Azenil® Capsules
Azenil ®200 mg/5 ml Suspension

NAME OF THE MEDICINAL PRODUCT

Azenil® Capsules
Azenil ®200 mg/5 ml Suspension

QUALITATIVE AND QUANTITATIVE COMPOSITION

Azenil capsules:
Each capsule contains Azithromycin dihydrate 262.05 mg equivalent to 250 mg azithromycin base.

Azenil 200mg/5ml suspension:
Contains Azithromycin 209.64 mg/5ml equivalent to 200mg/5ml of azithromycin base in Powder for Oral Suspension.

Excipients with known effect:

Azenil capsules: Lactose, sodium
Azenil 200mg/5ml suspension: Sucrose, sodium

For the full list of excipients, see Description (9) in this leaflet.

PHARMACEUTICAL FORM

Azenil capsules- The capsule is printed in black ink with Pfizer on one end of shell and “ZTM 250” on the other end. These capsules are packed in PVC blister packs.

Azenil 200mg/5ml - Powder for suspension is presented as a dry powder which yields, on reconstitution with water, a white to off-white suspension.

The powder for oral suspension is packed in polyethylene bottles.

1 INDICATIONS AND USAGE

Infections caused by susceptible organisms in lower respiratory tract including bronchitis and pneumonia, skin and soft tissue infections, otitis media, upper respiratory tract infections including sinusitis and pharyngitis, tonsilitis, also in the treatment of uncomplicated genital infections due to chlamydia trachomatis.

1.1 Limitations of Use

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 nosocomial 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).

1.2 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Azenil (azithromycin) and other antibacterial drugs, Azenil (azithromycin) should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

Oral azithromycin should be administered as a single daily dose. The period of dosing with regard to infection is given below.

Administration of azithromycin capsules following a substantial meal reduces bioavailability by at least 50%. Therefore, in common with many other antibiotics, each dose of the capsules should be taken at least 1 hour before or 2 hours after food.

Powder for oral suspension can be taken with or without food.

In Adults:
For the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis*, the dose is 1000 mg as a single oral dose.

For all other indications in which the oral formulation is administered, the total dosage of 1500 mg should be given as 500 mg 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 daily on days 2 to 5.

In Children:

Children over 45kg body weight and adults, including elderly patients: The total dose of azithromycin is 1500mg which should be given over three days (500mg once daily).

In uncomplicated genital infections due to *Chlamydia trachomatis*, the dose is 1000mg as a single oral dose.

In general, the total dose in children is 30 mg/kg. Treatment for pediatric streptococcal pharyngitis should be dosed at a different regimen (see below).
The total dose of 30 mg/kg should be given as a single daily dose of 10 mg/kg daily for 3 days, or given over 5 days with a single daily dose of 10 mg/kg on day 1, then 5 mg/kg on days 2-5.

As an alternative to the above dosing, treatment for children with acute otitis media can be given as a single dose of 30 mg/kg.

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 per day dose. However, penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including prophylaxis of rheumatic fever.

For children weighing less than 15 kg, azithromycin suspension should be measured as closely as possible. For children weighing 15 kg or more, azithromycin suspension, should be administered according to the guide provided below. There is no information on children less than 6 months of age.

AZITHROMYCIN SUSPENSION 30 mg/kg Total Treatment Dose			
Weight (kg)	**3-Day Regimen**	**5-Day Regimen**	**Bottle Size (mg)**
< 15	10 mg/kg once daily on days 1-3.	10 mg/kg on day 1, then 5 mg/kg once daily on days 2-5.	600
15-25	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.	600
26-35	300 mg (7.5 ml) once daily on days 1-3.	300 mg (7.5 ml) on day 1, then 150 mg (3.75 ml) once daily on days 2-5.	900
36-45	400 mg (10 ml) once daily on	400 mg (10 ml) on day 1, then 200 mg	

	days 1-3.	(5 ml) once daily on days 2-5.	600x2
> 45	Dose as per adults.	Dose as per adults.	600+900

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

SPECIAL POPULATIONS:

In the Elderly: The same dosage as in adult patients is used in the elderly. Elderly patients may be more susceptible to development of torsades de pointes arrhythmia than younger patients.

In Patients with Renal Impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 - 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min) .

In 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. Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin.

3 CONTRAINDICATIONS

3.1 Hypersensitivity
AZENIL is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug, or to any of the excipients listed in section9.

3.2 Hepatic Dysfunction
AZENIL is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

4 WARNINGS AND PRECAUTIONS

4.1 Hypersensitivity
Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy. *[see Contraindications (3.1)]*

Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is presently unknown.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.

4.2 Hepatotoxicity
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

4.3 Infantile Hypertrophic Pyloric Stenosis (IHPS)
Following the use of azithromycin in neonates (treatment up to 42 days of life), IHPS has been reported. Direct parents and caregivers to contact their physician if vomiting or irritability with feeding occurs.

4.4 QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

4.5 Cardiovascular Death

Some observational studies have shown an approximately two-fold increased short-term potential risk of acute cardiovascular death in adults exposed to azithromycin relative to other antibacterial drugs, including amoxicillin. The five-day cardiovascular mortality observed in these studies ranged from 20 to 400 per million azithromycin treatment courses. This potential risk was noted to be greater during the first five days of azithromycin use and does not appear to be limited to those patients with preexisting cardiovascular diseases. The data in these observational studies are insufficient to establish or exclude a causal relationship between acute cardiovascular death and azithromycin use. Consider balancing this potential risk with treatment benefits when prescribing Azenil..

4.6 *Clostridioides difficile*-Associated Diarrhea (CDAD)

Clostridioides difficile-associated diarrhea has been reported with use of nearly all antibacterial agents, including Azenil, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

4.7 Exacerbation of Myasthenia Gravis

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

4.8 Use in Sexually Transmitted Infections

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

4.9 Development of Drug-Resistant Bacteria

Prescribing AZENIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

4.10 Important information regarding some of the excipients in the medicine

Patients with rare hereditary problems of galactose intolerance, fructose intolerance total lactase deficiency, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

5 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hypersensitivity *[see Warnings and Precautions (4.1)]*
- Hepatotoxicity *[see Warnings and Precautions (4.2)]*
- Infantile Hypertrophic Pyloric Stenosis (IHPS) *[see Warnings and Precautions (4.3)]*
- QT Prolongation *[see Warnings and Precautions (4.4)]*
- Cardiovascular Death *[see Warnings and Precautions (4.5)]*
- *Clostridioides difficile*-Associated Diarrhea (CDAD) *[see Warnings and Precautions (4.6)]*
- Exacerbation of Myasthenia Gravis *[see Warnings and Precautions (4.7)]*

5.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious adverse reactions of angioedema and cholestatic jaundice were reported. Approximately 0.7% of the patients (adults and pediatric patients) from the 5-day multiple-dose clinical trials discontinued AZENIL (azithromycin) therapy because of treatment-related adverse reactions. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related adverse reactions was 0.6%. In clinical trials in pediatric patients given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related adverse reactions was approximately 1%. Most of the adverse reactions leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. *[see Clinical Studies (12.2)]*

Adults

Multiple-dose regimens: Overall, the most common treatment-related adverse reactions in adult patients receiving multiple-dose regimens of AZENIL were related to the gastrointestinal system with diarrhea/loose stools (4 to 5%), nausea (3%), and abdominal pain (2 to 3%) being the most frequently reported.

No other adverse reactions occurred in patients on the multiple-dose regimens of AZENIL with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.
Genitourinary: Monilia, vaginitis, and nephritis.
Nervous System: Dizziness, headache, vertigo, and somnolence.
General: Fatigue.
Allergic: Rash, pruritus, photosensitivity, and angioedema.

Single 1-gram dose regimen:
Overall, the most common adverse reactions in patients receiving a single-dose regimen of 1 gram of AZENIL were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Adverse reactions that occurred in patients on the single 1-gram dosing regimen of AZENIL with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Pediatric Patients

Single and Multiple-dose regimens: The types of adverse reactions in pediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in pediatric patients.

Acute Otitis Media: For the recommended total dosage regimen of 30 mg/kg, the most frequent adverse reactions (≥1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea, and rash. *[see Dosage and Administration (2)* and *Clinical Studies (12.2)]*

The incidence, based on dosing regimen, is described in the table below:

Dosage Regimen	Diarrhea %	Abdominal Pain %	Vomiting %	Nausea %	Rash %
1-day	4.3%	1.4%	4.9%	1.0%	1.0%
3-day	2.6%	1.7%	2.3%	0.4%	0.6%
5-day	1.8%	1.2%	1.1%	0.5%	0.4%

Community-Acquired Pneumonia: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent adverse reactions attributed to treatment were diarrhea/loose stools, abdominal pain, vomiting, nausea, and rash.

The incidence is described in the table below:

Dosage Regimen	Diarrhea/Loose stools %	Abdominal Pain %	Vomiting %	Nausea %	Rash %
5-day	5.8%	1.9%	1.9%	1.9%	1.6%

Pharyngitis/Tonsillitis: the most frequent adverse reactions attributed to treatment were diarrhea, vomiting, abdominal pain, nausea, and headache, when the drug was given at a dosage regimen of 12mg/kg on days 1-5 (this dosage regimen is higher than that approved in Israel).

The incidence is described in the table below:

Dosage Regimen	Diarrhea %	Abdominal Pain %	Vomiting %	Nausea %	Rash %	Headache %
5-day	5.4%	3.4%	5.6%	1.8%	0.7%	1.1%

With any of the treatment regimens, no other adverse reactions occurred in pediatric patients treated with AZENIL with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Cardiovascular: Chest pain.
Gastrointestinal: Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools, and oral moniliasis.
Hematologic and Lymphatic: Anemia and leukopenia.
Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, and insomnia.
General: Fever, face edema, fatigue, fungal infection, malaise, and pain.
Allergic: Rash and allergic reaction.
Respiratory: Cough, pharyngitis, pleural effusion, and rhinitis.
Skin and Appendages: Eczema, fungal dermatitis, pruritus, sweating, urticaria, and vesiculobullous rash.
Special Senses: Conjunctivitis.

5.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of azithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported with azithromycin during the postmarketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria, and angioedema.
Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension. There have been reports of QT prolongation and torsades de pointes, and cardiovascular death.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.
General: Asthenia, paresthesia, fatigue, malaise, and anaphylaxis
Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.
Hematopoietic: Thrombocytopenia.
Liver/Biliary: Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure. *[see Warnings and Precautions (4.2)]*

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation, and syncope.
Psychiatric: Aggressive reaction and anxiety.
Skin/Appendages: Pruritus, serious skin reactions including erythema multiforme, AGEP, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and DRESS.
Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus, and reports of taste/smell perversion and/or loss.

5.3 Laboratory Abnormalities

Adults:
Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils, and blood glucose; elevated serum creatine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils, and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH, and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline. When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 5000 patients, four patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

Pediatric Patients:
One, Three, and Five Day Regimens
Laboratory data collected from comparative clinical trials employing two 3-day regimens (30 mg/kg or 60mg/kg in divided doses over 3 days), or two 5-day regimens (30 mg/kg or 60mg/kg in divided doses over 5 days) were similar for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1-5%. Laboratory data for patients receiving 30 mg/kg as a single dose were collected in one single center trial. In that trial, an absolute neutrophil count between 500-1500 cells/mm^3 was observed in 10/64 patients receiving 30 mg/kg as a single dose, 9/62 patients receiving 30 mg/kg given over 3 days, and 8/63 comparator patients. No patient had an absolute neutrophil count <500 cells/mm^3.

In multiple-dose clinical trials involving approximately 4700 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

6 DRUG INTERACTIONS

6.1 Nelfinavir

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. *[see Adverse Reactions (5)]*

6.2 Warfarin

Spontaneous postmarketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

6. 3 Potential Drug-Drug Interaction with Macrolides

Interactions with digoxin, colchicine or phenytoin have not been reported in clinical trials with azithromycin. No specific drug interaction studies have been performed to evaluate potential drug-drug interaction. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug

interactions when digoxin, colchicine or phenytoin are used with azithromycin careful monitoring of patients is advised.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

Available data from published literature and postmarketing experience over several decades with azithromycin use in pregnant women have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). Developmental toxicity studies with azithromycin in rats, mice, and rabbits showed no drug-induced fetal malformations at doses up to 4, 2, and 2 times, respectively, an adult human daily dose of 500 mg based on body surface area. Decreased viability and delayed development were observed in the offspring of pregnant rats administered azithromycin from day 6 of pregnancy through weaning at a dose equivalent to 4 times an adult human daily dose of 500 mg based on body surface area (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Available data from published observational studies, case series, and case reports over several decades do not suggest an increased risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes with azithromycin use in pregnant women. Limitations of these data include the lack of randomization and inability to control for confounders such as underlying maternal disease and maternal use of concomitant medications.

Animal Data

Azithromycin administered during the period of organogenesis did not cause fetal malformations in rats and mice at oral doses up to 200 mg/kg/day (moderately maternally toxic). Based on body surface area, this dose is approximately 4 (rats) and 2 (mice) times an adult human daily dose of 500 mg. In rabbits administered azithromycin at oral doses of 10, 20, and 40 mg/kg/day during organogenesis, reduced maternal body weight and food consumption were observed in all groups; no evidence of fetotoxicity or teratogenicity was observed at these doses, the highest of which is estimated to be 2 times an adult human daily dose of 500 mg based on body surface area.

In a pre- and postnatal development study, azithromycin was administered orally to pregnant rats from day 6 of pregnancy until weaning at doses of 50 or 200 mg/kg/day. Maternal toxicity (reduced food consumption and body weight gain; increased stress at parturition) was observed at the higher dose. Effects in the offspring were noted at 200 mg/kg/day during the postnatal development period (decreased viability, delayed developmental landmarks). These effects were not observed in a pre- and postnatal rat study when up to 200 mg/kg/day of azithromycin was given orally beginning on day 15 of pregnancy until weaning.

7.2 Lactation

Risk Summary

Azithromycin is present in human milk (see Data). Non-serious adverse reactions have been reported in breastfed infants after maternal administration of azithromycin (see Clinical Considerations). There are no available data on the effects of azithromycin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for AZENIL and any potential adverse effects on the breastfed infant from AZENIL or from the underlying maternal condition.

Clinical Considerations

Advise women to monitor the breastfed infant for diarrhea, vomiting, or rash.

Data

Azithromycin breastmilk concentrations were measured in 20 women after receiving a single 2 g oral dose of azithromycin during labor. Breastmilk samples collected on days 3 and 6 postpartum as well as 2 and 4 weeks postpartum revealed the presence of azithromycin in breastmilk up to 4 weeks after dosing. In another study, a single dose of azithromycin 500 mg was administered intravenously to 8 women prior to incision for cesarean section.

Breastmilk (colostrum) samples obtained between 12 and 48 hours after dosing revealed that azithromycin persisted in breastmilk up to 48 hours.

7.3 Pediatric Use

[see Clinical Pharmacology (10.3), and Dosage and Administration (2)]

Safety and effectiveness in the treatment of pediatric patients with acute otitis media, acute bacterial sinusitis and community-acquired pneumonia under 6 months of age have not been established. Use of AZENIL for the treatment of acute bacterial sinusitis and community-acquired pneumonia in pediatric patients (6 months of age or greater) is supported by adequate and well-controlled trials in adults

Pharyngitis/Tonsillitis: Safety and effectiveness in the treatment of pediatric patients with pharyngitis/tonsillitis under 2 years of age have not been established.

7.4 Geriatric Use

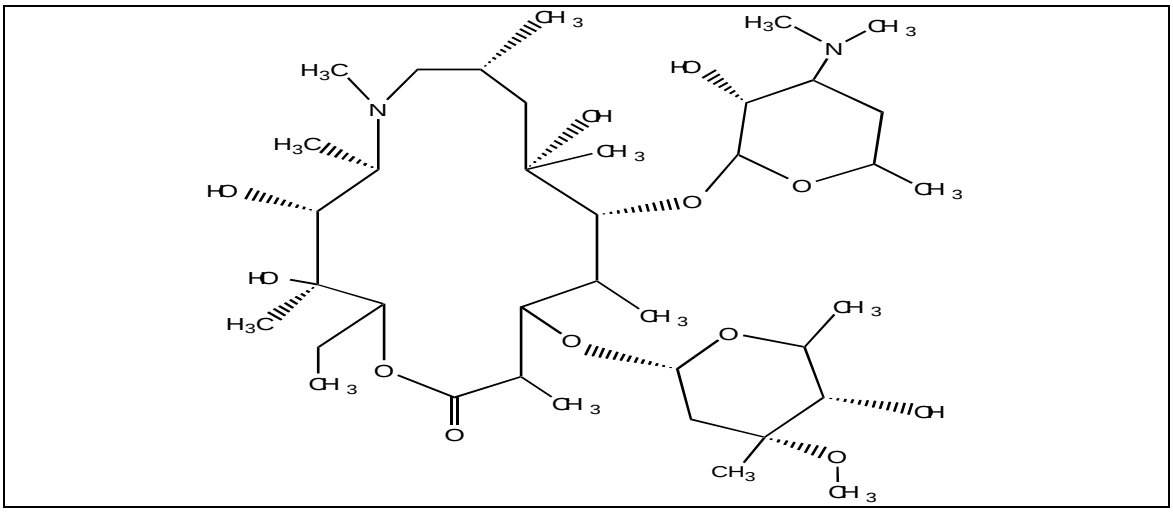
In multiple-dose clinical trials of oral azithromycin, 9% of patients were at least 65 years of age (458/4949) and 3% of patients (144/4949) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients. *[see Warnings and Precautions (4.4)]*

8 OVERDOSAGE

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

9 DESCRIPTION

Azenil (azithromycin capsules and azithromycin for oral suspension) contain the active ingredient azithromycin, a macrolide antibacterial drug, for oral administration. Azithromycin has the chemical name (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopy ranosyl]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 C38H72N2O12, 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 C38H72N2O12•2H2O and a molecular weight of 785.0.

Azenil is supplied as capsules containing azithromycin dihydrate equivalent to 250 mg azithromycin and the following inactive ingredients: anhydrous lactose, maize starch, magnesium stearate, sodium lauryl sulphate as excipients. The capsule shell contains gelatin and titanium dioxide.

Azenil for oral suspension is supplied in bottles containing azithromycin dihydrate powder equivalent to 200 mg/5 ml azithromycin base and the following inactive ingredients: sucrose, sodium phosphate tribasic anhydrous, hydroxypropyl cellulose, xanthan gum, artificial cherry, creme de vanilla and banana flavors.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Azithromycin is a macrolide antibacterial drug. *[see Microbiology (10.4)]*

10.2 Pharmacodynamics

Based on animal models of infection, the antibacterial activity of azithromycin appears to correlate with the ratio of area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for certain pathogens (*S. pneumoniae* and *S. aureus*). The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with azithromycin.

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with oral azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

10.3 Pharmacokinetics

Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were AUC_{0-72}=4.3 (1.2) mcg·hr/mL; C_{max}=0.5 (0.2) mcg/mL; T_{max}=2.2 (0.9) hours. Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.

In a two-way crossover study, 12 adult healthy volunteers (6 males, 6 females) received 1500 mg of 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). Due to limited serum samples on day 2 (3-day regimen) and days 2-4 (5-day regimen), the serum concentration-time profile of each subject was fit to a 3-compartment model and the $AUC_{0-\infty}$ for the fitted concentration profile was comparable between the 5-day and 3-day regimens.

	3-Day Regimen		**5-Day Regimen**	
Pharmacokinetic Parameter [mean (SD)]	**Day 1**	**Day 3**	**Day 1**	**Day 5**
C_{max} (serum, mcg/mL)	0.44 (0.22)	0.54 (0.25)	0.43 (0.20)	0.24 (0.06)
Serum $AUC_{0-\infty}$ (mcg·hr/mL)	17.4 (6.2)*		14.9 (3.1)*	
Serum $T_{1/2}$	71.8 hr		68.9 hr	

*Total AUC for the entire 3-day and 5-day regimens.

Absorption

The absolute bioavailability of azithromycin 250 mg capsules is 38%.

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase C_{max} by 23% but had no effect on AUC.

When azithromycin oral suspension was administered with food to 28 adult healthy male subjects, C_{max} increased by 56% and AUC was unchanged.

Distribution
The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL.

The antibacterial activity of azithromycin is pH related and appears to be reduced with decreasing pH, However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Azithromycin has been shown to penetrate into human tissues, including skin, lung, tonsil, and cervix. Extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, very low concentrations were noted in cerebrospinal fluid (less than 0.01 mcg/mL) in the presence of noninflamed meninges.

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 IV doses declined in a polyphasic pattern resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Specific Populations
Patients with Renal Impermeant
Azithromycin pharmacokinetics was investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg capsules), 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).
Patients with Hepatic Impairment
The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

Male and Female Patients
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 parameters in older volunteers (65 to 85 years old) were similar to those in young adults (18 to 40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. *[see Geriatric Use (7.4)]*

Pediatric Patients
In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 in two groups of pediatric patients (aged 1-5 years and 5-15 years, respectively). The mean pharmacokinetic parameters on day 5 were C_{max}=0.216 mcg/mL, T_{max}=1.9 hr, and AUC_{0-24}=1.822 mcg·hr/mL for the 1 to 5-year-old group and were C_{max}=0.383 mcg/mL, T_{max}=2.4 hr, and AUC_{0-24}=3.109 mcg·hr/mL for the 5 to 15-year-old group.

In another study, 33 pediatric patients received doses of 12 mg/kg/day (maximum daily dose 500 mg) for 5 days, of whom 31 patients were evaluated for azithromycin pharmacokinetics following a low fat breakfast. In this study,

azithromycin concentrations were determined over a 24 hr period following the last daily dose. Patients weighing above 41.7 kg received the maximum adult daily dose of 500 mg. Seventeen patients (weighing 41.7 kg or less) received a total dose of 60 mg/kg. The following table shows pharmacokinetic data in the subset of pediatric patients who received a total dose of 60 mg/kg.

Pharmacokinetic Parameter [mean (SD)]	**5-Day Regimen (12 mg/kg for 5 days)**
N	**17**
C_{max} (mcg/mL)	0.5 (0.4)
T_{max} (hr)	2.2 (0.8)
AUC_{0-24}(mcg·hr/mL)	3.9 (1.9)

Single dose pharmacokinetics of azithromycin in pediatric patients given doses of 30 mg/kg have not been studied. *[see Dosage and Administration (2)]*

Drug Interaction Studies
Drug interaction studies were performed with 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 1 and the effects of other drugs on the pharmacokinetics of azithromycin are shown in Table 2.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 1. No dosage adjustment of drugs listed in Table 1 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 2. *[see Drug Interactions (6.3)]*

Table 1. 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_{max}	**Mean AUC**
Atorvastatin	10 mg/day for 8 days	500 mg/day orally on days 6-8	12	0.83 (0.63 to 1.08)	1.01 (0.81 to 1.25)
Carbamazepine	200 mg/day for 2 days, then 200 mg twice a day for 18 days	500 mg/day orally for days 16-18	7	0.97 (0.88 to 1.06)	0.96 (0.88 to 1.06)
Cetirizine	20 mg/day for 11 days	500 mg orally 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 orally twice a day for 21 days	1200 mg/day orally on days 8-21	6	1.44 (0.85 to 2.43)	1.14 (0.83 to 1.57)
Efavirenz	400 mg/day for 7 days	600 mg orally on day 7	14	1.04*	0.95*
Fluconazole	200 mg orally single dose	1200 mg orally single dose	18	1.04 (0.98 to 1.11)	1.01 (0.97 to 1.05)
Indinavir	800 mg three times a day for 5 days	1200 mg orally on day 5	18	0.96 (0.86 to 1.08)	0.90 (0.81 to 1.00)
Midazolam	15 mg orally on day 3	500 mg/day orally for 3 days	12	1.27 (0.89 to 1.81)	1.26 (1.01 to 1.56)
Nelfinavir	750 mg three times a day for 11 days	1,200 mg orally on day 9	14	0.90 (0.81 to 1.01)	0.85 (0.78 to 0.93)
Sildenafil	100 mg on days 1 and 4	500 mg/day orally for 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 orally 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 orally twice a day for 15 days	500 mg orally 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 orally on day 1, then 250 mg/day on day 2	12	1.06*	1.02*
Trimethoprim/ Sulfamethoxazole	160 mg/800 mg/day orally for 7 days	1200 mg orally on day 7	12	0.85 (0.75 to 0.97)/0.90	0.87 (0.80 to 0.95/0.96

Table 1. 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_{max}	**Mean AUC**
				(0.78 to 1.03)	(0.88 to 1.03)
Zidovudine	500 mg/day orally for 21 days	600 mg/day orally for 14 days	5	1.12 (0.42 to 3.02)	0.94 (0.52 to 1.70)
Zidovudine	500 mg/day orally for 21 days	1200 mg/day orally for 14 days	4	1.31 (0.43 to 3.97)	1.30 (0.69 to 2.43)

* - 90% Confidence interval not reported

Table 2. Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs. *[see Drug Interactions (6)]*					
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_{max}	**Mean AUC**
Efavirenz	400 mg/day for 7 days	600 mg orally on day 7	14	1.22 (1.04 to 1.42)	0.92*
Fluconazole	200 mg orally single dose	1,200 mg orally single dose	18	0.82 (0.66 to 1.02)	1.07 (0.94 to 1.22)
Nelfinavir	750 mg three times a day for 11 days	1,200 mg orally on day 9	14	2.36 (1.77 to 3.15)	2.12 (1.80 to 2.50)

* - 90% Confidence interval not reported

10.4 Microbiology

Mechanism of Action
Azithromycin acts by binding to the 23S rRNA of the 50S ribosomal subunit of susceptible microorganisms inhibiting bacterial protein synthesis and impeding the assembly of the 50S ribosomal subunit.

Resistance
Azithromycin demonstrates cross resistance with erythromycin. The most frequently encountered mechanism of resistance to azithromycin is modification of the 23S rRNA target, most often by methylation. Ribosomal modifications can determine cross resistance to other macrolides, lincosamides, and streptogramin B (MLS_B phenotype).

Antimicrobial Activity
Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

Gram-Positive Bacteria
- *Staphylococcus aureus*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*

Gram-Negative Bacteria
- *Haemophilus ducreyi*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Neisseria gonorrhoeae*

Other Bacteria
- *Chlamydophila pneumoniae*
- *Chlamydia trachomatis*
- *Mycoplasma pneumoniae*

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for azithromycin against isolates of similar genus or organism group. However, the efficacy of azithromycin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria
- Beta-hemolytic streptococci (Groups C, F, G)
- Viridans group streptococci

Gram-Negative Bacteria
- *Bordetella pertussis*
- *Legionella pneumophila*

Anaerobic Bacteria
- *Prevotella bivia*
- *Peptostreptococcus species*

Other Bacteria
- *Ureaplasma urealyticum*

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. In fertility studies conducted in male and female rats, oral administration of azithromycin for 64 to 66 days (males) or 15 days (females) prior to and during cohabitation resulted in decreased pregnancy rate at 20 and 30 mg/kg/day when both males and females were treated with azithromycin. This minimal effect on pregnancy rate (approximately 12% reduction compared to concurrent controls) did not become more pronounced when the dose was increased from 20 to 30 mg/kg/day (approximately 0.4 to 0.6 times the adult daily dose of 500 mg based on body surface area) and it was not observed when only one animal in the mated pair was treated. There were no effects on any other reproductive parameters, and there were no effects on fertility at 10 mg/kg/day. The relevance of these findings to patients being treated with azithromycin at the doses and durations recommended in the prescribing information is uncertain.

11.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) in dogs and rats treated with azithromycin at doses which, expressed on the basis of body surface area, are similar to or less than the highest recommended adult human dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (50 mg/kg/day dose) at the observed maximal plasma concentration of 1.3 mcg/mL (1.6 times the observed C_{max} of 0.821 mcg/mL at the adult dose of 2 g). Similarly, it has been shown in the dog (10 mg/kg/day dose) at the observed maximal serum concentration of 1 mcg/mL (1.2 times the observed C_{max} of 0.821 mcg/mL at the adult dose of 2 g). Phospholipidosis was also observed in neonatal rats dosed for 18 days at 30 mg/kg/day, which is less than the pediatric dose of 60 mg/kg based on the surface area. It was not observed in neonatal rats treated for 10 days at 40 mg/kg/day with mean maximal serum concentrations of 1.86 mcg/mL, approximately 1.5 times the C_{max} of 1.27 mcg/mL at the pediatric dose. Phospholipidosis has been observed in neonatal dogs (10 mg/kg/day) at maximum mean whole blood concentrations of 3.54 mcg/mL, approximately 3 times the pediatric dose C_{max}. The significance of these findings for animals and for humans is unknown.

12 CLINICAL STUDIES

12.1 Adult Patients

Acute Bacterial Exacerbations of Chronic Bronchitis

In a randomized, double-blind controlled clinical trial of acute exacerbation of chronic bronchitis (AECB), azithromycin (500 mg once daily for 3 days) was compared with clarithromycin (500 mg twice daily for 10 days). The primary endpoint of this trial was the clinical cure rate at Days 21- 24. For the 304 patients analyzed in the modified intent-to-treat analysis at the Days 21-24 visit, the clinical cure rate for 3 days of azithromycin was 85% (125/147) compared to 82% (129/157) for 10 days of clarithromycin.

The following outcomes were the clinical cure rates at the Days 21-24 visit for the bacteriologically evaluable patients by pathogen:

Pathogen	Azithromycin (3 Days)	Clarithromycin (10 Days)
S. pneumoniae	29/32 (91%)	21/27 (78%)
H. influenzae	12/14 (86%)	14/16 (88%)
M. catarrhalis	11/12 (92%)	12/15 (80%)

Acute Bacterial Sinusitis

In a randomized, double-blind, double-dummy controlled clinical trial of acute bacterial sinusitis, azithromycin (500 mg once daily for 3 days) was compared with amoxicillin/clavulanate (500/125 mg three times a day for 10 days). Clinical response assessments were made at Day 10 and Day 28. The primary endpoint of this trial was prospectively defined as the clinical cure rate at Day 28. For the 594 patients analyzed in the modified intent to treat analysis at the Day 10 visit, the clinical cure rate for 3 days of azithromycin was 88% (268/303) compared to 85% (248/291) for 10 days of amoxicillin/clavulanate. For the 586 patients analyzed in the modified intent to treat analysis at the Day 28 visit, the clinical cure rate for 3 days of azithromycin was 71.5% (213/298) compared to 71.5% (206/288), with a 97.5% confidence interval of –8.4 to 8.3, for 10 days of amoxicillin/clavulanate.

In an open label, non-comparative study requiring baseline transantral sinus punctures, the following outcomes were the clinical success rates at the Day 7 and Day 28 visits for the modified intent to treat patients administered 500 mg of azithromycin once daily for 3 days with the following pathogens:

Clinical Success Rates of Azithromycin (500 mg per day for 3 Days)

Pathogen	Day 7	Day28
S. pneumoniae	23/26 (88%)	21/25 (84%)
H. influenzae	28/32 (87%)	24/32 (75%)
M. catarrhalis	14/15 (93%)	13/15 (87%)

12.2 Pediatric Patients

From the perspective of evaluating pediatric clinical trials, Days 11-14 were considered on-therapy evaluations because of the extended half-life of azithromycin. Days 11-14 data are provided for clinical guidance. Days 24-32 evaluations were considered the primary test of cure endpoint.

Pharyngitis/Tonsillitis
In three double-blind controlled studies, conducted in the United States, azithromycin (12 mg/kg once a day for 5 days) was compared to penicillin V (250 mg three times a day for 10 days) in the treatment of pharyngitis due to documented Group A β-hemolytic *streptococci* (GABHS or *S. pyogenes*). Azithromycin was clinically and microbiologically statistically superior to penicillin at Day 14 and Day 30 with the following clinical success (i.e., cure and improvement) and bacteriologic efficacy rates (for the combined evaluable patient with documented GABHS):

Three U.S. Streptococcal Pharyngitis Studies
Azithromycin vs. Penicillin V
EFFICACY RESULTS

	Day 14	**Day 30**
Bacteriologic Eradication:		
Azithromycin	323/340 (95%)	255/330 (77%)
Penicillin V	242/332 (73%)	206/325 (63%)
Clinical Success (cure plus improvement):		
Azithromycin	336/343 (98%)	310/330 (94%)
Penicillin V	284/338 (84%)	241/325 (74%)

Approximately 1% of azithromycin-susceptible *S. pyogenes* isolates were resistant to azithromycin following therapy.

Acute Otitis Media

Efficacy using azithromycin given over 5 days (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5).

Trial 1
In a double-blind, controlled clinical study of acute otitis media performed in the United States, azithromycin (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5) was compared to amoxicillin/clavulanate potassium (4:1). For the 553 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the Day 11 visit was 88% for azithromycin and 88% for the control agent. For the 521 patients who were evaluated at the Day 30 visit, the clinical success rate was 73% for azithromycin and 71% for the control agent.

Trial 2
In a non-comparative clinical and microbiologic trial performed in the United States, where significant rates of beta-lactamase producing organisms (35%) were found, 131 patients were evaluable for clinical efficacy. The combined clinical success rate (i.e., cure and improvement) at the Day 11 visit was 84% for azithromycin. For the 122 patients who were evaluated at the Day 30 visit, the clinical success rate was 70% for azithromycin.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. The following clinical success rates were obtained from the evaluable group:

Pathogen		
	Day 11	**Day 30**
	Azithromycin	**Azithromycin**
S. pneumoniae	61/74 (82%)	40/56 (71%)
H. influenzae	43/54 (80%)	30/47 (64%)
M. catarrhalis	28/35 (80%)	19/26 (73%)
S. pyogenes	11/11 (100%)	7/7 (100%)
Overall	177/217 (82%)	97/137 (73%)

Trial 3

In another controlled comparative clinical and microbiologic study of otitis media performed in the United States, azithromycin (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5).was compared to amoxicillin/clavulanate potassium (4:1). This study utilized two of the same investigators as Protocol 2 (above), and these two investigators enrolled 90% of the patients in Protocol 3. For this reason, Protocol 3 was not considered to be an independent study. Significant rates of beta-lactamase producing organisms (20%) were found. Ninety-two (92) patients were evaluable for clinical and microbiologic efficacy. The combined clinical success rate (i.e., cure and improvement) of those patients with a baseline pathogen at the Day 11 visit was 88% for azithromycin vs. 100% for control; at the Day 30 visit, the clinical success rate was 82% for azithromycin vs. 80% for control.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. At the Day 11 and Day 30 visits, the following clinical success rates were obtained from the evaluable group:

	Day 11		**Day 30**	
Pathogen	**Azithromycin**	**Control**	**Azithromycin**	**Control**
S. pneumoniae	25/29 (86%)	26/26 (100%)	22/28 (79%)	18/22 (82%)
H. influenzae	9/11 (82%)	9/9 (100%)	8/10 (80%)	6/8 (75%)
M. catarrhalis	7/7 (100%)	5/5 (100%)	5/5 (100%)	2/3 (66%)
S. pyogenes	2/2 (100%)	5/5 (100%)	2/2 (100%)	4/4 (100%)
Overall	43/49 (88%)	45/45 (100%)	37/45 (82%)	30/37 (81%)

Efficacy using azithromycin given over 3 days (10 mg/kg/day).

Trial 4
In a double-blind, controlled, randomized clinical study of acute otitis media in pediatric patients from 6 months to 12 years of age, azithromycin (10 mg/kg per day for 3 days) was compared to amoxicillin/clavulanate potassium (7:1) in divided doses q12h for 10 days. Each patient received active drug and placebo matched for the comparator.

For the 366 patients who were evaluated for clinical efficacy at the Day 12 visit, the clinical success rate (i.e., cure plus improvement) was 83% for azithromycin and 88% for the control agent. For the 362 patients who were evaluated at the Days 24-28 visit, the clinical success rate was 74% for azithromycin and 69% for the control agent.

Efficacy using azithromycin 30 mg/kg given as a single dose

Trial 5
A double-blind, controlled, randomized trial was performed at nine clinical centers. Pediatric patients from 6 months to 12 years of age were randomized 1:1 to treatment with either azithromycin (given at 30 mg/kg as a single dose on Day 1) or amoxicillin/clavulanate potassium (7:1), divided q12h for 10 days. Each child received active drug, and placebo matched for the comparator.

Clinical response (Cure, Improvement, Failure) was evaluated at End of Therapy (Days 12-16) and Test of Cure (Days 28-32). Safety was evaluated throughout the trial for all treated subjects. For the 321 subjects who were evaluated at End of Treatment, the clinical success rate (cure plus improvement) was 87% for azithromycin, and 88% for the comparator. For the 305 subjects who were evaluated at Test of Cure, the clinical success rate was 75% for both azithromycin and the comparator.

Trial 6
In a non-comparative clinical and microbiological trial, 248 patients from 6 months to 12 years of age with documented acute otitis media were dosed with a single oral dose of azithromycin (30 mg/kg on Day 1).

For the 240 patients who were evaluable for clinical modified Intent-to-Treat (MITT) analysis, the clinical success rate (i.e., cure plus improvement) at Day 10 was 89% and for the 242 patients evaluable at Days 24-28, the clinical success rate (cure) was 85%.

Presumed Bacteriologic Eradication		
	Day 10	**Days 24-28**
S. pneumoniae	70/76 (92%)	67/76 (88%)
H. influenzae	30/42 (71%)	28/44 (64%)
M. catarrhalis	10/10 (100%)	10/10 (100%)

Overall	110/128 (86%)	105/130 (81%)

13 HOW SUPPLIED/STORAGE AND HANDLING

Capsules: Capsules for oral administration are available as plain white opaque No. 0 hard gelatin capsules. The capsule is printed in black ink with Pfizer on one end of shell and "ZTM 250" on the other end. These capsules are packed in PVC blister packs.

Package sizes: 6 capsules

Powder for Oral Suspension: Azithromycin powder for oral suspension is presented as a dry powder which yields, on reconstitution with water, a white to off-white suspension.
The powder for oral suspension is packed in polyethylene bottles.

Package sizes: Azenil 200mg/5ml suspension - 600mg azithromycin powder for 15 ml suspension.
Azenil 200mg/5ml suspension- 900mg azithromycin powder for 22.5ml suspension

Each package contains: 10 ml oral dosing syringe, 5ml teaspoon and a measuring cup.

Not all packages may be marketed.

Shelf-Life

Capsules: The expiry date of the product is indicated on the packaging materials

Powder for Oral Suspension: The expiry date of the product is indicated on the packaging materials . After reconstitution of the powder, the product should be used within 5 days.

Special Precautions for Storage

Capsules: Store below 25°C.

Powder for Oral Suspension: Store below 25°C for the powder and the reconstituted suspension.

Special precautions for disposal and other handling

Capsules: The capsules should be swallowed whole.

Powder for Oral Suspension: Tap the bottle to loosen the powder.
To the 600-mg bottle, add 9 ml of water; to the 900-mg bottle add 12 ml of water.
Shake well. Shake immediately prior to use.

14 LICENCE HOLDER: Pfizer PFE pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

15 LICENSE NUMBER:

Azenil Capsules: 117-66-29827
Azenil 200mg/5ml suspension: 118-26-29828

Revised on 12/2021 according to MoH guidelines