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

Azithromycin Tablets I.P.

TRULIMAX®

1. GENERIC NAME

Azithromycin Tablet I.P.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Azithromycin Dihydrate IP equivalent to 250 mg/500 mg of Azithromycin on anhydrous basis.

All strengths/presentations mentioned in this document might not be available in the market.

List of Excipients

Pregelatinized Starch I.P.
Dibasic Calcium Phosphate, anhydrous I.P.
Croscarmellose Sodium I.P.
Magnesium Stearate I.P.
Sodium Lauryl Sulfate I.P.
White Opadry II (Y-30-18037)*

*Note: White Opadry II (Y-30-18037) is a film coating system supplied by Colorcon Inc., and contains:
Lactose monohydrate
HPMC 2910/Hypromellose 15 cP
Titanium dioxide
Triacetin/Glycerol triacetate.

3. DOSAGE FORM AND STRENGTH

250 mg/ 500 mg film-coated tablets

® Trademark Proprietor: Pfizer Products Inc., USA
Licensed User: Pfizer Limited, India.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in skin and soft tissue infections, in otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx; however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present).

In sexually transmitted diseases in men and women, azithromycin is indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated in the treatment of uncomplicated genital infection due to non-multi-resistant *Neisseria gonorrhoeae*; concurrent infection with *Treponema pallidum* should be excluded.

Azithromycin is indicated in the treatment of uncomplicated multidrug resistant enteric fever.

4.2 Posology and Method of Administration

Posology

The dose and duration of treatment is established according to age, weight, severity and location of infection and susceptibility of the microorganism.

The dose and duration of treatment is given below. Other presentations are available for the different dosing schedules.

Adults and paediatric population weighing over 45 kg

	Dosing schedule 1**	**Dosing schedule 2****
▪ *Acute bacterial sinusitis ▪ Pharyngotonsillitis ▪ Acute otitis media ▪ Chronic bronchitis ▪ Community-acquired pneumonia ▪ Skin and soft tissue infections	Duration of treatment: 3 days. Administer 500 mg per day in a single dose.	Duration of treatment: 5 days. *Day 1*: administer 500 mg per day in a single dose. *Days 2-5*: administer 250 mg per day in a single dose.
▪ Urethritis (gonococcal or non-gonococcal) ▪ Cervicitis	Duration of treatment: 1 day. Administer 1,000 mg per day in a single dose. In case of infection with *N. gonorrhoea*, administer the same dose in combination with Ceftriaxone (250 mg).	Not applicable

▪ Chancroid	Duration of treatment: 1 day. Administer 1,000 mg per day in a single dose.	Not applicable

*Sinusitis, treatment is indicated in adults and adolescents over 16 years.
**The size of the bottle for administering dosage in adults is 37.5 mL.

For suspected *Neisseria gonorrhoeae* infection, the recommended dose is 1,000 mg in combination with Ceftriaxone (250 mg).

Paediatric population weighing under 45 kg

The use of Zithromax 200 mg/5 mL powder for oral suspension is recommended.

The total recommended dose in the paediatric population for children over 1 year old is 30 mg/kg, administered in a single daily dose of 10 mg/kg for 3 consecutive days.

Alternatively, the same dose may be administered for a period of 5 days, administering a single dose of 10 mg/kg on the first day, continuing with a single dose of 5 mg/kg/day for the remaining 4 days.

Streptococcal pharyngitis in children over 2 years, 10 mg/kg or 20 mg/kg for 3 days, without exceeding the maximum daily dose of 500 mg.

The dosing schedule according to weight is as follows:

Weight (kg)	**Dosing schedule 1**	**Dosing schedule 2**	**Size of bottle (mL)**
<15*	Administer 10 mg/kg per day in a single dose.	*Day 1*: administer 10 mg/kg in a single dose *Days 2-5*: administer 5 mg/kg in a single dose	15 mL
15-25	200 mg (5 mL) in a single dose	*Day 1*: 200 mg (5 mL) in a single dose *Days 2-5*: 100 mg (2.5 mL) in a single dose	15 mL
26-35	300 mg (7.5 mL) in a single dose	*Day 1*: 300 mg (7.5 mL) in a single dose *Days 2-5*: 175 mg (3.75 mL) in a single dose	30 mL
36-45	400 mg (10 mL) in a single dose	*Day 1*: 400 mg (10 mL) in a single dose *Days 2-5*: 200 mg (5 mL) in a single dose	30 mL
>45	Adult dose	Adult dose	37.5 mL

*The dose for children weighing under 15 kg should be measured as accurately as possible.

Elderly patients

For elderly patients, the same dose as for adults can be administered. As elderly patients may have arrhythmogenic conditions, particular caution is recommended due to the risk of developing cardiac arrhythmia and *torsades de pointes* (see section 4.4).

Patients with renal insufficiency
Dose adjustment is not required in patients with mild to moderate renal insufficiency (glomerular filtration rate of 10–80 mL/min) (see section 4.4).

Patients with liver failure
Dose adjustment is not necessary in patients with mild to moderate liver failure (Child-Pugh class A or B) (see section 4.4).

Method of administration:
For oral administration.

Zithromax 500 mg tablets
This medicinal product should be administered as a single daily dose. The tablets must be swallowed whole with water and may be taken with or without food.

Zithromax 250 mg hard capsules
This medicinal product should be administered as a single daily dose. The hard capsules must be swallowed whole with water at least 1 hour before or 2 hours after eating. Taking the capsules with food reduces bioavailability by 50%.

Zithromax 200 mg/5 mL powder for oral suspension in bottle
Reconstitute before use. For reconstitution instructions before administration, see section 8.4. Reconstitution produces an almost white suspension with a cherry/banana and vanilla aroma. This medicinal product may be taken with or without food.

Zithromax 250 mg, 500 mg, 1,000 mg powder for oral suspension in sachets
This medicinal product should be administered as a single daily dose. Add the contents of the sachet to a glass containing a small amount of water and mix well. The reconstituted suspension must be swallowed immediately with or without food.

4.3 Contraindications

Hypersensitivity to azithromycin, erythromycin, any other macrolide or ketolide antibiotics, or to any of the excipients listed in section 2.

4.4 Special Warnings and Precautions for Use

Allergic reactions

As with erythromycin and other macrolides, on rare occasions severe allergic reactions, including angioedema and anaphylaxis (rarely fatal), and dermatologic reactions such as acute generalised exanthematous pustulosis (AGEP) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with

azithromycin have resulted in recurrent symptoms which have required a prolonged period of observation and treatment.

If an allergic reaction occurs, the medicinal product should be discontinued, and appropriate therapy should be instituted. Doctors should be aware that the allergic symptoms may reappear when symptomatic treatment is discontinued.

Hepatotoxicity

Since the liver is the principal route of elimination of azithromycin, azithromycin should be used with caution in patients with significant liver disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported (see section 4.8). Some patients may have a pre-existing liver disease or may have taken other hepatotoxic medicinal products.

If the signs and symptoms of liver dysfunction appear, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests should be performed immediately. Azithromycin administration should be discontinued if liver dysfunction or the signs and symptoms of liver dysfunction appear.

Ergotamine derivatives

In patients receiving ergotamine derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There is no data concerning the possibility of an interaction between ergotamine and azithromycin. However, because of the theoretical possibility of developing ergotism, azithromycin and ergotamine derivatives should not be coadministered.

Superinfection

As with other antibiotics, vigilance for signs of super-infection with non-susceptible microorganisms, 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. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

Clostridium difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *Clostridium difficile* cause an increase in morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require a colectomy. CDAD must be considered in all patients who present with diarrhoea after antibiotic treatment. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Renal insufficiency

In patients with severe renal insufficiency (glomerular filtration rate <10 mL/min) a 33% increase in systemic exposure to azithromycin has been observed (see section 5.3). Azithromycin should therefore be used with caution in these patients.

QT interval prolongation

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been observed in treatment with macrolides, including azithromycin (see section 4.8). Therefore since the following situations can lead to an increased risk of ventricular arrhythmia (including *torsades de pointes*), which can cause a cardiac arrest, azithromycin must be used with caution in patients with pre-existing arrhythmia disorders (especially in women and elderly patients), such as patients:

- with congenital or documented QT interval prolongation.
- who are currently receiving treatment with other active substances that may prolong QT interval such as class IA (quinidine and procainamide) and class III antiarrhythmics (dofetilide amiodarone and sotalol), cisapride terfenadine, antipsychotic agents (such as pimozide), antidepressants (such as citalopram) and anti-infective agents (fluoroquinolones such as moxifloxacin or levofloxacin and chloroquine).
- with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia.
- with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

The following recommendations should be considered before prescribing azithromycin:

Azithromycin film-coated tablets and hard capsules are not suitable for the treatment of severe infections which rapidly require a high concentration of the antibiotic in the blood.

In areas of elevated erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other macrolides.

Paediatric population
The safety and efficacy of azithromycin in the prevention of treatment of *Mycobacterium avium* complex (MAC) infection has not been established in children.

Infantile hypertrophic pyloric stenosis (IHPS) has been reported following the use of azithromycin in neonates (treatment up to 42 days old). Parents and carers must be told to contact their doctor if vomiting or irritability on feeding occur.

Zithromax 500 mg tablets contain lactose

Patients with a hereditary galactose intolerance, Lapp lactase deficiency (deficiency observed in some Lapp populations) or glucose-galactose malabsorption should not take this medicinal product.

Zithromax 250 mg hard tablets contain lactose

Patients with a hereditary galactose intolerance, Lapp lactase deficiency (deficiency observed in some Lapp populations) or glucose-galactose malabsorption should not take this medicinal product.

Zithromax 200 mg/5 mL powder for oral suspension in bottle contains sucrose, glucose and ethanol.

This medicinal product contains sucrose. Patients with a hereditary fructose intolerance (HFI), glucose-galactose absorption problems or sucrase-isomaltase deficiency should not take this medicinal product.

This medicinal product contains glucose. Patients with glucose-galactose absorption problems should not take this medicinal product.

This medicinal product contains 0.012% ethanol (alcohol) corresponding to 0.59 mg/5 mL of oral suspension.

Zithromax powder for oral suspension in sachets contains sucrose, glucose and ethanol.

Zithromax 250 mg powder for oral suspension

This medicinal product contains sucrose. Patients with a hereditary fructose intolerance (HFI), glucose-galactose absorption problems or sucrase-isomaltase deficiency should not take this medicinal product.

This medicinal product contains glucose. Patients with glucose-galactose absorption problems should not take this medicinal product.

This medicinal product contains 0.03% ethanol (alcohol) corresponding to 0.38 mg per sachet.

Zithromax 500 mg powder for oral suspension

This medicinal product contains sucrose. Patients with a hereditary fructose intolerance (HFI), glucose-galactose absorption problems or sucrase-isomaltase deficiency should not take this medicinal product.

This medicinal product contains glucose. Patients with glucose-galactose absorption problems should not take this medicinal product.

This medicinal product contains 0.03% ethanol (alcohol) corresponding to 0.76 mg per sachet.

Zithromax 100 mg powder for oral suspension

This medicinal product contains 9,642.43 mg of sucrose. Patients with a hereditary fructose intolerance (HFI), glucose-galactose absorption problems or sucrase-isomaltase deficiency should not take this medicinal product.

Patients with diabetes mellitus should take into account that this medicinal product contains 9,642.43 mg of sucrose per sachet.

This medicinal product contains glucose. Patients with glucose-galactose absorption problems should not take this medicinal product.

This medicinal product contains 0.03% ethanol (alcohol) corresponding to 1.51 mg per sachet.

This medicinal product contains 0.003% (w/w) ethanol (alcohol) corresponding to 0.38 mg, 0.76 mg and 1.51 mg for each 250 mg, 500 mg and 1,000 mg sachet respectively.

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 observed although peak plasma concentrations were reduced by approximately 25%. Patients in treatment with oral azithromycin and antacids should not take the medicinal products simultaneously.

Cetirizine

In healthy volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state did not produce any pharmacokinetic interaction or significant changes in the QT interval.

Didanosine

Coadministration of daily doses of 1,200 mg/day of azithromycin with 400 mg/day of 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 of serum digoxin levels, is necessary during treatment with azithromycin and after its discontinuation.

Zidovudine

Single 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin had a slight effect on the plasma pharmacokinetics and urinary excretion of zidovudine or its glucuronide metabolite. However, the 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.

Medicinal products which are known to prolong the QT interval

Azithromycin must be used with caution in patients being treated with medicinal products which are known to prolong the QT interval, cisapride, terfenadine, class IA and III antiarrhythmics, tricyclic antidepressants, antipsychotics and some anti-infective agents due to the increased risk of ventricular arrhythmia (see section 4.4).

Ergotamine derivatives

There is a theoretical possibility of interaction between azithromycin and ergotamine derivatives (see section 4.4) and therefore their concomitant use is not recommended.

Cytochrome P450

Azithromycin does not interact significantly with the hepatic cytochrome P450 enzyme system. It appears there are no pharmacokinetic drug interactions like those observed with erythromycin and other macrolides. Hepatic cytochrome P450 induction and inactivation *via* cytochrome-metabolite complex do not occur with azithromycin.

Pharmacokinetic studies have been conducted between azithromycin and the following medicinal products 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). However, post-marketing cases of rhabdomyolysis have been reported in patients receiving azithromycin with statins.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effects on the plasma levels of carbamazepine or its active metabolite were observed in patients concomitantly receiving azithromycin.

Cimetidine

No alterations in azithromycin pharmacokinetics were observed in a study investigating the effects of a single dose of cimetidine (administered 2 hours before azithromycin). Therefore, this medicinal product can be administered concomitantly with azithromycin.

Coumarin-type oral anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. There have been reports in the post-marketing period of potentiated anticoagulation after the coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, close monitoring of the prothrombin time is therefore recommended when azithromycin is used in patients treated with coumarin-type oral anticoagulants.

Cyclosporin

In a pharmacokinetic study with healthy volunteers who were administered a 500 mg/day oral dose of azithromycin for 3 days followed by a single 10 mg/kg oral dose of cyclosporin, significant increases in cyclosporin C_{max} and AUC_{0-5} were observed. Consequently, caution should be exercised when administering these medicinal products concomitantly. If coadministration of these medicinal products is necessary, cyclosporin plasma levels should be monitored and the dose adjusted accordingly.

Efavirenz

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

Fluconazole

Coadministration of a single dose of 1,200 mg of azithromycin did not alter the pharmacokinetics of a single dose of 800 mg of fluconazole. The 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 1,200 mg of azithromycin had no statistically significant effect on the pharmacokinetics of 800 mg of indinavir administered 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 dose of 15 mg of midazolam.

Nelfinavir

The administration of 1,200 mg of azithromycin during steady-state nelfinavir (750 mg three times daily) produced an increase in azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required when they are administered concomitantly.

Rifabutin

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either medicinal product.

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

Sildenafil

In 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 main circulating metabolite.

Terfenadine

Pharmacokinetic studies have not reported any 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 was no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline were coadministered to healthy volunteers.

Triazolam

In 14 healthy volunteers, the administration of azithromycin 500 mg (Day 1) and 250 mg (Day 2) with 0.125 mg of triazolam (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 (160 mg/800 mg) for 7 days with 1,200 mg of azithromycin on day 7 had no significant effect on peak concentrations, total exposure or urinary elimination of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

4.6 Use in Special Populations

Pregnancy

There are insufficient data on the use of azithromycin in pregnant women. In reproductive toxicity studies in animals, azithromycin was shown to cross the placenta, but no teratogenic effects were observed. The safety of using the active substance azithromycin during pregnancy has not been confirmed. Therefore, azithromycin should only be used during pregnancy if the benefit outweighs the risk.

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.

Fertility

In fertility studies conducted in rats, reduced pregnancy rates were observed following the administration of azithromycin. The clinical relevance of this finding in humans is unknown.

4.7 Effects on Ability to Drive and Use Machines

Zithromax has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects

The table below lists the adverse reactions identified during clinical trials and post-marketing surveillance (in italics) according to the MedDRA system organ class convention. Within each frequency group they have been ordered according to their clinical importance. The frequencies have been defined as: 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 group, 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

MedDRA system organ class	**Very common (≥1/10)**	**Common (≥1/100, <1/10)**	**Uncommon (≥1/1,000, <1/100)**	**Rare (≥1/10,000, <1/1,000)**	**Not known (cannot be estimated from available data)**
Infections and infestations			Candidiasis, *vaginal infection,* pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis		Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders			Leukopaenia, neutropaenia, eosinophilia		*Thrombocytopaenia*, haemolytic anaemia
Immune system disorders			Angioedema, hypersensitivity		*Anaphylactic reaction* (see section 4.4)
Metabolism and nutrition disorders			*Anorexia*		
Psychiatric disorders			*Nervousness*, insomnia	*Agitation*	*Aggression, anxiety,* deliria, hallucination
Nervous system disorders		*Headache*	*Dizziness, somnolence, dysgeusia, paraesthesia*		*Syncope, convulsions, hypoaesthesia, psychomotor hyperactivity, anosmia, ageusia, parosmia,* myasthenia gravis (see section 4.4)
Eye disorders			Visual disturbance		

Ear and labyrinth disorders			*Deafness*, ear disorder, *vertigo*		*Hearing impairment, including deafness, tinnitus*
Cardiac disorders			*Palpitations*		*Torsades de pointes* (see section 4.4), *arrhythmia* (see section 4.4) *including ventricular tachycardia, QT interval prolongation in the ECG* (see section 4.4)
Vascular disorders			Hot flushes		*Hypotension*
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis		
Gastrointestinal disorders	*Diarrhoea*	*Vomiting*, abdominal pain, nausea	*Constipation*, dysphagia, flatulence, *dyspepsia*, gastritis, abdominal distension, dry mouth, belching, mouth ulcers, salivary hypersecretion		*Pancreatitis*, *change in tongue colour*
Hepatobiliary disorders				Abnormal liver function	*Liver failure (rarely fatal)* (see section 4.4)*, fulminant hepatitis, hepatic necrosis.*
Skin and subcutaneous tissue disorders			*Rash, pruritus, urticaria*, dermatitis, dry skin, hyperhidrosis	*Photosensitivity reactions, drug reaction with eosinophilia and systemic symptoms (DRESS),* acute generalised exanthematous pustulosis (AGEP)	*Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme*
Musculoskeletal and connective tissue disorders			Osteoarthritis, myalgia, back pain, neck pain		*Arthralgia*
Renal and urinary disorders			Dysuria, renal pain		*Acute kidney failure, interstitial nephritis*
Reproductive system and breast disorders			Metrorrhagia, testicular disorder		

General disorders and administration site conditions			*Oedema, asthenia, general illness, fatigue*, face oedema, chest pain, pyrexia, pain, peripheral oedema		
Investigations		Decreased lymphocyte count, increased eosinophil count, decreased blood bicarbonate, increased basophils, increased monocytes, increased neutrophils	Increased aspartate aminotransferase, alanine aminotransferase, increased urea and creatinine in blood , hyperbilirubinaemia, abnormal blood potassium, increased blood alkaline phosphatase, increased chloride, increased glucose, increased platelets, decreased hematocrit, increased bicarbonate, abnormal sodium		
Injury, poisoning and procedural complications			Post-procedural complications		

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.

4.9 Overdose

Adverse reactions experienced at higher than recommended doses were very 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 activated carbon, general symptomatic measures and general supportive measures for vital functions are indicated..

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

Pharmacotherapeutic group: antibacterials for systemic use: macrolides. ATC code: J01FA10

Azithromycin is the first of a subclass of the macrolide antibiotics, known as azalides.

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

Azithromycin binds to the 23S ribosomal RNA (rRNA) of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis.

5.2 Pharmacodynamic Properties

Generally, the resistance of different species of bacteria to macrolides occurs via three mechanisms associated with alteration of the site of action, modification of the antibiotic or alteration of antibiotic transport (efflux pump). The efflux pump in streptococci corresponds to the presence of *mef* genes and leads to limited resistance to macrolides (M phenotype). Modification in the target is controlled by methylases encoded by *erm* genes.

Mechanism of Resistance:

The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are alteration of the site of action (often by methylation of 23S rRNA) and the efflux pump. The appearance of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, group A beta-haemolytic streptococci, *Enterococcus* spp. and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).

Penicillin-susceptible strains of *S. pneumoniae* are more likely to be susceptible to azithromycin than penicillin-resistant strains of *S. pneumoniae*. Methicillin-resistant *S. aureus* (MRSA) is less likely to be susceptible to azithromycin than methicillin-susceptible strains of *S. aureus* (MSSA).

The induction of significant resistance in both *in vitro* and *in vivo* models is rare, with the increase in dilution in MIC for *S. pyogenes, H. influenzae* and *Enterobacteriaceae* =1, while after 9 sub-lethal doses of active substance and three increases in dilution for *S. aureus* the development of *in vitro* resistance caused by mutation is rare.

Breakpoints

Criteria for susceptibility to azithromycin for typical bacterial pathogens based on the minimum inhibitory concentration (MIC) according to EUCAST [European Committee on Antimicrobial Susceptibility Testing, v 6.0 (01.01.2016)] are listed in the table below:

	MIC (mg/L)	
	Susceptible	**Resistant**
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (groups A, B, C and G)	≤ 0.25	> 0.5
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.125	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

The prevalence of acquired resistance may vary geographically and with time and therefore local information about the resistance is desirable for selected species, particularly when treating severe infections. If necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the medicinal product is questionable in some types of infection.

Species for which acquired resistance may be a problem: the prevalence of resistance is equal to or greater than 10% in at least one country in the European Union.

Table: Antibacterial spectrum for azithromycin.

Commonly susceptible species

Gram-positive aerobic microorganisms
Corynebacterium diphtheriae
Streptococcus pneumoniae
susceptible to erythromycin
susceptible to penicillin
Streptococcus pyogenes
susceptible to erythromycin

Gram-negative aerobic microorganisms
Bordetella pertussis
Escherichia coli (ETEC)
Escherichia coli (EAEC)
Haemophilus influenzae
Haemophilus ducreyi
Legionella spp.
Moraxella catarrhalis
susceptible to erythromycin
intermediate susceptibility to erythromycin
Pasteurella multocida

Anaerobic microorganisms
Fusobacterium nucleatum
Fusobacterium necrophorum
Prevotella spp.
Porphyromonas spp.
Propionibacterium spp.

Other microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Listeria spp.
Mycobacterium avium complex
Mycoplasma pneumoniae
Ureaplasma urealyticum

Species for which acquired resistance may be a problem
Gram-positive aerobic microorganisms
Staphylococcus aureus
susceptible to methicillin
Coagulase-neg. *Staphylococci*
susceptible to methicillin+
Streptococcus pneumoniae
intermediate susceptibility to penicillin
resistant to penicillin
intermediate susceptibility to erythromycin
Streptococcus pyogenes
intermediate susceptibility to erythromycin
Viridans streptococci
intermediate susceptibility to penicillin

Gram-negative aerobic microorganisms
Moraxella catarrhalis
resistant to erythromycin
Neisseria gonorrhoeae

Anaerobic microorganisms
Peptostreptococcus spp.

Inherently resistant organisms

Gram-positive aerobic microorganisms
Corynebacterium spp.
Enterococcus spp.
Staphylococci MRSA, MRSE
Streptococcus pneumoniae
resistant to erythromycin
resistant to penicillin and erythromycin
Streptococcus pyogenes
resistant to erythromycin
Viridans streptococci
resistant to penicillin
resistant to erythromycin

Gram-negative aerobic microorganisms
Pseudomonas aeruginosa

Anaerobic microorganisms
Bacteroides fragilis group

+ Resistance over 50%

5.3 Pharmacokinetic Properties

Absorption

The bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are reached after 2-3 hours.

Distribution

Orally administered azithromycin is widely distributed throughout the body. Pharmacokinetic studies have demonstrated that tissue concentrations of azithromycin are considerably higher than plasma concentrations (up to 50 times the observed peak plasma concentration). This indicates that azithromycin binds broadly to tissues (steady-state distribution volume is approximately 31 l/kg).

The average peak plasma concentration (C_{max}) after administration of a single 500 mg dose is approximately 0.4 µg/mL, 2-3 hours after administration. There is no accumulation in the plasma/serum at the recommended dose. Accumulation occurs in the tissues where levels are much greater than in plasma/serum. Three days after the administration of 500 mg as a single dose or in divided 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 were measured in lung, prostate, tonsil and plasma, respectively.

Peak average concentrations measured in peripheral leucocytes are greater than the MIC90 of the most common pathogens.

In experimental *in vitro* and *in vivo* studies, azithromycin accumulates in phagocytes. Release is promoted by active phagocytosis. In animal models, this process seems to contribute to the accumulation of azithromycin in tissue. Binding of azithromycin to plasma proteins in serum is variable and ranges from 52% at 0.005 µg/mL to 18% at 0.5 µg/mL, depending on the serum concentration.

Biotransformation and Elimination

The plasma terminal 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 in the urine over a period of 3 days, the majority 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 along with 10 metabolites (formed by N- and O-demethylation, by hydroxylation of the desosamine and glucose rings, or by hydrolysis of the cladinose conjugate). A comparison of HPLC methods and a microbiological assay suggests that the metabolites do not play a significant role in the microbiological activity of azithromycin.

Pharmacokinetics in Special Populations

Elderly

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

In elderly volunteers (>65 years), higher (29%) AUC values than in younger volunteers (<45 years) were always observed after a 5-day treatment. However, these differences are not regarded as clinically relevant; dose adjustment is therefore not recommended.

Renal insufficiency

Following a single oral dose of 1 g of azithromycin, the mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively, in subjects with mild to moderate renal insufficiency (glomerular filtration rate of 10-80 mL/min) compared with normal renal function (glomerular filtration rate >80 mL/min). In subjects with severe renal insufficiency (glomerular filtration rate <10 mL/min), the mean C_{max} and AUC_{0-120} increased by 61% and 35%, respectively, compared to normal values (see section 4.2).

Liver failure

In patients with mild to moderate liver failure, there is no evidence of marked changes in the serum pharmacokinetics of azithromycin compared to that of patients with normal liver function. In these patients, the urinary recovery of azithromycin appears to increase, possibly to compensate for the reduction in hepatic clearance. There are no data regarding the use of azithromycin in more severe cases of liver failure (see section 4.2).

Paediatric population

The pharmacokinetics have been studied in children from 4 months to 15 years old who took capsules, granules or suspension. The C_{max} obtained with 10 mg/kg on day 1 followed by 5 mg/kg on days 2 to 5 was slightly less than that of adults with 224 µg/L after 3 days in children from 0.6 to 5 years and 383 µg/L in children between 6 and 15 years. The $t_{1/2}$ at 36 h in older children was within the range expected for adults (see section 4.2).

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

In animal studies using exposures 40 times greater than those reached with clinical therapeutic doses, azithromycin was observed to cause reversible phospholipidosis, but as a general rule there were no associated toxicological consequences. The relevance of this finding for humans taking azithromycin in accordance with the recommendations is unknown.

Electrophysiological studies have shown that azithromycin prolongs the QT interval.

Carcinogenic potential

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential

There is no evidence of a potential for genetic and chromosomal mutations in *in vivo* and *in vitro* models.

Reproductive toxicity

No teratogenic effects were observed in embryotoxicity studies in rats after the oral administration of azithromycin. In rats, azithromycin doses of 100 and 200 mg/kg of bodyweight/day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations have been observed after the administration of 50 mg/kg/day of azithromycin.

7. DESCRIPTION

Trulimax 250 mg: Smooth, well-formed white to off white film coated, oval shaped tablet with "T 250" debossed on one side and plain on the other side.

Trulimax 500 mg: Smooth, well-formed white to off white film coated, oval shaped tablet with "T 500" debossed on one side and break line on the other side.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

24 Months.

8.3 Packaging Information

Trulimax 250 mg: 0.02 mm Alufoil- 0.250 mm clear PVC blister containing 6 Tablets.

Trulimax 500 mg: 0.02 mm Alufoil- 0.250 mm clear PVC blister containing 3 Tablets.

8.4 Storage and Handling Instructions

Store below 30°C.

Instruction for Use/Handling

The tablets should be swallowed whole.

9. PATIENT COUNSELLING INFORMATION

Azithromycin tablets can be taken with or without food. Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously. The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur. Patients should be counseled that antibacterial drugs including azithromycin should only be used to treat bacterial

infections. They do not treat viral infections (e.g., the common cold). When azithromycin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by azithromycin or other antibacterial drugs in the future. Diarrhea is a common problem caused by antibacterials which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

10. DETAILS OF MANUFACTURER

Pfizer Limited
Plot No. L-137, Phase III-A,
Verna Industrial Estate, Verna,
Goa - 403 722

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Marketing Authorization no. MF-17/2013 dated 06-Mar-2013

12. DATE OF REVISION

November 2020