

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Tirabycin

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Roxithromycin 150 mg / tab

Roxithromycin  $C_{41}H_{76}N_2O_{15}$   
(3R, 4S, 5S, 6R, 7R, 9R, 11S, 12R, 13S, 14R) - 4- [(2,6-dideoxy-3-C, 3-O-dimethyl -a-L-ribohexopyranosyl) oxy] -14 -ethyl -7,12,13 -trihydroxy -10 -[(E)- [(2-methoxyethoxy) methoxy] imino]- 3,5,7,9,11,13 -hexamethyl- 6-[(3,4,6 -trideoxy -3-dimethylamino -β-D-xylohexopyranosyl) -oxy] oxacyclo tetradecan-2-one.

### 3. PHARMACEUTICAL FORM

Film coated tablets

### 4. CLINICAL PARTICULARS

#### 4.1. Indications

Tirabycin is indicated for the treatment of infections due to microorganisms sensitive to roxithromycin, especially the following:

- Upper respiratory tract infections: pharyngitis and tonsillitis due to *Streptococcus pyogenes*. Acute nasosinusitis due to *Streptococcus pneumoniae*.
- Low respiratory tract infections: acute bacterial aggravation of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*. For patients with respiratory tract infections, when there is suspicion for infection due to *H. influenzae*, empirical therapy is not recommended. Pneumonia due to *Mycoplasma pneumoniae*, *Streptococcus pneumoniae* and *Chlamydia pneumoniae*.
- Genital tract infections except gonococcal ones
- Non-complicated skin and soft tissues infections due to *Streptococcus pyogenes* or *Staphylococcus aureus*. Abscesses usually need surgical drainage.

#### 4.2. Posology and method of administration

**Administration** : For oral administration.

**Dosage** : The usual dosage for adults is 300 mg daily, divided in two doses every 12 hours, on an empty stomach or 15 minutes before meals.

Tirabycin tablets should be taken with an adequate quantity of water.

*The administration of Tirabycin f.c.tabs 150 mg is not recommended in children.*

#### Dosage for adults in special cases

##### *Use in the elderly:*

Elimination half life is prolonged. However after repeated doses of 150 mg every 12 hours maximum plasma level at equilibrium stage as well as the area under the curve in the meantime of two doses do not differ from those achieved in young patients. Therefore the dosage in elderly is similar to those in other adult patients.

The usual dosage for elderly is 300 mg daily, divided in two doses every 12 hours.

##### *Patients with hepatic insufficiency:*

The administration of the drug is not indicated in patients with severe hepatic insufficiency. In the case that administration of Tirabycin is considered unavoidable, the dosage should be reduced to half the usual daily dose.

Roxithromycin must be used with caution in patients with mild to moderate hepatic insufficiency.

Liver tests should be performed regularly in patients showing signs of hepatic dysfunction or if there is history of hepatic function decrease in former treatment with roxithromycin. If these parameters worsen during treatment with roxithromycin, discontinuing therapy should be taken into consideration

***Patients with renal insufficiency :***

In cases of renal insufficiency, if renal excretion is low (renal excretion of roxithromycin and its metabolites reaches almost 10% of the orally administered dose), there is no demand for changing the dosage.

**4.3. Contraindications**

Tirabacin is contra-indicated in the following cases :

- Patients with known hypersensitivity to roxithromycin or macrolides
- Patients undergoing treatment with vasoconstrictive ergotamine alkaloids, and especially ergotamine and dihydroergotamine (see Interactions)
- Patients undergoing treatment with cisapride, terfenadine, astemizole, pimozide
- Pregnancy and lactation (see 4.6.)
- 300 mg tablets are contra-indicated for patients with severe hepatic insufficiency.
- in children

**4.4. Special warnings and special precautions for use**

In case of hypokalaemia, disturbed ventral conductivity, cardiac arrhythmia and known QT interval prolongation, roxithromycin should only be administered after exact diagnosis and with caution.

Severe vasoconstriction (“ergotism”) with potential torsade de pointes has been reported following simultaneous administration of macrolides and vasoconstrictive drugs. The use of these medicines must always be excluded before the administration of roxithromycin (see Interactions).

In cases of pseudomembranous colitis manifesting itself as serious and persistent diarrhoea, roxithromycin therapy should be discontinued. Antiperistaltic drugs are contra-indicated.

If therapy exceeds the 14 days, there should be regular renal, hepatic and haematological tests.

**4.5. Drug Interactions and other forms of interaction**

***Contra-indicated co-administrations:***

- Vasoconstrictors (see “Special warnings and precautions”).
- Lincomycin
- *Terfenadine:*

Some macrolides have shown pharmacokinetic interaction with terfenadine leading to its increased plasma levels. As a result severe ventral arrhythmia and torsades de pointes has been reported. Even though such a reaction with roxithromycin has not been observed, and clinical trials in a small amount of volunteers showed no signs of pharmacokinetic interactions or alterations in the electrocardiogram, co-administration of roxithromycin and terfenadine is contra-indicated.

- *Astemizole, cisapride, pimozide:*

These drugs are metabolized in the liver by the CYP 3A4 enzyme. As macrolides inhibit this enzyme, concomitant administration of the above mentioned drugs with macrolides may increase risk of cardiac rhythm disorders (QT interval prolongation, ventral arrhythmia, torsade de pointes). Therefore, they should not be co-administered with roxithromycin.

Although roxithromycin has limited ability to inhibit the CYP3A enzymes, the possibility of clinical interaction between roxithromycin and the above drugs cannot be excluded with certainty. Therefore, roxithromycin’s co-administration with these drugs is contra-indicated.

***Co-administrations that require caution:***

- In voluntary studies, interaction with warfarin has not been observed. However, in patients taking roxithromycin and vitamin K antagonists, increased prothrombin time or increased INR have been observed, which may be caused by the infection. It would be

advisable to monitor INR during concomitant therapy of roxithromycin and vitamin K antagonists.

- In an in vitro study, it was observed that roxithromycin may displace disopyramide, which is bound to protein. This in vivo phenomenon may result in the increase of free plasma disopyramide levels. Therefore, there should be monitoring of the electrocardiogram and, if possible, of disopyramide plasma concentrations.
- *Digoxin and other cardiotonic glycosides:*  
Healthy volunteer studies showed that roxithromycin might increase digoxin absorption. Very rarely this activity, common for other macrolides, may result in toxicity from cardiac glycosides. The symptoms may be nausea, vomiting, diarrhoea, headache or dizziness. Cardiac glycoside toxicity can also reveal cardiac conductivity or / and cardiac rhythm disorders. Therefore, for patients treated with roxithromycin and digoxin or other cardiotonic glycosides, there should be monitoring of the electrocardiogram and, if possible, of the cardiac glycoside plasma levels. This is necessary if the symptoms occurred indicate cardiac glycoside overdose.

***Co-administrations that must be taken into consideration:***

- Roxithromycin, as other macrolides, may increase the elimination half-life of midazolam, as well as the area under the curve of concentration vs time. For this reason, midazolam activity may be enhanced and prolonged in patients taking roxithromycin. There is no evidence of interaction between roxithromycin and triazolam.
- Small increase of ciclosporin A plasma levels has been observed, which does not require dosage changes.
- Roxithromycin's use in patients receiving high theophylline doses might be related to an increase in plasma theophylline levels and may enhance theophylline's toxicity. Pharmaceutical therapeutic control of theophylline concentrations is recommended, especially when theophylline levels before treatment are higher than 15 µg/ml.
- **Contraceptives**  
In rare cases, some antibiotics may reduce the activity of orally administered contraceptives as they interfere in intestinal bacterial hydrolysis of conjugated steroids, thus reducing the re-absorbance of non-conjugated steroids. In this case, active steroid plasma levels may be decreased. This rare interaction may occur in women with high biliary excretion of conjugated steroids. About 60 pregnancies occurred in English women, who orally received contraceptives while simultaneously taking antibiotics, especially ampicillin, amoxicillin and tetracyclines. There have been negative studies with co-trimoxazole, roxithromycin and clarithromycin, even though in very few cases.
- In case of co-administration with bromocriptine or cabergoline, increase of their plasma levels and possible enhancement of antiparkinsonian activity, or appearance of overdose symptoms (dyskinesia) should be taken into consideration.

***Other co-administrations:***

- A clinically significant interaction with carbamazepine, ranitidine, magnesium hydroxide and aluminum hydroxide has not been observed
- The absorption of the drug is not affected when Roxithromycin is given before meals.

**4.6. Administration during Pregnancy and Lactation.**

**Pregnancy**

Animal trials have not shown teratogenic or embryotoxic action for doses up to 200 mg/kg body weight per day or 40 times the treating dose for man.

The safety of roxithromycin towards the foetus has not been established for human pregnancy.

**Lactation**

A small quantity of roxithromycin is excreted in human breast milk. For this reason, lactation or nursing mother's treatment should be discontinued.

**4.7. Effects on ability to drive and operate machines**

As there is a possibility of dizziness occurring, special care is necessary during treatment with Tirabacin.

#### 4.8. Adverse reactions

The following side effects have been reported during treatment:

- Gastro-intestinal disturbances such as: nausea, vomiting, epigastralgia, diarrhoea and in very rare cases with blood signs.
- In isolated cases symptoms of pancreatitis have occurred. Most of those patients had received other drugs for which pancreatitis is a common side effect.
- Dizziness, headache and paraesthesia
- Possible slight increase of AST – ALT transferase or / and alkaline phosphatase. Cholestatic or in very rare cases hepatocellular hepatitis.
- In very rare cases, as with other macrolides, hypersensitivity reactions, such as skin eruptions, rash, agoneurotic oedema, bronchial spasm, anaphylactic reactions, increase of eosinophils.
- In very rare cases, purpura, lymphopenia, increase of thrombocytes.
- Possible fungi development
- As with other macrolides, taste and/or olfaction disturbances have been reported.
- Re-infection : as with other antibiotics, roxithromycin administration, especially if it is prolonged, may result in the development of non-sensitive microorganisms. It is essential to monitor the patient's state periodically. In case of re-infection during treatment, necessary measures should be taken.

#### 4.9. Overdosage

In case of overdosage general measures should be taken, such as gastric lavage and symptomatic treatment. There is no special antidote.

### 5. PHARMACOLOGICAL PROPERTIES

Roxithromycin is a semi-synthetic antimicrobial substance of the macrolide group.

#### 5.1. Pharmacodynamic properties

Antimicrobial activity: The natural antimicrobial spectrum of roxithromycin is the following:

a. Usually sensitive strains:

- *Streptococcus A (streptococcus pyogenes)*
- *Streptococcus C*
- *Streptococcus G*
- *Streptococcus mitis, sanguis, viridans*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- *Neisseria gonorrhoeae*
- *Bordetella pertussis*
- *Moraxella catarrhalis*
- *Corynebacterium diphtheriae*
- *Listeria monocytogenes*
- *Clostridium*
- *Mycoplasma pneumoniae*
- *Pasteurella multocida*
- *Chlamydia trachomatis, psittaci and pneumoniae*
- *Ureoplasma urealyticum*
- *Legionella pneumophila*
- *Helicobacter pylori*
- *Gardnerella vaginalis*

b. Strains with variable sensitivity:

- *Haemophilus influenzae (usually resistant)*
- *Bacteroides fragilis*
- *Vibrio cholerae*
- *Staphylococcus aureus, Staphylococcus coagulase negative (not resistant to methycillin)*
- *Staphylococcus epidermidis*

c. Resistant strains:

- *Enterobacteria*
- *Pseudomonas spp*
- *Acinetobacter spp*

## 5.2. Pharmacokinetic properties

### ***Absorbance***

Roxithromycin is rapidly absorbed. The antibiotic is present in the serum 15 minutes after administration. Maximum serum level is achieved 2,2 hours after administration of 150 mg on an empty stomach.

When roxithromycin is orally administered on an empty stomach in the form of 300 mg tablet, it is rapidly absorbed. Roxithromycin is more stable than other macrolides in an acidic environment. In healthy individuals maximal serum level is achieved within 1,5 hours ( $t_{max}$ ) after oral administration of 300 mg.

Absorbance is reduced with food, therefore it is recommended to take the tablets before meals.

### ***Distribution***

After the administration of 1 tablet of 150 mg in healthy individuals the pharmacokinetic parameters are as following:

- mean maximum plasma concentration: 6,6 mg/l
- mean concentration (12 hours after administration): 1,8 mg/l
- mean elimination half life: 10,5 hours

After repeated administration in healthy individuals (150 mg every 12 hours for 10 days), steady state plasma levels are achieved between the 2<sup>nd</sup> and the 4<sup>th</sup> day. Steady state plasma levels are as following:

- maximum level: 9,3 mg/l
- minimum level: 3,6 mg/l

### ***Plasma concentrations***

After the administration of 1 tablet of 300 mg in healthy individuals, the average maximum plasma level ( $C_{max}$ ) is 9,7 mg/l. This value is achieved within about 1,5 hours ( $T_{max}$ ). Within 12 hours the remaining concentration is 2,9 mg/ml and in 24 hours 1,2 mg/l.

After the administration of 300 mg every 24 hours for 11 days the maximum roxithromycin plasma concentration ( $C_{max}$ ) is 10,9 mg/l: this value is smaller than the expected because roxithromycin follows non linear kinetics even during the equilibrium stage. During the equilibrium stage the remaining concentration (24 hours) is 1,7 mg/l.

Elimination half life in adults is  $11,2 \pm 4,4$  hours.

### ***Diffusion in tissues***

Diffusion in tissues is sufficient especially in the lungs: 5,6 and 3,7 mg/Kg, in tonsils: 2,6 and 1,7 mg/Kg, in the prostate: 2,8 and 2,4 mg/kg. These concentrations were present 6 and 12 hours after repeated administration of 150 mg roxithromycin.

### ***Penetration in tissues***

Tissue penetration is sufficient especially in the lungs, tonsils and prostate, 6 and 12 hours after repeated administration of roxithromycin.

### ***Blood Protein binding***

96%. Roxithromycin is bound mainly with  $\alpha$ -1 acid glycoprotein. This bond is saturated when roxithromycin concentration exceeds 4 mg/l.

Small portions of roxithromycin are traced in breast milk, smaller than 0,05% of the administered dose. Some roxithromycin is detected in breast milk, lower than 0.05% of the administered dose.

### ***Metabolism***

Roxithromycin is only partially metabolised, given that more than 50% of the initial substance is excreted unchanged. Three metabolites have been traced in the urine and bile: descladinose roxithromycin is the main metabolite and N-mono and N-didemethyl roxithromycin are less

predominant. The proportion with which roxithromycin and the 3 metabolites are excreted in the urine and bile is the same.

### ***Excretion***

Roxithromycin excretion is predominantly biliary. 72 hours after oral administration of roxithromycin labelled with carbon  $^{14}\text{C}$ , 12% of the radioactivity is excreted in the urine, while the rest is excreted in the bile.

### ***Pharmacokinetics in special patient groups***

***Elderly:*** After the administration of 1 tablet of 300 mg, maximal plasma concentration ( $C_{\text{max}}$ ) of roxithromycin is on average 17,8 mg/l and is achieved within about 1,5 hours. The remaining concentration within 24 hours is 5,2 mg/l.

In the elderly elimination half-life is on average double. Variation from the linear kinetics is more intense in the elderly, where the observed increase in plasma concentration after repeated administration is smaller than the expected. This may well be caused by saturation of the bonds of roxithromycin into plasma proteins.

### ***Renal insufficiency***

After the administration of 1 tablet of 300 mg, the maximal plasma concentration of roxithromycin ( $C_{\text{max}}$ ) is 10,2 mg/l, and it is achieved within 2,2 hours. The remaining concentration within 24 hours is 3,4 mg/l.

Elimination half-life is 16 hours.

### ***Patients with severe hepatic insufficiency***

After oral administration of one tablet of 150 mg the elimination half-life is increased to 25 hours.

## **5.3. Preclinical safety data (toxicological properties)**

Roxithromycin exhibits small toxicity after acute administration ( $\text{LD}_{50}$  with about 750 mg/kg orally in mice, 1000 – 1700 mg/kg orally in rats, and > 2000 mg/kg orally in dogs).

After repeated administration the main target-organs were liver and pancreas.

Effect on liver was more obvious in dogs than in rats, in doses ranging from 180 mg/kg daily for 1 month to 100 mg/kg daily for 6 months compared to 400 and 125 mg/kg daily respectively for rats. Results with these dosages were more obvious in dogs than in rats.

Effect on the pancreas was detected in the endocrine part in rats but was more intense in the exocrine part in dogs. These phenomena were observed after administration of high doses or for long periods.

In rats some effect on teeth was also observed.

Original toxicological data also showed that roxithromycin did not show any teratogenic effect on mice, rats, rabbits, and no mutagenic action was observed.

It has been reported that roxithromycin, as erythromycin, causes an in vitro QRS prolongation, which is concentration-dependent. This effect has not been observed in man, but is considered clinically possible.

## **6. PHARMACEUTICAL DATA**

### **6.1. Excipients**

Hypromellose, Poloxalcol, Polyvidone 30, Silicon dioxide colloidal, Magnesium stearate, Talc, Maize starch.

Coating : Hypromellose, Dextrose anhydrous, Titanium dioxide E 171, Propylene glycol.

### **6.2. Incompatibilities**

Not reported.

### **6.3. Shelf Life**

The product has a shelf life of 36 months under normal conditions in the market packaging.

**6.4. Special precautions for storage**

Tirabycin should be stored at room temperature (< 25°C) in a dry place, away from the reach of children.

**6.5. Nature and contents of container**

White, round, film coated tablets in PVC/aluminium blister printed with the product's characteristics. Each box contains one blister of 10 tablets and a patient information leaflet.

**6.6. Instruction for use**

There are no special instructions.

**7. MARKETING AUTHORISATION HOLDER**

Kleva SA, 189, Parnithos Ave., 136.71 Athens, Tel.: (+30) 210 2402404-7, Fax: (+30) 210 2460206

**Representative of the Marketing Authorisation Holder:**

Actavis Ltd., B16 Bulebel Industrial Estate, Zejtun ZTN 08, Tel: (+356) 21693533

**8. MARKETING AUTHORISATION NUMBER**

122/02601

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

{To be advised}

**10. DATE OF REVISION OF THE TEXT**

April 2005