For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

TORTHROCIN

1. Generic Name

Azithromycin Tablets I.P.

2. Qualitative and quantitative composition

TORTHROCIN 250

Each film coated tablet contains:

Azithromycin (anhydrous)……. 250mg

(as Azithromycin dihydrate I.P.)

Colours: Titanium Dioxide I.P. and Yellow Oxide of Iron

The excipients used are Dibasic Calcium Phosphate Dihydrate, Croscarmellose Sodium, Povidone, Starch, Magnesium Stearate, Sodium Lauryl Sulphate, Hydroxy Propyl Methyl Cellulose, Purified Talc, Titanium Dioxide, Ferric Oxide, Propylene Glycol, Isopropyl Alcohol, Methylene Chloride.

TORTHROCIN 500

Each film coated tablet contains:

Azithromycin (anhydrous)……. 500mg

(as Azithromycin dihydrate I.P.)

Colour: Titanium Dioxide I.P.

The excipients used are Dibasic Calcium Phosphate Anhydrous, Maize Starch, Sodium Starch Glycolate, Sodium Lauryl Sulphate, Povidone, Polyvinylpyrrolidon Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Titanium Dioxide, Propylene Glycol, Purified Talc, Isopropyl Alcohol, Dichloromethane.

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: Azithromycin 250 mg / 500 mg

4. Clinical particulars

4.1 Therapeutic indication

It is indicated for the treatment of uncomplicated multidrug resistant enteric fever only.

4.2 Posology and method of administration

Posology

Azithromycin dose must be taken as prescribe by physician.

Azithromycin should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below.

Adults, children and adolescents with a body weight of 45 kg or over:

The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5.

In the case of uncomplicated Chlamydia trachomatis urethritis and cervicitis, the dosage is 1000 mg as a single oral dose.

For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

Children and adolescents with a body weight below 45 kg:

Azithromycin tablets are not suitable for patients under 45 kg body weight. Other dosage forms are available for this group of patients.

Elderly patients

For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

Patients with renal impairment:

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min).

Patients with hepatic impairment:

Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin.

Method of administration

For oral use.

Azithromycin Film-coated Tablets are for oral administration only. The tablets can be taken with or without food. The tablets should be taken with ½ glass of water.

4.3 Contraindications

Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient listed.

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions including

angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

Prolongation of the QT interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation (see section 4.8); therefore caution is required when treating patients:

- With congenital or documented QT prolongation.

- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes Ia and III, cisapride and terfenadine.

- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia

- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Superinfection:

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms including fungi is recommended.

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis.

Strains of C. difficile producing hypertoxins A and B contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for C. difficile should be considered.

Streptococcal infections

Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to Streptococcus pyogenes and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.

Renal impairment

In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Co-administration with hydroxychloroquine or chloroquine

Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality.

4.5 Drugs interactions

Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine: In healthy volunteers, coadministration of a 5-day regimen of azithromycin with 20 mg cetirizine at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine): Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine: Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergot derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 4.4).

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

Atorvastatin: Co administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase-inhibition assay).

Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of 15 mg warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin Cmax and AUC0-5 were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in AUC0-∞. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz: Coadministration of a single dose of 600 mg azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole: Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Indinavir: Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam: In healthy volunteers, coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Nelfinavir: Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.

Rifabutin: Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8).

Sildenafil: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and Cmax of sildenafil or its major circulating metabolite.

Terfenadine: Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

Theophylline: There is no reported evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam: In reported studies 14 healthy volunteers, coadministration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole: Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Hydroxychloroquine and chloroquine: Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine. Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

4.6 Use in special population (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the foetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Breast-feeding

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery.

However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable effects

Azithromycin is well tolerated with a low incidence of side effects.

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

very common ≥ 1/10	**common** ≥ 1/100 to < 1/10	**uncommon** ≥ 1/1,000 to < 1/100	**rare** ≥ 1/10,000 to <1/1,000	**very rare** < 1/10,000	**not known** frequency cannot be estimated from available data
Infections and infestations					
		Candidiasis, oral candidiasis, vaginal infection			Pseudomembranous colitis
Blood and lymphatic system disorders					
		Leukopenia, neutropenia			Thrombocytopenia, haemolytic anaemia
Immune system disorders					
		Angioedema, hypersensitivity			Anaphylactic reaction
Metabolism and nutrition disorders					
	Anorexia				
Psychiatric disorders					
		Nervousness	Agitation		Aggression anxiety
Nervous system disorders					
	Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia somnolence, insomnia			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia,

					Myasthenia gravis
Eye disorders					
	Visual impairment				
Ear and labyrinth disorders					
	Deafness	Hearing impaired, tinnitus	Vertigo		
Cardiac disorders					
		Palpitations			Torsades de pointes arrhythmia including ventricular tachycardia.
Vascular disorders					
					Hypotension
Gastrointestinal disorders					
Diarrhoea, abdominal pain, nausea, flatulence	Vomiting, dyspepsia	Gastritis, constipation			Pancreatitis, tongue discoloration
Hepatobiliary disorders					
		Hepatitis	Hepatic function abnormal		Hepatic failure (which has rarely resulted in death), hepatitis fulminant, hepatic necrosis, jaundice cholestatic
Skin and subcutaneous tissue disorders					
	Rash, pruritus	Stevens-Johnson syndrome, photosensitivity reaction, urticaria	Acute generalised exanthematous pustulosis (AGEP) *§, DRESS (Drug reaction with eosinophilia and systemic symptoms) *§		Toxic epidermal necrolysis, erythema multiforme.
Musculoskeletal and connective tissue disorders					
	Arthralgia				
Renal and urinary disorders					
					Renal failure acute, nephritis interstitial
General disorders and administration site conditions					

	Fatigue	Chest pain, oedema, malaise, asthenia			
Investigations					
	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal			Electrocardiogram QT prolonged

*****ADR identified post-marketing

§ ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3".

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

Symptoms

The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment

In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. Pharmacological properties

5.1 Mechanism of Action

The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides. ATC code: J01FA10.

Mode of action

Azithromycin is a macrolide antibiotic belonging to the azalide group.

The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0.

Mechanism of resistance:

Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Azithromycin demonstrates cross resistance with erythromycin resistant gram positive isolates. A decrease in macrolide susceptibility over time has been noted particularly in Streptococcus pneumoniae and Staphylococcus aureus. Similarly, decreased susceptibility has been observed among Streptococcus viridans and Streptococcus agalactiae (Group B) streptococcus against other macrolides and lincosamides.

Breakpoints

Azithromycin susceptibility breakpoints for typical bacterial pathogens, as published by EUCAST are:

Organism	**MIC breakpoint (mg/L)**	
	Susceptible (S≤)	**Resistant (R>)**
Staphylococcus spp.	1	2
Streptococcus spp. (Group A, B, C, G)	0.25	0.5
Streptococcus pneumoniae	0.25	0.5
Haemophilus influenzae	0.12	4
Moraxella catarrhalis	0.25	0.5
Neisseria gonorrhoeae	0.25	0.5

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and 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 the agent in at least some types of infections is questionable.

Table: Antibacterial spectrum of Azithromycin

Commonly susceptible species
Aerobic Gram-positive microorganisms

Staphylococcus aureus Methycillin-susceptible
Streptococcus pneumoniae Penicillin-susceptible
Streptococcus pyogenes **(Group A)**
Aerobic Gram-negative microorganisms
Haemophilus influenzae *Haemophilus parainfluenzae*
Legionella pneumophila
Moraxella catarrhalis
Neisseria gonorrhoeae
Pasteurella multocida
Anaerobic microorganisms
Clostridium perfringens
Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.
Other microorganisms
Chlamydia trachomatis
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae Penicillin-intermediate Penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci **MRSA, MRSE***
Anaerobic microorganisms
Bacteroides fragilis group

* Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

Paediatric population

Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

5.3 Pharmacokinetic properties

Absorption

Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (Cmax) after a single dose of 500 mg is approximately 0.4 µg/ml.

Distribution

Orally administered azithromycin is widely distributed throughout the body.

In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues. Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 µg/g, 0,6-2,3 µg/g, 2,0-2,8 µg/g and 0-0,3 µg/ml have been measured in resp. lung, prostate, tonsil and serum.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

Elimination

The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

Approximately 12% of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile. Ten metabolites have been identified (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggest that the metabolites do not play a role in the microbiological activity of azithromycin.

Pharmacokinetics in Special populations:

Renal Insufficiency

Following a single oral dose of azithromycin 1 g, mean Cmax and AUC0-120 increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80ml/min). In subjects with severe renal impairment, the mean Cmax and AUC0-120 increased 61% and 35% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

In elderly volunteers (> 65 years) higher (29%) AUC values have been measured after a 5 day treatment than in younger volunteers (< 45 years). These differences are not regarded as clinically relevant; dose adjustment is therefore not recommended.

Infants, toddlers, children and adolescents

Pharmacokinetics has been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the Cmax achieved is slightly lower than in adults, with 224 µg/l in children aged 0.6-5 years and after 3 days dosing, and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

Mutagenic potential:

There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

Reproductive toxicity:

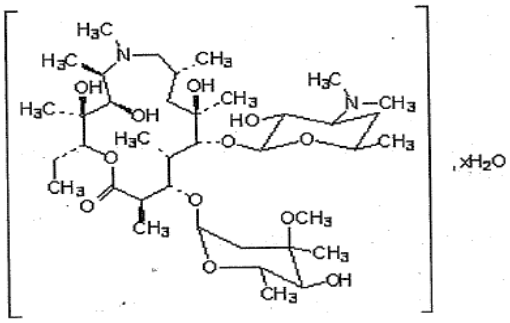
In reported animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal

weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

7. Description

TORTHROCIN 250

Azithromycin is (2R,3S,4R,5R,8R,10R,11R,12S,13R,14R)- 13-[2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3 (dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-l-oxa-6-azacyclopentadecan-15-one monohydrate or dihydrate. Its chemical formula is $C_{38}H_{72}N_2O_{12}..xh_2O$, the molecular weight is 749.0 g/mol and the chemical structure is:



TORTHROCIN 250

TORTHROCIN 250 is light yellow coloured, circular shaped, biconvex, film coated tablets plain on both sides. The excipients used are Dibasic Calcium Phosphate Dihydrate, Croscarmellose Sodium, Povidone, Starch, Magnesium Stearate, Sodium Lauryl Sulphate, Hydroxy Propyl Methyl Cellulose, Purified Talc, Titanium Dioxide, Ferric Oxide, Propylene Glycol, Isopropyl Alcohol, Methylene Chloride.

TORTHROCIN 500

TORTHROCIN 500 is White coloured, capsule shaped, biconvex, film -coated tablets plain on one side and central breakline on the other side. The excipients used are Dibasic Calcium Phosphate Anhydrous, Maize Starch, Sodium Starch Glycolate, Sodium Lauryl Sulphate, Povidone, Polyvinylpyrrolidon Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Titanium Dioxide, Propylene Glycol, Purified Talc, Isopropyl Alcohol, Dichloromethane.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

TORTHROCIN 250 is available in blister strip of 6 tablets

TORTHROCIN 500 is available in blister strip of 5 tablets

8.4 Storage and handing instructions

Store below 25°C. Protected from moisture.

Keep out of reach of children.

9. Patient Counselling Information

TORTHROCIN

(Azithromycin Tablets I.P.)

- Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 9.4.

What is in this leaflet

9.1 What TORTHROCIN is and what it is used for

The active substances of TORTHROCIN is Azithromycin belongs to a group of medicines called macrolide antibiotics.

TORTHROCIN is used to treat the treatment of uncomplicated multidrug resistant enteric fever only.

How to take TORTHROCIN

9.2 What you need to know before you take TORTHROCIN

Do not use TORTHROCIN:

If you are allergic to azithromycin dihydrate orany other macrolide antibiotic such as erythromycin or clarithromycin or to any of the other ingredients of this medicine.

Warnings and precautions

Talk to your doctor or pharmacist before taking Azithromycin if:
• you have severe liver problems: your doctor may need to monitor your liver function or stop the treatment
• you have severe kidney problems
• you have heart problems
• your blood levels of potassium or magnesium are too low
• you develop signs of another infection
• you are taking any ergot derivatives such as ergotamine (to treat migraine) as these medicines should not be taken together with azithromycin (see section "Other medicines and Azithromycin")
• you have a certain type of muscle weakness called myasthenia gravis.
Tell your doctor immediately if you feel your heart beating in your chest or have an abnormal heartbeat, or get dizzy or faint or suffer from any muscle weakness when taking Azithromycin.

If you develop diarrhoea or loose stools during or after treatment, tell your doctor at once. Do not take any medicine to treat your diarrhoea without first checking with your doctor. If your diarrhoea continues, please inform your doctor.

Other medicines and TORTHROCIN:

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, in particular:

• antacids - used for heartburn and indigestion

• ergotamine - used for migraine, should not be taken at the same time as serious side effects may develop (with numbness or tingling sensations in the limbs, muscle cramps, headaches, convulsions, abdominal or chest pain).

• warfarin or similar medicines - used to thin the blood. Azithromycin can thin the blood even more
• terfenadine - used to treat hay fever or skin allergy, should not be taken at the same time as this may cause severe heart problems (shown on an ECG)
• zidovudine or nelfinavir - used to treat HIV infections. Taking nelfinavir with Azithromycin may mean that you get more of the side effects listed in this leaflet
• rifabutin - used to treat tuberculosis (TB)
• quinidine - used to treat heart rhythm problems
• ciclosporin - used to stop your body rejecting an organ transplant. Your doctor will regularly check your blood levels of ciclosporin and may change your dose
• hydroxychloroquine or chloroquine (used to treat conditions including rheumatoid arthritis, or to treat or prevent malaria): Taking these medicines at the same time as azithromycin may increase the chance of you getting side effects that affect your heart.

Tell your doctor or pharmacist if you are taking any of the following medicines. Azithromycin can make the effects of these other medicines stronger. Your doctor may change your dose:
• digoxin - used to treat cardiac impairment

• colchicine - used for gout and familial Mediterranean fever.

TORTHROCIN with food and drink

This medicine can be taken with or without food.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

There are no data available about the influence of azithromycin on the ability to drive or operate machines. However, Azithromycin Tablets may cause dizziness and seizures so make sure you are not affected before driving or operating machinery

9.3 How to take TORTHROCIN

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure. The tablets can be taken with or without food. The tablets should be taken with half a glass of water. Always continue with the course even if you feel better. If your infection gets worse or you do not start to feel better within a few days or a new infection develops, go back and see your doctor.

If you take more TORTHROCIN

If you have taken too much TORTHROCIN, contact your doctor, pharmacist or go to your nearest hospital immediately. Symptoms of overdose are loss of hearing, feeling sick or being sick and diarrhoea. In case of overdose, admission into hospital may be necessary.

If you forget to take TORTHROCIN

If you forget to take TORTHROCIN, take your dose as soon as possible. If it is almost time for the next dose, just skip that dose and take the next one when it is due. If in doubt, please contact your doctor or pharmacist. If you have to skip a dose, still take all of your tablets. This means that you will finish your course a day later.

Do not take a double dose to make up for a forgotten dose.

If you stop taking TORTHROCIN

Never stop the treatment with TORTHROCIN on your own, but first discuss this with your doctor. If you stop taking TORTHROCIN too soon, the infection may return. Take the tablets for the full time of treatment, even when you begin to feel better.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

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9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you have any of the below symptoms of a severe allergic reaction stop taking this medicine and tell your doctor immediately or go to the casualty department at your nearest hospital.

Uncommon (may affect up to 1 in 100 people):

• swelling of the face, lips, tongue, throat, hands, feet or genitals

• blistering of the skin, mouth, eyes and genitals (Stevens-Johnson syndrome).

Rare (may affect up to 1 in 1,000 people):

• skin rash accompanied by other symptoms such as fever, swollen glands and an increase in a type of white blood cell (eosinophilia). A rash appears as small, itchy red bumps (Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)).

Not known (frequency cannot be estimated from the available data):

• sudden difficulty in breathing, speaking and swallowing

• extreme dizziness or collapse

• severe rash involving reddening, peeling and swelling of the skin (Toxic Epidermal Necrolysis).

If you experience any of the following serious side effects, contact your doctor as soon as possible as you may need urgent medical attention.

Uncommon (may affect up to 1 in 100 people):

• inflammation of the liver (hepatitis)

• signs of infection such as a sore throat and high temperature caused by a reduction in the number of white blood cells (leukopenia or neutropenia).

Rare (may affect up to 1 in 1,000 people):

• skin eruption that is characterised by the rapid appearance of red skin studded with small pustules (small blisters filled with white/yellow fluid) (Acute Generalised Exanthematous Pustulosis (AGEP)).

Not known (frequency cannot be estimated from the available data):

• severe or prolonged diarrhoea, which may have blood or mucus in it. This can be a sign of a serious bowel inflammation. This is something that can occasionally happen after taking antibiotics

• reduced number of red blood cells due to destruction (haemolytic anaemia); unusual bruising or bleeding caused by a reduction in the number of platelets (thrombocytopenia)

• yellowing of the skin or whites of the eyes (jaundice) or liver failure (rarely life-

threatening)

• inflammation of the pancreas, which causes severe pain in the abdomen and back

• inflammation of the kidney or kidney failure, increased or reduced urine output, or traces of blood in your urine

• a skin rash that has raised patches or blisters and may be itchy (erythema multiforme)

• rapid (ventricular tachycardia) or irregular heart beat, sometimes being life-threatening, changes of the heart rhythm found by an electro-cardiogram (QT prolongation and torsade de pointes).

Other side effects include:

Very common (may affect more than 1 in 10 people):

• diarrhoea

• abdominal pain

• feeling sick (nausea)

• wind (flatulence).

Common (may affect up to 1 in 10 people):

• lack of appetite (anorexia)

• feeling dizzy

• headache

• sensation of pins and needles or numbness (paraesthesia)

• changes in your sense of taste

• visual impairment

• deafness

• being sick (vomiting), stomach pain or cramps, loss of appetite, problems digesting your food

• skin rashes and itching

• joint pain (arthralgia)

• fatigue

• change in the quantity of the white blood cells and the concentration of bicarbonate in the blood.

Uncommon (may affect up to 1 in 100 people):

• yeast infection of the mouth or vagina (thrush)

• nervousness

• reduced sense of touch (hypoaesthesia)

• feeling drowsy (somnolence)

• having difficulty sleeping (insomnia)

• hearing loss or ringing in your ears

• palpitations

• inflammation of the lining of the stomach (gastritis)

• constipation

• skin more sensitive to sunlight than normal

• urticaria

• chest pain

• swelling (oedema)

• general feeling of being unwell (malaise)

• weakness (asthenia)

• change in liver enzyme levels and blood levels.

Rare (may affect up to 1 in 1,000 people):

• feeling agitated

• spinning sensation (vertigo)

• abnormal liver function.

Not known (frequency cannot be estimated from the available data):

• aggression or anxiety

• fainting (syncope)

• fits (convulsions)

• feeling hyperactive

• change in your sense of smell (anosmia, parosmia)

• change in your sense of taste (ageusia)

• exacerbation or aggravation of muscle weakness (myasthenia gravis)

• low blood pressure

• your tongue changes colour.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine.

9.5 How to store TORTHROCIN.

Store below 25°C. Protected from moisture.

Keep out of reach of children.

9.6 Contents of the pack and other information

What TORTHROCIN contains

TORTHROCIN consists of Azithromycin (anhydrous) comes in the strengths containing 250/500 mg of TORTHROCIN.

TORTHROCIN 250

It is light yellow coloured, circular shaped, biconvex, film coated tablets plain on both sides. The excipients used are Dibasic Calcium Phosphate Dihydrate, Croscarmellose Sodium, Povidone, Starch, Magnesium Stearate, Sodium Lauryl Sulphate, Hydroxy Propyl Methyl Cellulose, Purified Talc, Titanium Dioxide, Ferric Oxide, Propylene Glycol, Isopropyl Alcohol, Methylene Chloride.

TORTHROCIN 500

It is White coloured, capsule shaped, biconvex, film -coated tablets plain on one side and central breakline on the other side. The excipients used are Dibasic Calcium Phosphate Anhydrous, Maize Starch, Sodium Starch Glycolate, Sodium Lauryl Sulphate, Povidone, Polyvinylpyrrolidon Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Titanium Dioxide, Propylene Glycol, Purified Talc, Isopropyl Alcohol, Dichloromethane.

TORTHROCIN 250 is available in blister strip of 6 tablets

TORTHROCIN 500 is available in blister strip of 5 tablets

10 Details of manufacturer

Manufactured by:

Uni Medicolabs

21, 22, Pharmacity,

Selaqui, Dehradun-248 011,

(Uttarakhand), India.

11 Details of permission or licence number with date

55/UA/SC/P-2008 issued on 06.02.2020

12 Date of revision

Not Applicable

MARKETED BY

Torrent Pharmaceuticals Ltd.