SCHEDULING STATUS: S4

PROPRIETARY NAME AND DOSAGE FORM:

ZITHROMAX 500 mg Tablets

ZITHROMAX IV Powder for solution for infusion

COMPOSITION:

Each ZITHROMAX 500 mg tablet contains azithromycin dihydrate equivalent to 500 mg azithromycin base.

Each ZITHROMAX IV vial contains 500 mg of azithromycin (as the dihydrate), providing 100 mg/ml solution following reconstitution.

Inactive excipients:

ZITHROMAX 500 mg tablets contain pregelatinised starch, calcium phosphate dibasic anhydrous, croscarmellose sodium, magnesium stearate/sodium lauryl sulphate blend and film-coated with white Opadry® which contains lactose, hydroxypropyl methylcellulose, triacetin and titanium dioxide.
Contains sugar (lactose).

ZITHROMAX IV contains citric acid and sodium hydroxide.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Mode of action:

Azithromycin is an azalide, a subclass of the macrolide antibiotics. Chemically it is derived by insertion of a nitrogen atom into 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.

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

Cardiac electrophysiology:

QTc interval-prolongation was studied in a randomised, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1 000 mg) alone or in combination with azithromycin (500 mg, 1 000 mg, and 1 500 mg once daily). Coadministration of azithromycin significantly increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95 % upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1 000 mg and 1 500 mg azithromycin, respectively.

Mechanism of resistance:

The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

Efflux pumps occur in a number of bacteria, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher MICs) and staphylococci. In streptococci and enterococci, an efflux pump that recognises 14 - and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef*(A) genes.

Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive organisms. Ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in *viridans streptococci* and in *Streptococcus agalactiae.*

Azithromycin has *in vitro* activity against:

Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible organisms).

Aerobic and facultative Gram-negative bacteria.

In vitro resistance to azithromycin*:*

Azithromycin-resistant organisms are encountered relatively frequently among aerobic and facultative Gram-positive bacteria, in particular among methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae* (PRSP).

Pseudomonas spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* , . . *Pneumocystis jirovecii* and *Toxoplasma gondii* infections*.*

In vitro sensitivity does not necessarily imply *in vivo* efficacy.

Pharmacokinetic properties:

Absorption:

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37 %. No significant decrease in bio-availability was observed when azithromycin was administered with a meal. The time taken to peak plasma levels is 2 - 3 hours.

In patients hospitalised with community acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/ml, the mean Cmax ± S.D. achieved was 3,63 ± 1,60 μg/ml, while the 24-hour trough level was 0,20 ± 0,15 μg/ml, and the AUC_{24} was 9,60 ± 4,80 μg·h/ml.

The mean C_{max}, 24-hour trough and AUC_{24} values were 1,14 ± 0,14 μg/ml, 0,18 ± 0,02 μg/ml, and 8,03 ± 0,86 μg· h/ml, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml.

Distribution:

Kinetic studies of variable times ranging from hours to days after oral intake have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the medicine is highly tissue bound. Concentrations in target tissues such as lung, tonsil and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

Elimination:

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. Approximately 12 % of an intravenously administered dose is excreted in the urine over 3 days as azithromycin, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged medicine following oral administration. Very high concentrations of unchanged medicine have been found in human bile, together with 10 metabolites, formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

In a multiple-dose study in 12 normal volunteers utilising a 500 mg (1 mg/ml) one-hour intravenous-dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11 % after the 1st dose and 14 % after the 5th dose. These values are greater than the reported 6 % excreted unchanged in urine after oral administration of azithromycin.

Pharmacokinetics in special patient groups:

Renal impairment:

The pharmacokinetics of azithromycin in adult patients with mild-to-moderate renal impairment (GFR 10 – 80 ml/min) were not affected following a single 1 g dose of immediate release azithromycin. Statistically significant differences in AUC_{0-120} (8,8 mg × hr/ml vs. 11,7 mg × hr/ml), C_{max} (1,0 mg/ml vs. 1,6 mg/ml) and CLr (2,3

ml/min/kg vs. 0,2 ml/min/kg) were observed between the group with severe renal impairment (GFR < 10 ml/min) and the group with normal renal function.

Hepatic impairment:

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. The urinary clearance of azithromycin appears to increase in these patients, perhaps to compensate for reduced hepatic clearance. Azithromycin has not been studied and should not be used in patients with severe hepatic impairment.

Elderly:

Elderly volunteers (> 65 years) had slightly higher AUC values than in young volunteers (< 40 years) after a 5-day regimen, but these are not considered clinically significant, and hence no dose adjustment is recommended.

INDICATIONS:

Adults:

ZITHROMAX tablets are indicated for mild to moderate infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis due to *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae* or *Staphylococcus aureus* and pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae*; uncomplicated skin and soft tissue infections; sinusitis due to *Haemophilus influenzae, Streptococcus pneumoniae* or *Staphylococcus aureus*; and as an alternative to first line therapy of pharyngitis/tonsillitis.

ZITHROMAX IV is indicated for the treatment of community acquired pneumonia caused by susceptible organisms, including *Legionella pneumophila*, in patients who require initial intravenous therapy.

Zithromax IV should only be used when the oral route is not suitable.

In sexually transmitted diseases in men and women, ZITHROMAX tablets are indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis* and chancroid due to *Haemophilus ducreyi*.

Children 1 year and over:

ZITHROMAX tablets are indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms in children over 45 kg (ZITHROMAX suspension is recommended in children under 45 kg).

The safety and effectiveness of ZITHROMAX IV for the treatment of infections in children has not been established.

CONTRAINDICATIONS:

ZITHROMAX is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin, any of the macrolide antibiotics, or to any excipient listed under COMPOSITION.

Because of the theoretical possibility of ergotism, ZITHROMAX and ergot derivatives should not be co-administered.

Use in hepatic impairment:

As the liver is the principal route of excretion of ZITHROMAX, it should not be prescribed in patients with hepatic disease.

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity:

Serious allergic reactions, including angioedema and anaphylaxis and dermatologic reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported. Some of these reactions with ZITHROMAX have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, ZITHROMAX should be discontinued and appropriate therapy should be instituted. Medical practitioners to 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 ZITHROMAX should be undertaken with caution in patients with hepatic disease (see CONTRAINDICATIONS).

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure, some of which have resulted in death, have been reported. Discontinue ZITHROMAX immediately if signs and/or symptoms of hepatitis occur.

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 ergot and ZITHROMAX. However, because of the theoretical possibility of ergotism, ZITHROMAX and ergot derivatives should not be co-administered (see CONTRAINDICATIONS).

Superinfection:

Observation for signs of superinfection with non-susceptible organisms, including fungi, is recommended.

Pseudomembranous colitis:

Pseudomembranous colitis has been reported and may range in severity from mild to life-threatening. Therefore it is important to consider this diagnosis in patients with diarrhoea subsequent to administration of ZITHROMAX.

***Clostridium difficile*-associated diarrhoea:**

Clostridium difficile-associated diarrhoea (CDAD) due to overgrowth of *Clostridium difficile* in the gut, has been reported with use of ZITHROMAX, and may range in severity from mild diarrhoea to fatal colitis.

If CDAD is suspected or confirmed, ongoing ZITHROMAX use should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated.

Renal impairment:

In patients with a creatinine clearance < 30, a 33 % increase in systemic exposure to ZITHROMAX was observed (see PHARMACOLOGICAL ACTION). Acute renal failure and interstitial nephritis have been reported (see SIDE EFFECTS).

Prolongation of the QT interval:

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac dysrhythmia and Torsade de Pointes, have been seen in treatment with other macrolides including ZITHROMAX (see SIDE EFFECTS).

Prescribers should specifically consider the risk of QT prolongation, which can be fatal in at-risk groups including:

- Patients with congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval such as antidysrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- Patients with clinically relevant bradycardia, cardiac dysrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to medicine-associated effects on the QT interval

Use in children under 1 year of age:

The safety and efficacy of oral ZITHROMAX preparations in children less than 1 year have not been established.

The safety and effectiveness of ZITHROMAX IV for the treatment of infections in children has not been established.

Intravenous administration:

Azithromycin powder for solution for infusion should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. Do not administer as an intravenous bolus or an intramuscular injection (see DOSAGE AND DIRECTIONS FOR USE).

All volunteers who received infusate concentrations above 2,0 mg/ml experienced local infusion site reactions and therefore, higher concentrations should be avoided.

Lactose intolerance:

ZITHROMAX contains lactose monohydrate and should not be given to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Effects on ability to drive and use machines:

Side effects such as dizziness, convulsions, vertigo, somnolence, and syncope have been reported with usage of ZITHROMAX. These side effects may affect a patient's ability to drive or operate machinery.

INTERACTIONS:

Ergot derivatives:

Because of the theoretical possibility of ergotism, ZITHROMAX and ergot derivatives should not be coadministered (see CONTRAINDICATIONS and WARNINGS AND SPECIAL PRECAUTIONS).

Cetirizine:

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

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to be associated with the pharmacokinetic medicine interactions seen with erythromycin. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Pharmacokinetic studies have been conducted between azithromycin and the following medicines 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 in patients receiving azithromycin with statins have been reported.

Efavirenz:

Coadministration of a 600 mg single dose of 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 1 200 mg ZITHROMAX did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of ZITHROMAX were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18 %) of ZITHROMAX was observed.

Indinavir:

Coadministration of a single dose of 1 200 mg ZITHROMAX had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Midazolam:

In healthy volunteers, coadministration of ZITHROMAX 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetic properties and pharmacodynamic properties of a single 15 mg dose of midazolam.

Nelfinavir:

Coadministration of ZITHROMAX (1 200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased ZITHROMAX concentrations. No clinically significant adverse effects were observed and although a dose adjustment of ZITHROMAX is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of ZITHROMAX is warranted.

Sildenafil:

In normal healthy male volunteers, there was no evidence of an effect of ZITHROMAX (500 mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its major circulating metabolite.

Triazolam:

In 14 healthy volunteers, coadministration of ZITHROMAX 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 (160 mg/800 mg) for 7 days with ZITHROMAX 1 200 mg on day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. ZITHROMAX serum concentrations were similar to those seen in other studies.

Special administration advised with the following:

Antacids:

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with ZITHROMAX, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 24 %. In patients receiving both ZITHROMAX and antacids, the medicines should not be taken simultaneously. ZITHROMAX tablets should be taken at least 1 hour before or 2 hours after an antacid.

Administration of oral antacids is not expected to affect the disposition of ZITHROMAX given intravenously.

Cimetidine:

A single dose of cimetidine administered 2 hours before ZITHROMAX had no effect on the pharmacokinetics of ZITHROMAX.

No pharmacokinetic interactions were reported in studies of ZITHROMAX co-administered with:

Carbamazepine, methylprednisolone, didanosine (dideoxyinosine), theophylline, rifabutin (however coadministration of ZITHROMAX and rifabutin was associated with the development of neutropenia. A causal relationship to its combination with ZITHROMAX has not been established (see SIDE EFFECTS)) and

zidovudine (single 1 000 mg doses and multiple 1 200 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).

Special precautionary monitoring is advised with the following:

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 C_{max} and AUC_{0-5} were found to be significantly elevated (C_{max} increase by 24 % and AUC_{0-5} was 5 107 and 4 210 ngh/ml with and without azithromycin, respectively, $p \leq 0.05$). Consequently, caution should be exercised before co-administration of these two medicines. If coadministration is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

P-glycoprotein substrates:

Concomitant administration of ZITHROMAX with P-glycoprotein substrates such as digoxin or dabigatran, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if ZITHROMAX and P-glycoprotein substrates such as digoxin or dabigatran are administered concomitantly, the possibility of elevated serum medicine concentrations should be considered. Clinical monitoring and serum monitoring of digoxin levels during treatment with ZITHROMAX and after its discontinuation are necessary.

Some of the macrolide antibiotics have been reported to impair the metabolism of digoxin (in the gut) in some patients. Therefore, in patients receiving concomitant ZITHROMAX, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

Warfarin:

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. However there have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of ZITHROMAX and warfarin. Although

a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when ZITHROMAX is used in patients receiving coumarin-type oral anticoagulants.

PREGNANCY AND LACTATION:

The safety and efficacy of ZITHROMAX in pregnancy and lactation have not been established.

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 ZITHROMAX 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, ZITHROMAX should be used during pregnancy only if clearly needed.

Lactation:

ZITHROMAX 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 characterised the pharmacokinetics of ZITHROMAX excretion into human breast milk.

ZITHROMAX should only be used in lactating women where adequate alternatives are not available.

ZITHROMAX IV should only be used in pregnant or lactating women where adequate alternatives are not available.

DOSAGE AND DIRECTIONS FOR USE:

ZITHROMAX tablets:

ZITHROMAX should be administered as a single daily dose with or without food.

ZITHROMAX tablets should be taken whole.

Adults:

For all indications other than sexually transmitted diseases, the total dose is 1,5 g which should be given as 500 mg daily for 3 days.

For sexually transmitted diseases caused by *Chlamydia trachomatis* or *Haemophilus ducreyi*, the dose is 1 g given as a single dose.

For uncomplicated genital infections caused by non-multiresistant *N. gonorrhoea*, the dose is 1 g given as a single oral dose.

Use in the elderly:

Normal adult dosage is recommended. Elderly patients may be more susceptible to development of Torsade de Pointes arrhythmia than younger patients (see WARNINGS AND SPECIAL PRECAUTIONS).

Use in children:

Children over 45 kg - dose as per adults.

This formulation is not suitable for children under 45 kg.

ZITHROMAX IV:

For more severe infections, the recommended dose of ZITHROMAX IV for the treatment of adult patients with community acquired pneumonia requiring hospitalisation due to the indicated organisms is 500 mg as a single daily dose by the intravenous route for at least two days. Intravenous therapy should be followed by azithromycin by the oral route as a single daily dose of 500 mg to complete a 7 to 10 day course of therapy. The timing of the conversion to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

Use in elderly:

No dosage adjustment is necessary in elderly patients requiring ZITHROMAX therapy. Elderly patients may be more susceptible to development of Torsade de Pointes dysrhythmia than younger patients (see WARNINGS AND SPECIAL PRECAUTIONS).

Use in children:

The safety and effectiveness of ZITHROMAX IV for the treatment of infections in children has not been established.

Administration:

ZITHROMAX IV after reconstitution and dilution is for intravenous infusion only.

ZITHROMAX IV should not be given as a bolus or as an intramuscular injection.

The infusate concentration and rate of infusion for azithromycin powder for solution for infusion should be either 1 mg/ml over 3 hours or 2 mg/ml over 1 hour.

Preparation of the solution for intravenous administration is as follows:

Reconstitution:

Prepare the initial solution of azithromycin powder for solution for infusion by adding 4,8 ml of sterilised Water For Injections to the 500 mg vial and shaking the vial until all of the medicine is dissolved. It is recommended that a standard 5 ml (non-automated) syringe be used to ensure that the exact amount of 4,8 ml of sterilised Water for Injections is dispensed. Each ml of reconstituted solution contains 100 mg azithromycin.

The reconstituted infusion should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the solution should be discarded.

Dilute this solution further prior to administration as instructed below:

Dilution:

To provide azithromycin over a concentration range of 1,0 - 2,0 mg/ml, transfer 5 ml of the 100 mg/ml azithromycin solution into the appropriate amount of any of the diluents listed below.

Final infusion solution concentration (mg/ml)	Amount of diluent (ml)
1,0 mg/ml	500 ml
2,0 mg/ml	250 ml

The reconstituted solution can be diluted with:

0,9 % Sodium chloride

0,45 % Sodium chloride

5 % Dextrose in Water

Lactated Ringer's Solution

5 % Dextrose in 0,45 % Sodium chloride with 20 mEq KCl

5 % Dextrose in Lactated Ringer's Solution

5 % Dextrose in 0,3 % Sodium chloride

5 % Dextrose in 0,45 % Sodium chloride

It is recommended that a 500 mg dose of azithromycin powder for solution for infusion, diluted as above, be infused over a period of not less than 60 minutes.

ZITHROMAX IV reconstituted solution may be diluted using the instructions and compatible infusion solutions provided above. Other intravenous substances, additives or medications should not be added to ZITHROMAX IV, or infused simultaneously through the same intravenous line.

SIDE EFFECTS:

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

In clinical trials, the following undesirable effects have been reported. The side effects were categorised utilising the incidence rate as follows:

Common: ≥ 1/100 and < 1/10 (≥ 1 % and < 10 %)

Uncommon: ≥ 1/1 000 and < 1/100 (≥ 0,1 % and < 1 %)

Rare: ≥ 1/10 000 and < 1/1000 (≥ 0,01 % and < 0,1 %)

System organ class	**ZITHROMAX tablets** **Side effects**	**ZITHROMAX IV** **Side effects**
Blood and lymphatic system disorders		

System organ class	**ZITHROMAX tablets** **Side effects**	**ZITHROMAX IV** **Side effects**
Rare	Neutropenia	Neutropenia
Eye disorders		
Rare	Abnormal vision	Abnormal vision
Ear and labyrinth disorders		
Rare	Hearing impairment including hearing loss, deafness and/or tinnitus	Hearing impairment including hearing loss, deafness and/or tinnitus
Cardiac disorders		
Rare	Chest pains, dysrhythmias including ventricular tachycardia, palpitations, QT prolongation, Torsade de Pointes	Chest pains, dysrhythmias including ventricular tachycardia, palpitations, QT prolongation, Torsade de Pointes
Gastrointestinal disorders		
Common	Abdominal discomfort (pain/ cramps), diarrhoea, nausea	Abdominal discomfort (pain/ cramps), diarrhoea, nausea, vomiting
Uncommon	Flatulence, loose stools, vomiting	Flatulence
Rare	Malaena	Loose stools, malaena
Hepatobiliary disorders		
Common		Abnormal liver function

System organ class	**ZITHROMAX tablets** **Side effects**	**ZITHROMAX IV** **Side effects**
Rare	Abnormal liver function	
Skin and subcutaneous tissue disorders		
Uncommon	Rash	Rash
Rare	Allergic reactions, angioedema	Allergic reactions, angioedema
Renal and urinary disorders		
Rare	Nephritis	Nephritis
General disorders and administration site conditions		
Common		Local pain and inflammation at the site of infusion

In post-marketing experience, the following additional undesirable effects have been reported:

System organ class	**ZITHROMAX tablets** **Side effects**	**ZITHROMAX IV** **Side effects**
Infections and infestations	Moniliasis, vaginitis	Moniliasis, vaginitis
Blood and lymphatic system disorders	Thrombocytopenia	Thrombocytopenia

System organ class	**ZITHROMAX tablets** **Side effects**	**ZITHROMAX IV** **Side effects**
Immune system disorders	Anaphylaxis	Anaphylaxis
Metabolism and nutrition disorders	Anorexia	Anorexia
Psychiatric disorders	Nervousness, aggressive reaction, agitation, anxiety	Nervousness, aggressive reaction, agitation, anxiety
Nervous system disorders	Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paraesthesia, somnolence, syncope, taste/smell perversion and/or loss	Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paraesthesia, somnolence, syncope, taste/smell perversion and/or loss
Ear and labyrinth disorders	Deafness, tinnitus, impaired hearing, vertigo	Deafness, tinnitus, impaired hearing, vertigo

System organ class	ZITHROMAX tablets Side effects	ZITHROMAX IV Side effects
Cardiac disorders	Palpitations, dysrhythmias including ventricular tachycardia, QT prolongation, Torsade de Pointes	Palpitations, dysrhythmias including ventricular tachycardia, QT prolongation, Torsade de Pointes
Vascular disorders	Hypotension	Hypotension
Gastrointestinal disorders	Vomiting/ diarrhoea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, tongue discolouration	Vomiting/diarrhoea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, tongue discolouration
Hepatobiliary disorders	Hepatitis and cholestatic jaundice, hepatic necrosis and hepatic failure, which have rarely resulted in death	Hepatitis and cholestatic jaundice, hepatic necrosis and hepatic failure, which have resulted in death
Skin and subcutaneous tissue disorders	Allergic reactions including pruritus, rash, photosensitivity, oedema, urticaria, angioedema, serious skin reactions	Allergic reactions including pruritus, rash, photosensitivity, oedema, urticaria, angioedema, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis

System organ class	ZITHROMAX tablets Side effects	ZITHROMAX IV Side effects
	including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis	
Musculoskeletal disorders	Arthralgia	Arthralgia
Renal and urinary disorders	Interstitial nephritis, acute renal failure	Interstitial nephritis, acute renal failure
General disorders	Asthenia, fatigue, malaise	Asthenia, fatigue, malaise

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. Typical symptoms of overdosage with macrolide antibiotics include hearing loss, severe nausea, vomiting and diarrhoea. Gastric lavage and general supportive measures are indicated.

IDENTIFICATION:

ZITHROMAX 500 mg tablets are oval, white scored film-coated tablets embossed with “ZTM 500” on one side and “PFIZER” on the other side.

ZITHROMAX IV (Powder for solution for infusion) is a white to off-white cake powder. The reconstituted solution is clear and colourless, visually free of undissolved matter and essentially free from particles of foreign matter.

PRESENTATION:

ZITHROMAX 500 mg tablets: PVC blister packs of 2 or 3 tablets in an outer cardboard carton.

ZITHROMAX IV (azithromycin powder for solution for infusion) is packaged in single use 10 ml clear and colourless glass vial and closed with a rubber stopper and aluminium over-seal.

STORAGE INSTRUCTIONS:

ZITHROMAX tablets:

Store at or below 30 °C.

Keep out of reach of children.

ZITHROMAX IV:

Store at or below 25 °C.

Keep out of reach of children.

Keep vial in original packaging until use.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours at 30 °C. When diluted according to the instructions the diluted solution is chemically and physically stable for 24 hours at or below 30 °C or for 7 days if stored under refrigeration (5 °C). However, from a microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution and dilution has taken place in controlled and validated aseptic conditions.

REGISTRATION NUMBER:

ZITHROMAX 500 mg tablets: 31/20.1.1/0045

ZITHROMAX IV: 36/20.1.1/0190

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

Licensed from: Pliva, Zagreb, Croatia

DATE OF PUBLICATION OF THE PACKAGE INSERT:

Date of Registration:

ZITHROMAX 500 mg tablets: 17 June 1997

ZITHROMAX IV: 25 April 2003

Date of last Council approval: 16 October 2018

Zithromax 500 mg tablets:
NAMIBIA: S2
Reg. No.: 04/20.1.1/1251

Zithromax IV:
BOTSWANA: S2
Reg. No.: BOT0300580

Zithromax 500 mg tablets:
ZIMBABWE: PP
Reg. No.: 2001/7.2.5/3954

Zithromax IV:
ZIMBABWE: PP
Reg. No.: 2010/7.2.5/4647

Zithromax IV:
NAMIBIA: S2
Reg. No.: 06/20.1.1/0212

Zithromax 500 mg tablets:
Zambia:
Reg No.: 120/002

Zithromax 500 mg tablets:
BOTSWANA: S2
Reg. No.: BOT9900450