

SUMMARY OF THE PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Roximstad 150 mg, film-coated tablets

Roximstad 300 mg, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Roximstad 150 mg:

One film-coated tablet contains 150 mg roxithromycin.

Excipients with known effects

One film-coated tablet contains 1.8 mg lactose monohydrate.

Roximstad 300 mg:

One film-coated tablet contains 300 mg roxithromycin.

Excipients with known effects

One film-coated tablet contains 3.6 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Roximstad 150 mg:

Round, white, biconvex film-coated tablet.

Roximstad 300 mg:

Oblong white, capsule shaped coated tablet with off white core with a score line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Roximstad is indicated for the treatment of infections due to roxithromycin-susceptible microorganisms. Such infections include:

Respiratory infections: Community-acquired pneumonia, in particular pneumonia caused by *Mycoplasma pneumoniae*, *Chlamydophila psittaci* (ornithosis) or *Chlamydophila pneumoniae* (TWAR).

Tonsillitis, pharyngitis and acute otitis media in patients with hypersensitivity to beta lactam antibiotics, or when such treatment is considered unsuitable for other reasons.

Urogenital infections caused by *Chlamydia trachomatis*.

Skin and soft tissue infections such as furunculosis, pyoderma, impetigo, erysipelas in patients with hypersensitivity to beta lactam antibiotics, or when such treatment is considered unsuitable for other reasons.

Consideration should be given to official/national guidance regarding antibacterial resistance and the appropriate use and prescription of antibacterial agents.

4.2 Posology and method of administration

Posology

The tablet should be taken at least 15 minutes before a meal to ensure maximal absorption. Normal dosage is 150 mg twice daily (every 12th hour).

Patients with pneumonia may be treated with the dosage regimen 300 mg once daily.

Renal impairment

In patients with renal insufficiency no change in dosage is necessary.

Hepatic impairment

Roxithromycin should be used with caution in subjects with mild to moderate hepatic insufficiency. The use of roxithromycin is not recommended in patients with severe hepatic insufficiency (**see section 4.4**). If use of roxithromycin is essential because of clinical reasons in this patient group, half of the usual dose a day (= 150 mg) may be administered.

Parameters of hepatic function must be controlled regularly in patients with signs of liver dysfunction or in case hepatic functional impairment has occurred on previous therapy with roxithromycin. If the parameters deteriorate during administration of Roximstad, discontinuation of therapy should be considered.

Elderly patients

No change in dosage is necessary.

Paediatric patients

In children with a body weight of more than 40 kg the dosage should be the same as in adults.

In children with a body weight of less than 40 kg, Roximstad is not recommended.

Roximstad tablets are not suitable for administration to children under 6 years, for whom other pharmaceutical forms are available.

Method of administration

For oral use.

Duration of treatment

As a rule Roximstad is administered for a further 3 or 4 days after improvement of the clinical symptoms.

Therapy over at least 10 days is indicated in the treatment of infections with β -haemolytic streptococci in order to prevent late complications (e.g. rheumatic fever, glomerulonephritis).

4.3 Contraindications

Hypersensitivity to macrolides or to any of the excipients listed in section 6.1.

Concomitant administration of roxithromycin and any of the following substances is contraindicated:

- Vasoconstrictive ergot alkaloid derivatives (such as ergotamine and dihydroergotamine) (see section 4.5)
- Medicinal products with narrow therapeutic windows and which are substrates of CYP3A4 (cisapride, pimozide, astemizole and terfenadine (see sections 4.4 and 4.5).

Roxithromycin is contraindicated in patients with a history of congenital or a family history of long QT syndrome (if not excluded by ECG) and in patients with known acquired QT interval prolongation (see also section 4.4).

4.4 Special warnings and precautions for use

Warnings

Severe vasoconstriction ("ergotism") with possibly necrosis of the extremities has been reported when macrolides antibiotics have been associated with vasoconstrictive ergot alkaloids. Absence of treatment by these alkaloids must always be checked before prescribing roxithromycin (see section 4.4).

Precautions

As with other macrolides, due to a potential to increase QT interval, roxithromycin should be used with care in patients with coronary heart disease, a history of ventricular arrhythmias, uncorrected hypokalaemia and/or hypomagnesaemia, bradycardia (< 50 bpm).

Caution is warranted when roxithromycin is administered to patients taking:

- QT interval prolonging agents (see section 4.5). These include Class IA (e.g. quinidine, procainamide, disopyramide) and Class III (e.g. dofetilide, amiodarone) antiarrhythmic agents, citalopram, tricyclic antidepressants, methadone, some antipsychotics (e.g. phenothiazines), fluoroquinolones (e.g. moxifloxacin), some antifungals (e.g. fluconazole, pentamidine), and some antiviral drugs (e.g. telaprevir).
- Potent CYP 3A4 inhibitors such as protease inhibitors and ketoconazole.

The use of roxithromycin is not recommended in patients with severe hepatic insufficiency (e.g. cirrhosis of the liver with hepatitis and/or ascites). If use of roxithromycin is essential because of clinical reasons in this patient group please refer for dosage to section 4.2. Parameters of hepatic function must be controlled regularly in patients with signs of liver dysfunction or in case hepatic functional impairment has occurred on previous therapy with roxithromycin. If the parameters deteriorate during administration of roxithromycin i.e. increase in liver enzymes and/or bilirubin (jaundice), discontinuation of therapy should be considered.

Roxithromycin should be used with caution in patients with mild-moderate liver impairment.

Clostridium difficile-associated disease: Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with roxithromycin, may be symptomatic of pseudo-membranous colitis. If pseudo-membranous colitis is suspected, roxithromycin therapy must be stopped immediately. Antiperistaltics are contraindicated.

Anaphylactic reactions including angioedema have been reported for roxithromycin. Anaphylactic reactions can progress to a life threatening shock, even after the first administration. In these cases roxithromycin should be discontinued and suitable treatment (e.g. treatment for shock) initiated.

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis (AGEP), have been reported with roxithromycin. If symptoms or signs of AGEP, SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, roxithromycin treatment should be discontinued.

Roxithromycin has been shown to prolong the QT interval on the electrocardiogram in some patients and to cause ventricular tachycardia (e.g. torsade de pointes). If signs of cardiac arrhythmia occur during treatment with roxithromycin, treatment should be stopped and an ECG should be performed.

As with other macrolide antibiotics, roxithromycin may exacerbate or aggravate myasthenia gravis. Patients with myasthenia gravis taking roxithromycin should be advised to immediately seek medical attention if they experience exacerbation of their symptoms. Roxithromycin must then be discontinued and supportive care administered as medically indicated.

Renal excretion of roxithromycin and its metabolites accounts for approximately 10 % of an oral dose. The dosage should be kept unchanged in renal insufficiency.

It is not necessary to adjust the dosage in the elderly.

The effects of the medicinal product in children have not been documented. Roximstad 150/300 mg is not intended for use in children and patients with a body weight of less than 40 kg.

Especially during therapy exceeding a period of 14 days, routine kidney, liver and blood laboratory tests should be performed regularly (see section 4.8).

Excipients

Roximstad contains lactose-monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

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

4.5 Interaction with other medicinal products and other forms of interaction

Associations contraindicated

Roxithromycin is a weak inhibitor of CYP3A4, increasing midazolam AUC by 47 %. A possible clinical relevant inhibition of CYP3A4, leading to increased exposure of concomitantly administered medicines that are substrates of this enzyme, cannot be excluded in some individuals. Therefore, co-administration of cisapride, ergot alkaloid derivatives, pimozone, astemizole and terfenadine is contraindicated, and caution is warranted when roxithromycin is co-administered with other medicinal products with narrow therapeutic window metabolised by CYP3A .

Astemizole/cisapride/pimozone

Other drugs, such as astemizole, cisapride or pimozone, which are metabolised by hepatic CYP3A isozyme have been associated with QT interval prolongation and/or cardiac arrhythmias (typically Torsades de pointes) as a result of increase in their serum level subsequent to interaction with significant inhibitors of this isozyme, including some macrolide antibacterials. Although roxithromycin has no or limited ability to complex CYP3A and therefore to inhibit the metabolism of other drugs processed 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, concomitant use of these substances with roxithromycin is therefore contraindicated (see section 4.3).

Terfenadine

Some macrolides interact with terfenadine, with increased serum concentration of terfenadine as a consequence. This may cause serious ventricular arrhythmia, such as Torsade de pointes. Although this kind of reaction has not been demonstrated with roxithromycin and studies with a limited number of healthy volunteers have shown no pharmacokinetic interaction or relevant ECG-changes, the combination of roxithromycin and terfenadine is contraindicated (see section 4.3).

Ergot alkaloids

Concomitant medication of roxithromycin and ergot alkaloid derivatives (such as ergotamine and dihydroergotamine) could lead to severe vasoconstriction ("ergotism") with possibly necrosis of the extremities. The combination is contraindicated (see section 4.3).

Associations not recommended

Medicinal products with a potential to prolong the QT interval

Caution is warranted when roxithromycin is administered to patients taking other medicinal products with the potential to prolong the QT interval (see section 4.4). These include Class IA (e.g. quinidine, procainamide, disopyramide) and Class III (e.g. dofetilide, amiodarone) antiarrhythmic agents, citalopram, tricyclic antidepressants, methadone, some antipsychotics (e.g. phenothiazines), fluoroquinolones (e.g. moxifloxacin), some antifungals (e.g. fluconazole, pentamidine), and some antiviral drugs (e.g. telaprevir).

Warfarin and other anticoagulantia

No interaction with warfarin has been found in studies of healthy volunteers, however, increases in prothrombin time or International Normalised Ratio (INR), which may be explained either as an

interaction with roxithromycin or by the infectious episode (per se), have been reported in patients treated with roxithromycin and vitamin K antagonists. It is prudent practice to monitor INR during combined treatment with roxithromycin and vitamin K antagonists.

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. Therefore the ECG and, if possible, the serum levels of disopyramide should be controlled.

Precautions for use

Digoxin and other cardiac glycosides

A study in healthy volunteers has shown that roxithromycin may increase the absorption of digoxin. A similar phenomenon has been described for other macrolides and may very rarely result in cardiac glycoside toxicity. This may be manifested by symptoms such as nausea, vomiting, diarrhoea, headache or dizziness; cardiac glycoside toxicity may also elicit heart conduction and/or rhythm disorders. Consequently, in patients treated with roxithromycin and digoxin or any other cardiac glycoside, ECG and, if possible, the serum level of the cardiac glycoside should be monitored. This is mandatory if symptoms suggesting cardiac glycoside overdosage have occurred.

Roxithromycin, like other macrolides, should be used with caution in patients receiving Class IA and III antiarrhythmics.

HMG-CoA Reductase Inhibitors

When roxithromycin and an HMGCoA reductase inhibitor (statin) are combined, there is a potential risk of muscle related adverse events, such as rhabdomyolysis due to a possible increase of the statin exposure.

Caution should be exercised when a statin is combined with roxithromycin and patients should be monitored for signs and symptoms of myopathy.

Associations to be taken into account

Cyclosporine

In a clinical study to assess the effects of roxithromycin on cyclosporine exposure, 8 heart transplant recipients treated with cyclosporine for at least 1 month received roxithromycin 150 mg bid for 11 days. Roxithromycin caused a 50 % increase in plasma cyclosporine concentrations that progressively decreased on roxithromycin discontinuation. Cyclosporine dosage adjustment is in general not necessary.

Midazolam

Co-administration of roxithromycin (300 mg daily) and midazolam (15 mg orally) increased the midazolam (a sensitive CYP3A4 substrate) AUC by 47 %, which may lead to enhanced midazolam effects.

Theophylline

A slight increase has been detected in plasma concentrations of theophylline, but this does not generally require alteration of the usual dosage.

Roxithromycin use in patients who are receiving high doses of theophylline may be associated with an increase in serum theophylline levels and potentiate theophylline toxicity. Therapeutic drug monitoring of theophylline concentrations is recommended, especially when pre-treatment levels of theophylline are higher than 15 µg/ml.

Bromocriptine

Roxithromycin may increase the AUC and plasma concentrations of bromocriptine, which could lead to an increased risk for adverse effects of the compound.

Rifabutin

Roxithromycin can increase the plasma concentration of rifabutin.

Others

Carbamazepine, ranitidine, aluminium or magnesium hydroxide

There is no clinically significant interaction with carbamazepine, ranitidine, aluminium or magnesium hydroxide.

Contraceptives

Some antibiotics could in rare cases decrease the effect of oral contraceptives by interference with the bacterial hydrolysis of steroid conjugates in the intestine, thereby reducing the reabsorption of unconjugated steroid. The plasma levels of active steroid may then decrease. This rare interaction could occur in women with high biliary elimination of steroid conjugates. About 60 pregnancies have occurred in English women on oral contraceptives when antibiotics have been taken concomitantly, in particular ampicillin, amoxicillin and tetracyclines.

There are negative studies of clinical interactions to assess the effects of trimethoprim-sulphamethoxazole, roxithromycin and clarithromycin and oral contraceptives containing oestrogens and progestogens, although in very few subjects.

4.6 Fertility, pregnancy and lactation

Pregnancy

Studies in several animal species have not shown any teratogenic or foetotoxic effects at doses up to 200 mg/kg/day, or 40 times the human therapeutic dose. The safety of roxithromycin for the foetus has not been established in human pregnancy.

Roxithromycin should not be used during pregnancy unless clearly indicated.

Breast-feeding

There is no clinical experience on use during lactation: only very small amounts of roxithromycin (less than 0.05 % of the dose taken) are excreted into maternal milk. Breast-feeding or treatment of the mother should therefore be discontinued as necessary.

4.7 Effects on ability to drive and use machines

Car drivers and machine users should be informed about the risk of dizziness. Visual impairment and vision blurred may also have an effect on a patient's ability to drive or operate machinery (see section 4.8).

4.8 Undesirable effects

The total frequency of side effects is about 4 % (150 mg x 2) and 10 % (300 mg x 1) respectively. 3 % and 7 % respectively are gastrointestinal side effects, i.e. the frequency is increased with dosing once daily.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as:

Very common	($\geq 1/10$)
Common	($\geq 1/100$ to $< 1/10$)
Uncommon	($\geq 1/1,000$ to $\leq 1/100$)
Rare	($\geq 1/10,000$ to $\leq 1/1,000$)
Very rare	($\leq 1/10,000$)
Not known	(cannot be estimated from the available data).

System organ class	Common	Uncommon	Rare	Not known (Post-marketing experiences)
Infections and infestations				Superinfections with resistant bacteria or fungi on long-term use, Clostridium difficile colitis (pseudo membranous colitis; see section 4.4).
Blood and lymphatic disorders		Eosinophilia.	Changes in blood count.	Agranulocytosis, Neutropenia, Thrombocytopenia.
Immune system disorders			Angioedema, Anaphylactic reaction (see section 4.4).	Anaphylactic shock.
Psychiatric disorders				Confusional state (confusion), Hallucination, Psychosis.
Nervous system disorders	Headache, Dizziness.		Taste disorders (dysgeusia, ageusia), Smell disorders (parosmia, anosmia).	Paraesthesia.
Eye disorders				Visual impairment, Vision blurred.
Ear and labyrinth disorders				Deafness transitory, Hypoacusis, Vertigo, Tinnitus.
Cardiac disorders ⁽¹⁾				QT-prolongation, Ventricular tachycardia and Torsade de pointes (see section 4.4).
Respiratory, thoracic and mediastinal disorders			Bronchospasm.	
Gastrointestinal disorders	Nausea, Epigastric pain, Dyspepsia, Diarrhoea (see section 4.4).	Vomiting, Obstipation, Flatulence.		Anorexia, Haemorrhagic pancreatitis.

System organ class	Common	Uncommon	Rare	Not known (Post-marketing experiences)
Hepatobiliary disorders			Cholestatic hepatitis, Hepatocellular acute hepatitis (see section 4.4), Pancreatitis.	Jaundice (see section 4.4).
Skin and subcutaneous tissue disorders	Rash.	Redness, Urticaria, Erythema multiforme.	Eczema.	Pruritus, Purpura, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis (AGEP).
Musculoskeletal and connective tissue disorder				Myasthenia gravis (see section 4.4).
General disorders and administration site conditions			Weakness, Discomfort.	
Investigations		Increased transaminases and/or alkaline phosphatases and/or bilirubin (see section 4.4).		

⁽¹⁾ As with other macrolides, cases of QT prolongation, ventricular tachycardia and torsades de pointes were rarely reported for roxithromycin.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Toxicity

Low acute toxicity, but there is limited experience of overdose.

Symptoms

Nausea, vomiting and diarrhoea. Undesirable effects such as headache and dizziness may appear and become potentiated by overdose.

Treatment

If necessary gastric lavage and treatment with carbon. Symptomatic treatment. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Roxithromycin a semi-synthetic macrolide with a 14-membered lactone ring.

ATC code J01FA06

Mechanism of action

Roxithromycin's mode of action is exerted by inhibiting protein synthesis through binding to the 50S subunit of the bacterial ribosome. The antibacterial effect results herefrom.

PK/PD relationship

Primarily, the effectivity depends on the duration during which the serum level is above the Minimum Inhibitory Concentration (MIC) for the microorganism.

Mechanisms of resistance

Resistance against roxithromycin can be due to the following mechanisms:

- Efflux: Increase in the number of efflux pumps in the cytoplasmic membrane can result in resistance. Only 14- and 15-membered lactone rings (M-phenotype) are affected by this.
- Alteration of target structure: Methylation of the 23S rRNS decreases the affinity for ribosomal binding site. This results in resistance against macrolides (M), lincosamides (L) und streptogramin B (MLS_B-phenotype).
- The enzymatical deactivation of macrolides is only of secondary clinical relevance.

Among M phenotype there is complete cross-resistance between roxithromycin, azithromycin, clarithromycin, and erythromycin, respectively. Among MLS_B phenotype cross-resistance with clindamycin and streptogramin B exists additionally.

Breakpoints

Minimum inhibitory concentration (MIC) breakpoint established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

<i>Staphylococcus</i> spp.	$S \leq 1.0 \text{ mg/L}$ and $R > 2.0 \text{ mg/L}$
<i>Streptococcus</i> spp., group A, B, C and G	$S \leq 0.5 \text{ mg/L}$ and $R > 1.0 \text{ mg/L}$
<i>Streptococcus pneumoniae</i>	$S \leq 0.5 \text{ mg/L}$ and $R > 1.0 \text{ mg/L}$
<i>Haemophilus influenzae</i> *	$S \leq 1.0 \text{ mg/L}$ and $R > 16 \text{ mg/L}$
<i>Moraxella catarrhalis</i>	$S \leq 0.5 \text{ mg/L}$ and $R > 1.0 \text{ mg/L}$

*The correlation between *H. influenzae* macrolide MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type *H. influenzae* as intermediate

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species. Therefore, local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of roxithromycin in at least some types of infections is questionable.

Commonly susceptible species
<i>Aerobic Gram-positive microorganisms</i>
<i>Streptococcus pyogenes</i> ¹
<i>Aerobic Gram-negative microorganisms</i>
<i>Haemophilus influenzae</i>
<i>Moraxella catarrhalis</i>
<i>Other microorganisms</i>

<i>Chlamydia trachomatis</i> [°]
<i>Chlamydophila pneumoniae</i> [°]
<i>Chlamydophila psittaci</i>
<i>Legionella pneumophila</i> [°]
<i>Mycoplasma pneumoniae</i> [°]
Species for which acquired resistance may be a problem
<i>Aerobic Gram-negative microorganisms</i>
<i>Staphylococcus aureus</i> (Methicillin-susceptible)
<i>Staphylococcus aureus</i> (Methicillin-resistant) ⁺
<i>Streptococcus pneumoniae</i>
Inherently resistant organisms
<i>Aerobic Gram-negative microorganisms</i>
<i>Escherichia coli</i>
<i>Klebsiella</i> spp.
<i>Pseudomonas aeruginosa</i>
<i>Other microorganisms</i>
<i>Mycoplasma hominis</i>

[°] Natural intermediate susceptibility.

⁺ High rates of resistance (> 50 %) have been observed in one or more regions within the EU.

¹ Resistance rate in some studies ≥ 10 %

5.2 Pharmacokinetic properties

Absorption

For maximal absorption the tablet should be taken at least 15 minutes before a meal. Roxithromycin displays non-linear kinetics, and AUC and C_{max} do not increase in proportion to dose. Following single doses of 150 mg and 300 mg to healthy volunteers mean C_{max} values were in the range of 5.8 – 10.1 µg/ml and 7.2 – 12.0 µg/ml, respectively; under multiple dosing for up to 15 days there is marginal accumulation with mean C_{max} values of 6.57 – 9.3 µg/ml (150 mg) and 10.4 – 10.9 µg/ml (300 mg). Maximum plasma concentration is reached after about 1-2 hours.

The binding to plasma proteins at clinically relevant concentrations is 80-96 %. Roxithromycin binds with high affinity mainly to acid alpha-1-glycoproteins (saturated binding) and with low affinity to albumin (unsaturated binding): The binding is concentration dependent at concentrations above 4 mg/ml.

Distribution

Roxithromycin exhibits good penetration into various tissues and body fluids. High tissue concentrations have been observed in lungs, tonsils, sinus mucosa, prostate and uterus, 6 and 12 hours after administration in multiple dose studies. Roxithromycin accumulates into macrophages and polymorphonuclear neutrophils; intracellular/extracellular concentration ratios range from 14 to 190. The passage over the blood-brain-barrier is limited.

The half-life following single doses is reported to range from 6.3-16 h at doses of 150-450 mg. Following multiple dosing the half-life is reported to be 12-13 h, resulting in therapeutic plasma concentrations at the recommended dosages.

Biotransformation and elimination

More than half of the administered dose is excreted unchanged. Roxithromycin is mainly metabolised by the liver. Three metabolites have been identified in faeces and urine; descladinose roxithromycin, N-monodemethyloxithromycin and N-dimethyloxithromycin.

After oral dosage, roxithromycin is mainly eliminated in faeces and partly by the lungs. Only a small part of the dose is excreted in the urine. The dose should therefore be kept unchanged for patients with renal insufficiency.

In patients with impaired liver function, the half-life can be prolonged to about 25 hours and $C_{\max}$ increases after an oral dosage of 150 mg (see section 4.2). In end-stage renal disease $C_{\max}$ was not altered as compared to healthy subjects.

In infants or children receiving roxithromycin 2.5 mg/kg bid for 6 days mean $C_{\max}$ values were 10.1 µg/ml (5 – 13 months of age), 8.7 µg/ml (2 – 4 years of age), and 8.8 µg/ml (5 – 12 years of age), respectively.

5.3 Preclinical safety data

Roxithromycin, like erythromycin, has been shown *in vitro* to cause a concentration-dependent QRS prolongation. Such effects have not been seen in humans, but have been regarded as possible in clinical use.

There are no other preclinical data concerning general toxicity, reproduction effects and genotoxicity, relevant for the prescriber, except those already included under other headings in the summary of product characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core: microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, polaxamer 188, povidone, talc, magnesium stearate.

Coat: lactose monohydrate, hypromellose, macrogol 4000, titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

5 years

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and content of container

PVC aluminium blister

Pack sizes:

150 mg: 5, 10, 12, 14, 16, 20, 28, 30, 50, 60, 90, 100, 250 and 500 tablets

300 mg: 5, 6, 7, 10, 14, 16, 20, 28, 30, 50, 60, 90, 100, 250 and 500 tablets

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG
Stadastraße 2-18
D-61118 Bad Vilbel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

150 mg	16952
300 mg	16953

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

2001-01-26 / 2010-06-16

10. DATE OF REVISION OF THE TEXT

2020-11-19