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

MACROTOR

1. Generic Name

Azithromycin Tablets I.P.

2. Qualitative and quantitative composition

MACROTOR 250
Each film coated tablet contains:
Azithromycin Dihydrate I.P.
equivalent to Azithromycin 250 mg
Excipients q.s.
Colours: Lake of Quinoline Yellow and Titanium Dioxide I.P.

Other inactive ingredients are: microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, sodium lauryl sulphate, silicon dioxide, magnesium stearate, hydroxy propyl methyl celulose, PEG -6000, talc, titanium dioxide, quinoline yellow.

MACROTOR 500
Each film coated tablet contains:
Azithromycin Dihydrate I.P.
equivalent to Azithromycin 500 mg
Excipients q.s.
Colours: Lake of Quinoline Yellow and Titanium Dioxide I.P.

Other inactive ingredients are: microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, sodium lauryl sulphate, silicon dioxide, magnesium stearate, hydroxy propyl methyl celulose, PEG -6000, talc, titanium dioxide, quinoline yellow.

3. Dosage form and strength

Dosage form: Film coated Tablets

Strength: 250 mg and 500 mg

4. Clinical particulars

4.1 Therapeutic indication

Macrotor is indicated for the treatment in uncomplicated multidrug resistant enteric fever only. The treatment of the following infections when known or likely to be due to one or more susceptible microorganisms:

- Bronchitis
- Community-acquired pneumonia
- Acute bacterial sinusitis
- Pharyngitis/tonsillitis

- Otitis media
- Skin and soft tissue infections
- Uncomplicated genital infections due to Chlamydia trachomatis.

4.2 Posology and method of administration

Posology

Macrotor should be taken at least one hour before or two hours after meals since it may bind to food and not be absorbed from the intestine.

Children over 45kg body weight and adults, including elderly patients: The total dose of Azithromycin is 1500mg which should be given over three days (500mg once daily). In uncomplicated genital infections due to Chlamydia trachomatis, the dose is 1000mg. For most infections, Azithromycin is taken once daily for a relatively short course of treatment (usually five days). The first dose is often a "double dose," twice as much as the remainder of the doses given. For acute bacterial sinusitis, Azithromycin can be taken once daily for three days.

Renal failure

No dose adjustment is necessary in patients with mild to moderate (GFR 10-80 ml/min) or severe (GFR < 10 ml/min) renal impairment.

Hepatic failure

Since Azithromycin is metabolized 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.

Geriatric patient

Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

4.3 Contraindications

- Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic.
- Azithromycin is contraindicated in patients with a history of cholestatic jaundice / hepatic dysfunction associated with prior use of azithromycin.
- Symptomatic infection.
- Symptoms suggestive of other STIs e.g. any unusual genital or anal swellings or lesions.
- Children aged under 16 years.
- Renal or hepatic impairment.
- History of cardiac disease.
- Individuals receiving ciclosporin, digoxin, ergotamine, terfenadine, theophylline, disopyramide, rifabutin and coumarin anticoagulant therapy, such as warfarin.
- Individuals receiving azithromycin for treatment of other infections.
- Pregnancy and breast feeding.

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; 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 Iaand 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.

4.5 Drugs interactions

Antacids:

In a reported 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 reported 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 HIVpositive 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. Pharmacokinetic studies showed that azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.
Atorvastatin:
Coadministration 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 reported 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 reported 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 reported 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 reported 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 C_{max} and AUC_{0-5} 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:
In a reported study 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 C_{max} (18%) of azithromycin was observed.
Indinavir:
Coadministration of a single dose of 1200 mg azithromycin reported to had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone:
In a reported pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.
Midazolam:
In reported study of 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:
In a reported study 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:
In a reported study 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.
Sildenafil:
In reported study of normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.
Terfenadine:
In a reported pharmacokinetic studies 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 study of 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:
In a reported study 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.

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

Pregnancy
There are no adequate data from the use of azithromycin in pregnant women. In reported reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore, Azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breast-feeding

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with Azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

Fertility

In reported fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

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 reported 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.

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

Azithromycin is a macrolide antibiotic belonging to the azalide group.

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.

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.

5.2 Pharmacodynamic properties

Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding anitrogen atom to the lactone ring of erythromycin A. The chemical name of Azithromycin is 9-deoxy-9a-aza-9amethyl- 9a-homoerythromycin A. The molecular weight is 749.0. 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.

5.3 Pharmacokinetic properties

Absorption

Bioavailability after oral administration is approximately 37%. Peak plasma concentration attained in 2-3 hours after taking the medicinal product. The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 μg/ml.

Distribution

Orally administered Azithromycin is widely distributed throughout the body. In reported 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/ml serum. The mean volume of distribution at steady state has been calculated to be 31.1 l/kg.

In reported 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.

Metabolism and 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 of Azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged Azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N - and O - demethylation, hydroxylation of desosamine – and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of Azithromycin are not microbiologically active.

Pharmacokinetics in Special populations:

Renal Insufficiency

Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} 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 C_{max} and AUC_{0-120} increased 61% and 35% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no reported 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 were not regarded as clinically relevant; dose adjustment is therefore not recommended.

Infants, toddlers, children and adolescents

In reported pharmacokinetics studies 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 C_{max} 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:

In reported 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.

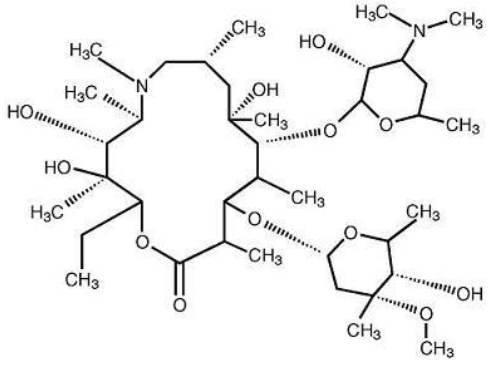
Reproductive toxicity:

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

Macrotor contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name 2R, 3S, 4R, 5R, 8R, 10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3- C-me t h y l - 3 -O-me t h y l - α - L - r i b o - h e x o p y r a n o s y l) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-1 1-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexo pyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.

Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is C38H72N2O12, and its molecular weight is 749.00. Azithromycin has the following structural formula:



8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

Macrotor 250 is available in blister of 6 tablets.
Macrotor 500 is available in blister of 3 tablets.

8.4 Storage and handing instructions

Store in a dry place below 25ºC. Keep out of reach of children.

9. Patient counselling information

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 or pharmacist.

• **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 or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What MACROTOR is and what it is used for

Azithromycin belongs to a group of medicines called macrolide antibiotics. It is indicated for the treatment in uncomplicated multidrug resistant enteric fever only.
The treatment of the following infections when known or likely to be due to one or more susceptible microorganisms:

- Bronchitis
- Community-acquired pneumonia
- Acute bacterial sinusitis
- Pharyngitis/tonsillitis
- Otitis media
- Skin and soft tissue infections

- Uncomplicated genital infections due to Chlamydia trachomatis.

You must talk to a doctor if you do not feel better or if you feel worse.

9.2 What you need to know before you take MACROTOR

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.

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.

Azithromycin 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.
There is insufficient information available about the use of azithromycin during pregnancy. Therefore you should not use Azithromycin during pregnancy, unless explicitly advised by your doctor.
Azithromycin is partially passed through the mother's milk.
It is not known whether azithromycin may have adverse effects on the breast-fed infant. Breast-feeding should therefore be discontinued during treatment with Azithromycin. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Breast-feeding may be resumed thereafter.
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 MACROTOR

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 recommended dose

For adults, children and adolescents with a body weight of 45kg or over 500mg (two 250mg or one 500mg tablets) once daily for three days with a total dose of 1500mg. Alternatively, our doctor may decide to prescribe the total dose of 1500mg over a period of 5 days, with 500mg the first day and 250mg on days 2 to 5.

For infections of the neck of the womb and urethra caused by Chlamydia trachomatis One dose of 1000mg (four 250mg or two 500mg tablets).

Children and adolescents under 45kg

Azithromycin tablets should not be taken by children or adolescents weighing less than 45kg. Other dosage forms are available for this group of patients.

Patients with kidney or liver problems

You should tell your doctor if you have kidney or liver problems as your doctor may need to alter the normal dose.

Method of administration

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 Azithromycin than you should

If you have taken too much Azithromycin, 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 Azithromycin

If you forget to take Azithromycin, 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 Azithromycin

Never stop the treatment with Azithromycin on your own, but first discuss this with your doctor. If you stop taking Azithromycin 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.

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 mucous 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 heartbeat, 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 and 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 or pharmacist. 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 MACROTOR

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the carton after expiry. The expiry date refers to the last day of that month.
This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

9.6 Contents of the pack and other information

What **MACROTOR** contains

The active substances **MACROTOR** is Azithromycin 250 mg and 500 mg.

Other inactive ingredients are: microcrystalline cellulose, croscarmellose sodium, pregelatinized starch, sodium lauryl sulphate, silicon dioxide, magnesium stearate, hydroxy propyl methyl celulose, PEG -6000, talc, titanium dioxide, quinoline yellow

10. Details of manufacturer

Manufactured in India by:

TORRENT PHARMACEUTICALS LTD.
32 No. Middle Camp, NH-10
East District, Gangtok, Sikkim-737 135.

11. Details of permission or licence number with date

M/564/2010 dated 23.12.2016

12. Date of revision

October/2020

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/MACROTOR 250, 500mg/Oct-20/02/PI