OF ANTIMICROBIAL ACTIVITY

The MIC breakpoints differentiating susceptible strains from intermediate strains, and intermediate strains from resistant strains, are as follows:

S ≤1 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 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 the 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-positive aerobes	
Bacillus cereus	
Corynebacterium diptheriae	
Enterococci	50 - 70 %
Rhodococcus equi	
Methicillin-susceptible 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	
Mobiluncus	
Peptostreptococcus	30 - 40 %
Porphyromonas	
Prevotella	
Propionibacterium acnes	
Miscellaneous	
Borrelia burgdorferi	
Chlamydia	
Coxiella	
Leptospires	
Mycoplasma pneumoniae	
Treponema pallidum	
MODERATELY SUSCEPTIBLE SPECIES (intermediate susceptibility in vitro)	

Gram-negative aerobes Haemophilus Neisseria gonorrhoeae **Anaerobes** Clostridium perfringens **Miscellaneous** Ureaplasma urealyticum	
RESISTANT SPECIES **Gram-positive aerobes** Corynebacterium jeikeium Nocardia asteroides **Gram-negative aerobes** Acinetobacter Enterobacteria Pseudomonas **Anaerobes** Fusobacterium **Miscellaneous** Mycoplasma hominis	

Roxithromycin has *in vitro* and *in vivo* activity on Toxoplasma gondii.
In vitro, roxithromycin shows moderate activity on *Mycobacterium avium*.

* 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

A bioequivalence studyshowed that the following dosage forms are bioequivalent:

- 50 mg sachet,
- 50 mg tablet,
- 150 mg tablet,

The formulae for 100 mg and 150 mg tablets are homothetic. Therefore, no bioequivalence study was carried out.

Absorption

Roxithromycin is rapidly adsorbed. It has been shown to be stable in acidic media and can be found in the plasma after 15 minutes. .

Peak plasma concentrations are reached within 2.2 hours after administration of 150 mg on an empty stomach. It has been shown that taking the medicine 15 minutes before meals does not change the pharmacokinetic profile in healthy subjects.

Distribution

- After administration of one tablet as a single dose in healthy subjects, the pharmacokinetic parameters are as follows:
  - mean peak plasma concentration: 6.6 mg/L
  - mean concentration (12 hours after a single dose): 1.8 mg/L
  - mean elimination half-life is 10.5 hours
- After administration of repeated doses in the healthy subjects (150 mg every 12 hours

for 10 days) steady state in plasma is reached between the 2nd and 4th day.At steady-state, plasma concentrations are as follows:

- peak concentration: 9.3 mg/L
- minimum concentration: 3.6 mg/L

As the drug does not accumulate, the daily dose can be taken as 2 divided doses, 12 hours apart, which makes it possible to achieve antibiotic plasma concentrations that are effective against susceptible microorganisms for 24 hours.

Macrolides penetrate and accumulate in phagocytes (neutrophils, monocytes, peritoneal and alveolar macrophages).
In humans, concentrations in phagocytes are high. These properties account for roxithromycin activity on intracellular bacteria.

- Tissue distribution

The drug is well distributed in tissue, especially lung tissue, tonsils and prostatic tissue, 6 and 12 hours after repeated doses of roxithromicyn.

- Plasma protein binding:

96%: roxithromycin mainly binds to alpha 1-acid glycoprotein. This bond is saturable and decreases when roxithromycin concentration exceeds 4 mg/L.

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Very small amounts of roxithromycin, i.e. less than 0.05% of the administered dose, are excreted in breast milk.

Metabolism
Roxithromycin is relatively poorly metabolized (by CYP3A); more than half the drug is excreted unchanged. Three metabolites have been identified in urine and feces: descladinose roxithromycin is the main metabolite, and N-mono and N-didemethyl roxithromycin are minor metabolites. The proportions of roxithromycin and its three metabolites are similar in the urine and feces.
Based on *in vitro* studies, roxithromycin demonstrated weak inhibition of CYP3A, but did not inhibit CYP1A2, CYP2C9, CYP2C19 or CYP2D6.

Elimination

Roxithromycin is mainly eliminated by the fecal route: Seventy-two hours after oral administration of 14C-radiolabeled roxithromycin, urinary excretion of radioactivity accounts for only 12% of the total amount eliminated in the urine and the feces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Maize starch, Hydroxypropyl cellulose, , Povidone, Hypromellose, Talc,
Colloidal anhydrous silica, Magnesium stearate, , Anhydrous glucose, Propylene glycol, Titanium dioxide, Poloxamer.

6.2 Shelf life

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

6.3 Special precaution for storage

Do not store above 25°C.

7. MARKETING AUTHORISATION HOLDER

Sanofi-aventis Israel ltd. P.O.B. 8090 Netanya 4250499

8. Manufacturer: Sanofi Winthrop Industrie, France

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