Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azithromycin Pfizer 200 mg/5 ml Powder for Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Following reconstitution as directed, each 5 ml of suspension contains 200 mg azithromycin (as dihydrate).

Excipients with known effect:
Azithromycin Pfizer 200 mg/5 ml Powder for Oral Suspension contains 3.87g sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Oral Suspension.

A dry white powder.

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):

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see section 4.4 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

Posology

Azithromycin Pfizer should be given as a single daily dose.

Azithromycin Pfizer Suspension can be taken with or without 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).

Paediatric population
In children under 45 kg body weight:
Azithromycin Pfizer Suspension should be used for children under 45 kg. There is no information on children less than 6 months of age. The dose in children is 10 mg/kg as a single dose for 3 days.

Up to 15 kg: Measure the dose as closely as possible using 10 ml oral dosing (less than syringe provided. The syringe is graduated in 0.25 ml divisions, 3 years) providing 10 mg of azithromycin in every graduation.

For children weighing more than 15 kg, Azithromycin Pfizer should be administered using the spoon provided according to the following guidance:

15-25 kg: 5 ml (200 mg) given as 1 x 5 ml spoonful, once daily for 3 days. (3-7 years)

26-35 kg: 7.5 ml (300 mg) given as 1 x 7.5 ml spoonful, once daily for 3 days. (8-11 years)

36-45 kg: 10 ml (400 mg) given as 1 x 10 ml spoonful, once daily for 3 days. (12-14 years)

Over 45 kg: Dose as per adults.

See section 6.5, for appropriate pack size to use depending on age/body weight of child.

The specially supplied measure should be used to administer Azithromycin Pfizer Suspension to children.

Renal impairment
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 and section 5.2).

Hepatic impairment
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).

Method of administration
Azithromycin Pfizer Suspension is for oral administration only.

4.3 Contraindications

Hypersensitivity to azithromycin or any of the macrolide or ketolide antibiotics, or to any of the excipients listed in section 6.1.

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

Because of the theoretical possibility of ergotism, Azithromycin Pfizer 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), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with Azithromycin Pfizer 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 depointes, 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 preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity form mild diarrhoea 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Streptococcal infections: Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.

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 Azithromycin Pfizer should be undertaken with caution in patients with impaired liver function or concomitantly receiving potentially hepatotoxic agents.

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

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Azithromycin Pfizer capsules are for oral administration only.

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 Azithromycin Pfizer and antacids, Azithromycin Pfizer 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 Azithromycin Pfizer had no effect on the pharmacokinetics of azithromycin.

Ciclosporin: In a pharmacokinetic study with healthy volunteers who 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 co-administration is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Digoxin: Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. Therefore, in patients receiving concomitant Azithromycin Pfizer, a related azalide antibiotic, 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, Azithromycin Pfizer (azithromycin) and ergot derivatives should not be administered.

Atorvastatin: Co-administration 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).

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

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

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.

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

Theophylline: Theophylline levels may be increased in patients taking Azithromycin Pfizer.

Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, Azithromycin Pfizer did not alter the anticoagulant effect of a single dose of 15 mg warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to 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 six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to 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.).

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 1200 mg azithromycin 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

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 was found. There are no adequate and well controlled studies in pregnant women.

Since animal studies are not necessarily predictive of human response, Azithromycin Pfizer (azithromycin) should be used in pregnancy only if clearly needed.

Breast-feeding
No data on secretion of azithromycin in breast milk are available. As many drugs are excreted in human milk, Azithromycin Pfizer (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 were adequate alternatives are not available.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that Azithromycin Pfizer may have an effect on a patient's ability to drive or use machines.

4.8 Undesirable effects

Azithromycin Pfizer 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)
Aggressiveness, 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 arrhythmias 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).

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, discoloration 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 instances 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 cutaneous adverse reactions such as erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis.
Very Rare (<1/10,000)
DRESS

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), candidiasis, fatigue, malaise.

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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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

General properties
Pharmacotherapeutic group: Antibacterials for systemic use. ATC code: J01FA10

Mode of action:
Azithromycin Pfizer is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to 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. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

Mechanism of resistance:
Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Complete cross resistance exists among *Streptococcus pneumoniae*, betahaemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant S. *aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints
Azithromycin susceptibility breakpoints for typical bacterial pathogens are:

NCCLS:

- Susceptible ≤ 2mg/l; resistant ≥ 8mg/l
- *Haemophilus* spp.: susceptible ≤ 4mg/l
- *Streptococcus pneumoniae* and *Streptococcus pyogenes:*

Susceptible ≤ 0.5 mg/l; resistant ≥ 2 mg/l

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Table: Antibacterial spectrum of Azithromycin

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus Methicillin-susceptible
Streptococcus pneumoniae Penicillin-susceptible
Streptococcus pyogenes **(Group A)**
Aerobic Gram-negative microorganisms
Haemophilus influenzae *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 Penicillin-intermediate Penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci **MRSA, MRSE***
Anaerobic microorganisms
Bacteroides fragilis group

* Methicillin-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 to 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

Hyprolose
Sodium phosphate tribasic anhydrous
Sucrose
Xantham gum

Flavours:
Artificial banana
Artificial cherry
Artificial crème de vanilla

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
Once reconstituted with water, Azithromycin Pfizer suspension has a shelf-life of 5 days.

6.4 Special precautions for storage

Dry Powder for Oral Suspension: Do not store above 30 ºC.
Reconstituted Powder for Oral Suspension: Do not store above 25 °C. Do not refrigerate or freeze.

6.5 Nature and contents of container

15 ml (600 mg), 22.5 ml (900 mg), 30 ml (1200 mg) polypropylene container with child resistant screw cap (with or without tamper evident seal), in a carton box. Pack contains a multi-dosing spoon.

15 ml (600 mg) containers also contain a 10 ml oral dosing syringe with detachable adaptor.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Azithromycin Pfizer Powder for Oral suspension is a dry white powder which reconstitutes with water to give a cherry/banana flavoured suspension with a slight vanilla odour.

600 mg (15 ml) Pack. Reconstitute with 9 ml of water to give 15 ml suspension.

900 mg (22.5 ml) Pack. Reconstitute with 12 ml of water to give 22.5 ml suspension.

1200 mg (30 ml) Pack. Reconstitute with 15 ml of water to give 30 ml suspension.

When dispensing the 15 ml pack, advice should be given as to whether the dose should be measured using the oral dosing syringe or the spoon provided and on correct usage. If the dose is to be given using the oral dosing syringe, before dispensing, the syringe adaptor should be detached from the syringe and inserted into the bottle neck and the cap replaced.

When dispensing 22.5 ml and 30 ml packs, advice should be given as to the correct usage of the multidosing spoon.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
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Kent CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0019/093/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th July 2013

10 DATE OF REVISION OF THE TEXT

January 2016