

# azithromycin for injection

For I.V. infusion only

Rx only

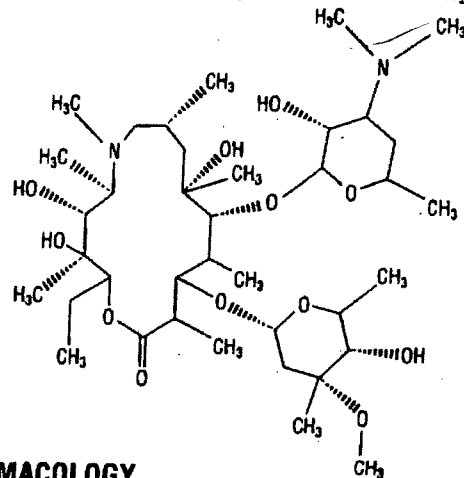
To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin and other bacterial drugs, azithromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

## DESCRIPTION

Azithromycin for injection contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for intravenous injection. Azithromycin has the chemical name (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- $\alpha$ -*L*-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-hepta-methyl-11-[[[3,4,6-trideoxy-3-(dimethylamino)- $\beta$ -*D*-xylo-hexopyranosyl]oxy]-1-oxa-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. Azithromycin has the following structural formula:

Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of  $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$  and a molecular weight of 785.0.

Azithromycin for injection consists of azithromycin dihydrate and the following inactive ingredients: citric acid and sodium hydroxide. Azithromycin for injection is supplied in lyophilized form in a 10-mL vial equivalent to 500 mg of azithromycin for intravenous administration. Reconstitution, according to label directions, results in approximately 5 mL of azithromycin for intravenous injection with each mL containing azithromycin dihydrate equivalent to 100 mg of azithromycin.



## CLINICAL PHARMACOLOGY

### Pharmacokinetics

In patients hospitalized 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  $C_{max} \pm S.D.$  achieved was  $3.63 \pm 1.60 \mu\text{g/mL}$ , while the 24-hour trough level was  $0.20 \pm 0.15 \mu\text{g/mL}$ , and the  $AUC_{24}$  was  $9.60 \pm 4.80 \mu\text{g}\cdot\text{h/mL}$ .

The mean  $C_{max}$ , 24-hour trough and  $AUC_{24}$  values were  $1.14 \pm 0.14 \mu\text{g/mL}$ ,  $0.18 \pm 0.02 \mu\text{g/mL}$ , and  $8.03 \pm 0.86 \mu\text{g}\cdot\text{h/mL}$ , respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/mL. Similar pharmacokinetic values were obtained in patients hospitalized with community-acquired pneumonia that received the same 3-hour dosage regimen for 2-5 days.

Table 1. Plasma Concentrations ( $\mu\text{g/mL} \pm S.D.$ ) After the Last Daily Intravenous Infusion of 500 mg Azithromycin

Infusion Concentration, Duration	Time after starting the infusion (hr)								
	0.5	1	2	3	4	6	8	12	24
2 mg/mL, 1 hr <sup>a</sup>	2.98	3.63	0.60	0.40	0.33	0.26	0.27	0.20	0.20
	$\pm 1.12$	$\pm 1.73$	$\pm 0.31$	$\pm 0.23$	$\pm 0.16$	$\pm 0.14$	$\pm 0.15$	$\pm 0.12$	$\pm 0.15$
1 mg/mL, 3 hr <sup>b</sup>	0.91	1.02	1.14	1.13	0.32	0.28	0.27	0.22	0.18
	$\pm 0.13$	$\pm 0.11$	$\pm 0.13$	$\pm 0.16$	$\pm 0.05$	$\pm 0.04$	$\pm 0.03$	$\pm 0.02$	$\pm 0.02$

- <sup>a</sup> = 500 mg (2 mg/mL) for 2-5 days in community-acquired pneumonia patients
- <sup>b</sup> = 500 mg (1 mg/mL) for 5 days in healthy subjects

The average  $CL_T$  and  $V_d$  values were 10.18 mL/min/kg and 33.3 L/kg, respectively, in 18 normal volunteers receiving 1000 to 4000-mg doses given as 1 mg/mL over 2 hours.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg intravenous azithromycin showed only an 8% increase in  $C_{max}$  but a 61% increase in  $AUC_{24}$  reflecting a threefold rise in  $C_{24}$  trough levels.

Following single oral doses of 500 mg azithromycin (two 250 mg capsules) to 12 healthy volunteers,  $C_{max}$ , trough level, and  $AUC_{24}$  were reported to be 0.41  $\mu\text{g/mL}$ , 0.05  $\mu\text{g/mL}$ , and 2.6  $\mu\text{g}\cdot\text{h/mL}$ , respectively. These oral values are approximately 38%, 83%, and 52% of the values observed following a single 500-mg I.V. 3-hour infusion ( $C_{max}$ : 1.08  $\mu\text{g/mL}$ , trough: 0.06  $\mu\text{g/mL}$ , and  $AUC_{24}$ : 5.0  $\mu\text{g}\cdot\text{h/mL}$ ). Thus, plasma concentrations are higher following the intravenous regimen throughout the 24-hour interval. The pharmacokinetic parameters on day 5 of azithromycin 250-mg capsules following a 500-mg oral loading dose to healthy young adults (age 18-40 years old) were as follows:  $C_{max}$ : 0.24  $\mu\text{g/mL}$ ,  $AUC_{24}$ : 2.1  $\mu\text{g}\cdot\text{h/mL}$ . Azithromycin 250 mg capsules are no longer commercially available. Azithromycin 250 mg tablets are bioequivalent to 250 mg capsules in the fasting state.

Median azithromycin exposure ( $AUC_{0-288}$ ) in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following 1,500 mg of oral azithromycin, administered in single daily doses over either 5 days (two 250 mg tablets on day 1, followed by one 250 mg tablet on days 2-5) or 3 days (500 mg per day for days 1-3) to 12 healthy volunteers, was more than a 1000-fold and 800-fold greater than in serum, respectively.

#### Distribution

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  $\mu\text{g/mL}$ .

Tissue concentrations have not been obtained following intravenous infusions of azithromycin. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios following oral administration of azithromycin are shown in the following table:

**Table 2. Azithromycin Concentrations Following a 500 mg Dose (Two 250 mg Capsules) in Adults**

Tissue or Fluid	Time After Dose (hr)	Tissue or Fluid Concentration ( $\mu\text{g/g}$ or $\mu\text{g/mL}$ ) <sup>1</sup>	Corresponding Plasma or Serum Level ( $\mu\text{g/mL}$ )	Tissue (Fluid) Plasma (Serum) Ratio <sup>1</sup>
Skin	72-96	0.4	0.012	35
Lung	72-96	4.0	0.012	>100
Sputum*	2-4	1.0	0.64	2
Sputum**	10-12	2.9	0.1	30
Tonsil***	9-18	4.5	0.03	>100
Tonsil****	180	0.9	0.006	>100
Cervix*****	19	2.8	0.04	70

<sup>1</sup> High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial 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.

\* Sample was obtained 2-4 hours after the first dose.

\*\* Sample was obtained 10-12 hours after the first dose.

\*\*\* Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.

\*\*\*\* Sample was obtained 19 hours after a single 500 mg dose.

Tissue levels were determined following a single oral dose of 500 mg azithromycin in 7 gynecological patients. Approximately 17 hours after dosing, azithromycin concentrations were 2.7 µg/g in ovarian tissue, 3.5 µg/g in uterine tissue, and 3.3 µg/g in salpinx. Following a regimen of 500 mg on the first day followed by 250 mg daily for 4 days, concentrations in the cerebrospinal fluid were less than 0.01 µg/mL in the presence of non-inflamed meninges.

#### **Metabolism**

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

#### **Elimination**

Plasma concentrations of azithromycin following single 500 mg oral and I.V. doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues.

In a multiple-dose study in 12 normal volunteers utilizing 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. Biliary excretion is a major route of elimination for unchanged drug, following oral administration.

#### **Special Populations**

##### **Renal Insufficiency**

Azithromycin pharmacokinetics were investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1,000 mg dose of azithromycin, mean  $C_{max}$  and  $AUC_{0-120}$  increased by 5.1% and 4.2%, respectively in subjects

with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean  $C_{max}$  and  $AUC_{0-120}$  increased 61% and 35%, respectively in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). (See **DOSAGE AND ADMINISTRATION**.)

#### **Hepatic Insufficiency**

The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established.

#### **Gender**

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

#### **Geriatric Patients**

Pharmacokinetic studies with intravenous azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen.

#### **Pediatric Patients**

Pharmacokinetic studies with intravenous azithromycin have not been performed in children.

#### **Drug-Drug Interactions**

Drug interaction studies were performed with oral azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 3 and the effect of other drugs on the pharmacokinetics of azithromycin are shown in Table 4.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 3. No dosage adjustment of drugs listed in Table 3 is recommended when co-administered with azithromycin.

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the  $C_{max}$  and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 4. (See **PRECAUTIONS - Drug Interactions**.)

**Table 3. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin**

Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (with/without azithromycin) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00	
				Mean C <sub>max</sub>	Mean AUC
Atorvastatin	10 mg/day x 8 days	500 mg/day PO on days 6-8	12	0.83 (0.63 to 1.08)	1.01 (0.81 to 1.25)
Carbamazepine	200 mg/day x 2 days, then 200 mg BID x 18 days	500 mg/day PO for days 16-18	7	0.97 (0.88 to 1.06)	0.96 (0.88 to 1.06)
Cetirizine	20 mg/day x 11 days	500 mg PO on day 7, then 250 mg/day on days 8-11	14	1.03 (0.93 to 1.14)	1.02 (0.92 to 1.13)
Didanosine	200 mg PO BID x 21 days	1,200 mg/day PO on days 8-21	6	1.44 (0.85 to 2.43)	1.14 (0.83 to 1.57)
Efavirenz	400 mg/day x 7 days	600 mg PO on day 7	14	1.04*	0.95*
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	1.04 (0.98 to 1.11)	1.01 (0.97 to 1.05)
Indinavir	800 mg TID x 5 days	1,200 mg PO on day 5	18	0.96 (0.86 to 1.08)	0.90 (0.81 to 1.00)
Midazolam	15 mg PO on day 3	500 mg/day PO x 3 days	12	1.27 (0.89 to 1.81)	1.26 (1.01 to 1.56)
Nelfinavir	750 mg TID x 11 days	1,200 mg PO on day 9	14	0.90 (0.81 to 1.01)	0.85 (0.78 to 0.93)
Rifabutin	300 mg/day x 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	See footnote below	NA
Sildenafil	100 mg on days 1 and 4	500 mg/day PO x 3 days	12	1.16 (0.86 to 1.57)	0.92 (0.75 to 1.12)
Theophylline	4 mg/kg IV on days 1, 11, 25	500 mg PO on day 7, 250 mg/day on days 8-11	10	1.19 (1.02 to 1.40)	1.02 (0.86 to 1.22)
Theophylline	300 mg PO BID x 15 days	500 mg PO on day 6, then 250 mg/day on days 7-10	8	1.09 (0.92 to 1.29)	1.08 (0.89 to 1.31)
Triazolam	0.125 mg on day 2	500 mg PO on day 1, then 250 mg/day on day 2	12	1.06*	1.02*
Trimethoprim/Sulfamethoxazole	160 mg/800 mg/day PO x 7 days	1,200 mg PO on day 7	12	0.85 (0.75 to 0.97)/ 0.90 (0.78 to 1.03)	0.87 (0.80 to 0.95)/ 0.96 (0.88 to 1.03)
Zidovudine	500 mg/day PO x 21 days	600 mg/day PO x 14 days	5	1.12 (0.42 to 3.02)	0.94 (0.52 to 1.70)
Zidovudine	500 mg/day PO x 21 days	1,200 mg/day PO x 14 days	4	1.31 (0.43 to 3.97)	1.30 (0.69 to 2.43)

NA - not available

\* 90% confidence interval not reported

Mean rifabutin concentrations one-half day after the last dose of rifabutin were 60 ng/mL when co-administered with azithromycin and 71 ng/mL when co-administered with placebo.

**Table 4. Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs (See PRECAUTIONS - Drug Interactions.)**

Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (with/without co-administered drug) of Azithromycin Pharmacokinetic Parameters (90% CI); No Effect = 1.00	
				Mean C <sub>max</sub>	Mean AUC
Efavirenz	400 mg/day x 7 days	600 mg PO on day 7	14	1.22 (1.04 to 1.42)	0.92*
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	0.82 (0.66 to 1.02)	1.07 (0.94 to 1.22)
Nelfinavir	750 mg TID x 11 days	1,200 mg PO on day 9	14	2.36 (1.77 to 3.15)	2.12 (1.80 to 2.50)
Rifabutin	300 mg/day x 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	See footnote below	NA

NA - not available

\* 90% confidence interval not reported

Mean azithromycin concentrations one day after the last dose were 53 ng/mL when coadministered with 300 mg daily rifabutin and 49 ng/mL when coadministered with placebo.

#### **Microbiology**

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for azithromycin for injection.

#### **Aerobic and facultative Gram-positive microorganisms**

*Staphylococcus aureus*

*Streptococcus pneumoniae*

NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant staphylococci are resistant to azithromycin.