LETAZITH CAPSULES

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

(EACH CAPSULE CONTAINS AZITHROMYCIN DIHYDRATE EQUIVALENT TO AZITHROMYCIN 250 MG)

Country of Origin: Ghana

Document number: SPC/QA/087/01

SUMMARY OF PRODUCT CHARACTERISTICS FOR LETAZITH CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

Letazith Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Azithromycin Dihydrate equivalent to 250 mg of Azithromycin

The formulation contains Lactose Monohydrate
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Capsule
White powder filled in white coloured size 'O' capsules with a black print 'Letazith' on both cap and body

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Letazith is used for the treatment of lower respiratory infections like community acquired pneumonia upper respiratory infections like pharyngitis/tonsillitis, otitis media, bronchitis, uncomplicated skin and skin structure infections due to staphylococcus and streptococcus, sexually transmitted diseases like non-gonococcal urethritis and cervicitis due to chlamydia and mycobacterial infections.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Each dose of Letazith capsules should be swallowed whole at least 1 hour before or 2 hours after food with a glass of water.

Posology

The usual dose is:
Adults and children with body weight of 45 kg and above:
The recommended dose is 500 mg (2 capsules) taken together, once a day for 3 days.

For some diseases such as chlamydia. Your doctor will ask you to take a single dose of 1000 mg taken all together in one day only. For gonorrhea, the recommended dose is 1 g or 2 g of azithromycin in combination with 250 or 500 mg of ceftriaxone

Letazith Capsules should not be given to children less than 45 kg. Possible dose adjustment regimen may be considered in patients with kidney or liver problems although no studies have been conducted regarding treatment of such patients with azithromycin. It should however be considered that azithromycin is metabolised in the liver and excreted in the bile. Patients should make sure that they complete the entire prescription of Letazith, even if they start feeling better. This will ensure that the infection is completely treated.

4.3 Contraindications

Letazith is contra-indicated in patients with a known hypersensitivity to azithromycin or any macrolide or ketolide antibiotics, erythromycin, or to any excipients thereof as (for example) mentioned in this document

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 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. 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 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; 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 I and III, cisapride and terfenadine
- With electrolyte disturbance, particularly in case of hypokalaemia 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 diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea 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 diarrhoea 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.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

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

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: 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.

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 co-administration 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.

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 Cmax, 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 Pregnancy, lactation and Fertility

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these 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 Letazith may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Azithromycin is well tolerated with a low incidence of side 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** ≥ 1/1,000 to < 1/100	**rare** ≥ 1/10,000 to <1/1,000	**very rare** < 1/10,000	**not known** frequency cannot be estimated from available data
Infections and infestations					
		Candidiasis Oral candidiasis Vaginal infection			*Pseudomembranous colitis* (see 4.4)
Blood and lymphatic system disorders					
		Leukopenia Neutropenia			*Thrombocytopenia, Haemolytic anaemia*
Immune system disorders					
		Angioedema Hypersensitivity			*Anaphylactic reaction*(see section 4.4.)
Metabolism and nutrition disorders					
		Anorexia			
Psychiatric disorders					
		Nervousness	Agitation		*Aggression* *Anxiety*

Nervous system disorders					
	Headache, Dizziness, Paraesthesia, Dysgeusia	Somnolence, Hypoaesthesia, Insomnia			*Syncope Convulsion, Psychomotor hyperactivity Anosmia Ageusia Parosmia myasthenia gravis*(see 4.4)
Eye disorders					
	Visual impairment				
Ear and labyrinth disorders					
	Deafness				

Hearing impairment,

Tinnitus					
Cardiac disorders					
		Palpitations			*Torsades de pointes* (see section 4.4), *Arrhythmia* (see section 4.4) *including ventricular tachycardia.*
Vascular disorders					
					Hypotension
Gastrointestinal disorders					
Diarrhoea, Abdominal pain, Nausea, Flatulence	Vomiting, Dyspepsia	Constipation, Gastritis			*Pancreatitis Tongue discoloration*
Hepatobiliary disorders					
		Hepatitis	Hepatic function abnormal		*Hepatic failure (see section 4.4)*, which has rarely resulted in death *Hepatitis fulminant Hepatic necrosis Jaundice cholestatic*

Skin and subcutaneous tissue disorders					
	Rash Pruritus	Stevens-Johnson Syndrome, photosensitivity reaction, Urticaria	Acute generalised exanthematous pustulosis (AGEP)	DRESS	Toxic epidermal necrolysis (TEN), *Erythema multiforme*
Musculoskeletal and connective tissue disorders					
	Arthralgia				
Renal and urinary disorders					
					Renal failure acute *Nephritis interstitial*
General disorders and administration site conditions					
	Fatigue	Oedema, Asthenia, Malaise, Chest pain			
Investigations					
	Lymphocyte count decreased, Eosinophil count increased, Blood bicarbonate decreased	Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood bilirubin increased, Blood urea increased, Blood creatinine increased, Blood potassium abnormal			*Electrocardiogram QT prolonged* (see section 4.4)

2.5.9 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:

Antibacterials for systemic use.

ATC code: J01FA10

Mode of action:

Azithromycin 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 binding to the ribosomal 50S sub-unit and thus inhibiting the translocation of peptides.

Cardiac Electrophysiology:

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Coadministration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

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*, beta-haemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *Staphylococcus aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints

Azithromycin susceptibility breakpoints for typical bacterial pathogens:

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 influenza, 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:

Following oral administration, the bioavailability of azithromycin is approximately 37 %. Peak plasma levels are reached after 2-3 hours after taking the medicinal product.

Distribution:

Orally administered azithromycin is widely distributed over the whole body.

Pharmacokinetic studies have shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma) than in the plasma. This indicates that the substance is extensively bound in the 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 follows the tissue depletion half-life of 2 to 4 days.

Approximately 12 % of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days.Particually high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites have been identified (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by cleavage of the 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.

<u>Carcinogenic potential:</u>

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 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 Monohydrate, Starch, Talc, Magnesium Stearate, Sodium Lauryl Sulphate, Kollidon – CL, Cab – O - Sil

6.2 Incompatibilities

Not Known

6.3 Shelf life

A tentative shelf life of 2 years is proposed for Letazith® capsules.

6.4 Special precautions for storage

Letazith® capsules should be stored in cool dark place below 30^{o}C in the original package and should be kept out of reach and sight of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Letazith® is filled into size '0' white hard gelatin capsule shells with black print, 'LETAZITH' on both body and cap printed in black colour. It is supplied in pack of 6 capsules per printed Aluminium/clear PVC blister pack placed in each inner carton box, 10 inner carton boxes in an outer carton box (secondary packaging material).

6.6 Special precautions for disposal and other handling

There are no special requirements for disposal and handling of Letazith Capsules however, it should be handled with care. Medicines should however not be disposed of via wastewater or household waste. Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

Letap Pharmaceuticals Limited.,
P. O. Box 3346, Plot 107, Graphic Road, Accra, Ghana
Tel: +233-0302-225838/224613 Fax: +233-0302-224693
Email: Letap.group@gmail.com

8. DATE OF LAST REVISION

August 2019