PROFESSIONAL INFORMATION LEAFLET: ZITHRACT

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

Zithract 500 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains: 500 mg of azithromycin (as dihydrate)

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

Pink coloured, capsule shaped film coated tablets, plain on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

ZITHRACT tablets are indicated for mild to moderate infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis due to *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae* or *Staphylococcus aureus* and pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae*; uncomplicated skin and soft tissue infections; sinusitis due to *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Staphylococcus aureus*; and as an alternative to first line therapy of pharyngitis/tonsillitis.

In sexually transmitted diseases in men and women, ZITHRACT tablets are indicated in the treatment of uncomplicated genital infections due to Chlamydia trachomatis and chancroid due to *Haemophilus ducreyi*.

Children 1 year and over:

ZITHRACT tablets are indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms in children over 45 kg (an azithromycin suspension is recommended in children under 45 kg).

4.2 Posology and method of administration

ZITHRACT tablets:

ZITHRACT should be administered as a single daily dose with or without food.

ZITHRACT tablets should be taken whole.

Adults

For all indications other than sexually transmitted diseases, the total dose is 1,5 g which should be given as 500 mg daily for 3 days.

For sexually transmitted diseases caused by *Chlamydia trachomatis* or *Haemophilus ducreyi*, the dose is 1 g given as a single dose.

Special Populations

Use in patients with hepatic impairment:

ZITHRACT is contraindicated in patients with severe hepatic impairment (see section 4.3)

Use in the elderly:

Normal adult dosage is recommended. Elderly patients may be more susceptible to development of Torsade de Pointes dysrhythmia than younger patients (see section 4.4).

Use in children:

Children over 45 kg - dose as per adults.

This formulation is not suitable for children under 45 kg.

4.3 Contraindications

ZITHRACT is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin, any of the macrolide antibiotics, or to any excipient listed under section 6.1.

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

Use in hepatic impairment:

As the liver is the principal route of excretion of ZITHRACT, it should not be prescribed in patients with hepatic disease.

4.4 Special warnings and precautions for use

Hypersensitivity:

Serious allergic reactions, including angioedema and anaphylaxis and dermatologic reactions including Stevens - Johnson syndrome, Acute Generalised Exanthemateous Pustulosis (AGEP), Drug with Eosinophilic and systemic symptoms (DRESS) and toxic epidermal necrolysis have been reported. Some of these reactions with ZITHRACT have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, ZITHRACT should be discontinued and appropriate therapy should be instituted. Medical practitioners to be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity:
Since the liver is the principal route of elimination for azithromycin, ZITHRACT should not be used in patients with hepatic disease (see section 4.3).
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure, some of which have resulted in death, have been reported.
Discontinue ZITHRACT immediately if signs and/or symptoms of hepatitis occur.

Ergot derivatives:
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 ZITHRACT.
However, because of the theoretical possibility of ergotism, ZITHRACT and ergot derivatives should not be co-administered (see section 4.3).

Superinfection:
Observation for signs of superinfection with non-susceptible organisms, including fungi, is recommended.

Pseudomembranous colitis:
Pseudomembranous colitis has been reported and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients with diarrhoea subsequent to administration of ZITHRACT.

***Clostridium difficile*-associated diarrhoea:**
Clostridium difficile-associated diarrhoea (CDAD) due to overgrowth of *Clostridium difficile* in the gut, has been reported with use of ZITHRACT, and may range in severity from mild diarrhoea to fatal colitis.
If CDAD is suspected or confirmed, ongoing ZITHRACT use should be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated.

Renal impairment:

In patients with a creatinine clearance < 30, a 33 % increase in systemic exposure to ZITHRACT was observed (see section 5.2).

Acute renal failure and interstitial nephritis have been reported (see section 4.8)

Prolongation of the QT interval:

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac dysrhythmia and Torsade de Pointes, have been seen in treatment with other macrolides including ZITHRACT (see section 4.8).

Prescribers should specifically consider the risk of QT prolongation, which can be fatal in at-risk groups including:

- Patients with congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval such as antidysrhythmics of classes IA and III; antipsychotic medicines; antidepressants; and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- Patients with clinically relevant bradycardia, cardiac dysrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to medicine-associated effects on the QT interval
- Myasthenia gravis: exacerbation of symptoms of myasthenia gravis and new-onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Use in children under 1 year of age:

The safety and efficacy of oral ZITHRACT preparations in children less than 1 year have not been established.

4.5 Interaction with other medicines and other forms of interaction

Ergot derivatives:

Because of the theoretical possibility of ergotism, ZITHRACT and ergot derivatives should not be co-administered (see section 4.3 and section 4.4).

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.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to be associated with the pharmacokinetic medicine interactions seen with erythromycin.
Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

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

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 1 200 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 C_{max} (18 %) of azithromycin was observed.

Indinavir:
Co-administration of a single dose of 1 200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Midazolam:
In healthy volunteers, co-administration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetic properties and pharmacodynamics properties of a single 15 mg dose of midazolam.

Nelfinavir:
Co-administration of azithromycin (1 200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and although a dose adjustment of ZITHRACT is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of ZITHRACT is warranted.

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.

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 (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.

Special administration advised with the following:
Antacids:
In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 24 %. In patients receiving both ZITHRACT and antacids, the medicines should not be taken simultaneously. ZITHRACT tablets should be taken at least 1 hour before or 2 hours after an antacid.

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

No pharmacokinetic interactions were reported in studies of ZITHRACT co-administered with:
Carbamazepine, methylprednisolone, didanosine (dideoxyinosine), theophylline, rifabutin (however co-administration of ZITHRACT and rifabutin was associated with the development of neutropenia. A causal relationship to its combination with ZITHRACT has not been established (see section 4.8)) and *zidovudine* (single 1 000 mg doses and multiple 1 200 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).

Special precautionary monitoring is advised with the following:
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 (C_{max} increase by 24 % and AUC_{0-5} was 5 107 and 4 210 ngh/ml with and without azithromycin, respectively, $p \leq 0,05$). Consequently, caution should be exercised before co-administration of these two medicines.
If co-administration is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

P-glycoprotein substrates:
Concomitant administration of ZITHRACT with P-glycoprotein substrates such as digoxin or dabigatran has been reported to result in increased serum levels of the P-glycoprotein substrate.
Therefore, if ZITHRACT and P-glycoprotein substrates such as digoxin or dabigatran are administered concomitantly, the possibility of elevated serum medicine concentrations should be considered. Clinical monitoring and serum monitoring of digoxin levels during treatment with ZITHRACT and after its discontinuation are necessary.

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 ZITHRACT, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

Warfarin:
In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. However, there have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and warfarin. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when ZITHRACT is used in patients receiving coumarin-type oral anticoagulants.

4.6 Fertility, pregnancy and lactation
The safety and efficacy of ZITHRACT in pregnancy and lactation have not been established.

Pregnancy:
Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the foetus 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, ZITHRACT should be used during pregnancy only if clearly needed.

Lactation:
Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterised the pharmacokinetics of azithromycin excretion into human breast milk.
ZITHRACT should only be used in lactating women where adequate alternatives are not available.

4.7 Effects on ability to drive and use machines
Side effects such as dizziness, convulsions, vertigo, somnolence, and syncope have been reported with usage of ZITHRACT. These side effects may affect a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Table 1: Tabulated summary of adverse reactions

The following undesirable effects have been reported.

System Organ Class	**ZITHRACT Tablets Side Effects**
Blood and lymphatic system disorders	
Less frequent:	Neutropenia
Immune system disorders	
Less frequent:	Angioedema
Eye disorders	
Less frequent:	Abnormal vision
Ear and labyrinth disorders	
Less frequent:	Hearing impairment including hearing loss, deafness and/or tinnitus
Cardiac disorders	
Less frequent:	Chest pains, dysrhythmias including ventricular tachycardia, palpitations, QT prolongation, Torsade de Pointes
Gastrointestinal disorders	
Frequent:	Abdominal discomfort (pain/ cramps), diarrhoea, nausea
Less frequent:	Flatulence, loose stools, vomiting, malaena
Hepatobiliary disorders	
Less frequent:	Abnormal liver function
Skin and subcutaneous tissue disorders	
Less frequent:	Rash, allergic reactions
Renal and urinary disorders	

Less frequent:	Nephritis

In post-marketing experience, the following additional undesirable effects have been reported with frequency unknown:

System Organ Class	ZITHRACT Tablets Side Effects
Infections and infestations	Moniliasis, vaginitis
Blood and lymphatic system disorders	Thrombocytopenia
Immune system disorders	Anaphylaxis
Metabolism and nutrition disorders	Anorexia
Psychiatric disorders	Nervousness, aggressive reaction, agitation, anxiety
Nervous system disorders	Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paraesthesia, somnolence, syncope, taste/smell perversion and/or loss
Ear and labyrinth disorders	Deafness, tinnitus, impaired hearing, vertigo
Cardiac disorders	Palpitations, dysrhythmias including ventricular tachycardia, QT prolongation, Torsade de Pointes
Vascular disorders	Hypotension
Gastrointestinal disorders	Vomiting/ diarrhoea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, tongue discolouration
Hepatobiliary disorders	Hepatitis and cholestatic jaundice, hepatic necrosis and hepatic failure, which have rarely resulted in death

Skin and subcutaneous tissue disorders	Allergic reactions including pruritus, rash, photosensitivity, oedema, urticaria, angioedema, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal disorders	Arthralgia
Renal and urinary disorders	Interstitial nephritis, acute renal failure
General disorders *Frequent:*	Asthenia, fatigue, malaise

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions. Suspected adverse reactions can be reported to Actor Pharma (Pty) Ltd via email: pharmacovigilance@actorpharma.co.za or telephonically on 011 312 3812. Suspected adverse reactions can also be reported to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose
Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. Typical symptoms of overdosage with macrolide antibiotics include hearing loss, severe nausea, vomiting and diarrhoea. General supportive measures are indicated.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
PHARMACOLOGICAL CLASSIFICATION:
A 20.1.1 Broad and medium spectrum antibiotics

Azithromycin is an azalide, a subclass of the macrolide antibiotics. Chemically it is derived by insertion of a nitrogen atom into 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.
Azithromycin binds to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology:
QTc interval-prolongation was studied in a randomised, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1 000 mg) alone or in combination with azithromycin (500 mg, 1 000 mg, and 1 500 mg once daily). Co-administration of azithromycin significantly 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, 1 000 mg and 1 500 mg azithromycin, respectively.

Efflux pumps occur in a number of bacteria, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher MICs) and staphylococci. In streptococci and enterococci, an efflux pump that recognises 14 - and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by mef(A) genes.
Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive organisms. Ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in *Viridans streptococci* and in *Streptococcus agalactiae*.

Azithromycin has *in vitro* activity against:
- Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible organisms).
- Aerobic and facultative Gram-negative bacteria.

In vitro resistance to azithromycin:

Azithromycin-resistant organisms are encountered relatively frequently among aerobic and facultative Gram- positive bacteria, in particular among methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin- resistant *Streptococcus pneumoniae* (PRSP).

Pseudomonas spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica*, *Pneumocystis jirovecii* and *Toxoplasma gondii* infections.
In vitro sensitivity does not necessarily imply *in vivo* efficacy.

5.2 Pharmacokinetic properties

Absorption

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37 %. No significant decrease in bioavailability was observed when azithromycin was administered with a meal. The time taken to peak plasma levels is 2 - 3 hours.

In patients hospitalised with community acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/ml, the mean C_{max} ± S.D. achieved was 3,63 ± 1,60 µg/ml, while the 24-hour trough level was 0,20 ± 0,15 µg/ml, and the AUC_{24} was 9,60 ± 4,80 µg·h/ml.
The mean C_{max}, 24-hour trough and AUC_{24} values were 1,14 ± 0,14 µg/ml, 0,18 ± 0,02 µg/ml, and 8,03 ± 0,86 µg·h/ml, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/ml.

Distribution

Kinetic studies of variable times ranging from hours to days after oral intake have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the medicine is highly tissue bound. Concentrations in target tissues such as lung, tonsil and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

Elimination

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. Approximately 12 % of an intravenously administered dose is excreted in the urine over 3 days as azithromycin, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged medicine following oral administration. Very high

concentrations of unchanged medicine have been found in human bile, together with 10 metabolites, formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

In a multiple-dose study in 12 normal volunteers utilising a 500 mg (1 mg/ml) one-hour intravenous dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11 % after the 1st dose and 14 % after the 5th dose. These values are greater than the reported 6 % excreted unchanged in urine after oral administration of azithromycin.

Pharmacokinetics in special patient groups:

Renal impairment:

The pharmacokinetics of azithromycin in adult patients with mild-to-moderate renal impairment (GFR 10 – 80 ml/min) were not affected following a single 1 g dose of immediate release azithromycin. Statistically significant differences in AUC_{0-120} (8,8 mg × hr/ml vs. 11,7 mg × hr/ml), C_{max} (1,0 mg/ml vs. 1,6 mg/ml) and CLr (2,3 ml/min/kg vs. 0,2 ml/min/kg) were observed between the group with severe renal impairment (GFR < 10 ml/min) and the group with normal renal function.

Hepatic impairment:

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. The urinary clearance of azithromycin appears to increase in these patients, perhaps to compensate for reduced hepatic clearance. Azithromycin has not been studied and should not be used in patients with severe hepatic impairment.

Elderly:

Elderly volunteers (> 65 years) had slightly higher AUC values than in young volunteers (< 40 years) after a 5-day regimen, but these are not considered clinically significant, and hence no dose adjustment is recommended.

5.3 Preclinical safety data

Nothing of relevance which is not included in other sections of the Professional Information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

microcrystalline cellulose, sodium lauryl sulphate, sodium starch glycollate, povidone, isopropyl alcohol, croscarmellose sodium, purified talc, magnesium stearate

Coating:

Lake ponceau 4R, titanium dioxide, purified talc, purified water, hypromellose and macrogols 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

PVC-PVDC / Aluminium blisters enclosed in an outer carton.

Pack size: 3 film-coated tablets.

6.6 Special precautions for disposal

No special requirement.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Actor Pharma (Pty) Ltd[1]
Royal Palm Business Estate
Unit 7, 646 Washington Street
Halfway House, Midrand, 1685
Gauteng, South Africa

8. REGISTRATION NUMBER(S)

48/20.1.1/0764

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 April 2021

10. DATE OF REVISION OF THE TEXT

Not applicable

[1] Company Registration number.: 2008/008787/07

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