SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Zetron® 250 mg Capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains: Azithromycin 250 mg.

Ingredient
Azithromycin Dihydrate
Lactose Anhydrous (DCL-21)
Corn starch
Magnesium Stearate
Sodium lauryl sulfate
Empty Hard Gelatin Capsule size '0' Light Brown / Light Brown

3. PHARMACEUTICAL FORM

Capsules:

Light brown opaque cap and light brown opaque body, size '0' hard gelatin capsules imprinted with "TC" containing white to off-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 Pharmacodynamic properties): - Bronchitis

- Community-acquired pneumonia
- Sinusitis
- Pharyngitis/tonsillitis (see 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

Method of administration:

Zetron should be given as a single daily dose. In common with many other antibiotics Zetron Capsules should be taken at least 1 hour before or 2 hours after 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: Zetron Capsules 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 metabolized 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).
Zetron Capsules are for oral administration only.

4.3 Contraindications

Zetron is contra-indicated in patients with a known 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.

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic edema 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 the 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 Undesirable effects). 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 co-administration 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 co-administrated.
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade's 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 repolarization (see Section 4.8 Undesirable effects); therefore, caution is required when treating patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substance known to prolong QT interval such as antiarrhytmics of classes Ia and III, cisapride and terfenadine
- With electrolyte disturbance, particularly in case of hypokalemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

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. Strains of *C. difficile* producing hypertoxin A and B 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. Therefore, CDAD must be considered in patients who present with diarrhea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for *C. difficile* should be considered.

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 Pharmacokinetic properties).

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).

Safety and efficacy for prevention or treatment of MAC in children have not been established.

Zetron capsules are for oral administration only.

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

4.5 Interactions 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.

Cetirizine: In healthy volunteers, co-administration 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)*: Co-administration 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: Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

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 derivatives: 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 precautions for use).

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

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).

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 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.

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 concurrent administration of these drugs. If coadministration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz: Co-administration 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: Co-administration 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 co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Indinavir: Co-administration 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, co-administration 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: 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 is required.
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).
Sildenafil: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its 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, co-administration 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: Co-administration 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

Teratogenic Effects. Pregnancy Category B

Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These doses, based on a mg/m^2 basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin 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, azithromycin should be used during pregnancy only if clearly needed.
There are no data on secretion in breast milk. As many drugs are excreted in human milk, azithromycin should not be used in the treatment of a lactating woman unless the physician feels that the potential benefits justify the potential risks to the infant.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Zetron is well tolerated with a low incidence of side effects.
The section 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: Infections and Infestations

Uncommon *(≥1/1,000 to <1/100)*
Candidiasis, oral candidiasis, vaginal infection
Not known *(cannot be estimated from available data)*
Pseudomembranous colitis (See Section 4.4)

Blood and Lymphatic System Disorders

Uncommon *(≥ 1/1,000 to < 1/100)*
Leukopenia, neutropenia
Not known *(cannot be estimated from available data)*
Thrombocytopenia, haemolytic anaemia

Immune System Disorders

Uncommon *(≥1/1,000 to <1/100)*
Angioedema, hypersensitivity
Not known *(cannot be estimated from available data) Anaphylactic reaction* (See Section 4.4)

Metabolism and Nutrition Disorders

Common *(> 1/100, < 1/10)*
Anorexia

Psychiatric Disorders

Uncommon *(≥1/1,000 to <1/100)* Nervousness
Rare *(> 1/10000, < 1/1000)*
Agitation
Not known *(cannot be estimated from available data)*
Aggression, anxiety

Nervous System Disorders

Common *(> 1/100, < 1/10)*
Dizziness, headache, paraesthesia, dysgeusia
Uncommon *(≥1/1,000 to <1/100)*
Hypoaesethesia, somnolence, insomnia
Not known *(cannot be estimated from available data)*
Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (See Section 4.4).

Eye Disorders

Common (> 1/100, < 1/10)
Visual impairment

Ear and Labyrinth Disorders

Common (> 1/100, < 1/10) Deafness
Uncommon *(≥1/1,000 to <1/100)*
Hearing impaired, tinnitus
Rare *(> 1/10000, < 1/1000)*
Vertigo

Cardiac Disorders

Uncommon *(≥1/1,000 to <1/100)*
Palpitations
Not known *(cannot be estimated from available data)*
Torsades de pointes (See Section 4.4), *arrhythmia* (See Section 4.4) including *ventricular tachycardia*
Vascular Disorders
Not known *(cannot be estimated from available data)*
Hypotension
Gastrointestinal Disorders
Very common *(≥1/10)* Diarrhea, abdominal pain, nausea, flatulence
Common *(> 1/100, < 1/10)*
Vomiting, dyspepsia
Uncommon *(> 1/1000, < 1/100)*
Gastritis, constipation
Not known *(cannot be estimated from available data)*
Pancreatitis, tongue discolouration
Hepatobiliary Disorders
Uncommon *(> 1/1000, < 1/100)*
Hepatitis
Rare *(> 1/10000, < 1/1000)*
Hepatic function abnormal
Not known *(cannot be estimated from available data)*
Hepatic failure (See Section 4.4), which has rarely resulted in death, *hepatitis fulminant, hepatic necrosis, jaundice cholestatic*
Skin and Subcutaneous Tissue Disorders
Common *(> 1/100, < 1/10)*
Pruritus and rash
Uncommon *(> 1/1000, < 1/100)*
Stevens-Johnson syndrome, photosensitivity reaction, urticaria
Not known *(cannot be estimated from available data)*
Toxic epidermal necrolysis, erythema multiforme
Musculoskeletal, Connective Tissue Disorders
Common *(> 1/100, < 1/10)*
Arthralgia
Renal and Urinary Disorders
Not known *(cannot be estimated from available data)*
Renal failure acute, nephritis interstitial
General disorders and Administration Site Conditions
Common *(> 1/100, < 1/10)*
Fatigue
Uncommon *(> 1/1000, < 1/100)*
Chest pain, oedema, malaise, asthenia
Investigations
Common *(> 1/100, < 1/10)*
Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased

Uncommon *(> 1/1000, < 1/100)*
Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal
Not known *(cannot be estimated from available data) Electrocardiogram QT prolonged* (See Section 4.4)

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

General properties
Antibacterial for systemic use. ATC code: J01FA10 Mode of action:
Zetron 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 ≤ 2 mg/l; resistant ≥ 8 mg/l
- *Haemophilus* spp.: susceptible ≤ 4 mg/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 2-3 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 invitro 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 fetal 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

Lactose
Maize starch
Sodium Lauryl Sulphate
Magnesium stearate

6.2 Incompatibilities

None known

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30 °C.

6.5 Nature and contents of container

One Aluminum-PVC/PVDC blister of six capsules, packed in printed carton with folded leaflet.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7.Marketing authorization holder

Tabuk Pharmaceutical Manufacturing Company.
P.O. Box 3633, Tabuk
Tel: 009661-4-4283030
Fax: 009661-4-4283031
Kingdom of Saudi Arabia

8. Marketing authorization number(s)

08402/08826/NMR/2021

9. Date of first authorization/renewal of the authorization

Date of first authorization in the country of origin (KSA): **Jan 31, 2023**

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