



MODULE 1

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

1. NAME OF THE MEDICINAL PRODUCT

1.1 (Invented) name of the medicinal product

AZITAR-500

1.2 Strength

Azithromycin Tablets USP

Each Film coated tablet contains,
Azithromycin (Dihydrate) USP 500 mg
eq. to Azithromycin anhydrous 500 mg
Excipients Q.S.
Colour: Titanium Dioxide B.P.

1.3 Pharmaceutical form

Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION



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Quantitative Composition

Sr. No.	Name of Ingredients	Sp.	Lab. Cl.	Over. Ages %	Std. Qty. In Kgs	Batch Qty. In Kgs	mg / tabs
DRY MIX							
1	Azithromycin Dihydrate Eq. to Azithromycin*	USP	500 mg		263.50		524.0
BINDER PREPRATION							
2	Povidone-30	BP			10.00	10.00	20.00
3	Isopropyl alcohol	BP			75.00 Lt.	75.00 Lt.	150.0

Sr. No.	Name of Ingredients	Sp.	Lab. Cl.	Over. Ages %	Std. Qty. In Kgs	Batch Qty. In Kgs	mg / tabs
Lubrication							
1	Purified Talc.	BP			7.00	7.00	14.00
2	Magnesium Stearate	BP			4.00	4.00	8.00
3	Cross Carmellose Sodium	BP			7.00	7.00	14.00
4	Sodium Starch Glycollate	BP			7.00	7.00	14.00
5	Colloidal Silicon Dioxide	BP			0.7	0.7	1.400
6	Microcrystalline Cellulose **	BP			52.3	52.3	104.6

*Label Claim of Azithromycin Dihydrate = $500 \times 1.048 = 524 \text{ mg}$

(Molecular weight of Azithromycin Dihydrate 785.02 and Azithromycin 749.00, so factor = $785.02/749.00 = 1.048$)

Calculation based on 100 % assay on as is basis, any increase or decrease in the quantity compensate with Microcrystalline Cellulose .

Film Coating Material

Sr. No.	Name of Ingredients	Sp.	Std. Qty. In Kgs	Batch Qty. In Kgs	Mg/tabs
1.	Titanium Dioxide	BP	2.00	2.00	4.000
2.	P.VP.K-30	BP	0.700	0.700	1.400
3.	Purified Talc	BP	1.50	1.50	3.000
4.	Purified Talc (For Dusting)	BP	1.00	1.00	2.000
5.	HPMC-15 cps	BP	5.25	5.25	10.500
6.	PEG-6000	BP	1.40	1.40	2.800
7.	Iso Propyl Alcohol	BP	65.00	65.00	130.000
8.	Methylene Di Chloride	BP	135.00	135.00	270.000



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3. PHARMACEUTICAL FORM

Tablet

Description

White coloured, Capsule shape film coated tablet having central break line on one side and Plain on other side.

4. CLINICAL PARTICULARS

Azithromycin is indicated for use in **adults** for the treatment of the following infections of mild to moderate severity:

1. Lower respiratory tract infections

- **acute bacterial bronchitis** due to *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*
- **community-acquired pneumonia** due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients suitable for outpatient oral treatment
- **community-acquired pneumonia caused by susceptible organisms in patients who require initial intravenous therapy**
In clinical studies, efficacy has been demonstrated against *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*.

2. Upper respiratory tract infections

- **acute sinusitis** due to *Streptococcus pneumoniae* or *Haemophilus influenzae*
- **acute streptococcal pharyngitis**
Note: penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin appears to be almost as effective in the treatment of streptococcal pharyngitis. However, substantial data establishing the efficacy of azithromycin in the subsequent prevention of rheumatic fever is not available at present.
- **acute otitis media**

3. Uncomplicated skin and skin structure infections

- **uncomplicated infections** due to *Staphylococcus aureus*, *Streptococcus pyogenes* or *Streptococcus agalactiae*
Surgical drainage is usually required for abscesses.

4. Sexually transmitted diseases

- **uncomplicated urethritis and cervicitis** due to *Chlamydia trachomatis* or non multi-resistant *Neisseria gonorrhoeae*
- **Note:** at the recommended dose, azithromycin cannot be relied upon to treat syphilis. As with other drugs for the treatment of non-gonococcal infections, azithromycin may mask or delay the symptoms of incubating syphilis and, therefore, concurrent infection with *Treponema pallidum*



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should be excluded. Appropriate tests should be performed for the detection of syphilis and treatment should be instituted as required.

5. **Pelvic inflammatory disease** caused by susceptible organisms (*Chlamydia trachomatis*, *Neisseria gonorrhoea*, *Mycoplasma hominis*), in patients who require initial intravenous therapy
6. ***Chlamydia trachomatis* conjunctivitis and trachoma**
7. **Prevention of infection due to *Mycobacterium avium-intracellulare* complex disease**, when used as the sole agent or in combination with rifabutin at its approved dose, in adults with HIV infection and CD4 cell count less than or equal to 75 cells/ μ L. Disseminated infection due to *Mycobacterium avium-intracellulare* complex should be excluded by a negative blood culture prior to the commencement of therapy.

Azithromycin is indicated for use in **children** for the treatment of the following infections:

1. **Lower respiratory tract infections**
2. **Upper respiratory tract infections**
3. **Uncomplicated skin and skin structural infections**
4. **Acute streptococcal pharyngitis or tonsillitis**
Note: penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. The 20 mg/kg azithromycin dose appears to be as effective as penicillin in the treatment of streptococcal pharyngitis. However, substantial data establishing the efficacy of azithromycin in the subsequent prevention of rheumatic fever are not available at present.
5. ***Chlamydia trachomatis* conjunctivitis and trachoma** in children 12 months or older, based on 20 mg/kg/dose
6. **Prevention of infection due to *Mycobacterium avium-intracellulare* complex disease**, when used as the sole agent or in combination with rifabutin at its approved dose, in children aged more than 12 years with HIV infection and CD4 cell count less than or equal to 75 cells/ μ L. Disseminated infection due to *Mycobacterium avium-intracellulare* complex should be excluded by a negative blood culture prior to the commencement of therapy.

4.2 Posology and Method of Administration:

Azithromycin is administered as a single daily dose, taken on an empty stomach.



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Adults

All indications (except the following), including outpatients initiated on oral treatment for community-acquired pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae*: total dose of 1.5 g, taken as 500 mg on day 1, then 250 mg daily on days 2 to 5, or alternatively as 500 mg daily for 3 days.

Following intravenous (IV) therapy for the treatment of community-acquired pneumonia: 500 mg as a single daily dose to complete a 7- to 10-day course of therapy.

Following IV therapy for the treatment of pelvic inflammatory disease: 250 mg as a single daily dose to complete a 7-day course of therapy.

Sexually transmitted uncomplicated urethritis and cervicitis due to *Chlamydia trachomatis* or susceptible *Neisseria gonorrhoeae*: 1 g as a single dose.

Conjunctivitis and trachoma due to *Chlamydia trachomatis*: 1 g either as a single dose or once weekly for up to three weeks

Prevention of disseminated MAC disease in adults with HIV infection: 1,200 mg taken as a single dose once weekly, either alone or in combination with rifabutin at its recommended dosage.

Children

All indications (except the following): 10 mg/kg as a single dose on the first day, followed by 5 mg/kg/day on days 2 to 5. For children weighing more than 45 kg, dose as per adults.

Streptococcal pharyngitis and tonsillitis: 20 mg/kg once daily for 3 consecutive days providing a total dose of 60 mg/kg over a 3-day treatment period. Do not exceed a daily dose of 500 mg. For children weighing more than 45 kg, dose as per adults.

Acute otitis media: total dose of 30 mg/kg, given as 30 mg/kg as a single dose or 10 mg/kg once daily for 3 days, or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on days 2 to 5. For children weighing more than 45 kg, dose as per adults.

Conjunctivitis and trachoma due to *Chlamydia trachomatis* in children aged 12 months or older: 20 mg/kg either as a single dose or once weekly for up to three weeks.

Prevention of disseminated MAC disease in children aged more than 12 years old with HIV infection: 1,200 mg taken as a single dose once weekly, either alone or in combination with rifabutin at its recommended dosage.

4.3 Contraindications

Patients with known hypersensitivity to azithromycin, erythromycin, any other macrolide or ketolide antibiotic, or to any component of the product

4.4 Special Warnings and special Precautions for use



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Community-acquired pneumonia

In the treatment of pneumonia, azithromycin has been shown to be safe and effective **only** in the treatment of community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy.

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as patients with the following conditions:

- cystic fibrosis
- nosocomially-acquired infections
- known or suspected bacteremia
- requiring hospital admission
- who are the elderly or debilitated
- significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including azithromycin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use, which may occur up to several weeks after cessation of therapy. Mild cases may respond to drug discontinuation alone. However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil[®]), may prolong and/or worsen the condition and should not be used.

4.5 Interaction with other medicinal products and other forms of interaction

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.

Drugs that should not be concomitantly administered with azithromycin:

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 up to 30%. In patients receiving azithromycin and antacids, the drugs should not be taken simultaneously.

Ergot - the theoretical possibility of ergotism contraindicates the concurrent use of azithromycin with ergot derivatives.

Drugs that require dosage adjustment when administered concomitantly with azithromycin:

Cyclosporin - in a pharmacokinetic study with healthy volunteers that were administered an oral dose of 500 mg/day of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose to be adjusted accordingly.

Drugs that have been studied with no clinically significant interaction shown:

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.

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.

Cimetidine - in a study investigating the effects of a single dose of cimetidine (given 2 hours before azithromycin) on the pharmacokinetics of azithromycin, no alteration of the pharmacokinetic parameters of azithromycin 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.

Didanosine - co-administration of 1,200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects for 2 weeks had no effect on the steady-state pharmacokinetics of didanosine as compared to placebo.

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. No dose adjustment is necessary when azithromycin is given with efavirenz.

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. No dose adjustment is necessary when azithromycin is given with fluconazole.

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. No adjustment of the dose is necessary when azithromycin is given with indinavir.

Methylprednisolone - in a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

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Midazolam - in healthy volunteers, co-administration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetic or pharmacodynamic variables of a single 15 mg dose of midazolam.

Nelfinavir - co-administration of 1,200 mg azithromycin and nelfinavir at steady-state (811 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and, thus, 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 with azithromycin and rifabutin. Although neutropenia has been associated with use of rifabutin, a causal relationship to the 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 C_{max} of sildenafil or its major circulating metabolite.

Terfenadine and astemizole - during the steady-state dosing of terfenadine, addition of azithromycin did not result in any significant changes in cardiac repolarisation (QTc interval) measured in normal subjects. However, there have been cases reported where the possibility of such an interaction could not be entirely excluded.

Theophylline - there was no evidence of any pharmacokinetic interaction when azithromycin and theophylline were co-administered to healthy volunteers.

Triazolam - in 14 healthy volunteers, after administering azithromycin 500 mg on day 1, co-administration of azithromycin 250 mg with triazolam 0.125 mg on day 2 had no significant effect on any of the pharmacokinetic variables for triazolam (when compared with triazolam plus placebo).

Trimethoprim and sulfamethoxazole - co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin 1,200 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. No dose adjustment is necessary.

Zidovudine - a single dose of azithromycin 1,000 mg or multiple doses of 1,200 mg or 600 mg did not affect the plasma pharmacokinetics or urinary excretion of zidovudine, or its glucuronide metabolite. However, azithromycin increased the concentrations of phosphorylated zidovudine, the active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear.

Other interactions:

Digoxin - 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 and digoxin, the possibility of raised digoxin levels should be borne in mind.

4.6 Pregnancy and lactation**Use in pregnancy (Category B1)**

No studies have been carried out in pregnant women. Azithromycin was not foetotoxic or teratogenic in mice and rats at doses that were moderately maternotoxic (up to 200 mg/kg/day). At 200 mg/kg/day, mouse and rat



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fetal tissues homogenate concentrations were 5- to 10-fold higher than corresponding maternal plasma concentrations.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in lactation

There is no data on the possible secretion of azithromycin into animal or human breast milk. However, azithromycin should only be used in lactating women where adequate alternatives are not available.

4.7 Effects on ability to drive and use machines

Azithromycin may cause dizziness and fatigue. Individual response should be determined before driving or performing tasks requiring alertness.

4.8 Undesirable effects**Clinical trials**

In clinical trials, most of the reported adverse events were mild to moderate in severity and were reversible on discontinuation of the drug. Approximately 0.7% of patients discontinued the azithromycin therapy because of treatment-related adverse events. Most of the adverse events leading to discontinuation were related to the gastrointestinal tract such as nausea, vomiting, diarrhoea or abdominal pain. Rare, but potentially serious, adverse events were angioedema (1 case) and cholestatic jaundice (1 case).

Hearing impairment has been reported in investigational studies, mainly where higher doses were used for prolonged periods of time. In those cases where follow-up information was available, the majority of these events were reversible.

1. Adults***Multiple-dose regimen***

The most frequently reported adverse events in patients receiving the multiple-dose regimen of azithromycin were related to the gastrointestinal system with diarrhoea or loose stools (5%), nausea (3%) and abdominal pain (3%) being the most frequently reported. No other side effects occurred in patients on the multiple-dose regimen with a frequency greater than 1%.

Side effects that occurred with a frequency of 1% or less included the following:

Allergic - rash, photosensitivity, angioedema

Cardiovascular - palpitations, chest pain

Gastrointestinal - dyspepsia, flatulence, vomiting, melaena, cholestatic jaundice

Genitourinary - moniliasis, vaginitis, nephritis

Nervous system - dizziness, headache, vertigo, somnolence

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General - fatigue
Single 1-gram dose regimen

The most frequently reported adverse events in patients receiving a single-dose regimen of 1 g of azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen. Adverse events that occurred in patients on the single 1-gram dosing regimen of azithromycin with a frequency of 1% or greater included diarrhoea/loose stools (7%), nausea (5%), abdominal pain (5%) vomiting (2%), vaginitis (2%) and dyspepsia (1%).

Laboratory abnormalities

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

Incidence \geq 1%: elevated serum creatinine phosphokinase, potassium, alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), lymphocytes and neutrophils; decreased neutrophils

Incidence $<$ 1%: leukopenia, neutropenia, thrombocytopenia; elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, lactate dehydrogenase, phosphate, monocytes, basophils, bicarbonate; decreased sodium and potassium.

When the follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose trials involving more than 3,000 patients, 3 patients discontinued the therapy due to treatment-related liver enzyme abnormalities, and 1 due to renal function abnormality.

HIV infected patients receiving prophylaxis for disseminated MAC

The most frequent (greater than 5% in any treatment group) treatment-related adverse events in this group are shown in the following table

	Study 155		Study 174		
	Placebo %	Azithromycin %	Azithromycin %	Rifabutin %	Combination therapy %
Adverse Event (AE)	N = 91	N = 89	N = 233	N = 236	N = 224
Diarrhoea	15.4	52.8	50.2	19.1	50.9
Loose stools	6.6	19.1	12.9	3.0	9.4
Nausea	11.0	32.6	27.0	16.5	28.1
Vomiting	1.1	6.7	9.0	3.8	5.8
Dyspepsia	1.1	9.0	4.7	1.7	1.8
Abdominal pain	6.6	27	32.2	12.3	31.7
Flatulence	4.4	9.0	10.7	5.1	5.8
Rash	2.2	3.4	6.0	8.1	9.8



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	Study 155		Study 174		
	Placebo %	Azithromycin %	Azithromycin %	Rifabutin %	Combination therapy %
Adverse Event (AE)	N = 91	N = 89	N = 233	N = 236	N = 224
Pruritus	3.3	0	3.9	3.4	7.6
Headache	0	0	3.0	5.5	4.5
Arthralgia	0	0	3.0	4.2	7.1
Subjects with AEs	31.9	79.8	78.1	59.7	83.5

The most common laboratory test abnormalities in this group were haematological (mainly decreases in haemoglobin and white cell count) and increases in AST and ALT.

2. Children

The side effect profile in children is comparable to that of adults. No new adverse events have been reported in children. In the treatment of streptococcal pharyngitis, the 20 mg/kg/day dose is associated with a higher rate of adverse events. These are mainly gastrointestinal and remain mild to moderate.

The following table indicates the adverse events that were reported at an occurrence of greater than or equal to 1% in a 3-day treatment, and where a causal relationship to treatment could not be ruled out.

Category of event	Event	Azithromycin (Study 96-001)	
		10 mg/kg* (N = 169)	20 mg/kg* (N = 165)
Gastrointestinal system disorders	Abdominal pain	2%	5%
	Diarrhoea	3%	6%
	Nausea	1%	3%
	Vomiting	7%	9%
General condition disorders	Allergic reaction	2%	-
Skin and accessory structures	Eczema	1%	-
	Rash	1%	-

3. Post-marketing experience

In post-marketing experience, the following adverse events have been reported:

Infections and infestations - moniliasis, vaginitis

Body as a whole - asthenia, anaphylaxis (rarely fatal), malaise

Cardiovascular - hypotension, arrhythmias including ventricular tachycardia (as seen with other macrolides), rare reports of QT prolongation and torsades de pointes (a causal relationship between azithromycin and all these effects has not been established)



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Central and peripheral nervous system - dizziness, somnolence, headache, syncope, convulsions (as seen with other macrolides), paraesthesia, hyperactivity

Gastrointestinal - vomiting or diarrhoea (rarely resulting in dehydration), dyspepsia, pancreatitis, anorexia, constipation, pseudomembranous colitis, rare reports of tongue discolouration

Genitourinary - acute renal failure, interstitial nephritis

Liver or biliary - hepatitis, cholestatic jaundice, hepatic necrosis, hepatic failure (rarely resulted in death) (a causal relationship has not been established)

Musculoskeletal - arthralgia

Psychiatric - aggressive reaction, nervousness, agitation, anxiety

Skin or appendages - pruritus, urticaria, oedema, serious skin reactions including erythema multiforme, rash, photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis

Special senses - vertigo, hearing disturbances* including hearing loss, deafness and/or tinnitus, taste or smell perversion and/or loss (a causal relationship has not been established)

* Hearing impairment has been reported with macrolide antibiotics.

4.9 Overdose

Most adverse events experienced in higher than recommended doses were similar in nature but may be more frequent than those seen at normal doses. The incidence of tinnitus and ototoxicity is more frequent in overdosage than at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

As with many cationic amphiphilic drugs, multiple doses of azithromycin have been shown to induce phospholipidosis in some tissues of mice, rats and dogs. This has been demonstrated in dogs at doses that were as low as 2 to 3 times greater than the recommended human dose, and in rats at doses comparable to the human doses. This effect is reversible after cessation of azithromycin treatment. The significance of these findings in humans with overdose of azithromycin is unknown.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Microbiology

Azithromycin demonstrates activity *in vitro* against a wide range of bacteria including the following:

Gram-positive aerobic bacteria - *Staphylococcus aureus*, *Streptococcus pyogenes* (group A beta-haemolytic streptococci), *Streptococcus pneumoniae*, alpha-haemolytic streptococci (viridans group) and other streptococci, and *Corynebacterium diphtheriae*. Azithromycin demonstrates cross resistance with erythromycin resistant-positive strains, including *Streptococcus faecalis* (enterococcus) and most strains of methicillin-resistant staphylococci.



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Gram-negative aerobic bacteria - *Haemophilus influenzae* (including beta-lactamase producing *Haemophilus influenzae*), *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Acinetobacter* species, *Yersinia* species, *Legionella pneumophila*, *Bordetella pertussis*, *Bordetella parapertussis*, *Shigella* species, *Pasteurella* species, *Vibrio cholerae* and *parahaemolyticus*, *Plesiomonas shigelloides*. Activities against *Escherichia coli*, *Salmonella enteritidis*, *Salmonella typhi*, *Enterobacter* species, *Aeromonas hydrophila* and *Klebsiella* species are variable and susceptibility tests should be performed.

Proteus species, *Serratia* species, *Morganella* species and *Pseudomonas aeruginosa* are usually resistant.

Anaerobic bacteria - *Bacteroides fragilis* and *Bacteroides* species, *Clostridium perfringens*, *Peptococcus* species, *Peptostreptococcus* species, *Fusobacterium necrophorum* and *Propionibacterium acnes*.

Organisms of sexually transmitted diseases - azithromycin is active against *Chlamydia trachomatis* and also shows good activity against *Treponema pallidum*, *Neisseria gonorrhoeae* and *Haemophilus ducreyi*.

Other organisms - *Borrelia burgdorferi* (Lyme disease agent), *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Campylobacter* species and *Listeria monocytogenes*.

Opportunistic pathogens associated with human immunodeficiency virus (HIV) infections - *Mycobacterium avium-intracellulare* complex.

Azithromycin demonstrates activity *in vivo* against the following bacteria:

Gram-positive aerobic bacteria - *Staphylococcus aureus*, *Streptococcus pyogenes* (group A beta-haemolytic streptococci), *Streptococcus pneumoniae*, alpha-haemolytic streptococci (viridans group) and other streptococci.

Gram-negative aerobic bacteria - *Haemophilus influenzae* (including beta-lactamase producing *Haemophilus influenzae*), *Haemophilus parainfluenzae*, *Moraxella catarrhalis*.

Other organisms - *Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*.

Opportunistic pathogens associated with HIV infections - *Mycobacterium avium-intracellulare* complex.

In Australia, macrolide resistance for *Streptococcus pneumoniae* and *Staphylococcus aureus* has been increasing since the late 1990's. Resistance rates of 15% or more are regularly reported. The use of macrolides should be guided by culture susceptibility results and practice guidelines.

Susceptibility testing

Dilution or diffusion techniques, either quantitative (minimal inhibitory concentration, MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. National Committee for Clinical Laboratory Standards). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited when the patient is given the recommended dose. A report of "Intermediate" indicates that the result should be considered equivocal, and if the micro-organism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body site where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation.



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A report of "Resistant" indicates that the pathogen is not likely to be inhibited when the patient is given the recommended dose. Other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Susceptibility testing for *Mycobacterium avium* complex (MAC)

The disk diffusion techniques and dilution methods for susceptibility testing against Gram-positive and Gram-negative bacteria should not be used for determining azithromycin MIC values against mycobacteria. *In-vitro* susceptibility testing methods and diagnostic products currently available for determining MIC values against MAC organisms have not been established or validated. Azithromycin MIC values will vary depending on the susceptibility testing method employed, composition and pH of media and the utilization of nutritional supplements. Breakpoints used to determine whether clinical isolates of *M. avium* or *M. intracellulare* are susceptible to azithromycin but have not been established.

Clinical trials

Disseminated MAC disease prophylaxis

In a placebo-controlled study, patients receiving azithromycin were less than one-half as likely to develop MAC bacteremia as those on placebo. The 1-year cumulative incidence rate of disseminated MAC disease was 8.24% on azithromycin and 20.22% on placebo.

In a comparative study, the risk of developing MAC bacteremia in patients receiving azithromycin was less than that observed for patients receiving rifabutin. Patients on a combination of azithromycin and rifabutin were approximately one-third as likely to develop MAC bacteremia as those patients receiving either agent alone. The 1-year cumulative incidence rate of disseminated MAC disease was 7.62% on azithromycin, 15.25% on rifabutin and 2.75% on azithromycin and rifabutin. However, patients receiving the combination were more likely to discontinue therapy due to poor tolerability.

Trachoma

Children and adults

Data from clinical trials and other published studies support the efficacy of 20 mg/kg to 1 g, taken either as a single dose or each week for three weeks, in the treatment of trachoma in children and adults. However, the single dose schedule has not been compared with the 3-weekly dosing schedule in clinical trials.

Repeat courses

While the statistically significant superiority of a single dose of azithromycin given as a single dose and repeated at 6 months versus a single dose of azithromycin to adults or children with active trachoma has not been determined, information from clinical trials suggests that the trachoma-free period may be extended by a repeat single dose of azithromycin at 6 months.

Pharyngitis or tonsillitis

In a clinical trial (Study 96-001), 501 children aged 2 to 12 years with a clinical diagnoses of acute tonsillitis received azithromycin 10 mg/kg/day or 20 mg/kg/day for 3 days, or penicillin V 50 mg/kg (in 3 divided doses) for 10 days. Similar clinical efficacy but greater bacteriological eradication was evident at the 20 mg/kg/day dose of azithromycin (maximum 500 mg daily). Group A beta-haemolytic streptococci (GABHS) eradication rates and clinical response rates are detailed below:

MODULE 1

Treatment	Day 14	Day 30
Azithromycin 10 mg/kg	57.8 %	56.8 %
Azithromycin 20 mg/kg	94.2 %	82.8 %
Penicillin V 50 mg/kg	84.2 %	81.6 %

4. Clinical response rates (success)

Treatment	Day 14
Azithromycin 10 mg/kg	94.1 %
Azithromycin 20 mg/kg	100.0%
Penicillin V 50 mg/kg	94.5%

5.2 Pharmacokinetic properties
Absorption

Following oral administration of a single 500 mg dose to fasted subjects, mean maximum serum concentration (C_{max}) of 0.24 to 0.87 $\mu\text{g/mL}$ was achieved in about 1.0 to 3.5 hours, with a mean area under the curve (AUC_{0-24}) of 3.05 $\mu\text{g}\cdot\text{hr/mL}$. The absolute bioavailability of azithromycin is 37%.

The extent of absorption is unaffected by co-administration with antacid. However, C_{max} is reduced by up to 30%. Administration of cimetidine (800 mg) 2 hours prior to azithromycin had no effect on the absorption of azithromycin.

Azithromycin did not affect the plasma levels or pharmacokinetics of carbamazepine, methylprednisolone, zidovudine or multiple oral doses of theophylline.

Distribution

Azithromycin is distributed widely throughout the body. Rapid movement of azithromycin from blood into tissues results in significantly higher azithromycin concentrations in tissue than in plasma (from 1 to 60 times the maximum observed concentration in plasma). It appears to be concentrated intracellularly. Concentrations in tissues, e.g. lung, tonsil and prostate, exceed the MIC_{90} for likely pathogens after a single dose of 500 mg, and remain high after serum or plasma concentrations decline to below detectable levels. Mean peak concentrations observed in peripheral leucocytes, the site of MAC infection, were 140 $\mu\text{g/mL}$ and remained above 32 $\mu\text{g/mL}$ for approximately 60 hours following a single 1,200 mg oral dose.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 $\mu\text{g/mL}$ to 7% at 2 $\mu\text{g/mL}$.

Metabolism

In vitro and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

Elimination

Serum concentrations decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. The high values for apparent steady-state volume of distribution (31.1 L/kg) and plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues. Azithromycin concentrations in the cerebrospinal fluid are very low. Concentrations in the peritoneal fluid are also very low.

**MODULE 1**

Approximately 12% of an intravenously administered dose is excreted in the urine over three days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug following oral administration. Very high concentrations of unchanged drug have been found, together with ten 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.

5.3 Preclinical safety data**Carcinogenesis, mutagenesis, impairment of fertility**

No studies have been done to determine the carcinogenic potential of azithromycin in animals. Azithromycin showed no genotoxic potential in a range of standard laboratory tests for gene mutations and chromosomal damage. In three fertility and general reproduction studies in rats, there was decreased fertility at doses of 20 and 30 mg/kg/day. The clinical significance of this is unknown.

6. PHARMACEUTICAL PARTICULARS**6.1 List of Excipients:**

- Povidone-30
- Isopropyl alcohol
- Purified Talc.
- Magnesium Stearate
- Cross Carmellose Sodium
- Sodium Starch Glycollate
- Colloidal Silicon Dioxide
- Microcrystalline Cellulose
- Titanium Dioxide
- P.VP.K-30
- Purified Talc
- Purified Talc (For Dusting)
- HPMC-15 cps
- PEG-6000
- Iso Propyl Alcohol
- Methylene Di Chloride



MODULE 1

6.2 Incompatibilities

None

6.3 Shelf life

36 months from the date of manufacturers

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

01 x 03's Alu pvc blister packed in a unit carton; such cartons are packed in a corrugated box.

6.6 Special precautions for disposal

Tablets should be handled with care.

Keep the medicine out of reach of children

7. REGISTRANT

Name of Registrant:

Maxtar Bio-Genics

Address of Office:

310, Pearls Corporate (W Mall),
Manglam Place ,Sector- 3,Rohini,
Delhi-85 India.

8. MANUFACTURER

Name of Manufacturer:

Maxtar Bio-Genics



MODULE 1

Address of Manufacturer:

K. No. 705, Nalagarh road, Malku Majra,
(Baddi), Tehsil Nalagarh ,Distt. Solan,
Himachal Pradesh - 173205
INDIA

9. DATE OF REVISION OF THE TEXT

Fresh Authorization