# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Zithromax 250 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: azithromycin.
The tablets contain azithromycin dihydrate equivalent to 250mg azithromycin.
Also contains lactose.
For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Film-coated Tablet
*Product imported from Greece:*
White, capsule shaped, film-coated tablets engraved ‘Pfizer’ on one side and 'ZTM 250' on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Azithromycin is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see section 5.1 Pharmacodynamic properties):

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see section 4.4 Special warnings and precautions for use, regarding streptococcal infections)
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to *Chlamydia trachomatis.*

Considerations should be given to official guidance regarding the appropriate use of antibacterial agents.

### 4.2 Posology and method of administration

Method of administration

Zithromax should be given as a single daily dose.

In common with many other antibiotics Zithromax tablets may be taken with food.

**Children over 45 kg body weight and adults, including elderly patients:** The total dose of azithromycin is 1500 mg which should be given over three days (500 mg once daily).

In uncomplicated genital infections due to Chlamydia trachomatis, the dose is 1000 mg as a single oral dose.

**In children under 45 kg body weight:**

Zithromax Tablets are not suitable for children under 45 kg.

**Renal failure:**
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 - 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min) (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties).

**Hepatic failure:**
Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin (see Section 4.4 Special warnings and precautions for use).

Zithromax Tablets are for oral administration only.

## 4.3 Contraindications

Zithromax is contra-indicated in patients with hypersensitivity to azithromycin or any of the macrolide or ketolide antibiotics, erythromycin, or to any excipients thereof as (for example) listed in Section 6.1 (List of Excipients).

Zithromax is contra-indicated in patients with serious impairment of hepatic function.

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

## 4.4 Special warnings and precautions for use

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

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation , see section 4.8.
As with any antibiotic, 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 form 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.

Use in renal impairment: In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed, see section 5.2.
Use in hepatic impairment: In patients with mild or moderate hepatic impairment, there is no evidence of marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients urinary recovery of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance. Hence no dose adjustment is recommended for patients with mild to moderate hepatic impairment.
Nonetheless, since the liver is the principal route of elimination for azithromycin, the use of Zithromax should be undertaken with caution in patients with impaired liver function or concomitantly receiving potentially hepatotoxic agents.

Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.87 g of sucrose.
Due to the sucrose content (3.87 g/ 5 ml of reconstituted suspension), this medicinal product is not indicated for persons with fructose intolerance (hereditary fructose intolerance), glucose-galactose malabsorption or saccharase-

isomaltase deficiency.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

**Antacids:** When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma fell by 25%. In patients receiving Zithromax and antacids, Zithromax should be taken at least 1 hour before or 2 hours after the antacid.

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

**Cimetidine:** A single dose of cimetidine administered 2 hours before Zithromax had no effect on the pharmacokinetics of azithromycin.

**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 (by 24% and 21% respectively), however no significant changes were seen in $AUC_{0-\infty}$. Consequently, caution should be exercised before considering co-administration of these two drugs. If coadministration is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

**Digoxin:** 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 and digoxin the possibility of raised digoxin levels should be borne in mind, and digoxin levels monitored.

**Ergot derivatives:** Because of the theoretical possibility of ergotism, Zithromax and ergot derivatives should not be coadministered.

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

**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.

**Terfenadine:** Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other anti-infectives in conjunction with terfenadine, pharmacokinetic interaction studies have been performed. These 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.

As with other macrolides, Zithromax should be administered with caution in combination with terfenadine.

**Theophylline:** Theophylline levels may be increased in patients taking Zithromax.

**Coumarin-type oral anticoagulants:** In a pharmacodynamic interaction study, Zithromax did not alter the anticoagulant effect of a single 15mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration 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.

**Zidovudine:** Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin did not affect 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.

**Didanosine:** Co-administration of daily doses of 1200 mg azithromycin with 400mg didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

**Rifabutin:** Co-administration 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).

**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.

**Trimethoprim/sulfamethoxazole:** Coadministration of trimethoprim/sulfamethoxazole (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

**Use in pregnancy:** Animal reproduction studies have been performed at doses up to moderate maternally toxic dose concentrations. In these studies, no evidence of harm to the foetus due to azithromycin was found. There are no adequate and well controlled studies in pregnant women.

Since animal studies are not necessarily predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

**Use in lactation:** No data on secretion of azithromycin in breast milk are available. As many drugs are excreted in human milk, Zithromax (azithromycin) should not be used in the treatment of lactating women unless the physician feels that the potential benefits justify the potential risks to the infant, and where adequate alternatives are not available.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Zithromax is well tolerated with a low incidence of side-effects.

**Blood and lymphatic system disorders**
*Rare (> 1/10000, < 1/1000)*
Thrombocytopenia. In clinical trials there have been occasional reports of periods of transient, mild neutropenia. However, a causal relationship with azithromycin treatment has not been confirmed.

**Psychiatric disorders**
*Rare (> 1/10000, < 1/1000)*
Agressiveness, agitation, anxiety and nervousness.

**Nervous system disorders**
*Uncommon (> 1/1000, < 1/100)*
Dizziness/vertigo, somnolence, headache, convulsions (which have also been found to be caused by other macrolides), syncope
*Rare (> 1/10000, < 1/1000)*
Paraesthesia, asthenia *and hypoesthesia*
Insomnia and hyperactivity.
There have been rare reports of taste/smell perversion and taste/smell loss during postmarketing surveillance; a causal relationship to azithromycin has not been established.

**Ear and labyrinth disorders**
*Rare (> 1/10000, < 1/1000)*
Macrolide antibiotics have been reported to have caused hearing damage. In some patients receiving azithromycin impaired hearing, deafness and ringing in the ears have been reported. Many of these cases relate to experimental studies in which azithromycin was used at large doses over prolonged periods. According to available follow-up reports, the majority of these problems however were reversible. Vertigo has been observed during postmarketing surveillance.

**Cardiac disorders**
*Rare (> 1/10000, < 1/1000)*
Palpitations and arrythmias including ventricular tachycardia (as seen with macrolides) have been reported. There have been rare reports of QT prolongation and torsades de pointes (see Section 4.4 Special warnings and precautions for use).

**Vascular disorders**
*Rare (> 1/10000, < 1/1000)*
Hypotension.

**Gastrointestinal disorders**
*Common (> 1/100, < 1/10)*
Nausea, vomiting, diarrhoea, abdominal discomfort (pain/cramps).
*Uncommon (> 1/1000, < 1/100)*
Loose stools, flatulence, digestive disorders, anorexia, dyspepsia.
*Rare (> 1/10000, < 1/1000)*
Constipation, discolouration of the tongue, pancreatitis.
Pseudomembranous colitis has been reported.

**Hepatobiliary disorders**
*Rare (> 1/10000, < 1/1000)*
Hepatitis and cholestatic jaundice have been reported, including abnormal liver function test values, as well as rare cases of hepatic necrosis and hepatic dysfunction, which in rare instances have resulted in death.

***Skin and subcutaneous tissue disorders***
*Uncommon (> 1/1000, < 1/100)*
Allergic reactions including pruritus and rash.
*Rare (> 1/10000, < 1/1000)*
Allergic reactions including angioneurotic oedema, urticaria and photosensitivity; serious skin reactions such as erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis.

***Musculoskeletal, connective tissue and bone disorders***
*Uncommon (> 1/1000, < 1/100)*
Arthralgia.

**Renal and urinary disorders**
*Rare (> 1/10000, < 1/1000)*
Interstitial nephritis and acute renal failure.

**Reproductive system and breast disorders**
*Uncommon (> 1/1000, < 1/100)*
Vaginitis.

**General disorders**
*Rare (> 1/10000, < 1/1000)*
Anaphylaxis including oedema (leads in rare cases to death, see section 4.4 Special warnings and precautions for use), candidiasis, fatigue, 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.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Table: Antibacterial spectrum of Azithromycin

| **Commonly susceptible species** |
|---|
| **Aerobic Gram-positive microorganisms** |
| *Staphylococcus aureus*<br>Methycillin-susceptible |
| *Streptococcus pneumoniae*<br>Penicillin-susceptible |
| *Streptococcus pyogenes* **(Group A)** |
| **Aerobic Gram-negative microorganisms** |
| *Haemophilus influenzae*<br>*Haemophilus parainfluenzae* |
| *Legionella pneumophila* |
| *Moraxella catarrhalis* |
| *Pasteurella multocida* |
| **Anaerobic microorganisms** |
| *Clostridium perfringens* |
| *Fusobacterium spp.* |
| *Prevotella spp.* |
| *Porphyromonas spp.* |
| **Other microorganisms** |
| *Chlamydia trachomatis* |
| **Species for which acquired resistance may be a problem** |
| **Aerobic Gram-positive microorganisms** |
| *Streptococcus pneumoniae*<br>Penicillin-intermediate<br>Penicillin-resistant |
| **Inherently resistant organisms** |
| |

| **Aerobic Gram-positive microorganisms** |
|---|
| *Enterococcus faecalis* |
| Staphylococci **MRSA, MRSE*** |
| **Anaerobic microorganisms** |
| Bacteroides fragilis group |

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

## 5.2 Pharmacokinetic properties

Absorption
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2-3 hours after taking the medicinal product.

Distribution
Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.

Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

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

Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O- demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

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

## 5.3 Preclinical safety data

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

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

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

Reproductive toxicity:
In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats,

azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Tablet Core:
Pregelatinised maize starch
Calcium phosphate dibasic anhydrous
Croscarmellose sodium
Sodium laurilsulfate
Magnesium stearate

Film-coating:
Lactose anhydrous
Hypromellose
Titanium dioxide (E171)
Triacetin

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

The shelf-life expiry date of this product shall be the date shown on the blister and outer package of the product on the market in the country of origin.

## 6.4 Special precautions for storage

Do not store above 30°C.

## 6.5 Nature and contents of container

Packs of 6 tablets. Aluminium/PVC blister strip, 6 tablets per strip, 1 strip in a carton box

## 6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

## 7 PARALLEL PRODUCT AUTHORISATION HOLDER

B & S Healthcare
Unit 4, Bradfield Road
Ruislip
Middlesex HA4 0NU
United Kingdom

## 8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1328/168/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th May 2012

## 10 DATE OF REVISION OF THE TEXT