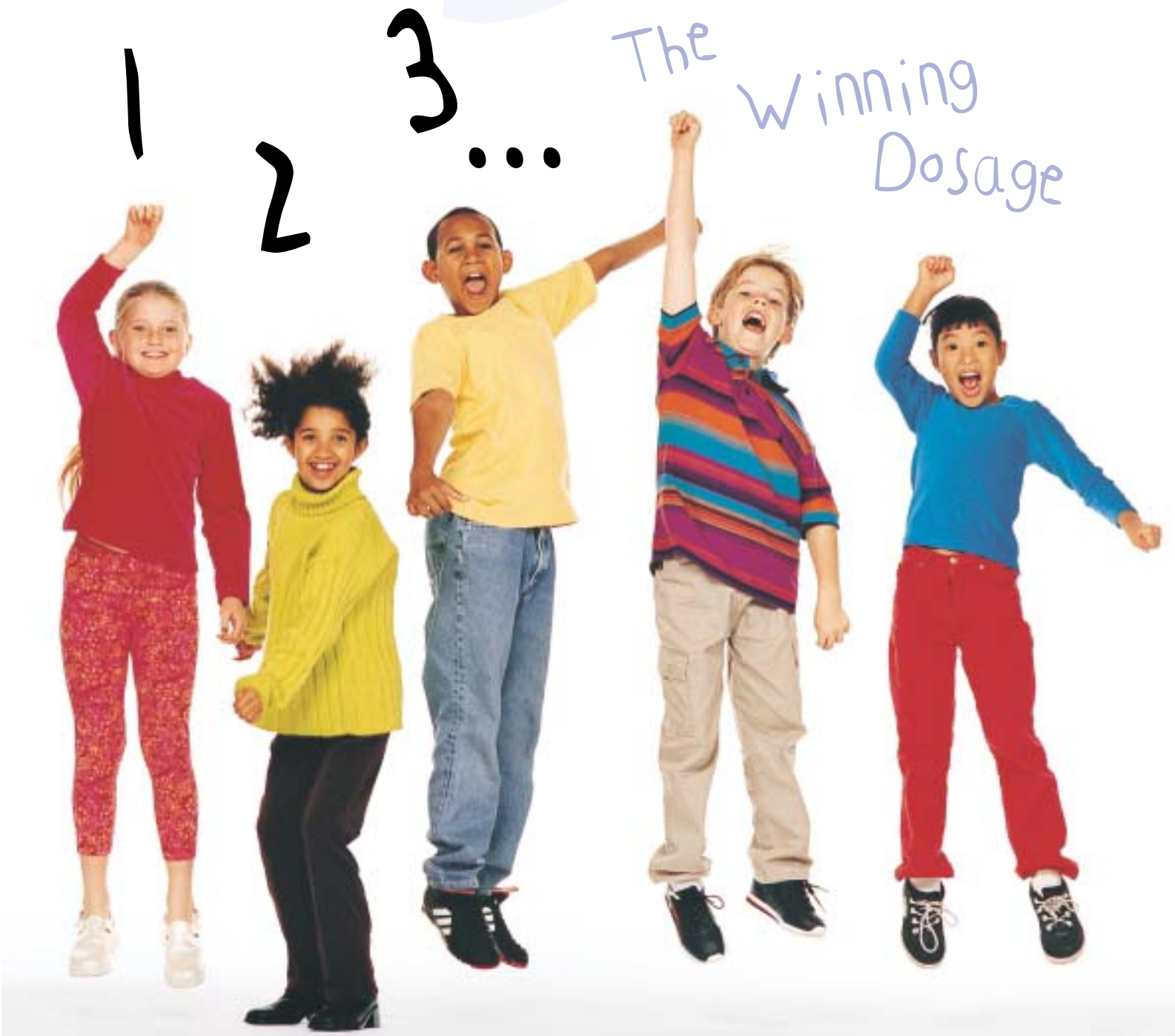
Pfizer

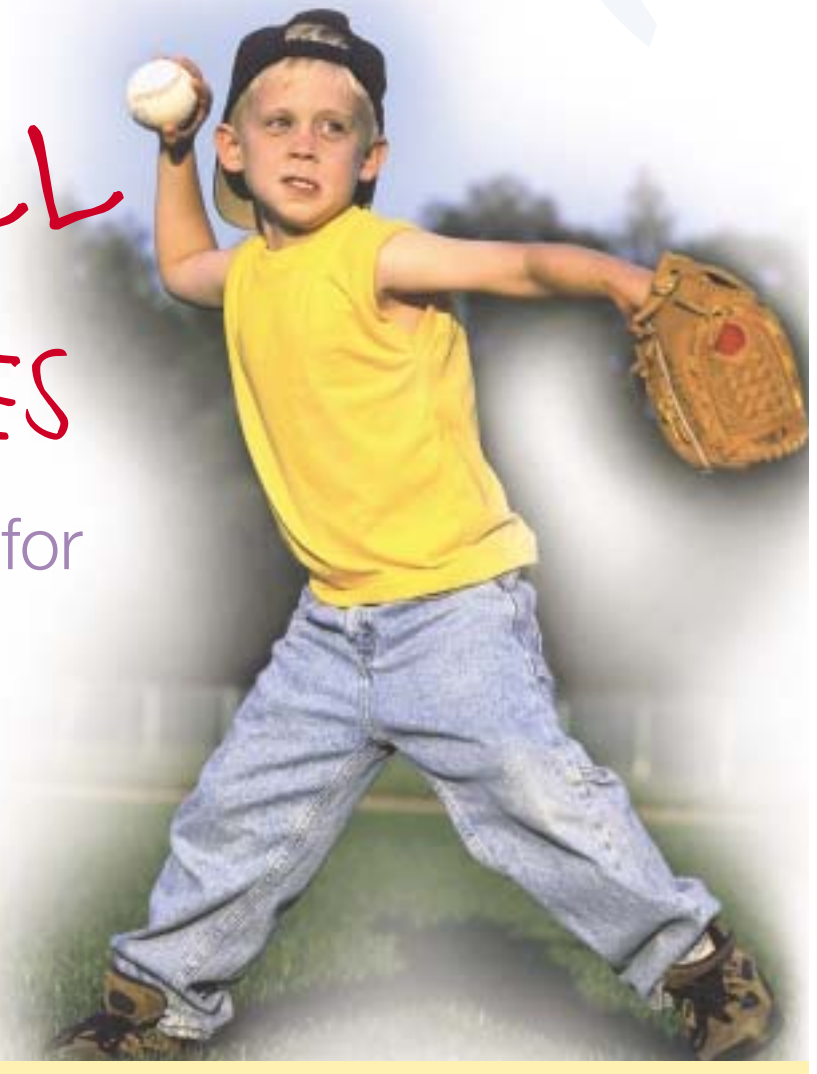
Azenil®

(azithromycin for oral suspension)

Once a day for three days…



COVER ALL your BASES



Consider Azenil first for

- Bacterial coverage
- Effect on pathogen
- Compliance and dosage
- Safety profile

Azenil indications and respiratory pathogens[1]

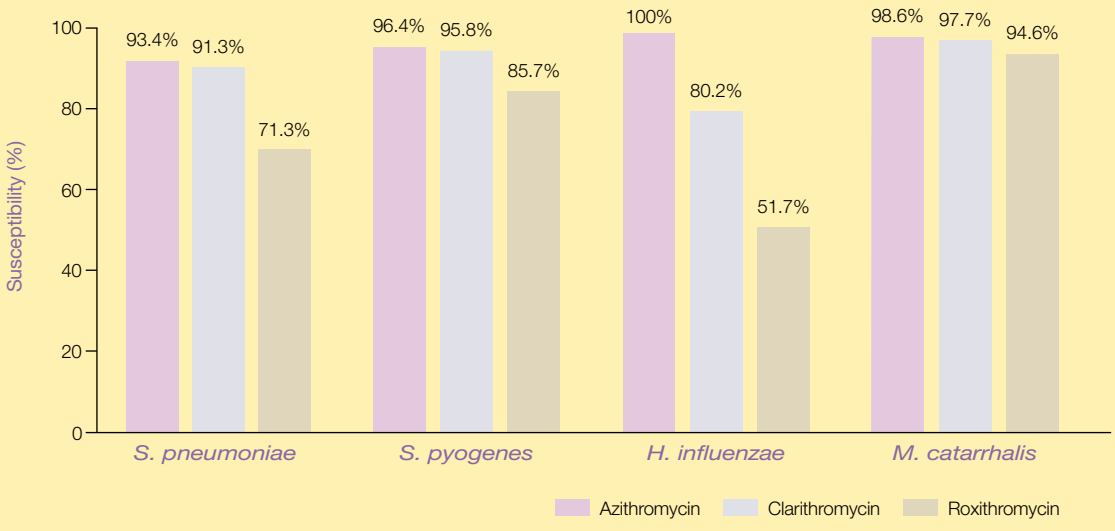
INDICATION	RESPIRATORY PATHOGENS					
	Haemophilus influenzae	*Streptococcus pneumoniae*	*Moraxella catarrhalis*	*Chlamydia pneumoniae*	*Mycoplasma pneumoniae*	*Streptococcus pyogenes*
ACUTE OTITIS MEDIA	●	●	●			
COMMUNITY-ACQUIRED PNEUMONIA (CAP)	●	●		●	●	
PHARYNGITIS						●

In vitro activity does not necessarily imply a correlation with clinical results.
Data on file

Key respiratory pathogens are susceptible to Azithromycin[1]

The Artemis project is a multinational study that monitors the susceptibilities of clinical isolates against antibiotics, including the macrolides.

ARTEMIS Project: comparative susceptibility against key respiratory pathogens



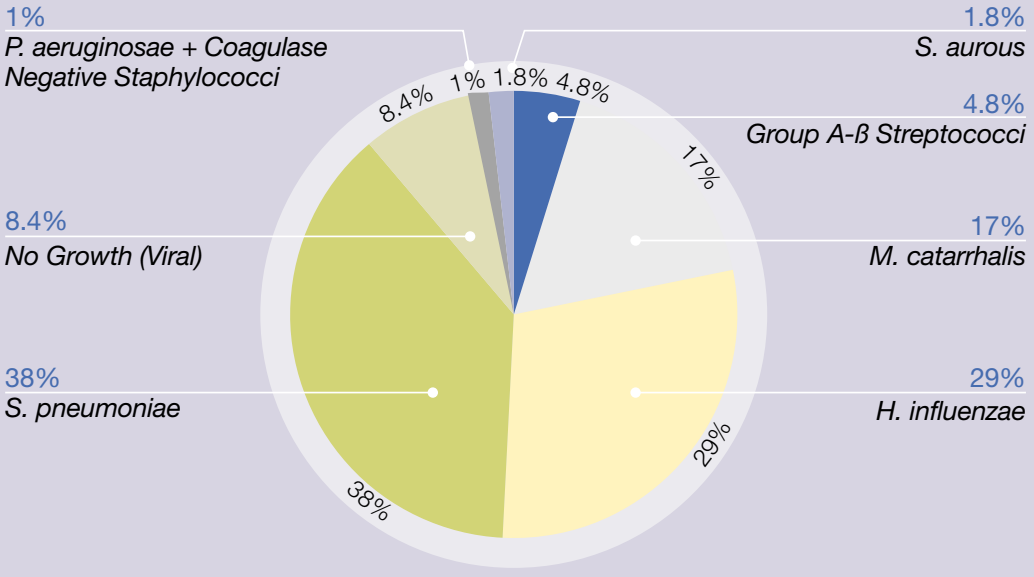
Data on file

1 x 3 The Winning Dosage

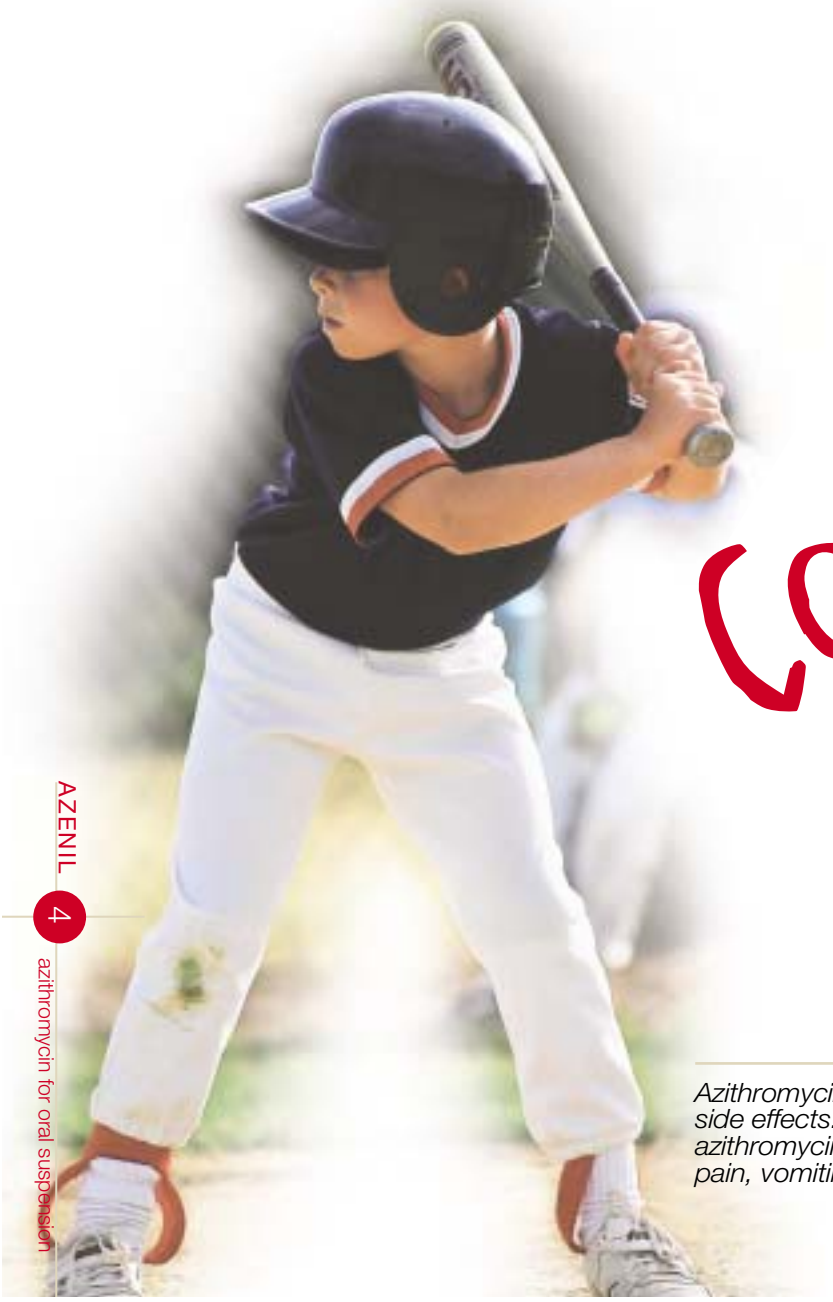
APPROPRIATE coverage for CAP, AOM and Pharyngitis*

* *Please see full prescribing information on last page.*

Key pathogens associated with acute otitis media[2]



(Adapted from Blumer, 1998)[2]



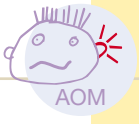
COVER ALL your BASES

Azithromycin is well tolerated with a low incidence of side effects. The most common side effects of azithromycin are diarrhea/loose stool, abdominal pain, vomiting, nausea and rash.

1 x 3 The Winning Dosage

CAP

Azenil is indicated for the treatment of pediatric community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.*



AOM

Azithromycin was reported to be the most potent of the macrolides tested (clarithromycin, roxithromycin, erythromycin, dirithromycin, josamycin and spiramycin) against *Haemophilus influenzae.*[3]

Pharyngitis

"Once daily oral dosage with azithromycin for 3 days yields drug concentrations in tonsillar and adenoid tissues that exceed the MIC_{90} of *S. pyogenes* and are maintained long after the end of dosing."[4]

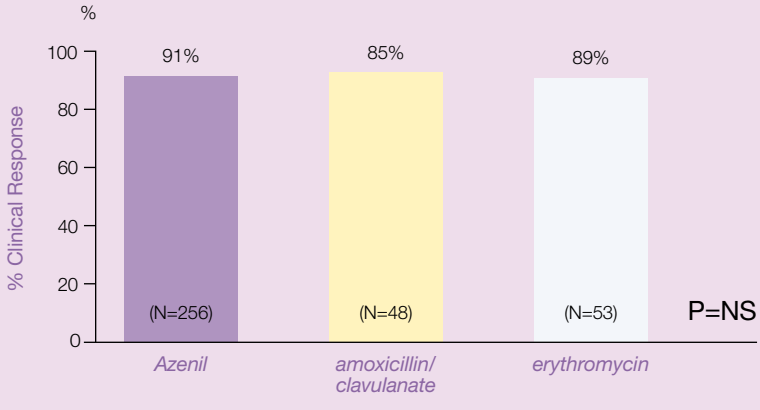
The **APPROPRIATE** coverage for key respiratory pathogens[1]

* *Please see full prescribing information on last page.*

Azenil Delivers Efficacy

ALL ACROSS THE BOARD

Clinical response rates in the treatment of children at 4 to 6 weeks post therapy[5]



A multicenter, parallel-group, double-blind trial comparing the efficacy of Azenil® (10 mg/kg on day 1 and 5 mg/kg on days 2 to 5) with Augmentin (40 mg/kg/day in 3 divided doses for 10 days) or erythromycin estolate (40 mg/kg/day tid for 10 days) in children with community-acquired pneumonia. (Adapted from Harris)[5]

The experts agree on Azenil (azithromycin) first line for outpatient CAP

The Centers for Disease Control (CDC) Therapeutic Working Group: recommended first-line therapies for outpatient CAP[6]

- Macrolide (AZITHROMYCIN, clarithromycin, or erythromycin)
- Doxycycline
- Oral B-lactam
- The CDC Therapeutic Working Group recommends reserving fluoroquinolones for use in CAP when:[6]
  - Treatment with another agent has failed; patient is allergic to alternative agents; or infection with highly resistant *Streptococcus pneumoniae* has been documented.

The Infectious Diseases Society of America: generally preferred treatment regimens for outpatient CAP[7]

- Macrolide (AZITHROMYCIN, clarithromycin,or erythromycin)
- Doxycycline
- Fluoroquinolones (gatifloxacin, levofloxacin, or moxifloxacin)

(Adapted from Bartlett et al.)[7]

The Canadian Infectious Diseases Society/Canadian Thoracic Society: recommended first-choice therapies for outpatient CAP[8]

- Outpatients without modifying factors: macrolide (AZITHROMYCIN, erythromycin, or clarithromycin)
- Outpatients with modifying factors: chronic obstructive lung disease without antibiotic or steroid use during prior 3 months: newer macrolide (AZITHROMYCIN, or clarithromycin)

(Adapted from Mandell et al.)[8]

The American Thoracic Society: recommended first-line therapies for outpatient CAP[9]

- Outpatients 60 years or younger without comorbidities: macrolide (AZITHROMYCIN, erythromycin, clarithromycin) or tetracycline

(Adapted from ATS Guidelines)[9]

The Stanford Guide to Antimicrobial Therapy 2000: suggested primary regimens for outpatient CAP[10]

- AZITHROMYCIN, or clarithromycin

(Adapted from Gilbert et al.)[10]

Oral azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially-acquired infections, patients with known or suspected bacteremia, patients requiring hospitilization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immundeficiency or functional asplenia)

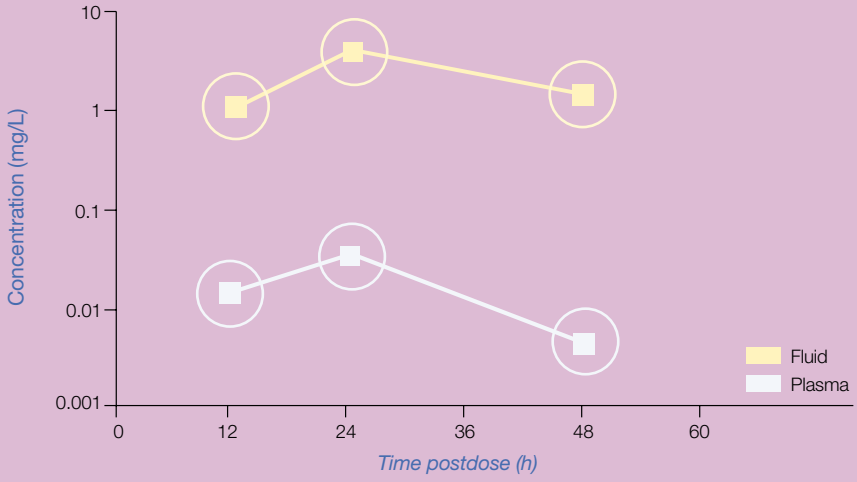
The most common side effects of Azenil are diarrhea/loose stools (5%), nausea (3%) and abdominal pain (3%)

"Azenil is an **APPROPRIATE** choice for the treatment of community-acquired pneumonia in children 6 months of age and older."[5]

Please see full prescribing information on last page.

Azithromycin concentration in middle ear fluid (MEF)[11]

Azithromycin concentrations in MEF and corresponding concentrations in plasma



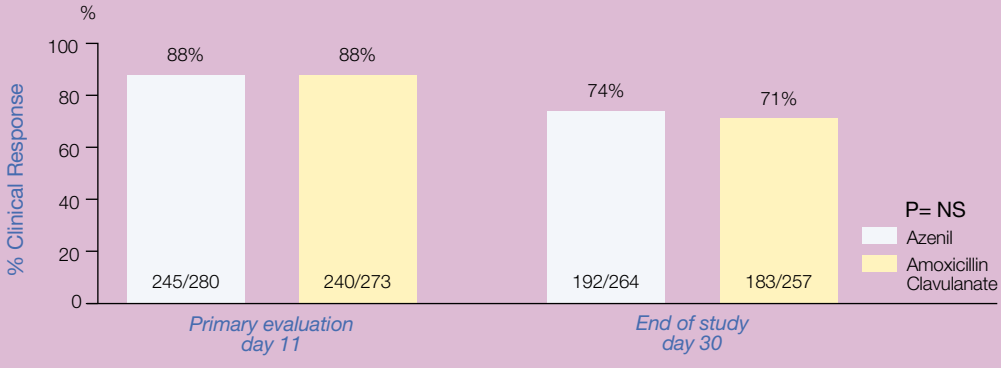
In an open-label study, the concentrations of azithromycin in middle ear effusions and plasma were determined in 29 children with a diagnosis of either secretory otitis media of at least 1 month's duration or AOM. Azithromycin (10 mg/kg) was administered as a single dose 12, 24 or 48 hours before the insertion of tympanostomy tubes to 17 children with SOM and once daily for 5 days to children with AOM.

Pukander J. Journal of Antimicrobial Chemotherapy (1996) 37. suppl. C. 53-61.

Azenil Delivers Efficacy

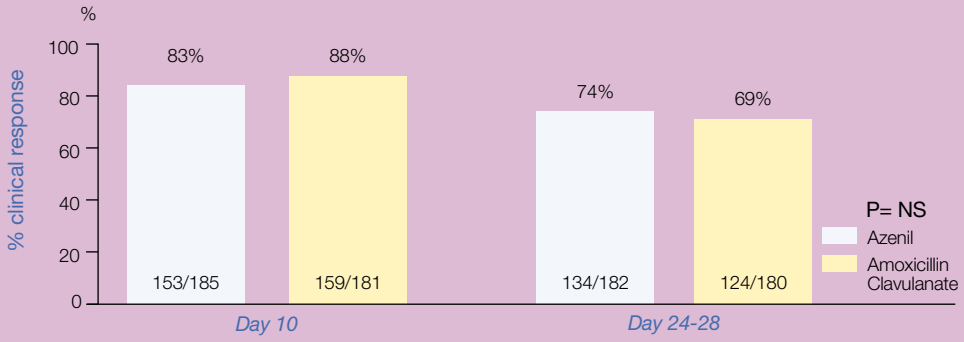
ALL ACROSS THE BOARD

Azenil delivers equal clinical efficacy to amoxicillin/clavulanate in treating AOM[13]



In a randomized, double-blind, double-dummy, multicenter study, 553 evaluable children with acute otitis media received Azenil oral suspension (10 mg/kg on day 1, 5 mg/kg qd on days 2 to 5) or amoxicillin/clavulanate (40 mg/kg day in 3 divided doses for 10 days) and were evaluated for clinical efficacy and safety. (Adapted from McLinn)[13]

Azenil given over 3 days is as effective as amoxicillin/clavulanate for treatment of AOM[12]



In a randomized, double-blind study, 373 evaluable children with acute otitis media received Azithromycin oral suspension (10 mg/kg/day) for 3 days or amoxicillin/clavulanate (45 mg/kg/day bid) for 10 days.

(Adapted from Dunne)[12]

Therapeutic efficacy of oral azithromycin in pediatric patients with AOM[14]

Reference	*Patient's age*	*AZM (%) AMC*		*Overall efficacy*
		Clinical success rate		
Arguelas et al, 1996	7 mos - 12 years	100	96	AZM = AMC
Aronovitz et al, 1996	2 - 15 years	88	100	AZM = AMC
Daniel et al, 1993	1 - 8 years	99	100	AZM = AMC
Khurana et al, 1998	1 - 13 years	92	90	AZM = AMC
Principi et al, 1995	4 mos - 10 years	93	94	AZM = AMC
Schaad et al, 1993	7 mos - 1 year	93	97	AZM = AMC
McLinn et al, 1996	1 - 15 years	88	88	AZM = AMC

Reference	*Patient's age*	*AZM (%) CLR*		*Overall efficacy*
Arguelas et al, 1997	9 mos - 11 years	100	96	AZM = CLR
Peterson et al, 1998	5 mos - 9 years	100	92	AZM = CLR
Ramet et al, 1995	5 mos - 6 years	99	99	AZM = CLR

AZM = azithromycin ; AMC = amoxicillin/clavulanate ; CLR = clarithromycin (Langtry)[14].

"Given as an oral suspension, Azenil once daily for 3 days is as well tolerated and effective as amoxicillin/clavulanic acid given 3 times a day for 10 days in the treatment of AOM"[15]

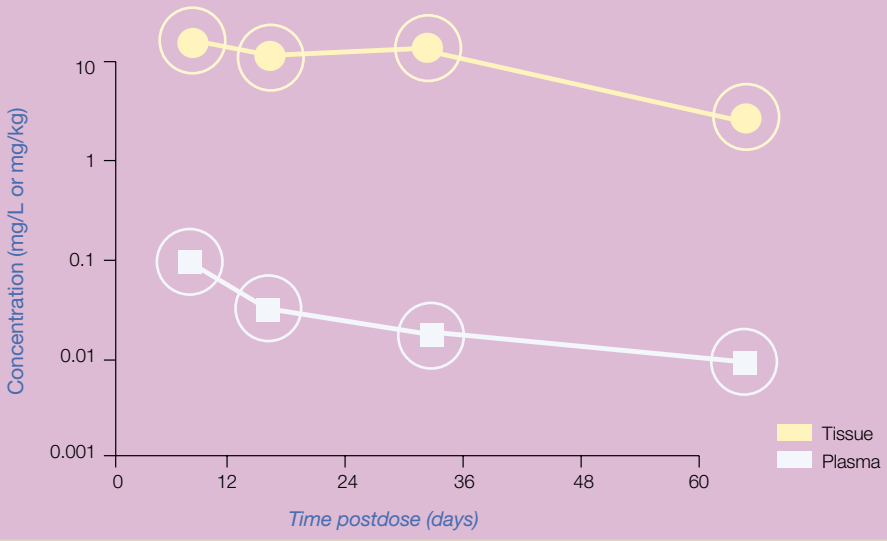
1 x 3 The Winning Dosage

(Zhanel, 2001)[15]

Please see full prescribing information on last page.

Azenil delivers good clinical results in treatment of pharyngitis

Azithromycin concentrations in tonsillar and adenoidal tissue and corresponding in plasma[16]

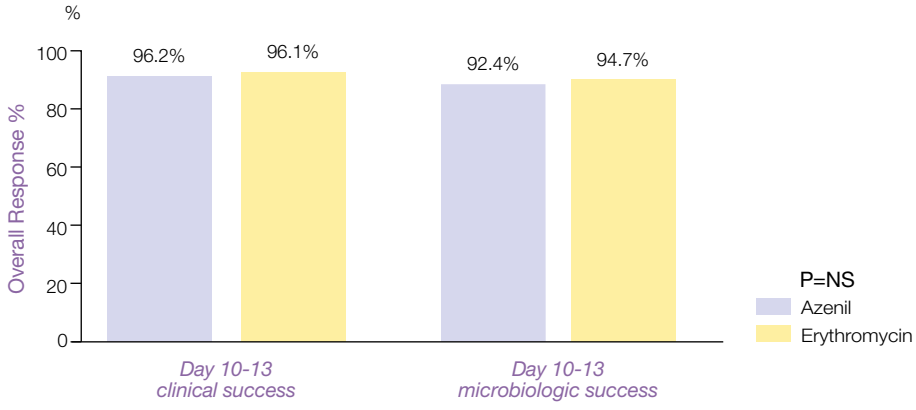


Azithromycin levels in tonsillar and/or adenoid tissue were determined in children who were scheduled for surgical removal of their tonsils and/or adenoids. The children received azithromycin oral suspension 10 mg/kg once daily x 3 days. Tissue and serum samples were obtained during surgery 1, 2, 4 or 8 days after the last dose of azithromycin.

Vaudaux BP Journal of Antimicrobial Chemotherapy (1996) 37. suppl. C. 45-51.

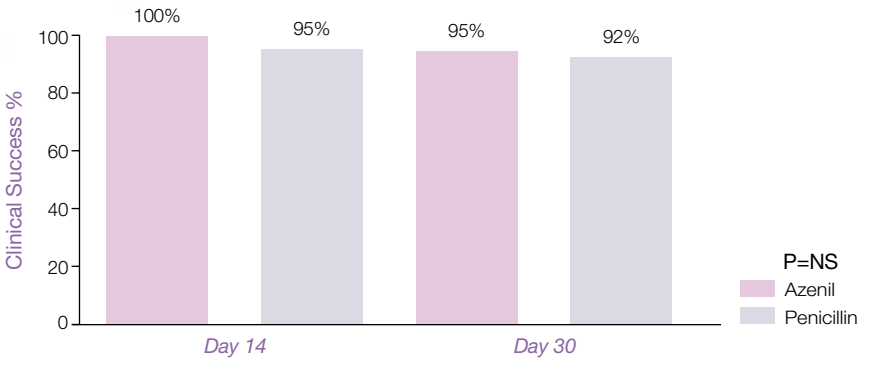
Azenil Delivers Efficacy ALL ACROSS THE BOARD

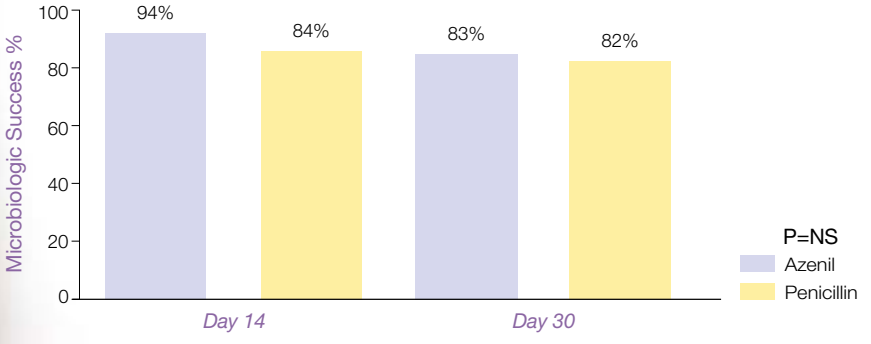
Azenil vs erythromycin in the treatment of pediatric patients with acute streptococcal pharyngitis[17]



In an open randomized multicenter study, 205 children with clinically-diagnosed streptococcal pharyngitis, received treatments of once-daily azithromycin 10 mg/kg/day for 3 days or 30-50 mg/kg/day erythromycin in 3 divided doses for 10 days. (Treadway, 1998)[17]

Azenil 20mg/kg per day is equivalent to 10-day penicillin V for pharyngitis[4]





Prospective, randomized, multicenter, double-blind trial included 501 children (aged 2-12 years) with GAS-TD (confirmed by rapid identification tests). Treatments were assigned by means of a centralized telephonic computer program. The primary endpoint was microbiologic response at end of treatment (day 14), classified as success (eradication of baseline GAS or persistence).[4]

Azithromycin is well tolerated with a low incidence of side effects. The most common side effects of azithromycin are diarrhea/loose stool, abdominal pain, vomiting, nausea and rash.

"3-day azithromycin 20 mg/kg/day is a more effective regimen than 3-day azithromycin 10 mg/kg/day and is equivalent to 10-day penicillin V for pediatric GAS-TP"

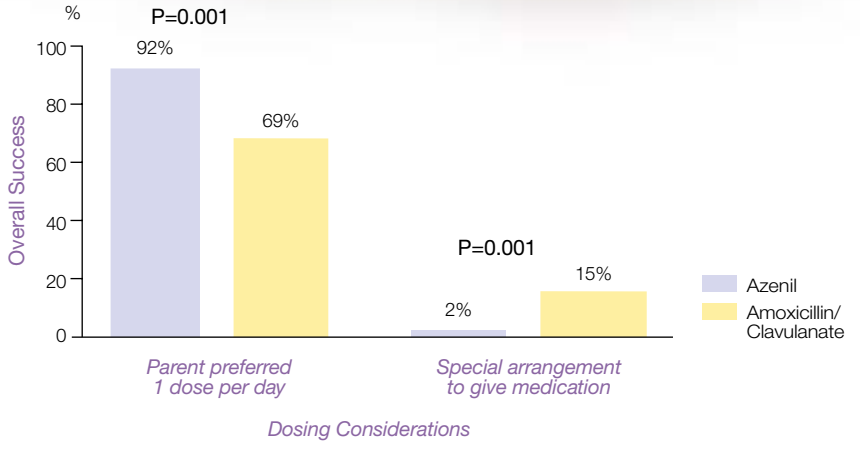
(Cohen, 2000)[4]

Please see full prescribing information on last page.

It's As Easy As 1-2-3

"Azenil is well accepted by family members, convenient to use and well suited to children"[18]

"Convenient to administer and well accepted by parents and children"[18]



In a randomized, multicenter, open-label, comparative study, 527 children aged 6 months to 12 years enrolled in day care or school with acute otitis media received powder for oral suspension forms of Azenil (azithromycin) (10 mg/kg on day 1 5 mg/kg qd on days 2-5) or amoxicillin/clavulanate (40 mg/kg day in 3 divided doses for 10 days). (Adapted from Khurana)[18]

CONVENIENCE

In a comparative trial of 3 days of Azenil, versus 10 days of clarithromycin, in the treatment of children with acute otitis media with effusion, 73% of the parents preferred to administer only 1 dose per day.[19]

"Azenil at 10 mg/kg once a day for 3 days is an attractive alternative in those situations in which patient compliance becomes an issue."[19]

(Adapted from Arguelas, 1997)[19]

Convenient dosage
Happy parents
Healthy kids

Please see full prescribing information on last page.

First to the Finish Line

Compliance rates improve as frequency decreases[20]

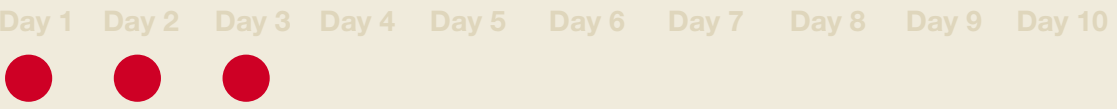
DOSING SCHEDULE	RELATIVE COMPLIANCE
QD	95%
BID	76%
TID	75%
ID	58%

(Adapted from Cockburn et al., 1987)

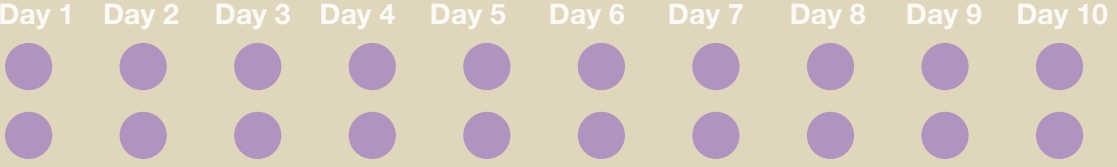
Azithromycin is well tolerated with a low incidence of side effects. The most common side effects of azithromycin are diarrhea/loose stool, abdominal pain, vomiting, nausea and rash.

Once a day 3-day dosage

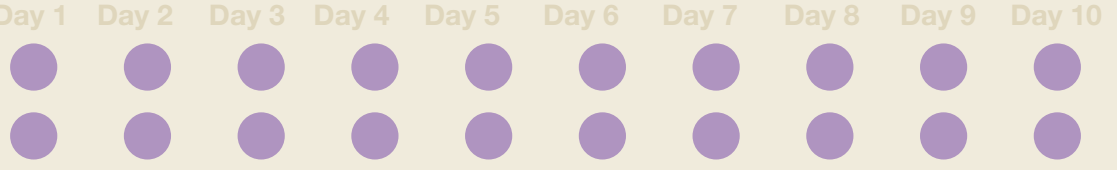
One full course of AZENIL*



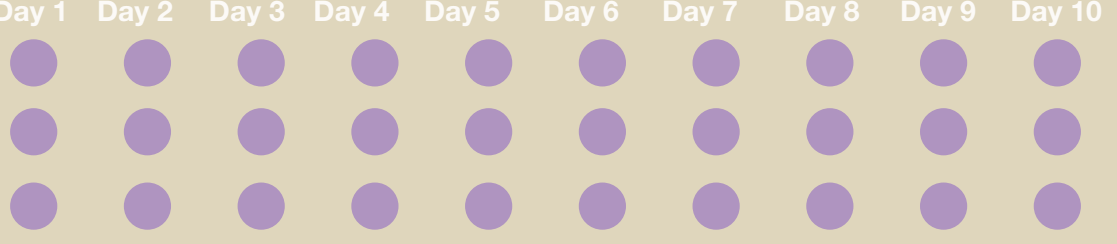
One full course of amoxicillin/clavulanate[21]



One full course of clarithromycin[21]



One full course of amoxicillin[21]



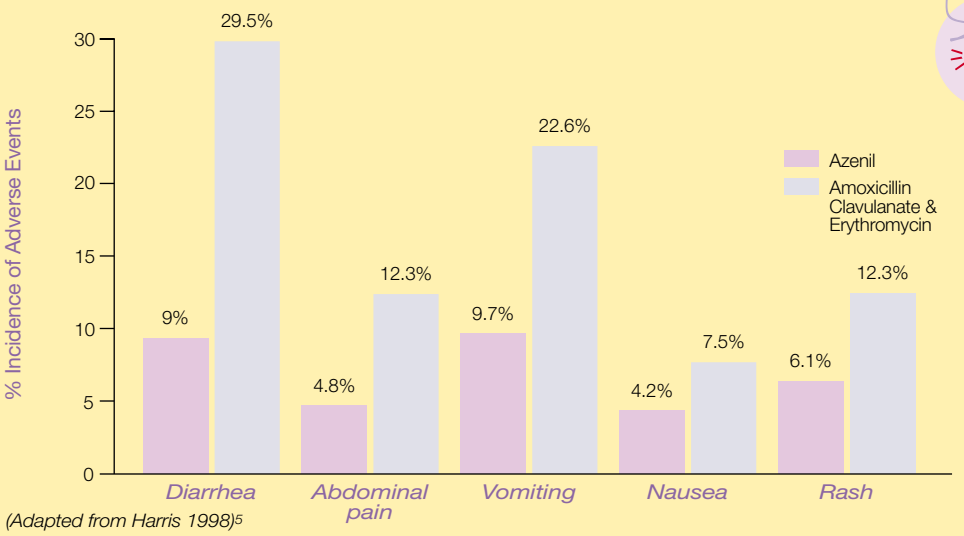
With the exception of the treatment of streptococcal pharyngitis, the total dosage in children is 30 mg/kg which should be given as a single dose of 10 mg/kg/daily for 3 days, or as an alternative, given over 5 days with a single dose of 10 mg/kg on day 1 then 5 mg/kg on days 2-5. For pediatric streptococcal pharyngitis, azithromycin is given as a single dose of 10 mg/kg or 20 mg/kg for 3 days.

The right dosage for better **COMPLIANCE**

** Please see full prescribing information on last page.*

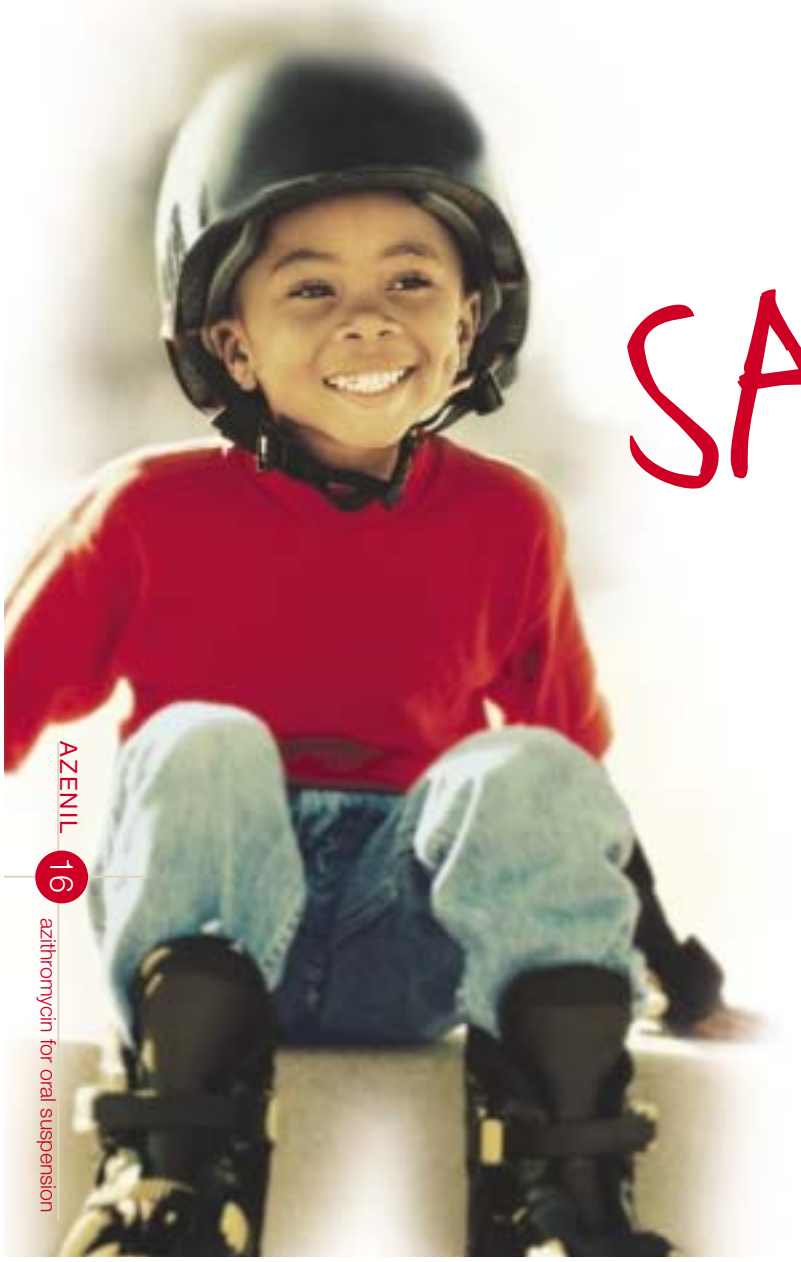
"Azithromycin had significantly fewer side effects than comparator drugs"[5]

Most common adverse events due to therapy vs. comparative agents[5]



(Adapted from Harris 1998)[5]

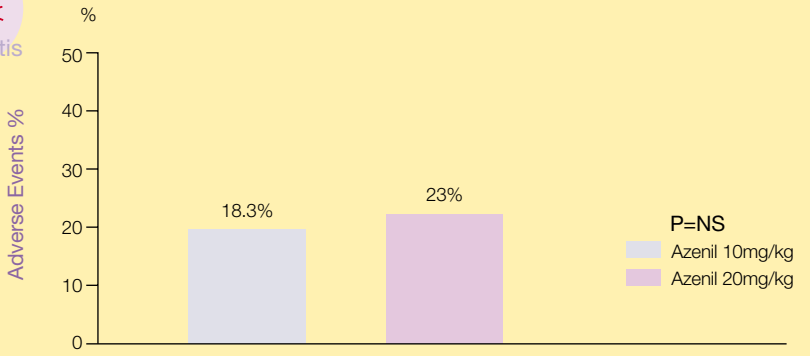
The majority of treatment-related adverse events were mild to moderate in severity and related to the gastrointestinal tract (diarrhea, vomiting, abdominal pain, nausea, anorexia).[5]



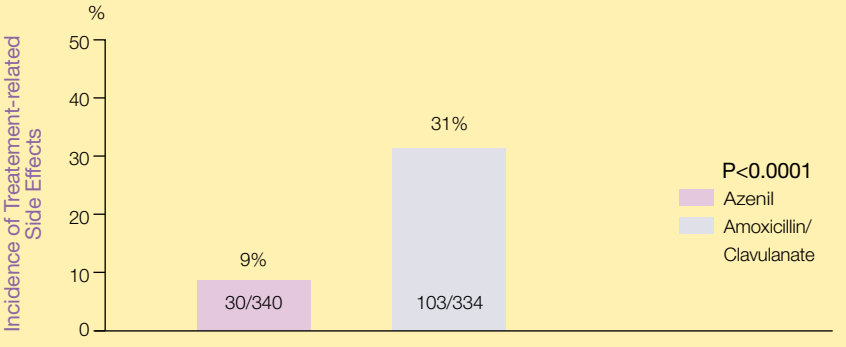
SAFETY comes FIRST

Incidence of treatment-related adverse events[4]

"Most treatment-related adverse events were gastrointestinal in nature and of mild to moderate severity."[4]



Azithromycin is significantly better tolerated than amoxicillin/clavulanate[13]



(McLinn, 1996)[13]

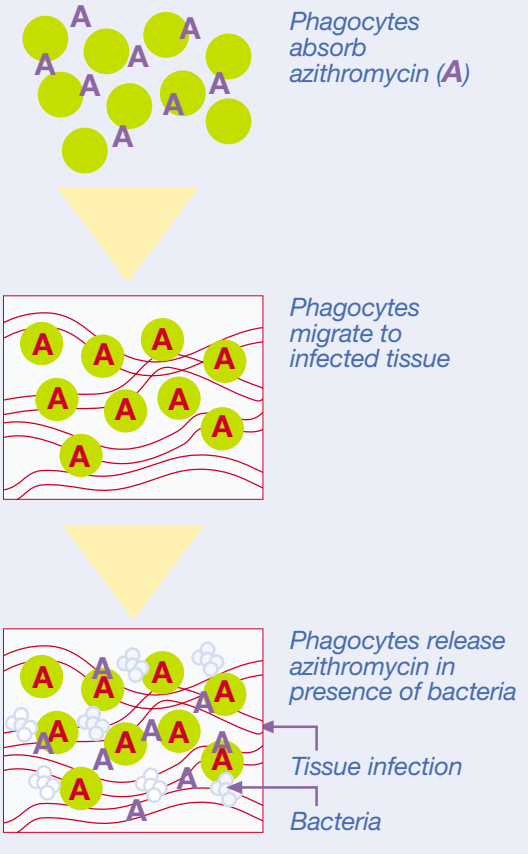
Safe, well-tolerated treatment for CAP, AOM and Pharyngitis

Azithromycin is well tolerated with a low incidence of side effects. The most common side effects of azithromycin are diarrhea/loose stool, abdominal pain, vomiting, nausea and rash.

Please see full prescribing information on last page.

HOW it WORKS...

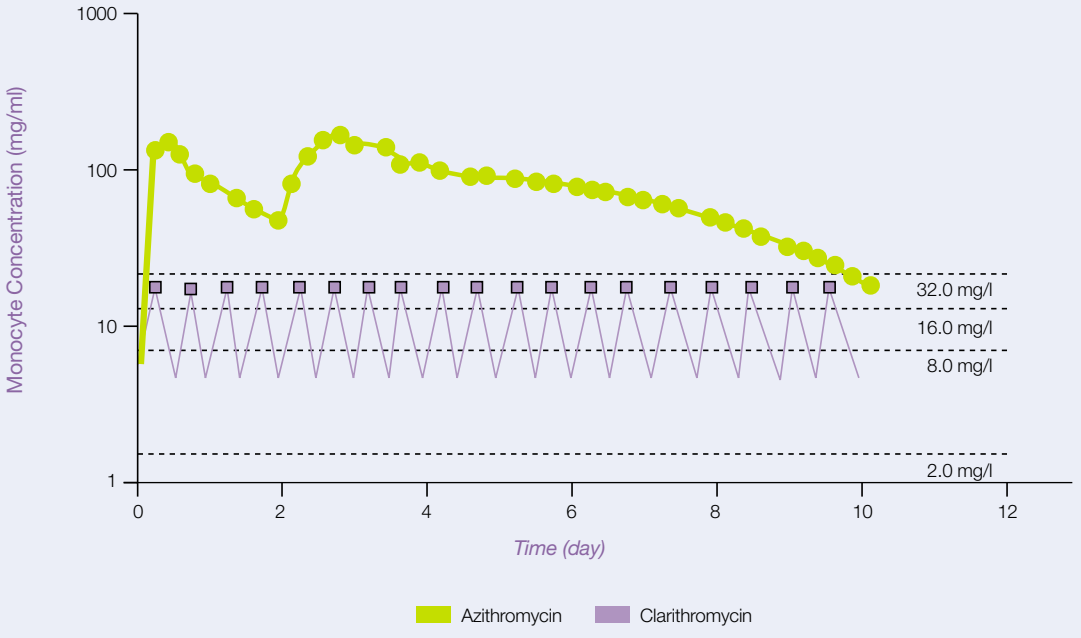
PHAGOCYTES MEDIATE THE TARGETED DELIVERY OF AZITHROMYCIN TO THE SITES OF INFECTION[22]



(Adapted from Schentag, 1991)[22]

Azenil releases quickly in tissue and reaches serum concentrations 100 times higher after a single 500 mg oral dose.[24]

Azithromycin concentration in monocytes



Anticipated concentration of Azenil in tissues and serum following 500 mg on day 1 and 250 mg on days 2-5.
(Adapted from Amsden, 1999)[23]

This difference between azithromycin and clarithromycin in the uptake and retention by phagocytic cells explains the absence of reports of clinical failures associated with azithromycin, even in the absence of high serum concentrations.

The high concentrations achieved by azithromycin in phagocytic cells maximize its activity against pathogens.

(Adapted from Amsden, 1999)[23]

Azenil has a **UNIQUE** pharmacokinetic profile.

Please see full prescribing information on last page.

Prescribing Information

AZENIL
CAPSULES
POWDER FOR ORAL SUSPENSION

Composition

Azenil Capsules

Each capsule contains:

Active Ingredient
Azithromycin (as dihydrate) 250 mg

Other Ingredients
Lactose, maize starch, magnesium stearate, sodium lauryl sulfate, gelatin, titanium dioxide, sulfur dioxide.

Azenil Powder for Oral Suspension

Each 5 ml contains:
Active Ingredient
Azithromycin (as dihydrate) 200 mg

Other Ingredients
Sucrose, artificial banana flavor, artificial creme de vanilla, sodium phosphate tribasic, artificial cherry, hydroxypropyl cellulose, xanthan gum.

Mechanism of Action

Azithromycin is the first of a class of antibiotics designated chemically as azalides. The mode of action of azithromycin is inhibition of protein synthesis in bacteria by binding to the 50s ribosomal subunit and preventing translocation of peptides.

Spectrum of activity azithromycin demonstrates activity in vitro against a wide range of bacteria including:

Gram-positive aerobic bacteria

Staphylococcus aureus, Streptococcus pyogenes (group A ß- hemolytic streptococci), Streptococcus pneumoniae, α-hemolytic streptococci (viridans group) and other streptococci, and corynebacterium diphtheriae. Azithromycin demonstrates cross resistance with erythromycin- resistant Gram-positive strains including Streptococcus fecalis (enterococcus).

Indications

Gram-negative aerobic bacteria

Hemophilus influenzae, Hemophilus parainfluenzae, Moraxella catarrhalis, Acinetobacter species, Yersinia species, Legionella pneumophila, Bordetella pertussis, Bordetella parapertussis, Shigella species, Pasteurella species, Vibrio cholera and parahemolyticus, 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 and 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 gonorrhoea and Hemophilus ducreyi.

Other Organisms: Borrelia burgdorferi (Lyme disease agent). Chlamydia pneumonia, Toxoplasma gondii, Mycoplasma pneumonia, Mycoplasma hominis, Ureaplasma urealyticum, Pneumocystis carinii, Myobacterium avium-intracellulare, Campylobacter species and Listeria monocytogenes.

Pharmacokinetics

Absorption and Distribution

Following oral administration in humans, azithromycin is widely distributed throughout the body: bioavailability is approximately 37%. Administration following a substantial meal reduces bioavailability by at least 50%. The time taken to peak plasma levels is 2-3 hours.

Pharmacokinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the drug is heavily 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. In animal studies, high azithromycin concentrations have been observed in phagocytes.

In experimental models, higher concentrations of azithromycin are released during active phagocytosis than from non-stimulated phagocytes. In animal models, this results in high concentrations of azithromycin being delivered to the site of infection.

Half-Life

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. In elderly volunteers (> 65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (< 40 years), but these are not considered clinically significant, and hence no dose adjustment is recommended.

Metabolism and Elimination

Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Very high concentrations of unchanged drug 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.

Indication

Azenil is indicated for infections caused by susceptible organisms: in lower respiratory tract infections including bronchitis and pneumonia, in skin and soft tissue infections, in otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of Streptococcus pyogenes pharyngitis, including the prophylaxis of rheumatic fever. Azenil is generally effective in the eradication of streptococci from the oropharynx, however, data establishing the efficacy of Azenil in the subsequent prevention of rheumatic fever are not available at present).

Note: Azenil 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 any of the following:
- Patients with nosocomially-acquired infections.
- Patients with known or suspected bacteremia.
- Patients requiring hospitalization.
- Elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

In sexually transmitted diseases in men and women, Azenil is indicated in the treatment of uncomplicated genital infections due to Chlamydia trachomatis. It is also indicated in the treatment of uncomplicated genital infection due to non-multiresistant Neisseria gonorrhea; concurrent infection with Treponema pallidum should be excluded.

Contraindications

The use of this product is contraindicated in patients with a history of allergic reactions to azithromycin or any of the macrolide antibiotics, or to any other ingredient of the preparation.

Warnings

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia of mild severity due to Streptococcus pneumonia or Hemophilus 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 any of the following:
- Patients with nosocomially-acquired infections.
- Patients with known or suspected bacteremia.
- Patients requiring hospitalization.
- Elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

Teratogenicity: animal reproduction studies have demonstrated that azithromycin crosses the placenta, but have revealed no evidence of harm to the fetus.

Use in Pregnancy

Safety of use during pregnancy has not been established. Therefore, azithromycin should be used in pregnant women only in the event that adequate alternatives are not available.

Use in Breastfeeding

There are no data on secretion in breast milk. Safety for use has not been established. Azithromycin should only be used in breastfeeding women where adequate alternatives are not available.

Use in Pediatrics

There is no information regarding use in children under 6 months of age.

Use in Patients with Impairment of Hepatic Function

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. In these patients, urinary recovery of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

Use in Patients with Impairment of Renal Function

In patients with mild renal impairment (creatinine clearance more than 40 ml/min), there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal renal function. There are no pharmacokinetic data regarding azithromycin usage in patients with a creatinine clearance <40 ml/min.

Adverse Reactions

Azithromycin is well tolerated with a low incidence of side effects.

Gastrointestinal - Diarrhea (rarely resulting in dehydration) and loose stools, dyspepsia, abdominal discomfort (pain/cramps), anorexia, nausea, vomiting, constipation and flatulence, Pseudomembranous colitis and rare reports of tongue discoloration.

Special Senses - Hearing impairment has been reported with macrolide antibiotics. There have been reports of hearing impairment, including hearing loss, deafness and or tinnitus in some patients receiving azithromycin. Many of these have been associated with prolonged use of high doses in investigational studies. In those cases where follow-up nformation was available, the majority of these events were reversible. There have been rare reports of taste perversion.

Genitourinary - Interstitial nephritis and acute renal failure.
Hematopoietic - Thrombocytopenia and most strains of methicillin- resistant Staphylococci.

Liver/Biliary - Abnormal liver function including hepatitis and cholestatic jaundice have been reported, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death. However, a causal relationship has not been established.

Musculoskeletal - Arthralgia.

Psychiatric - Aggressive reaction, nervousness, agitation and anxiety.

Reproductive - Vaginitis.

Central & Peripheral Nervous System - Dizziness/vertigo, convulsions (as seen with other macrolides), headache, somnolence, paresthesia and hyperactivity . White Blood Cell/RES - Transient episodes of mild neutropenia have occasionally been observed in clinical trials, although a causal relationship to azithromycin has not been established.

Skin/Appendages - Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria and angioedema. Rarely, serious skin reactions including erythema multiforme, Stevens-Johnson Syndrome and toxic epidermal necrolysis, have occurred.

Cadiovascular - Palpitations and arrhythmias including ventricular tachycardia (as seen with other macrolides) have been reported, although a causal relationship to azithromycin has not been established.

General - Asthenia has been reported, although a causal relationship has not been established, moniliasis and anaphylaxis (rarely fatal).

Precautions

Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. In patients with mild renal impairment (creatinine clearance more than 40 ml/min), there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal renal function. There are no data regarding azithromycin usage in patients with more severe renal impairment; thus, caution should be exercised before prescribing azithromycin in these patients. As with any antibiotic preparation, observation for signs of superinfection with nonsusceptible organisms, including fungi, is recommended. There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.

Azenil suspension contains 3.87 g. sucrose per 5 ml. This should be taken into consideration when administered to diabetics.

In high-dose animal studies, giving drug concentrations 40-fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Drug Interactions

Azithromycin/Antacids: In a phamacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations of azithromycin were reduced by up to 30%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Azithromycin/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 azithromycin concomitantly.

Azithromycin/Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Azithromycin/Coumarin-Type of 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 coadministartion of azithrimycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time.

Azithromycin/Cyclosporin: In the absence of conclusive data from pharmacokinetic or clinical studies investigating potential interaction between azithromycin and cyclosporin, caution should be exercised before concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Azithromycin/Didnosine: Coadministration of daily doses of 1200 mg azithromycin with didanosine in 6 subjects did not appear to affect the pharmacokinetics of didanosine as compared with placebo.

Azithromycin/Digoxin: Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. In patients receiving concomitant azithromycin or a related azalide antibiotic, together with digoxin, the possibility of raised levels should be borne in mind.

Azithromycin/Ergot: Due to theoretical possibiliy of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

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

Rifabutin: Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see sectiction “Adverse Reactions”).

Azithromycin/Theophylline: There is no evidence of any pharmacokinetic interaction when azithromycin and theophylline are coadministered to healthy volunteers.

Azithromycin/Terfenadine: Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

Azithromycin/Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin did not affect 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.

Dosage and Administration

Note

Azenil should be administered as a single daily dose. The period of dosing with regard to infection is given below. Administration following a substantial meal reduces bioavailability by at least 50%. Therefore, in common with many other antibiotics, each dose should be taken at least 1 hour before or 2 hours after food.

Azenil capsules should be swallowed whole.

Azenil capsules should only be administered to children weighing more than 45 kg.

Adults

For all indications except sexually transmitted diseases, the total dosage of 1.5 grams should be given as 500 mg (2 capsules) daily for 3 days. As an alternative, the same total dose can be given over 5 days with 500 mg given on day 1, then 250 mg (1 capsule) daily on days 2 to 5.

For the treatment of sexually transmitted diseases caused by Chlamydia trachomatis or susceptible Neisseria gonorrhoea, the dose is 1 gram (4 capsules) as a single oral dose.

Elderly

The same dosage as in adult patients is used in the elderly.

Patients with Renal Impairment

The same dosage as in patients with normal renal function may be used in patients with mild renal impairment (creatinine clearance more than 40 ml/ min). There are no data regarding azithromycin usage in patients with a creatinine clearance <40 ml/min.

Patients with Hepatic Impairment

The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment. (See also Warnings).

Children

With the single exception of the treatment of streptococcal pharyngitis, the total dosage in children is 30 mg/kg which should be given as a single daily dose of 10 mg/kg daily for 3 days, or as an alternative, given over 5 days with a single daily dose of 10 mg/kg on day 1, then 5 mg/kg on days 2-5.

Guidelines for Administering Azenil Suspension to Children

Note: Use the measuring spoon supplied for the product.

Weight (kg)	3-day Regimen	5-day Regimen	Bottle Size
Less then 15 (Under 3 Years)	10 mg/kg once daily on days 1-3	10 mg/kg once on day 1, then 5 mg/kg once daily on days 2-5.	15 ml (containing 600 mg azithromycin).
15-25 (3-7 Years)	200 mg (5 ml) once daily on days 1-3	200 mg (5 ml) on day 1, then 100 mg (2.5 ml) once daily on days 2-5.	15 ml (containing 600 mg azithromycin).
26-35 (8-11 Years)	300 mg (7.5 ml) once daily on days 1-3	300 mg (7.5 ml) once on day 1, then 150 mg (3.75 ml) once daily on days 2-5.	22.5 ml (containing 900 mg azithromycin).
36-45 (12-14 Years)	400 mg (10 ml) once daily on days 1-3	400 mg (10 ml) once on day 1, then 200 mg (5ml) once daily on days 2-5.	2x15 ml (containing 1200 mg azithromycin).
More then 45	Does as per adults		

For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective. However, a daily dose of 500 mg must not be exceeded. In clinical trials comparing these two dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg/day dose. However, penicillin is the usual drug of choice in the treatment of Streptococcus pyogenes pharyngitis, including prophylaxis of rheumatic fever.

Overdosage

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

Reconstitution of Azenil Powder for Oral Suspension

Tap the bottle to loosen the powder.
For the 15 ml size bottle (containing 600 mg of azithromycin)
Add 9 ml of water and shake.
For the 22.5ml size bottle (containing 900 mg of azithromycin)
Add 12 ml of water and shake.

Manufacturer

Teva Pharmaceutical Industries Ltd
P. O. Box 3190, Petach Tikva.

For

Pfizer Pharmaceuticals Israel Ltd.
9 Shenkar St. Hertzliya Pituach 46725, Israel
Azenil 250mg Capsules, 200mg/5ml Suspension, (31 January, 2000).

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AZENIL® (azithromycin for oral suspension)