PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

AZITHROMYCIN UNICORN 500 film coated tablets

Strength: 500 mg azithromycin dihydrate equivalent to 500 mg azithromycin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains azithromycin dihydrate equivalent to 500 mg azithromycin

Contains sugar: 10,80 mg lactose monohydrate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

White to off-white capsule shaped, film coated tablets, debossed with “AZ” and “500” on either side of the score line on one side and plain on the other side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AZITHROMYCIN UNICORN 500 is macrolide antibacterial medicine indicated in the treatment of 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.

AZITHROMYCIN UNICORN 500 is indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis* and/or non-multiresistance *Neisseria gonorrhoea* in sexually transmitted diseases. It is also indicated in the treatment of chancroid due to *Haemophilus ducreyi.*

Children 1 year and over:

AZITHROMYCIN UNICORN 500 is indicated in the treatment of bacterial exacerbations of pharyngitis/tonsillitis and otitis media caused by susceptible organisms in children over 45 kg.

4.2 Posology and method of administration

AZITHROMYCIN UNICORN 500 tablets should be taken whole as a single dose.

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 (2 x 500 mg) given as a single dose.

For uncomplicated genital infections caused by non-multiresistant *N. gonorrhoea,* the dose is 1 g given as a single oral dose.

Use in elderly:

No dosage adjustments are necessary for elderly patients.

Use in children:

For children over 45 kg body weight, the dose is as for adults. Note that this formulation is not suitable for children with a body weight of under 45 kg.

Method of Administration

These tablets can be taken orally, with or without food and in a single daily dose.

4.3 Contraindications

- Hypersensitivity to azithromycin, erythromycin, any of the macrolide or ketolide antibiotics, or any of the excipients (see section 2).
- **AZITHROMYCIN UNICORN 500** should not be co-administered with ergot derivatives due to the risk of ergotism.
- **AZITHROMYCIN UNICORN 500** is contraindicated in patients with liver disease.

4.4 Special warnings and precautions for use

Hypersensitivity:

Rare serious allergic reactions, such as anaphylaxis and angioedema, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome and toxic epidermal necrolysis have been reported in patients taking azithromycin. Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. These patients required prolonged periods of observation and symptomatic treatment. Allergic symptoms may recur after symptomatic therapy has been discontinued. These patients require prolonged periods of observation and symptomatic treatment.

Hepatotoxicity:

Cases of fulminant hepatitis potentially leading to life-threatening liver failure, have been reported (see section 4.8). In case of signs and symptoms of liver dysfunction, such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/investigations should be performed immediately. **AZITHROMYCIN UNICORN 500** should be stopped if liver dysfunction has emerged.

Prolongation of the QT interval:

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac dysrhythmia and torsade de pointes, have been reported with macrolides. Caution is required when treating patients:

• with congenital or documented QT prolongation;

• currently receiving treatment with another active substance known to prolong QT interval, such as dysrhythmic medicines classes IA (quinidine, procainamide) and III (dofetilide, amiodarone, sotalol), and cisapride;

• with electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesaemia;

• with clinically relevant bradycardia, cardiac dysrhythmia or severe cardiac insufficiency.

Elderly patients: elderly patients may be more susceptible to medicine-associated effects on the QT interval

Superinfection:

Patients treated with **AZITHROMYCIN UNICORN 500** should be closely monitored for signs or symptoms of superinfections (including fungi).

Clostridium difficile associated diarrhoea:

Clostridium difficile associated diarrhoea (CDAD) has been reported and may range in severity from mild diarrhoea to fatal pseudomembranous colitis (see section 4.8). Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of C. difficile. 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.

It is therefore important to consider the diagnosis of CDAD in patients who present with diarrhoea during or subsequent to treatment with **AZITHROMYCIN UNICORN 500**. Careful medical history is necessary, since CDAD has been reported to occur over two months after the administration of antibiotics. Discontinuation of therapy with **AZITHROMYCIN UNICORN 500** and appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of Clostridium difficile, and surgical evaluation should be instituted as clinically indicated.

Myasthenia gravis:

Exacerbation of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported (see section 4.8).

Renal impairment:

Caution should be taken when prescribing **AZITHROMYCIN UNICORN 500** to patients with renal impairment. Increased systemic exposure to **AZITHROMYCIN UNICORN 500** has been reported in patients with severe renal impairment (glomerular filtration rate (GFR) < 10 ml/min).

Sexually Transmitted Infections

AZITHROMYCIN UNICORN 500, at the recommended dose, should not be relied upon to treat syphilis. Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhoea performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

The safety of **AZITHROMYCIN UNICORN 500** in children under the age of 1 year has not

been established. **AZITHROMYCIN UNICORN 500** is not indicated for children weighing less than 45 kg (see section 4.1).

AZITHROMYCIN UNICORN 500 contains lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take **AZITHROMYCIN UNICORN 500.**

4.5 Interaction with other medicines and other forms of interaction

Co-administration of **AZITHROMYCIN UNICORN 500** with ergotamine or dihydroergotamine has been associated with acute ergot toxicity.

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

Macrolides, including azithromycin, have the potential to interact with a large number of medicines through their action on hepatic cytochrome P450 isoenzymes. Macrolides inhibit metabolism by microsomal cytochromes by competitive inhibition and by the formation of inactive complexes. Such interactions can occur with non-sedative antihistamines and cisapride.

An increase in the serum concentrations of ciclosporin, digoxin, hexobarbital or phenytoin has been reported with the concurrent use of azithromycin.

Caution should be exercised before co-administration of ciclosporin and azithromycin. If co-administration is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

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 **AZITHROMYCIN UNICORN 500**, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

There have been less frequent reports of an interaction in patients receiving **AZITHROMYCIN UNICORN 500** and terfenadine where the possibility of such an interaction could not entirely

be excluded.

Concurrent use with aluminium and magnesium containing antacids has decreased the peak serum concentration by approximately 24 %. **AZITHROMYCIN UNICORN 500** tablets should be taken at least 1 hour before or 2 hours after the antacid.

A single dose of cimetidine administered 2 hours before **AZITHROMYCIN UNICORN 500** had no effect on the pharmacokinetics of azithromycin.

Concurrent use of warfarin and azithromycin has been associated with increased anticoagulant effects. The prothrombin time of these patients should be monitored.

A variety of broad-spectrum antibiotics, including azithromycin have been reported to decrease oral contraceptive efficacy. It is recommended that additional contraceptive precautions should be used while taking, and for 7 days after stopping **AZITHROMYCIN UNICORN 500**. If these 7 days run into the last 7 days of the cycle, then the tablet free interval (or the 7 inert tablets) should be omitted and the next cycle of tablets started immediately.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

Breast feeding

The safety and efficacy of AZITHROMYCIN UNICORN 500 in breastfeeding has not been established.

Fertility

No fertility data available.

4.7 Effects on ability to drive and use machines

AZITHROMYCIN UNICORN 500 may cause dizziness, and vision impairment (see section 4.8). Patients should be advised not to drive or handle machines or tools if this happens.

4.8 Undesirable effects

System Organ Class	Frequency	Side effects

Blood and the lymphatic system disorders	*Less frequent*	Leukopenia, neutropenia, eosinophilia
	Frequency unknown	Thrombocytopenia, haemolytic anaemia
Infections and infestations	*Less frequent*	Candidiasis, oral candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis
	Frequency unknown	Pseudomembranous colitis
Immune system disorders	*Less frequent*	Angioedema, hypersensitivity
	Frequency unknown	Anaphylactic reaction
Metabolism and nutrition disorders	*Frequent*	Anorexia
Psychiatric disorders	*Less frequent*	Nervousness, agitation, restlessness
	Frequency unknown	Aggression, anxiety, somnolence, insomnia, delirium, hallucination
Nervous system disorders	*Frequent*	Dizziness, headache, paraesthesia, disgeusia
	Less frequent	Hypaesthesia, hyperkinesia
	Frequency unknown	Myasthenia gravis, syncope, convulsion, psychomotor hyperactivity, anosmia
Eye disorders	*Frequent*	Visual impairment
Ear and labyrinth disorders	*Frequent*	Deafness
	Less frequent	Hearing impairment (including tinnitus), ear disorder, vertigo, hearing loss
Cardiac disorders	*Less frequent*	Palpitations
	Frequency	Torsade de pointes, dysrhythmia

	unknown	(including ventricular tachycardia, prolonged electrocardiogram QT
Vascular disorders	*Less frequent*	Hot flushes
	Frequency unknown	Hypotension
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Dyspnoea, epistaxis, cough, pleural effusion
Gastrointestinal disorders	*Frequent*	Abdominal discomfort (pain/cramps), diarrhoea (rarely resulting in dehydration), nausea, vomiting, flatulence, dyspepsia, constipation, loose stools
	Less frequent	Gastritis, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion, pyloric stenosis
	Frequency unknown	Pseudomembranous colitis, taste disturbances, pancreatitis, tongue discolouration, melaena
Hepatobiliary disorders	*Less frequent*	Hepatitis
	Frequency unknown	Abnormal hepatic function, cholestatic jaundice, hepatic necrosis and hepatic failure, which have rarely resulted in death
Skin and subcutaneous tissue disorders	*Frequent*	Rash, pruritus
	Less frequent	Stevens-Johnson syndrome, photosensitivity reaction, urticaria, fungal dermatitis, dry skin, hyperhidrosis, eczema, sweating, vesiculobullous rash,

		AGEP, and DRESS
	Frequency unknown	Toxic epidermal necrolysis, erythema multiforme
Musculoskeletal, connective tissue and bone disorders	*Frequent*	Arthralgia
	Less frequent	Osteoarthritis, myalgia, back pain, neck pain
Renal and urinary disorders	*Less frequent*	Dysuria, renal pain
	Frequency unknown	Acute interstitial nephritis, renal failure
Reproductive system and breast disorders	*Less frequent*	Metrorrhagia, testicular disorder
General disorders and administrative site conditions	*Frequent*	Fatigue
	Less frequent	Face oedema, chest pain, pyrexia, peripheral pain, oedema, malaise, asthenia, fever
	Frequency unknown	Allergic reactions (including difficulty in breathing, swelling of the face, mouth, neck, hands or feet, skin rash)
Investigations	*Frequent*	Decreased: lymphocyte count, blood bicarbonate; increased: eosinophil count, basophils, monocytes, neutrophils
	Less frequent	Abnormal: blood potassium, sodium; decreased: haematocrit, bicarbonate; increased: aspartate aminotransferase, alanine aminotransferase, blood bilirubin, blood urea, blood creatinine, blood alkaline phosphatase, chloride, glucose, platelets, bicarbonate.

Injury and poisoning	*Less frequent*	Post procedural complications

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8. Reporting can also be done directly to Unicorn Pharmaceuticals at: vigilance@unicornpharma.co.za.

4.9 Overdose

There are no known symptoms of overdosage. Typical symptoms of overdosage include hearing loss, severe nausea, vomiting and diarrhoea. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

AZITHROMYCIN UNICORN 500 is an azalide antibiotic.

Azithromycin is a macrolide antibiotic which acts by inhibiting protein synthesis by binding reversibly to 50 S ribosomal subunits of sensitive microorganisms.

Mechanism of action

AZITHROMYCIN UNICORN (azithromycin tablets) contain the active ingredient azithromycin, a macrolide antibacterial drug, for oral administration. Azithromycin has the chemical name (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]-1oxa-6-azacyclopentadecan-15-one.

Azithromycin

is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is

$C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749,00.

Mechanisms 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.

Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive isolates.

A decrease in macrolide susceptibility over time has been noted particularly in *Streptococcus pneumoniae* and *Staphylococcus aureus*. Similarly, decreased susceptibility has been observed among *Streptococcus viridans* and *Streptococcus agalactiae* (Group B streptococcus) against other macrolides and lincosamides.

Resistant organisms:

- The incidence of resistance to azithromycin and other macrolides is higher among penicillin resistant strains than among penicillin-sensitive strains of bacteria;
- Azithromycin resistant isolates of Helicobacter pylori have emerged.
- H. pylori and Mycobacterium spp. genetic mutations, responsible for azithromycin resistance, have been identified.
- Resistance develops rapidly in Mycobacterium avium during azithromycin monotherapy.
- Systemic M. avium complex infection in AIDS patients, despite combined treatment, has been found to be resistant to azithromycin.
- Aerobic gram-positive microorganisms, namely Enterococcus faecalis and staphylococci MRSA, MRSE.

Anaerobic microorganisms, namely Bacteroides fragilis group.

5.2 Pharmacokinetic properties

Absorption:

Azithromycin is well absorbed and has a bioavailability of approximately 37 %. No significant decrease in bio-availability was observed when azithromycin was administered with a meal. Peak plasma concentrations are achieved 2 to 3 hours after a dose.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51 % at 0,02 mcg/mL to 7 % at 2 mcg/mL. The antibacterial activity of azithromycin is pH related and appears to be reduced with decreasing pH, However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Azithromycin has been shown to penetrate into human tissues, including skin, lung, tonsil, and cervix. Extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). High concentrations are taken up into white blood cells. Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, very low concentrations were noted in cerebrospinal fluid (less than 0.01 mcg/mL) in the presence of noninflamed meninges.

Biotransformation

Azithromycin undergoes some hepatic metabolism to inactive metabolites, but biliary excretion is the major route of elimination.

Elimination

Only 12 % of azithromycin is excreted unchanged in the urine. The plasma terminal half-life closely reflects the tissue depletion half-life of 2 to 4 days. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination.

In vitro sensitivity does not necessarily imply *in vivo* efficacy. Azithromycin demonstrates activity *in vitro* against a wide range of Gram-positive and Gram-negative bacteria including: *Staphylococcus aureus, Streptococcus pneumonia, Streptococcus, pyogenes* (Group A) and other Streptococcus species: *Haemophilus influenza, Moraxella catarrhalis, Legionella pneumophila, Bordetella pertussis, Borrelia burgdorferi, Haemophilus ducreyi*, and *Chlamydia trachomatis*. Azithromycin also demonstrates *in vitro* activity against *Mycoplasma pneumoniae* and *Treponema pallidum*.

5.3 Preclinical safety data

Not Applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients:

Calcium hydrogen phosphate anhydrous, croscarmellose sodium, hypromellose, magnesium stearate, Opadry White (containing hypromellose, lactose monohydrate, titanium dioxide, triacetin), pregelatinised starch, sodium lauryl sulphate.

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strip in outer carton until required for use.

6.5 Nature and contents of container

Hard tempered silver aluminium foil blister pack (PVC / PVdC) with heat sealable lacquer and white opaque PVC film coated with PVdC, containing 2, 3 or 10 tablets per blister strip.

One blister strip is placed in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

45/20.1.1/1076

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 November 2023

10 DATE OF REVISION OF THE TEXT

To be allocated