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 macrolides or to any of the excipients.
- Concomitant therapy with vasoconstrictive ergot alkaloids (see section 4.5).
- Concomitant use with drugs that may cause ventricular arrhythmias (torsades de pointes, prolonged QT interval) is contraindicated. Such drugs include for example terfenadine, astemizole, cisapride or pimozide (see section 4.5).
- Women breast-feeding an infant who is treated with cisapride (see Section 4.6)
4.4 Warnings and special precautions for use

Warnings

As this medicine contains glucose, it is contraindicated in patients with glucose-galactose malabsorption syndrome.

In certain conditions macrolides, including roxithromycin, have the potential to prolong the QT interval. Therefore roxithromycin should be used with caution in patients with congenital prolongation of the QT interval, with ongoing proarrhythmic conditions (i.e. uncorrected hypokalaemia or hypomagnesaemia, clinically significant bradycardia), and in patients receiving Class IA and III antiarrhythmic agents. (see section 4.5 and 4.8).

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

Administration of roxithromycin is not recommended in patients with hepatic insufficiency. If it must be administered in these subjects, regular liver function tests are warranted and, if necessary dose reduction.

Renal elimination of the active substance is low. There is therefore no need to adjust dosage in patients with renal insufficiency.

In elderly subjects, the elimination half-life is prolonged. However, after repeated administration of 150 mg every 12 hours, peak plasma concentrations and the area under the curve, at steady state between two doses, do not differ from those found in young subjects.

Dosage adjustment is therefore not necessary in elderly subjects.

Coadministration of roxithromycin with colchicine or dopaminergic ergot alkaloids is not recommended (see Section 4.5 Interactions with other medicinal products and other forms of interaction).

Like other macrolides, roxithromycin may have the potential to aggravate myasthenia gravis.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindicated combinations (see 4.3 Contraindications)

+ Ergotamine/ Dihydroergotamine
Concomitant use of roxithromycin and ergotamine or hidydroergotamine, may cause perfusion disturbances, especially in the fingers and toes. Absence of treatment by these alkaloids must always be checked before prescribing roxithromycin.

Concomitant use of these substances with roxithromycin is contraindicated

+ Terfenadine
Certain macrolides are capable of a pharmacokinetic interactions with terfenadine leading to increased serum concentrations of terfenadine. This may result in severe ventricular arrhythmias, typically torsade 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 association of roxithromycin and terfenadine is not recommended.
**Astemizole, Cisapride and Pimozide**
Concomitant use of roxithromycin with astemizole, cisapride and pimozide may increase the serum levels of these drugs. The increased serum levels of these drugs have been associated with cardiovascular adverse reactions, such as QT interval prolongation and arrhythmias. Therefore association of roxithromycin with these drugs is not recommended.

**Inadvisable combinations** (see 4.4 Special warnings)

- **Dopaminergic ergot alkaloids (bromocriptine, cabergoline, lisuride, pergolide)**
  Increased dopaminergic plasma concentrations with possible increased activity or appearance of symptoms of overdose.

- **Colchicine**
  Increased adverse effects of colchicine with potentially fatal consequences.

**Combinations requiring precautions for use**

- **Oral anticoagulants**
  Increased oral anticoagulant effect and increased risk of bleeding.
  INR should be monitored more frequently. Dosage adjustment of the oral anticoagulant may be necessary during treatment with the macrolide and after its discontinuation.

- **Ciclosporin**
  Risk of increased blood ciclosporin and creatinine concentrations.
  Blood ciclosporin concentrations should be assayed, renal function monitored and dosage adjusted during treatment with the macrolide and after its discontinuation.

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

- **Digoxin and other cardiac glycosides**
  Roxithromycin may increase the absorption of digoxin. This effect, common to other macrolides, may very rarely result in cardiac glycoside toxicity. This may be manifested by symptoms such as nausea, vomiting, diarrhea, headache or dizziness. Cardiac glycoside toxicity may also elicit heart conduction and/or rhythm disorders. Therefore in patients treated with roxithromycin and digoxin or other cardiac glycoside ECG, and if possible serum level of cardiac glycoside, should be monitored.

- **Class IA and III antiarrhythmic agents**
  Roxithromycin, like other macrolides, should be used with caution in patients receiving Class IA and III antiarrhythmic agents (see section 4.4).
**Combinations to be taken into account**

+ **Midazolam**
  Slightly increased sedative effect.

+ **Theophylline (and, by extrapolation, aminophylline)**
  Risk of increased blood theophylline concentrations, especially in children.

**Special INR imbalance-related issues**

Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotic therapy. The context of infection or of pronounced inflammation, the patient’s age and general state 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.

**4.6 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, clinical data are insufficient.

**Lactation**

The drug is excreted in human breast milk to a very limited extent. Therefore breastfeeding or treatment with roxithromycin should be discontinued as necessary.

Most macrolides have been found to be excreted in breast milk, at concentrations equal to or greater than plasma concentrations. However, the amounts ingested by the breast-fed newborn are low compared to pediatric dosages. An effect on the infant’s intestinal flora remains the greatest risk. Breast-feeding during treatment is therefore possible. Should the breast-fed infant develop gastro-intestinal 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 in the infant (torsades de pointes).

**4.7 Effects on the ability to drive vehicle or to use machine**

Vehicle drivers or machine users should be informed about risk of vertigo.

**4.8 Adverse effects:**

Adverse effects appear in about 4% of the patients at dose of 150 mg twice daily, and in about 10% at dose of 300 mg once daily. Of these adverse effects 3% and respectively 7% are gastrointestinal. Therefore the incidence is bigger at once daily dosing.
The following frequency rating has been used: Common ($\geq 1/100; <1/10$); uncommon ($\geq 1/1,000; <1/100$); rare ($\geq 1/10,000; <1/1,000$); very rare ($<1/10,000$).

<table>
<thead>
<tr>
<th>Disorder Category</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea, abdominal pain</td>
<td>Diarrhoea (sometimes bloody), vomiting</td>
<td>Fungal infections of gastrointestinal tract</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Anaphylactic shock</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Headache, dizziness, paraesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
<td>Bronchospasm</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>Cholestatic or hepatocellular acute hepatitis (sometimes with jaundice)</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td>Rash, urticaria</td>
<td>Angioedema</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td>Increase in ASAT, ALAT and/or alkaline phosphatase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The following adverse effects have been reported in post-marketing use (frequency unknown):

**Nervous system disorders:**
As with other macrolides, taste disturbance (including ageusia) and/or smell perversion (including anosmia) have been reported.

**Skin and subcutaneous tissue disorders:**
Erythema multiforme, purpura

**Gastrointestinal disorders:**
Symptoms of pancreatitis have been observed; most patients had received other drugs for which pancreatitis is a known adverse reaction. Dyspepsia.

**Blood and lymphatic system disorders:**
Eosinophilia

**Infections and infestations:**
Superinfection: As with other antibiotics, the use of roxithromycin, especially if prolonged, may result in overgrowth of non-susceptible organisms. repeated evaluation of the patient’s
condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

**Psychiatric disorders:**
Hallucinations

**Heart 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).

### 4.9 Overdose:

In case of overdosage: gastric lavage and symptomatic treatment: there is no specific antidote.

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIBACTERIALS FOR SYSTEMIC USE

ATC code: J01FA06 (J: anti-infective)

Roxithromycin is an antibiotic of the macrolide group.

**SPECTRUM OF ANTIMICROBIAL ACTIVITY**

The critical concentrations differentiating susceptible strains from intermediate strains and the latter from resistant strains are as follows:

S ≤1 mg/I and R > 4 mg/I.

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence of acquired resistance in France (&gt; 10%) (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SUSCEPTIBLE SPECIES</strong></td>
<td></td>
</tr>
<tr>
<td>Gram-positive aerobic</td>
<td></td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td></td>
</tr>
<tr>
<td>Corynebacterium diphtheriae</td>
<td></td>
</tr>
<tr>
<td>Enterococci</td>
<td></td>
</tr>
<tr>
<td>Rhodococcus equi</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus meti-S</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus meti-R*</td>
<td></td>
</tr>
<tr>
<td>Streptococcus B</td>
<td></td>
</tr>
<tr>
<td>Unclassified streptococcus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50 - 70 %</td>
</tr>
<tr>
<td></td>
<td>70 - 80 %</td>
</tr>
<tr>
<td></td>
<td>30 - 40 %</td>
</tr>
<tr>
<td>Category</td>
<td>Incidence of acquired resistance in France (&gt; 10%) (range)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------------------------------</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Borrelia burgdorferi</td>
<td></td>
</tr>
<tr>
<td>Chlamydia</td>
<td></td>
</tr>
<tr>
<td>Coxiella</td>
<td></td>
</tr>
<tr>
<td>Leptospires</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Treponema pallidum</td>
<td></td>
</tr>
<tr>
<td>MODERATELY SUSCEPTIBLE SPECIES</td>
<td>(intermediate susceptibility in vitro)</td>
</tr>
<tr>
<td>Gram-negative aerobic</td>
<td></td>
</tr>
<tr>
<td>Haemophilus</td>
<td></td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td></td>
</tr>
<tr>
<td>Anaerobic</td>
<td></td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
<td></td>
</tr>
<tr>
<td>RESISTANT SPECIES</td>
<td></td>
</tr>
<tr>
<td>Gram-positive aerobic</td>
<td></td>
</tr>
<tr>
<td>Corynebacterium jeikeium</td>
<td></td>
</tr>
<tr>
<td>Nocardia asteroides</td>
<td></td>
</tr>
</tbody>
</table>

- **Streptococcus pneumoniae** 35 - 70%
- **Streptococcus pyogenes** 16 - 31%

**Gram-negative aerobic**
- Bordetella pertussis
- Branhamella catarrhalis
- Campylobacter
- Legionella
- Moraxella

**Anaerobic**
- Actinomyces
- Bacteroides 30 - 60%
- Eubacterium
- Mobiluncus
- Peptostreptococcus 30 - 40%
- Porphyromonas
- Prevotella
- Propionibacterium acnes
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 study has shown a bioequivalence between the pharmaceutical forms:

- 50 mg sachets (powder for oral suspension)
- 50 mg tablets
- 150 mg tablets

The 100 mg tablet form being homothetic with the 150 mg tablet form no bioequivalence study has been performed.

**Absorption**

It is rapid. Roxithromycin is stable in acid media and present in the serum as soon as the 15th minute:

- C max is reached 2.2 hours after a fasting dose of 150 mg
- The absorption is not modified by food; it has been shown that the product administered ¼ hour before meal does not entail any modification on the pharmacokinetics in normal subject.

**Distribution and excretion**

- Pharmacokinetic parameters after administration of a single tablet of 150 mg in healthy subjects, are as follows:
  - maximal serum concentration (C max) is on average 6.6 mg/l
  - serum concentration 12 hours after administration is on average 1.8 mg/l
  - mean elimination half-life is 10.5 hours

After administration of repeated doses in the healthy subject (150 mg every 12 hours during 10 days) the steady state is reached between the 2nd and the 4th day.
The serum concentrations in steady state are as follows:

- Cmax 9.3 mg/ml
- Cmax 3.6 mg/ml

Because there is no accumulation of the product, the daily dosage may be administered in two doses, every 12 hours. By such a way the antibiotic plasma concentration is effective on the sensitive strains for 24 hours.

Tissue penetration

It is satisfying, especially in lung, tonsil and prostate, 6 to 12 hours after repeated 150 mg doses administration.

Macrolides enter and gather into the phagocytes (neutrophil polynuclear, monocytes, alveolar and peritoneal macrophage). Intra-phagocytic concentrations are high in man. These properties explain the activity of roxithromycin on intra-cellular bacteria.

Plasma binding

- Binding to plasma proteins is 96%. Roxithromycin is bound principally to 1-alpha-1-acid-glycoprotein. Plasma binding is saturable and is max with a roxithromycin plasma concentration above 4 mg/ml.
- There is a slight passage of roxithromycin into milk, less than 0.05 % of the administered dose.

Biotransformation:

Roxithromycin undergoes only slight biotransformation, more than half being excreted unchanged. Three compounds have been identified in the urine and faeces:

- descladinose roxithromycin, the most abundantly found metabolite
- two minor metabolites, N-monodemethylroxithromycin and N-didemethylroxithromycin. These three derivatives are found in the same proportions in the urine and faeces.

Excretion:

Elimination is principally by the faeces (65%). After roxithromycin C¹⁴ oral administration the urinary radioactivity is only 12 % of the whole excreted quantity in 72 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

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

6.2 Special precaution for storage

Do not store above 25°C
7. MARKETING AUTHORIZATION HOLDER

Sanofi-aventis Israel Ltd.
P.O.B. 8090 Netanya 42504

8. Manufacturer

Sanofi Winthrop Industrie, France