CORE SAFETY PROFILE (CSP)

Active Substance:	Azithromycin
Brand Names:	ZITHROMAX, ZITROMAX, , AZITROCIN, AZITROMAX, AZITROMICINA, AZADOSE, ULTREON, ZITHROMAX RETARD, ZMAX, ZETAMAC, ZITRAVAL, AZITHROMICINE, ZETAMAX
Pharmaceutical form(s)/strength:	250 mg, 500 mg and 600 mg film-coated tablets 250 mg hard capsules 100 mg, 150 mg, 250 mg, 300 mg, 400 mg, 500 mg, 1000 mg and 200 mg/5ml, powder for oral suspension 100 mg/ml and 500 mg/5ml powder for solution for infusion 2 g granules, prolonged release, for oral suspension
P-RMS:	Finland
Date:	28 February 2013
Supersedes:	Version approved on 23rd June 2009

4.2 Posology and method of administration

Do not administer as an intravenous bolus or an intramuscular injection (see Section 4.4 Special Warnings and Special Precautions for Use).

In the Elderly:

The same dosage as in adult patients is used in the elderly. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes. (**see Section 4.4 Special warnings and precautions for use).**

4.3 Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any excipient listed in Section 6.1 (List of excipients).

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

Since 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 (see Section 4.8) 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.

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

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

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which 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. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see Section 5.2 **Pharmacokinetic properties**).

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (See Section 4.8 **Undesirable effects**). Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as

pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

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 safety and efficacy of intravenous azithromycin for the treatment of infections in children has not been established.

Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex in children have not been established.

Intravenous Administration:

Azithromycin for injection 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 Section 4.2 Posology and method of administration and Section 6.6 Instructions for use and handling, and disposal).**

Azithromycin 40 mg/ml powder for oral suspension:

Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.87 g of sucrose.

Azithromycin 40 mg/ml powder for oral suspension contain sucrose (3.87 g / 5 ml of reconstituted suspension). Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Azithromycin capsules:

Azithromycin capsules contain Lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take Azithromycin capsules.

Azithromycin prolonged-release granules:

Azithromycin prolonged-release granules for oral suspension contain 19.36 g of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Azithromycin prolonged-release granules for oral suspension contain 148 mg of sodium.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and

antacids, the drugs should not be taken simultaneously. Co-administration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

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.

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

Digoxin (P-gp substrates): Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

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: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see Section 4.4 **Special warnings and special precautions for use**).

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

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

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

Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of 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.

Cyclosporin: 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 cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

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 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 had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

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

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

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

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

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

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

Terfenadine: Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such

an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

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

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

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

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of azithromycin in pregnant women. In 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.

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.

Fertility

In 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

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

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

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

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to < 1/100)	Rare (≥ 1/10,000 to <1/1,000)	Frequency Not Known
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			Leukopenia Neutropenia Eosinophilia		Thrombocytopenia Haemolytic anaemia
Immune System Disorders			Angioedema Hypersensitivity		Anaphylactic reaction (see section 4.4)
Metabolism and Nutrition Disorders			Anorexia		

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to < 1/100)	Rare (≥ 1/10,000 to <1/1,000)	Frequency Not Known
Psychiatric Disorders			Nervousness Insomnia,	Agitation	Aggression Anxiety Delirium Hallucination
Nervous System Disorders		Headache	Dizziness Somnolence Dysgeusia Paraesthesia		Syncope, convulsion Hypoestheia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see Section 4.4)
Eye Disorders			Visual impairment		
Ear and Labyrinth Disorders			Ear disorder Vertigo		Hearing impairment including deafness and/or tinnitus
Cardiac Disorders			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia (see section 4.4) including ventricular tachycardia Electrocardiogram QT prolonged (see section 4.4)
Vascular Disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea, Epistaxis		
Gastrointestinal Disorders	Diarrhea	Vomiting Abdominal pain Nausea	Constipation Flatulence Dyspepsia, Gastritis dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion		Pancreatitis Tongue discolouration
Hepatobiliary Disorders				Hepatic function abnormal Jaundice cholestatic	Hepatic failure (which has rarely resulted in death) (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and Subcutaneous Tissue Disorders			Rash Pruritus Urticaria, Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction	Stevens-Johnson syndrome Toxic epidermal necrolysis Erythema multiforme

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to < 1/100)	Rare (≥ 1/10,000 to <1/1,000)	Frequency Not Known
Musculoskeletal and Connective Tissue Disorders			Osteoarthritis, Myalgia Back pain Neck pain		Arthralgia
Renal and Urinary Disorders			Dysuria Renal pain		Renal failure acute Nephritis interstitial
Reproductive system and breast disorders			Metrorrhagia, Testicular disorder		
General Disorders and Administration Site Conditions		Injection site pain * Injection site inflammation	Oedema Asthenia Malaise Fatigue Face edema Chest pain Pyrexia Pain Peripheral edema		

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to < 1/100)	Rare (≥ 1/10,000 to <1/1,000)	Frequency Not Known
Investigations		Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline phosphatase increased Chloride increased Glucose increased platelets increased Hematocrit decreased Bicarbonate increased abnormal sodium		
Injury and poisoning			Post procedural complication		

* for powder for solution for infusion only

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

	Very Common (≥1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to < 1/100)**
Metabolism and Nutrition Disorders		Anorexia	
Nervous System Disorders		Dizziness Headache Paraesthesia Dysgeusia	Hypoesthesia
Eye Disorders		Visual impairment	
Ear and Labyrinth Disorders		Deafness	Hearing impaired Tinnitus
Cardiac Disorders			Palpitations
Gastrointestinal Disorders	Diarrhea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools		
Hepatobiliary Disorders			Hepatitis
Skin and Subcutaneous Tissue Disorders		Rash Pruritus	Stevens-Johnson syndrome Photosensitivity reaction
Musculoskeletal and Connective Tissue Disorders		Arthralgia	
General Disorders and Administration Site Conditions		Fatigue	Asthenia Malaise

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.