Product Monograph

Including Patient medication Information

[Pr]pms-AZITHROMYCIN

Azithromycin Tablets

Tablets, 250 mg and 600 mg, Oral

USP

Antibacterial Agent

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1. Indications, 1.1. Pediatrics	2026-08
4. Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	2026-08

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. Indications

pms-AZITHROMYCIN (azithromycin) is indicated in adults for treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the following diseases and specific conditions. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, see 4 Dosage and Administration for specific dosing recommendations.

Because some strains are resistant to azithromycin, when applicable, appropriate culture and susceptibility tests should be initiated before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with pms-AZITHROMYCIN may be initiated before results of these tests are known; once the results become available, antibiotic treatment should be adjusted accordingly.

Pharyngitis and tonsillitis caused by *Streptococcus pyogenes* (group A β-hemolytic streptococci) occurring in individuals who cannot use first line therapy.

NOTE: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is often effective in the eradication of susceptible strains of streptococci from the oropharynx. However, data establishing the efficacy of azithromycin in the subsequent prevention of rheumatic fever are not available at present.

Acute bacterial exacerbations of chronic obstructive pulmonary diseases caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

Community-acquired pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae, Mycoplasma pneumoniae* or *Chlamydia pneumoniae* in patients for whom oral therapy is appropriate.

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 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).

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes* or *Streptococcus agalactiae*.

Genitourinary tract infections
Urethritis and cervicitis due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

Patients should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Prevention of Disseminated *Mycobacterium Avium* Complex (MAC) Disease
Azithromycinalone or in combination with rifabutin at its approved dose, is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in persons with advanced HIV infections (MAC) disease in persons with advanced HIV infections (see 14 Clinical Trials).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of pms-AZITHROMYCIN and other antibacterial drugs, pms-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.

1.1. Pediatrics
Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of pms-AZITHROMYCIN tablets in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics
Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness. However, elderly patients may be more susceptible to development of torsade de pointes arrhythmias (see 7 Warnings and Precautions, Cardiovascular; 7.1.4 Geriatrics; 10 Clinical Pharmacology).

2. Contraindications

pms-AZITHROMYCIN is contraindicated:
- in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin
- in those with a hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibacterial agent, or to any ingredient in the formulation or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.

4. Dosage and Administrations

4.1. Dosing Considerations

pms-AZITHROMYCIN tablets is not bioequivalent and are not interchangeable with azithromycin sustained release due to a different pharmacokinetic profile.

Hepatic Impairment
No dose adjustment of pms-AZITHROMYCIN is recommended for patients with mild to moderate hepatic impairment. Azithromycin has not been studied in patients with severe hepatic impairment. Since the liver is the principal route of elimination for azithromycin, the use of pms-AZITHROMYCIN should be undertaken with caution in patients with impaired hepatic function (see 7 Warning and Precautions; and 10 Clinical Pharmacology).

Renal Impairment
No dosage adjustment of pms-AZITHROMYCIN is recommended for subjects with GFR 10-80 mL/min. The mean AUC_{0-120} increased 35% in subjects with GFR < 10 mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with GFR < 10 mL/min. No studies have been conducted in patients requiring hemodialysis (see 7 Warning and Precautions; and 10 Clinical Pharmacology).

4.2. Recommended Dose and Dosage Adjustment

DOSING in relation to FOOD
pms-AZITHROMYCIN Tablets can be taken with or without food.

Upper and Lower Respiratory Infections/Skin and Skin Structure Infections
The recommended dose of pms-AZITHROMYCIN for individuals 16 years of age or older in the treatment of mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease due to the indicated organisms is: either 500 mg per day for 3 days or 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5 for a total dose of 1.5 grams.

The recommended dose of pms-AZITHROMYCIN for the treatment of community-acquired pneumonia of mild severity, uncomplicated skin and skin structure infections, and for pharyngitis/tonsillitis (as second-line therapy) due to the indicated organisms is: 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5 for a total dose of 1.5 grams.

Genitourinary Infections
The recommended dose of pms-AZITHROMYCIN for the treatment of genital ulcer disease due to *Haemophilus ducreyi* (chancroid) and non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 gram (1,000 mg) oral dose of pms-AZITHROMYCIN. This dose can be administered as four 250 mg tablets.

The recommended dose of pms-AZITHROMYCIN for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* is: a single 2 gram (2,000 mg) dose of pms-AZITHROMYCIN. This dose can be administered as eight 250 mg tablets.

For Prevention of Disseminated *Mycobacterium Avium* Complex (MAC) Disease
The recommended dose of pms-AZITHROMYCIN for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease is 1,200 mg (two 600 mg tablets) taken once weekly. This dose of pms-AZITHROMYCIN may be continued with the approved dosage regimen of rifabutin.

4.5. Missed Dose

In case of missed dose, patients should not double the next dose.

5. Overdose

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

Ototoxicity and gastrointestinal adverse events may occur with an overdose of azithromycin.

Up to 15 grams cumulative dose of azithromycin over 10 days has been administered in clinical trials without apparent adverse effect.

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Oral	Tablet, 250 mg and 600 mg of azithromycin	Croscarmellose Sodium, Hypromellose, Lactose Anhydrous, Magnesium Stearate, Poloxamer 188, Povidone, Silicified Microcrystalline Cellulose, Polyethylene Glycol, Talc and Titanium Dioxide. 250 mg tablets also contain D & C Red No. 27, FD & C Blue No. 2, FD & C Red No. 40 and FD & C Yellow No. 6. 600 mg tablets also contain Polysorbate 80.

Description

250 mg: Each dark pink, coated, modified capsule-shaped tablet debossed with an "AZI" logo on one side and "250" on the other side, contains 250 mg of azithromycin.

600 mg: Each white to off-white, coated, modified capsule-shaped tablet debossed with a "P" logo on one side and "600" on the other side, contains 600 mg of azithromycin.

Packaging

pms-AZITHROMYCIN 250 mg film-coated tablets are available in HDPE bottles of 30 and 100 tablets and blister packs of 6 tablets.

pms-AZITHROMYCIN 600 mg film-coated tablets are available in HDPE bottles of 30 tablets.

7. Warnings and Precautions

General

- Azithromycin and ergot derivatives should not be coadministered due to the possibility that ergot toxicity may be precipitated by macrolide antibiotics. Acute ergot toxicity is characterized by severe peripheral vasospasm, including ischemia of the extremities, along with dysesthesia and possible central nervous system effects. The use of azithromycin with other drugs may lead to drug-drug interactions. For established or potential drug interactions, see 9 Drug Interactions section of the product monograph.

As with any antibacterial preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.

- Intramuscular use of azithromycin is not recommended; extravasation of drug into the tissues may cause tissue injury.

Carcinogenesis and Mutagenesis
Long term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no genotoxic or mutagenic potential in standard laboratory tests (see 16 Non-Clinical Toxicology).

Cardiovascular
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes,* have been seen in treatment with macrolides including azithromycin (see 8 Adverse Reactions). Prescribers should consider the risk of QT prolongation which can lead to fatal events when weighing the risks and benefits of azithromycin. Risk factors for *torsades de pointes* include patients:

- With a history of *torsade de pointes*
- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly may be more susceptible to drug-associated effects on the QT interval
- Exposed to higher plasma levels of azithromycin (e.g., receiving intravenous azithromycin, hepatobiliary impaired)

There is information that 'QT Related Adverse Events' may occur in some patients receiving azithromycin. There have been spontaneous reports from post-marketing experience of prolonged QT interval and *torsades de pointes* (see 8.5 Post-Market Adverse Reaction). These include but are not limited to: one AIDS patient dosed at 750 mg to 1 g daily experienced prolonged QT interval and *torsades de pointes*; a patient with previous history of arrhythmias who experienced *torsades de pointes* and subsequent myocardial infarction following a course of azithromycin therapy; and a pediatric case report of prolonged QT interval experienced at a therapeutic dose of azithromycin which reversed to normal upon discontinuation (see 10 Clinical Pharmacology, Cardiac Electrophysiology).

Endocrine and Metabolism

Lysosomal lipid storage diseases

In the absence of data on the metabolism and pharmacokinetics in patients with lysosomal lipid storage diseases (e.g., Tay-Sachs disease, Niemann-Pick disease) the use of azithromycin in these patients is not recommended.

Saccharide Intolerance

- Caution in diabetic patients
- Due to the lactose content in the tablet coating, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take the tablet formulation.

Gastrointestinal

A higher incidence of gastrointestinal adverse events (8 of 19 subjects) was observed when azithromycin was administered to a limited number of subjects with GFR < 10 mL/min.

Clostridioides difficile-associated disease

Clostridioides difficile-associated disease (CDAD) has been reported with use of many antibacterial agents including azithromycin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agents. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridioides difficile*. *Clostridioides difficile* produces toxins A and B which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridioides difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridioides difficile*. Surgical evaluation should be instituted as clinically indicated; as surgical intervention may be required in certain severe cases (see 8 Adverse Reactions).

Hematologic

Severe neutropenia (WBC < 1,000/mm^3) may adversely affect the distribution of azithromycin and its transport to the site of infection. Antibacterials with proven efficacy in this population should be used, as outlined by the relevant guidelines for treatment of patients with severe neutropenia. Efficacy and safety of azithromycin have not been studied in patients with severe neutropenia.

Hepatic/biliary/pancreatic
Since the liver is the principal route of elimination for azithromycin, the use of pms-AZITHROMYCIN should be undertaken with caution in patients with impaired hepatic function. Azithromycin has not been studied in patients with severe hepatic impairment (see 10 Clinical Pharmacology).

Hepatotoxicity
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Rare cases of acute hepatic necrosis requiring liver transplant or causing death have been reported in patients following treatment with oral azithromycin. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur (see 8 Adverse Reactions).

Immune
Allergic reactions may occur during and soon after treatment with azithromycin. 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. If an allergic reaction occurs, the drug should be discontinued, and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Monitoring and Laboratory Tests
Monitoring of QT/QTc intervals during treatment with pms-AZITHROMYCIN may be considered by the physician as appropriate.

Musculoskeletal
Exacerbations of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy. The use of pms-AZITHROMYCIN in patients with a known history of myasthenia gravis is not recommended.

Renal
The safety, efficacy and pharmacokinetics of azithromycin in patients with renal impairment have not been established. No dose adjustment is recommended for patients with GFR 10-80 mL/min. Caution should be exercised when azithromycin is administered to patients with GFR < 10 mL/min. This precaution is based on a clinical study of azithromycin immediate-release tablets, in which patients with GFR < 10 mL/min showed a significant (61%) increase in mean C_{max} and a significant (35%) increase in systemic exposure to azithromycin, and experienced a high incidence of gastrointestinal adverse events (8 of 19 clinical study subjects). Patients with GFR 10-80 mL/min showed only slightly increased serum azithromycin levels compared to patients with normal renal function.

Due to limited data in subjects with GFR < 10 mL/min, caution should be exercised when prescribing oral azithromycin in these patients (see 10 Clinical Pharmacology).

Reproductive Health:

- **Fertility**
  There are no adequate and well-controlled studies in humans. In fertility studies conducted in the rat, reduced pregnancy rates were noted following administration of azithromycin. The predictive value of these data to the response in humans has not been established (see 16 Non-Clinical Toxicology).

Sensitivity/Resistance

Prescribing pms-AZITHROMYCIN 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.

Skin

Serious allergic reactions, including angioedema, anaphylaxis, and dermatological reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermolysis, toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic symptoms (DRESS) have been reported rarely (with rare reports of fatalities), in patients on azithromycin therapy (see 2 Contraindications).

7.1. Special Populations

7.1.1. Pregnancy

Azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any potential risk to the fetus.

There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. While most studies do not suggest an association with adverse fetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy.

In animal reproduction studies in mice and rats, at azithromycin doses up to 200 mg/kg/day (moderately maternally toxic), effects were noted during the prenatal and postnatal development period (see 16 Non-Clinical Toxicology).

7.1.2. Breastfeeding

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed. However, the safety of azithromycin has not been studied in infants less than 6 months of age.

pms-AZITHROMYCIN should not be used in the treatment of breastfeeding women unless the expected benefit to the mother outweighs any potential risk to the infant. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Because azithromycin may accumulate in breast milk over time with continued pms-AZITHROMYCIN therapy, if the lactating mother is treated with azithromycin, the breast milk should be expressed and discarded during treatment.

7.1.3. Pediatrics

Pediatrics (< 18 years of age):
Studies evaluating the use of repeated courses of therapy have not been conducted. Safety data with the use of azithromycin at doses higher than proposed and for durations longer than recommended are limited to a small number of immunocompromised children who underwent chronic treatment.

Infantile hypertrophic pyloric stenosis (IHPS)
Following the use of azithromycin in neonates (treatment up to 42 days of life); infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Prevention of Disseminated *Mycobacterium Avium* Complex (MAC) Disease
Safety and efficacy of azithromycin for the prevention of MAC in children have not been established.

Limited safety data are available for 24 children 5 months to 14 years of age (mean 4.6 years) who received azithromycin for treatment of opportunistic infections. The mean duration of therapy was 186.7 days (range 13-710 days) at doses of < 5 to 20 mg/kg/day. Adverse events were similar to those observed in the adult population, most of which involved the gastrointestinal tract. While none of these children prematurely discontinued treatment due to a side effect, one child discontinued due to a laboratory abnormality (eosinophilia). Based on available pediatric pharmacokinetic data, a dose of 20 mg/kg in children would provide drug exposure similar to the 1,200 mg adult dose but with a higher C_{max}.

7.1.4. Geriatrics

The pharmacokinetics in elderly volunteers (age 65 to 85) were similar to those in younger volunteers (age 18 to 40) for the 5-day oral therapeutic regimen. Dosage adjustment does not appear to be necessary for elderly patients with normal renal and hepatic function receiving treatment with this dosage regimen. However, elderly patients may be more susceptible to development of torsade de pointes arrhythmias.

8. Adverse Reactions

8.1. Adverse Reaction Overview

The majority of side effects observed in controlled clinical trials involving patients (adults and children) treated with oral azithromycin were of a mild and transient nature. Approximately 0.7% of both adult patients (n=3,812) and children (n=2,878) from the 5-day multiple dose clinical trials discontinued azithromycin therapy because of drug related side effects. Discontinuation rates were slightly higher for PID patients receiving concomitant metronidazole therapy (4%).

In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.4%. In clinical trials in children given 30 mg/kg, orally either as a single dose (n=487) or over 3 days, (n=1,729) discontinuation from therapy due to treatment-related side effects was approximately 1%.

Most of the side effects leading to discontinuation in patients on oral therapy were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, along with abdominal pain, rashes. Potentially serious treatment-related side effects including angioedema and cholestatic jaundice occurred in less than 1% of patients.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Oral Regimen: Adults

Multiple-dose Regimens

In adult patients, the most common treatment-related side effects in patients receiving the 3 or 5 day oral multiple-dose regimens of azithromycin were related to the gastrointestinal system with diarrhea/loose stools (4-5%), nausea (3-4%), abdominal pain (2-3%), and vomiting (1%).

Treatment-related side effects that occurred with a frequency of 1% or less include:

Allergic:	pruritus
Cardiovascular:	hypertension
Gastrointestinal:	dry mouth, esophagitis, gastroenteritis, rectal hemorrhage, cholestatic jaundice
Genitourinary:	menorrhagia, urinary frequency, vaginitis
Nervous system:	dizziness
Special senses:	conjunctivitis

Single 1-gram Dose Regimen
In adult patients (n=904), side effects that occurred on the single one-gram dosing regimen of azithromycin with a frequency greater than 1% included diarrhea (6.1%), nausea (4.9%), abdominal pain (4.9%), vomiting (1.7%), vaginitis (1.3%), loose stools (1.2%), and dyspepsia (1.1%).

Single 2-gram Dose Regimen
Overall, the most common side effects in patients receiving a single 2-gram dose of azithromycin were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of a 1% or greater included nausea (18.2%), diarrhea/loose stools (13.8%), vomiting (6.7%), abdominal pain (6.7%), vaginitis (2.2%), dyspepsia (1.1%), and dizziness (1.3%). The majority of these complaints were mild in nature.

Prevention of *Mycobacterium Avium* Complex (MAC) Disease
Chronic therapy with azithromycin 1,200 mg weekly regimen: The nature of side effects seen with the 1,200 mg weekly dosing regimen for the prevention of *Mycobacterium avium* complex infection in severely immunocompromised HIV-infected patients were similar to those seen with short-term dosing regimens.

Incidence[1] (%) of Treatment Related* Adverse Events in HIV-Infected Patients Receiving Prophylaxis for Disseminated MAC**

	Study 155		Study 174		
	Placebo (n=91)	Azithromycin 1,200 mg weekly (n=89)	Azithromycin 1,200 mg weekly (n=233)	Rifabutin 300 mg daily (n=236)	Azithromycin & Rifabutin (n=224)
Mean Duration of Therapy (days)	303.8	402.9	315	296.1	344.4
Discontinuation of Therapy (%)	2.3	8.2	13.5	15.9	22.7
AUTONOMIC NERVOUS SYSTEM					
Mouth Dry	0	0	0	3.0	2.7
CENTRAL NERVOUS SYSTEM					
Dizziness	0	1.1	3.9	1.7	0.4
Headache	0	0	3.0	5.5	4.5
GASTROINTESTINAL					
Diarrhea	15.4	52.8	50.2	19.1	50.9
Loose Stools	6.6	19.1	12.9	3.0	9.4
Abdominal Pain	6.6	27	32.2	12.3	31.7
Dyspepsia	1.1	9	4.7	1.7	1.8
Flatulence	4.4	9	10.7	5.1	5.8
Nausea	11	32.6	27.0	16.5	28.1
Vomiting	1.1	6.7	9.0	3.8	5.8
GENERAL					
Fever	1.1	0	2.1	4.2	4.9
Fatigue	0	2.2	3.9	2.1	3.1
Malaise	0	1.1	0.4	0	2.2
MUSCULOSKELETAL					
Arthralgia	0	0	3.0	4.2	7.1

	Study 155		Study 174		
	Placebo (n=91)	Azithromycin 1,200 mg weekly (n=89)	Azithromycin 1,200 mg weekly (n=233)	Rifabutin 300 mg daily (n=236)	Azithromycin & Rifabutin (n=224)
PSYCHIATRIC					
Anorexia	1.1	0	2.1	2.1	3.1
SKIN & APPENDAGES					
Pruritus	3.3	0	3.9	3.4	7.6
Rash	3.2	3.4	8.1	9.4	11.1
Skin discoloration	0	0	0	2.1	2.2
SPECIAL SENSES					
Tinnitus	4.4	3.4	0.9	1.3	0.9
Hearing Decreased	2.2	1.1	0.9	0.4	0
Taste Perversion	0	0	1.3	2.5	1.3

* Includes those events considered possibly or probably related to study drug

** > 2% adverse event rates for any group

[1] Reflects the occurrence of ≥ 1 event during the entire treatment period

Side effects related to the gastrointestinal tract were seen more frequently in patients receiving azithromycin than in those receiving placebo or rifabutin. In one of the studies, 86% of diarrheal episodes were mild to moderate in nature with discontinuation of therapy for this reason occurring in only 9/233 (3.8%) of patients.

The most common side effects (greater than 1%) in adult patients who received sequential oral azithromycin in studies of **community-acquired pneumonia** were related to the gastrointestinal system: diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%).

In adult women who received sequential oral azithromycin in studies of **pelvic inflammatory disease**, the most common side effects (greater than 1%) were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most frequently reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was coadministered with metronidazole in these studies, a higher proportion of women experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%) and application site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).
Side effects that occurred with a frequency of 1% or less included:

Allergic: bronchospasm
Gastrointestinal: dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis
Nervous System: headache, somnolence
Special Senses: taste perversion

8.2.1. Clinical Trial Adverse Reactions – Pediatrics

Oral Regimen: Children

Single and Multiple-dose regimens
In children enrolled in controlled clinical trials in acute otitis media and *S. pyogenes* pharyngitis, the types of side effects were comparable to those seen in adults (see below). Different side effect incidence rates for the dosage regimens recommended in children were observed.

Acute Otitis Media: For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects (≥ 1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea and rash. The incidence, based on dosing regimen, is described in the table below:

Regimen	Subjects	Overall ADR Incidence	Diarrhea	Abdominal Pain	Vomiting	Nausea	Rash
1-Day	487	14%	4%	1%	5%	1%	1%
3-Day	1,395	7%	3%	2%	1%	< 1%	< 1%
5-Day	1,888	6%	2%	1%	1%	1%	< 1%

Community-Acquired Pneumonia: For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects attributed to treatment were diarrhea/loose stools, abdominal pain, vomiting/nausea and rash. The incidence is described in the table below:

Dosage Regimen	Subjects	Overall ADR Incidence	Diarrhea/ Loose stools	Abdominal Pain	Vomiting	Nausea	Rash
5-Day	323	12%	5.8%	1.9%	1.9%	1.9%	1.6%

Pharyngitis/tonsillitis: For the recommended total dosage regimen of 60 mg/kg, the most frequent side effects attributed to treatment were diarrhea, vomiting, abdominal pain, nausea and headache. The incidence is described in the table below:

Regimen	Subjects	Overall ADR Incidence	Diarrhea	Abdominal pain	Vomiting	Nausea	Rash	Headache
5-Day	447	17%	5%	3%	6%	2%	< 1%	1%

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

Allergic: Allergic reaction, photosensitivity, angioedema, erythema multiforme, pruritus and urticaria;
Cardiovascular: Palpitations, chest pain;
Gastrointestinal: Dyspepsia, flatulence, melena, constipation, anorexia, enteritis, loose stools, oral moniliasis and gastritis;

General:	Fatigue, face edema, fever, fungal infection, pain and malaise;
Genitourinary:	Monilia, vaginitis and nephritis;
Hematologic and Lymphatic:	Anemia, leukopenia
Liver/Biliary:	Liver function test abnormal, jaundice and cholestatic jaundice.
Nervous System:	Dizziness, vertigo, somnolence, agitation, nervousness, insomnia and hyperkinesia;
Respiratory:	Cough increased, pharyngitis, pleural effusion and rhinitis;
Skin and Appendages:	Eczema, fungal dermatitis, sweating and vesiculobullous rash;

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Oral Therapy:

Adults
Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials in patients were reported as follows:

With an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, monocytes, albumin and blood glucose, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT and AST (SGOT), BUN, creatinine, blood glucose, platelet count, eosinophils and monocytes.

With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, LDH and phosphate.

The majority of subjects with elevated serum creatine 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 4,500 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities, one for treatment-related elevated transaminases and triglycerides and one because of a renal function abnormality.

Prevention of *Mycobacterium Avium* Complex (MAC) Disease
In these immunocompromised patients with advanced HIV infection, it was sometimes necessary to assess laboratory abnormalities developing on study with additional criteria if baseline values were outside the normal range.

Prophylaxis Against Disseminated MAC Abnormal Laboratory Values

Criteria[a]		Study 155		Study 174		
		Placebo (n=88)	Azithromycin 1,200 mg weekly (n=89)	Azithromycin 1,200 mg weekly (n=208)	Rifabutin 300 mg daily (n=205)	Azithromycin & Rifabutin (n=199)
Hemoglobin	< 0.8 x LLN[b]	31%	30%	19%	26%	21%
Platelet Count	< 0.75 x LLN	19%	16%	11%	10%	16%
WBC Count	< 0.75 x LLN	48%	49%	60%	53%	60%
Neutrophils	< 0.5 x LLN	16%	28%	23%	20%	29%
	< 500/mm^3	6%	13%	5%	6%	8%
AST (SGOT)	> 2.0 x ULN[c]	28%	39%	33%	18%	30%
	> 200 U/L	10%	8%	8%	3%	6%
ALT (SGPT)	> 2.0 x ULN	24%	34%	31%	15%	27%
	> 250 U/L	2%	6%	8%	2%	6%

[a] secondary criteria also applied if baseline abnormal, as follows: Hemoglobin, 10% decrease; Platelet, 20% decrease; WBC count, 25% decrease; Neutrophils, 50% decrease; AST (SGOT), 50% increase; ALT (SGPT), 50% increase.

[b] lower limit of normal

[c] upper limit of normal

In a phase I drug interaction study performed in normal volunteers, 1 of 6 subjects given the combination of azithromycin and rifabutin, 1 of 7 given rifabutin alone and 0 of 6 given azithromycin alone developed a clinically significant neutropenia (< 500 cells/mm^3).

Children

One-, Three- and Five-Day Regimens

Laboratory data collected from 64 subjects receiving azithromycin in comparative clinical trials employing the 1-day regimen (30 mg/kg as a single dose), 1,198 and 169 subjects receiving azithromycin respectively employing the two 3-day regimens (30 mg/kg or 60 mg/kg in divided doses over 3 days) were similar for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1-5%.

Similar results were obtained in subjects receiving the two 5-day regimens. Overall, 1,948 and 421 patients were exposed to 30 mg/kg or 60 mg/kg, respectively in divided doses over 5 days. The data collected in the subset of azithromycin patients assessed for laboratory abnormalities were similar to those in all comparators combined with most clinically significant laboratory abnormalities occurring at incidences of 1-5%.

In a single center clinical trial, a decrease in absolute neutrophils was observed in the range of 21-29% for azithromycin regimens of 30 mg/kg given either as a single dose or over 3 days, as well as the comparator. No patients had significant neutropenia defined as an absolute neutrophil count < 500 cells/mm^3 (see 14 Clinical Trials).

In clinical trials involving approximately 4,700 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

8.5. Post-Market Adverse Reactions

The following adverse experiences have been reported in patients under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain or in patients treated with significantly higher than the recommended doses for prolonged periods.

In addition, because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency is not always possible.

Allergic:	Arthralgia, edema, anaphylaxis (with rare reports of fatalities) (see 7 Warning and Precautions), serum sickness, urticaria, vasculitis, angioedema;
Blood and the lymphatic system disorders:	Agranulocytosis, haemolytic anaemia, thrombocytopenia;
Cardiovascular:	Cardiac arrhythmias (including ventricular tachycardia), palpitations, hypotension. There have been rare reports of QT prolongation and *torsades de pointes* in patients receiving therapeutic doses of azithromycin, including a pediatric case report of QT interval prolongation which reversed to normal upon discontinuation (see 7 Warning and Precautions);
Gastrointestinal:	Anorexia, constipation, hypoglycaemia, dehydration, vomiting/diarrhea rarely resulting in dehydration, pancreatitis, pseudomembranous colitis, rare reports of tongue discoloration, pyloric stenosis / infantile hypertrophic pyloric stenosis (IHPS);
General:	Asthenia, paresthesia, fatigue, muscle pain;
Genitourinary:	Interstitial nephritis, acute renal failure, nephrotic syndrome, vaginitis;
Liver/Biliary:	Hepatitis fulminant. Abnormal liver function including drug-induced hepatitis and cholestatic jaundice have been reported. There have also been rare cases of hepatic necrosis and hepatic failure, which have resulted in death (see 7 Warning and Precautions);
Musculoskeletal and connective tissue disorders:	Myasthenia gravis;
Nervous System: *Psychiatric*	Hyperactivity, hypoesthesia, seizure, convulsions and syncope;

Disorders: Aggressive reaction, anxiety, nervousness, agitation, delirium, hallucinations;

Skin/Appendages: Serious skin reactions including erythema multiforme, exfoliative dermatitis, Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) (see 7 Warning and Precautions);

Special Senses: Hearing disturbances including hearing loss, hearing impaired, deafness and/or tinnitus, vertigo, taste/smell perversion and/or loss, abnormal vision.

9. Drug Interactions

9.2. Drug Interactions Overview

Drugs that cause QT prolongation
Caution is warranted when azithromycin is administered to a patient with a history of a significant cardiac repolarization disorder or who is taking other medicinal products that cause a prolonged QT interval (see 7 Warning and Precautions, Cardiovascular; and 8.5 Post-Market Adverse Reactions).

P-glycoprotein substrates
Concomitant administration of azithromycin with P-glycoprotein substrates may result in increased serum levels of P-glycoprotein substrates. Concomitant administration of P-glycoprotein inhibitors with azithromycin sustained-release form had minimal effect on the pharmacokinetics of azithromycin.

Hepatic cytochrome P450
Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the cytochrome P450-related drug interactions seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inhibition via cytochrome metabolite complex does not occur with azithromycin.

9.4. Drug-Drug Interactions

Established or Potential Drug-Drug Interactions

Proper name	Source of Evidence	Effect	Clinical comment
Antacids Aluminum and magnesium containing antacids	CT	Reduce the peak serum levels but not the extent of azithromycin absorption.	Azithromycin and these drugs should not be taken simultaneously.
Carbamazepine	CT	In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.	
Cetirizine	CT	In healthy male volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.	
Cimetidine	CT	Administration of a single dose of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption or on azithromycin pharmacokinetics.	
Coumarin-Type Oral Anticoagulants	CT	In a pharmacokinetic interaction study of 22 healthy men, a 5-day course of azithromycin did not affect the prothrombin time from a subsequently administered single 15 mg dose of warfarin. Spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants.	Prothrombin times should be carefully monitored while patients are receiving azithromycin and concomitantly-administered oral anticoagulants.
Cyclosporine	CT	In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporine, the resulting cyclosporine C_{max} and AUC_{0-5} were found to be significantly elevated.	Caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporine levels should be monitored, and the dose adjusted accordingly.
Didanosine	CT	Daily doses of 1,200 mg azithromycin had no effect on the pharmacokinetics of didanosine.	
Efavirenz	CT	Efavirenz, when administered at a dose of 400 mg for seven days produced a 22% increase in the C_{max} of azithromycin administered as a 600 mg single dose. AUC was not affected. Administration of a single 600 mg dose of azithromycin immediate-release had no effect on the pharmacokinetics of efavirenz given at 400 mg doses for seven days.	

Proper name	Source of Evidence	Effect	Clinical comment
Fluconazole	CT	A single dose of 1,200 mg azithromycin immediate-release did not alter the pharmacokinetics of a single 800 mg oral dose of fluconazole. Total exposure and half-life of 1,200 mg azithromycin were unchanged and C_{max} had a clinically insignificant decrease (18%) by coadministration with 800 mg fluconazole.	
HMG-CoA Reductase Inhibitors	CT	In healthy volunteers, coadministration of atorvastatin (10 mg daily) and azithromycin immediate-release (500 mg daily) did not alter plasma concentrations of atorvastatin (based on HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.	
Indinavir	CT	A single dose of 1,200 mg azithromycin immediate-release had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir three times daily for 5 days).	
Midazolam	CT	In healthy volunteers (N=12), coadministration of azithromycin immediate-release 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.	
Nelfinavir	CT	Coadministration of a single dose of 1,200 mg azithromycin immediate-release with steady-state nelfinavir (750 mg three times daily) produced an approximately 16% decrease in mean AUC_{0-8} of nelfinavir and its M8 metabolite. C_{max} was not affected. Coadministration of nelfinavir (750 mg three times daily) at steady-state with a single dose of 1,200 mg azithromycin immediate-release increased the mean $AUC_{0-\infty}$ of azithromycin by 113% and mean C_{max} by 136%.	Dose adjustment of azithromycin is not recommended. However, close monitoring for known side effects of azithromycin, when administered in conjunction with nelfinavir, is warranted.
P-glycoprotein inhibitors	CT	Co-administration of P-glycoprotein inhibitors (Vitamin E, Poloxamer 407, or Poloxamer 124) with azithromycin sustained release form (1 gram dose) had minimal effect on the pharmacokinetics of azithromycin.	

Proper name	Source of Evidence	Effect	Clinical comment
Rifabutin	CT	Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment with azithromycin and rifabutin.	Neutropenia has been associated with the use of rifabutin, but it has not been established if concomitantly-administered azithromycin potentiates that effect (see Adverse Reactions).
Sildenafil	CT	In normal healthy male volunteers, there was no evidence of a statistically significant effect of azithromycin immediate-release (500 mg daily for 3 days) on the AUC, C_{max}, T_{max}, elimination rate constant or subsequent half-life of sildenafil or its principal circulating metabolite.	
Theophylline	CT	Concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Azithromycin did not affect the pharmacokinetics of theophylline administered either as a single intravenous infusion or multiple oral doses at a recommended dose of 300 mg every 12 hours. There is one post-marketing report of supraventricular tachycardia associated with an elevated theophylline serum level that developed soon after initiation of treatment with azithromycin.	Until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.
Trimethoprim / Sulfamethoxazole	CT	Co-administration of trimethoprim/ sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin immediate-release 1,200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.	
Zidovudine	CT	Single 1 g doses and multiple 1,200 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.	

Legend: CT = Clinical Trial

Concomitant Therapy

The following drug interactions have not been reported in clinical trials with azithromycin and no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. Nonetheless, they have been observed with macrolide products, and there have been rare spontaneously reported cases with azithromycin and some of these drugs, in post-marketing experience. Until further data are developed regarding drug interactions, when pms-AZITHROMYCIN and these drugs are used concomitantly, careful monitoring of patients is advised both during and for a short period following therapy:

Antihistamines
Prolongation of QT intervals, palpitations or cardiac arrhythmias have been reported with concomitant administration of azithromycin and astemizole or terfenadine.

Cisapride, Hexobarbital, Phenytoin
Increased serum levels of hexobarbital, cisapride or phenytoin have been reported.

Digoxin and colchicine / P-glycoprotein substrates
Concomitant administration of some macrolide antibiotics with P-glycoprotein substrates, including digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Disopyramide
Azithromycin may increase the pharmacologic effect of disopyramide.

Ergot (ergotamine or dihydroergotamine)
Azithromycin and ergot derivatives should not be coadministered due to the possibility that ergot toxicity may be precipitated by some macrolide antibiotics. Acute ergot toxicity is characterized by severe peripheral vasospasm including ischemia of the extremities, along with dysesthesia and possible central nervous system effects.

Gentamicin
No data are available on the concomitant clinical use of azithromycin and gentamicin or other amphiphilic drugs which have been reported to alter intracellular lipid metabolism.

Triazolam
Azithromycin may decrease the clearance of triazolam and increase the pharmacologic effect of triazolam.

9.5. Drug-Food Interactions

Azithromycin tablets can be taken with or without food.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. Clinical Pharmacology

10.1. Mechanism of Action

Azithromycin a macrolide antibiotic of the azalide subclass, exerts its antibacterial action by binding to the 23S rRNA of the 50s ribosomal subunits of susceptible bacteria. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

10.2. Pharmacodynamics

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial. A total of 119 healthy subjects were enrolled (mean age of 35.5 years; range 18-55 years), of which 116 subjects (97 males) completed the study and were included in the analysis. Subjects were randomized to one of 5 treatments and received orally once daily for 3 days: placebo, chloroquine 600 mg base only, or chloroquine 600 mg base in combination with azithromycin 500 mg, 1,000 mg, and 1,500 mg. On Day 3, the azithromycin mean (%CV) plasma C_{max} values for the 500, 1,000 and 1,500 mg azithromycin dose regimens were 0.536 (33), 0.957 (31), and 1.54 (28) mcg/mL, respectively. Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the day 3 maximum mean (90% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the coadministration of 500 mg, 1,000 mg and 1,500 mg azithromycin, respectively.

10.3. Pharmacokinetics

No data exist in humans in regard to the extent of accumulation, duration of exposure, metabolism or excretory mechanisms of azithromycin in neural tissue such as the retina and the cochlea.

Adult Pharmacokinetics
Plasma concentrations of azithromycin decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. The prolonged half-life is likely due to extensive uptake and subsequent release of drug from tissues. Over the dose range of 250 to 1,000 mg orally, the serum concentrations are related to dose.

In adults, the following pharmacokinetic data have been reported:

DOSE/DOSAGE FORM	Subjects	C_{max} (mcg/mL)	T_{max} (hr)	AUC (mc.hr/mL)	$T_{1/2}$ (hr)
500 mg/250 mg tablet	12; fasted	0.34	2.1	2.49[a]	-
500 mg/250 mg tablet	12; fed	0.41	2.3	2.40[a]	-
1,200 mg/600 mg tablet	12; fasted	0.66	2.5	6.8[b]	40

[a] 0-48 hr
[b] 0-last

Absorption
Following oral administration, azithromycin is rapidly absorbed (T_{max} = 2-3 hours) and distributed widely throughout the body.

The absolute bioavailability is approximately 37%.

When azithromycin suspension was administered with food to 28 adult healthy male subjects, the rate of absorption (C_{max}) was increased by 56% while the extent of absorption (AUC) was unchanged. Food does not affect the absorption of azithromycin in the tablet dosage form. Azithromycin tablets can be taken with or without food.

Distribution
The serum protein binding of azithromycin is concentration dependent, decreasing from 51% at 0.02 mcg/mL to 7% at 2.0 mcg/mL. Following oral administration, azithromycin is widely distributed throughout the body with a steady-state apparent volume of distribution of 31.1 L/kg.

Rapid movement of azithromycin from blood into tissue results in significantly higher azithromycin concentrations in tissue than in plasma (up to 50 times the maximum observed concentration in plasma).

The long tissue half-life and large volume of distribution result from intracytoplasmic uptake and storage in lysosomal phospholipid complexes.

Metabolism
The majority of systemically available azithromycin is excreted unchanged in the bile. Metabolites of azithromycin were identified in bile but have not been studied further.

Elimination
Biliary excretion of azithromycin, predominantly as unchanged drug, is a main route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in the urine.

Special Populations and Conditions

- **Pediatrics:**

The safety and efficacy of pms-AZITHROMYCIN tablets in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Pharmacokinetics in children receiving a total dose of 30 mg/kg
The table below shows mean pharmacokinetic parameters on day 5 in children 1 to 5 years and 5 to 15 years of age when azithromycin oral suspension was dosed in the absence of food at a total dose of 30 mg/kg delivered as 10 mg/kg on day 1 and 5 mg/kg on days 2-5.

Pharmacokinetics in children given a total dose of 30 mg/kg delivered as a single dose have not been studied.

Pharmacokinetic parameters on day 5 at dosage 10 mg/kg (day 1) and 5 mg/kg (days 2-5)					
Age 1-5			Age 5-15		
C_{max} (mcg/mL)	T_{max} (hrs)	AUC_{0-24} (mcg.hr/mL)	C_{max} (mcg/mL)	T_{max} (hrs)	AUC_{0-24} (mcg.hr/mL)
0.216	1.9	1.822	0.383	2.4	3.109

Pharmacokinetics in children receiving a 60 mg/kg total dose
Two clinical studies enrolled 35 and 33 children respectively aged 3-16 years with pharyngitis/tonsillitis to determine the pharmacokinetics and safety of azithromycin for oral suspension in children when given 60 mg/kg in divided doses delivered as 20 mg/kg/day over 3 days or 12 mg/kg/day over 5 days with a maximum daily dose of 500 mg.

The following table shows pharmacokinetic data in the subset of children who received a total dose of 60 mg/kg. In both studies azithromycin concentrations were determined over a 24-hour period following the last daily dose.

Similarity of overall exposure ($AUC_{0-\infty}$) between the 3 and 5-day regimen is unknown.

	3-Day Regimen	5-Day Regimen
N	11[B]	17[B]
C_{max} (mcg/mL)	1.05 ± .44[a]	0.534 ± 0.361[a]
T_{max} (hr)	3 ± 2.0[a]	2.2 ± 0.8[a]
AUC_{0-24} (mcg x hr/mL)	7.92 ± 2.87[a]	3.94 ± 1.90[a]

[a] Arithmetic means
[B] maximum weight for 3-day regimen was ≤ 25 kg and for 5-day regimen was ≤ 41.7 kg

- **Geriatrics**

When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

- **Sex**

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

- **Hepatic Insufficiency**

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of oral azithromycin compared to those with normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase. Hence no dose adjustment is recommended for patients with mild to moderate hepatic impairment. Azithromycin has not been studied in patients with severe hepatic impairment.

- **Renal Insufficiency**

Azithromycin pharmacokinetics were investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1,000 mg dose of azithromycin, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively in subjects with GFR 10 to 80 mL/min compared to subjects with GFR >80 mL/min. The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively in subjects with GFR < 10 mL/min compared to subjects with GFR >80 mL/min.

11. Storage, Stability, and Disposal

Tablets

Store between 15°C and 30°C.

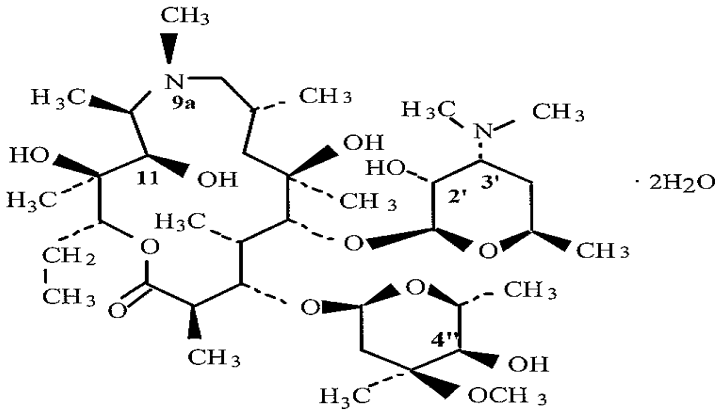
Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Proper name:	Azithromycin Dihydrate
Chemical name:	9-deoxo-9α-aza-9α-methyl-9α-homoerythromycin A dihydrate
Molecular formula:	$C_{38}H_{72}N_2O_{12}.\ 2H_2O$
Molecular mass:	785.0 g/mol

Structural formula:



Physicochemical properties

Description:	Azithromycin dihydrate is a white to off-white crystalline powder of uniform appearance. The aqueous solubility at pH 7.4 at 37°C is 39 mg/mL. The powder is non-hygroscopic.
pKa	8.48
Melting point:	125°C

14. Clinical Trials

14.1. Clinical Trial by Indication

Study Results
From the perspective of evaluating clinical trials because of the extended half-life of azithromycin, days 11-14 (10-13 days after completion of the one-day regimen, 8-11 days after completion of the three-day regimen or 6-9 days after completion of the five-day regimen) were considered on-therapy evaluations and are provided for clinical guidance. Day 21-30 evaluations were considered the primary test of cure endpoint. For patients with community-acquired pneumonia, Days 15-19 were considered as on-therapy evaluations. Days 28-42 were the cure endpoint.

Acute Bacterial Exacerbations of Chronic Bronchitis

Efficacy using azithromycin 500 mg over 3 days
In a randomized, double-blind controlled clinical trial of acute exacerbation of chronic bronchitis (AECB) in 404 adult patients, 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 Day 21-24. For the 377 patients analyzed in the MITT analysis at the Day 21-24 visit, the clinical cure rate for 3 days of azithromycin was 87% (162/186) compared to 85% (162/191) for 10 days of clarithromycin (95% CI for azithromycin-clarithromycin cure rate = -5.3, 9.8).

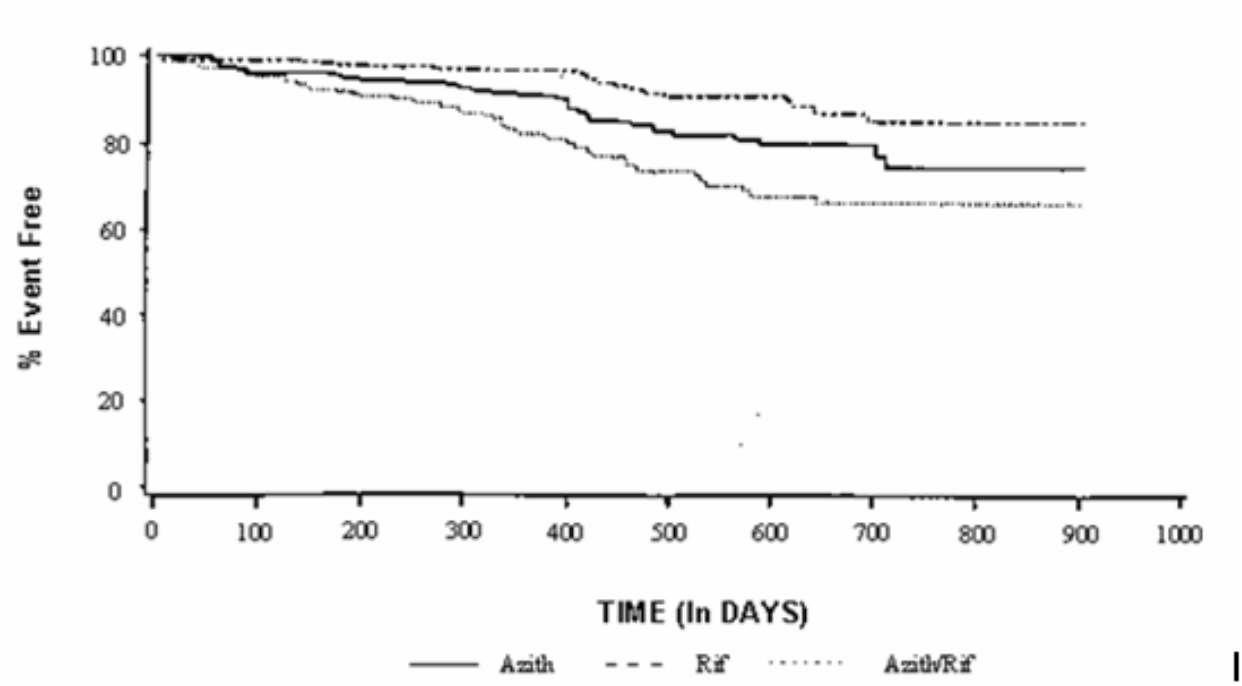
The following outcomes were the clinical cure rates at the Day 21-24 visit for the bacteriologically evaluable patients by pathogen:

Clinical Outcome by Baseline Pathogen		
Pathogen	**Azithromycin (3 days)**	**Clarithromycin (10 days)**
S. pneumonia	29/32 (91%)	21/27 (78%)
H. influenza	12/14 (86%)	14/16 (88%)
M. catarrhalis	11/12 (92%)	12/15 (80%)

In patients with advanced HIV infection for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease (see 1 Indications)

Two randomized, double-blind clinical trials were performed in patients with CD4 counts < 100 cells/mcL. The first study compared azithromycin (1,200 mg once weekly) to placebo and enrolled 182 patients with a mean CD4 count of 35 cells/mcL. The second study randomized 723 patients to either azithromycin (1,200 mg once weekly), rifabutin (300 mg daily) or the combination of both. The mean CD4 count was 51 cells/mcL. Endpoints included disseminated

MAC disease, the incidence of clinically significant disseminated MAC disease and discontinuations from therapy for drug-related side effects.



Azithromycin dihydrate
Time to Disseminated MAC Infection

MAC Bacteremia

In the first study, in the intent-to-treat analysis comparing azithromycin to placebo, patients randomized to azithromycin were one-half as likely to develop MAC as those who received placebo (p=0.004). The one-year cumulative incidence rate of disseminated MAC disease was 8.25% on azithromycin and 20.22% on placebo.

In the second study, in the intent-to-treat analysis comparing azithromycin, rifabutin and the combination of azithromycin/rifabutin, the risk of developing MAC bacteremia for patients assigned to azithromycin was also reduced by one-half relative to rifabutin (p=.005). Patients on the combination of azithromycin and rifabutin experienced a risk reduction of approximately two-thirds compared to rifabutin alone ($p < 0.001$). The one-year cumulative incidence rate of MAC infection was 7.62% on azithromycin, 15.25% on rifabutin and 2.75% on the combination.

In the placebo-controlled first study, all MAC isolates recovered within 30 days of the last dose of drug from patients randomized to azithromycin were sensitive to azithromycin. In the second study, 2 of 23 (8.7%) isolates received from patients randomized to azithromycin were resistant to azithromycin while none of the isolates received from patients randomized to rifabutin were resistant to azithromycin (p=0.14). None of the isolates recovered from patients randomized to the combination of azithromycin and rifabutin were resistant to azithromycin.

Clinically Significant Disseminated MAC Disease
In association with the decreased incidence of bacteremia, patients in the groups randomized to either azithromycin alone or azithromycin in combination with rifabutin showed reductions in the signs and symptoms of disseminated MAC disease, including fever or night sweats, weight loss and anemia.

Discontinuations from Therapy for Drug-Related Side Effects
In the first study, discontinuations for drug-related toxicity occurred in 8.2% of subjects treated with azithromycin and 2.3% of those given placebo (p=0.121). In the second study, more subjects discontinued from the combination of azithromycin and rifabutin (22.7%) than from azithromycin alone (13.5%; p=0.026) or rifabutin alone (15.9%).

14.2. Comparative Bioavailability Studies

A randomized, blinded, single center, single-dose, 2-way, crossover comparative bioavailability study of pms-AZITHROMYCIN tablets 600 mg (Pharmascience Inc.) and ZITHROMAX® tablets 600 mg (Pfizer Canada Inc.) was conducted in healthy adult subjects under fasting conditions. Comparative bioavailability data from 31 subjects that were included in the statistical analysis are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Azithromycin (1 x 600 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_{0-72} (ng·h/mL)	4294.89 4369.56 (20.25)	4408.29 4557.07 (25.75)	97.4	90.6-104.8
AUC_I (ng·h/mL)	5117.22 5181.32 (17.98)	5184.46 5352.50 (25.98)	98.7	91.5-106.4
C_{MAX} (ng/mL)	531.14 567.68 (36.20)	546.76 591.68 (39.55)	97.1	86.3-109.3
T_{MAX}[3] (h)	2.34 (38.29)	2.53 (43.87)		
$T_{½}$[4] (h)	35.12 (16.21)	32.89 (20.90)		

[1] pms-AZITHROMYCIN (azithromycin ethanolate), tablet, 600 mg (Pharmascience Inc, Canada)
[2] ZITHROMAX ® (azithromycin dihydrate), tablet, 600 mg (Pfizer Canada Inc., Canada)
[3] Expressed as the median only
[4] Expressed as the arithmetic mean (CV %) only

15. Microbiology

Mechanism of Resistance
The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

Spectrum of Activity
Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in 1 Indications.

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% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration MIC) less than or equal to the azithromycin susceptible breakpoint of ≤ 4mcg/mL. However, safety and effectiveness of azithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

Gram-positive bacteria
Beta-hemolytic streptococci (Groups C, F, G)
Viridans group streptococci

Gram-negative bacteria
Bordetella pertussis

Anaerobic bacteria
Peptostreptococcus species
Prevotella bivia

"Other" bacteria
Ureaplasma urealyticum
Legionella pneumophila
Mycoplasma hominis

Activity of Azithromycin against Mycobacterium avium complex (MAC)
In vitro azithromycin has demonstrated activity against Mycobacterium avium complex (MAC) bacteria. Azithromycin has also been shown to be active against phagocytized MAC bacteria in mouse and human macrophage cell cultures.

Susceptibility Testing Methods
When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports may differ from susceptibility data obtained from outpatient use, but could aid the physician in selecting the most effective antimicrobial.

Dilution Techniques
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method (broth or agar) or equivalent with standardized inoculum concentration and standardized concentration of azithromycin powder. The MIC values should be interpreted according to criteria provided in Table 1.

Diffusion Techniques
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure requires the use of standardized inoculum concentration. This procedure uses paper disks impregnated with 15-mcg azithromycin to test the susceptibility of bacteria to azithromycin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1: Susceptibility Interpretive Criteria for Azithromycin
Susceptibility Test Result Interpretive Criteria

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
Haemophilus influenzae[a]	≤ 4	-	-	≥ 12	-	-
Staphylococcus aureus	≤ 2	4	≥ 8	≥ 18	14 - 17	≤ 13
Streptococci including *S. pneumoniae*	≤ 0.5	1	≥ 2	≥ 18	14 - 17	≤ 13

Susceptibility to azithromycin must be tested in ambient air.
[a] Insufficient information is available to determine Intermediate or Resistant interpretive criteria
The ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues.

A report of "susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. A report of "intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

Quality Control
Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test. Standard azithromycin powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the azithromycin 15 mcg disks, the criteria in Table 2 should be achieved.

Table 2: Acceptable Quality Control Ranges for Azithromycin

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Haemophilus influenzaae ATCC* 49247	1.0 – 4.0	13 - 21
Staphylococcus aureus ATCC 29213	0.5 – 2.0	----
Staphylococcus aureus ATCC 25923	----	21 - 26
Streptococcus pneumoniae ATCC 49619	0.06 – 0.25	19 - 25

Susceptibility to azithromycin must be tested in ambient air.
*ATCC = American Type Culture Collection

16. Non-Clinical Toxicology

General Toxicology:

Acute Toxicity:
Adult animals (Mice and Rats)
Most mortality occurred within 1 to 2 hours and generally within 48 hours of dosing. At higher doses in mice, symptomatology included clonic convulsive activity, loss of righting reflex, gasping, and blanching prior to death.

Gross necropsy of mice or rats which died following intraperitoneal doses revealed yellowish or clear fluid in the pleural and peritoneal cavities. At necropsy on day 14 there were no gross pathological changes in either species aside from a few liver adhesions to the diaphragm.

Neonatal animals (Rats)
No deaths or remarkable clinical signs were observed in any animal during the 14-day observation period. All animals gained weight during the trial. At sacrifice on day 15, no remarkable gross findings were observed in any surviving rat.

Subacute Toxicity
Phospholipidosis has been observed in animals administered high doses of azithromycin. This effect is reversible after cessation of azithromycin treatment in animals. Despite light- and electron-microscopic correlates of phospholipidosis (myeloid figures and intracytoplasmic vacuoles) in many organs, only in dogs receiving 100 mg/kg/day for at least 2 months have kidney, liver, and gallbladder toxicity been seen. This dose in dogs results in tissue levels greater than 5,000 mg/g. Minimal increases in serum transaminase levels in rats and dogs at

20 mg/kg/day and above have also been seen, but are consistent with findings previously reported for erythromycin. Special attention has been given to the effects of phospholipidosis in the retina, including studies of azithromycin, 30 and 100 mg/kg/day for 6 and 2 months, respectively, in dogs. No evidence was elicited of deleterious effects of azithromycin on vision, pupillary reflex or retinal vasculature. The detection of phospholipidosis in the choroid plexus and dorsal root ganglion was not associated with degenerative or functional changes.

In animal studies, treatment with azithromycin is associated with accumulation in various tissues, including the extra-cranial neural ganglia (i.e., retina and sympathetic nervous system). Tissue accumulation is both dose and time dependent, and is associated microscopically with the development of phospholipidosis (intra-lysosomal drug phospholipid complexes). The only evidence in animals that azithromycin is associated with alterations of intracellular phospholipid metabolism has been the documentation of small increases in phospholipid content after prolonged treatment (6 months) or exaggerated doses. Phospholipidosis has been observed at total cumulative doses only 2 multiples of the clinical doses. One month after withdrawal of treatment the concentration of azithromycin and the presence of phospholipidosis in tissue, including the retina, is at or near predose levels.

Genotoxicity

Azithromycin was examined in several genetic toxicology assays for induction of gene mutations in microbial and mammalian cells and for chromosomal mutations *in vivo* and *in vitro*. No evidence of genotoxic activity was observed in any of the following assays:

Microbial Assay: Tests were conducted on strains TA 1535, TA 1537, TA 98 and TA 100 of *Salmonella typhimurium* at concentrations up to 2 mcg/plate (higher concentrations cause bacterial growth inhibition) in the presence and absence of Aroclor-stimulated rat or mouse liver microsomal enzymes. Additional tests were performed using the same strains of *Salmonella* spp. and urine from mice treated orally with up to 200 mg/kg of azithromycin.

Mammalian Cell Gene Mutation Assay: The L5178Y Mouse Lymphoma Assay for gene mutations at the thymidine kinase locus was conducted at concentrations of 36-360 mcg/mL to cytotoxicity in the presence and absence of rat liver microsomal enzymes.

***In Vitro* Cytogenetics Assay:** The clastogenic activity of azithromycin was evaluated in human lymphocytes *in vitro* exposed up to toxic concentrations of 40 mcg/mL in the presence and 7.5 mcg/mL in the absence of rat liver microsomal enzymes.

***In Vivo* Cytogenetics Assay:** Azithromycin was examined for clastogenic activity in the bone marrow cells of male and female CD-1 mice treated orally at 200 mg/kg, and sacrificed at 6, 24 or 48 hours post-treatment.

Carcinogenicity

Long-term toxicology studies to assess the carcinogenicity potential have not been conducted.

Reproductive and developmental toxicology
In animal reproduction studies in mice and rats, at azithromycin doses up to 200 mg/kg/day (moderately maternally toxic), effects were noted in the rat at 200 mg/kg/day, during the prenatal development period (delayed ossification) and during the postnatal development period (decreased viability, delayed developmental landmarks, differences in performance of learning task). The 200 mg/kg/day dose in mice and rats is approximately 0.5-fold and 1-fold, respectively, the single adult oral dose of 2 g, based on mg/m^2 (body surface area). Pharmacokinetic data from the 200 mg/kg/day dose level in these studies showed that azithromycin crossed the placenta and distributed to fetal tissue at 5 to 9-fold the maternal plasma C_{max} of 2 mcg/mL

Special Toxicology

Antigenicity Studies
Azithromycin was tested for the induction of a systemic anaphylaxis reaction in guinea pigs and in rabbits. Azithromycin did not have antigenic potential under the conditions used in the studies.

17. Supporting Product Monographs

1. ZITHROMAX® (tablets, 250 mg, and 600 mg; powder for suspension 100 mg/5 mL and 200 mg/5 mL; powder for injection, 500 mg/vial), submission control 270217, Product Monograph, Pfizer Canada ULC, April 27, 2023.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-AZITHROMYCIN
Azithromycin Tablets
Read this carefully before you start taking **pms-AZITHROMYCIN** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **pms-AZITHROMYCIN**.

What is pms-AZITHROMYCIN used for?
pms-AZITHROMYCIN is an antibiotic medicine used to treat the following types of **mild to moderate** infections **by certain microorganisms** in adults such as bronchitis, certain types of skin infections, strep throat (pharyngitis, tonsillitis), genitourinary infections, disseminated mycobacterium avium complex (MAC) disease in people with HIV, and pneumonia.

Antibacterial drugs like pms-AZITHROMYCIN treat only bacterial infections. They do not treat viral infections such as the common cold.

How does pms-AZITHROMYCIN work?
pms-AZITHROMYCIN helps stop the growth of the bacteria that cause infection. It gets into infected tissue where it is released slowly over time, so the medicine keeps fighting bacteria for many days after the last dose is taken. This is why pms-AZITHROMYCIN may be taken for as short a time as one day.

What are the ingredients in pms-AZITHROMYCIN?
Medicinal ingredient: Azithromycin dihydrate
Non-medicinal ingredients:

250 mg tablets: Croscarmellose Sodium, D&C Red No. 27, FD&C Blue No. 2, FD&C Red No. 40, FD&C Yellow No.6, Hypromellose, Lactose Anhydrous, Magnesium Stearate, Poloxamer 188, Povidone, Silicified Microcrystalline Cellulose, Polyethylene Glycol, Talc and Titanium Dioxide.

600 mg tablets: Croscarmellose Sodium , Hypromellose, Lactose Anhydrous, Magnesium Stearate, Poloxamer 188, Povidone, Silicified Microcrystalline Cellulose, Polyethylene Glycol, Polysorbate 80, Talc and Titanium Dioxide.

pms-AZITHROMYCIN comes in the following dosage forms:
Tablets: 250 mg and 600 mg.

Do not use pms-AZITHROMYCIN if:

- you have a history of liver problems when you have used azithromycin.
- you are hypersensitive (allergic) to azithromycin, or any macrolide or ketolide antibiotic (including erythromycin) or any other ingredient of pms-AZITHROMYCIN (see What are the ingredients in pms-AZITHROMYCIN).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-AZITHROMYCIN. Talk about any health conditions or problems you may have, including if you:

- have a known prolonged heart cycle (interval) (QT prolongation)
- are currently taking medication known to prolong QT interval (prolong your heart cycle) such as antiarrhythmics (drugs to regulate your heartbeat such as class IA: quinidine, procainamide and class III; dofetilide, amiodarone, sotalol); antipsychotic agents; antidepressants; and fluoroquinolones (a class of antibiotics)
- have a history of life-threatening irregular heartbeat
- have constantly low levels of potassium or magnesium in your blood
- have a history for heart problems such as slow heart rate, irregular heartbeat or cardiac insufficiency (your heart has a hard time pumping blood to your body)
- are pregnant or think you are pregnant,
- are breast feeding or planning to breastfeed. Azithromycin is excreted in human breast milk. It is not known if pms-AZITHROMYCIN could affect your baby. Discuss with your doctor.
- have ever had any liver or kidney problems
- have a weak immune system
- have ever had an allergic reaction to any medicines, including antibiotics such as erythromycin
- have myasthenia gravis (a chronic autoimmune neuromuscular disease which causes muscle weakness)
- have hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption as this product contains lactose.

Other warnings you should know about:

If you develop diarrhea during or after treatment with pms-AZITHROMYCIN, tell your doctor at once. Do not use any medicine to treat your diarrhea without first checking with your doctor.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with pms-AZITHROMYCIN:

- Warfarin (or other anticoagulant medicine);
- Cyclosporin (used to suppress the immune system to prevent and treat rejection in organ or bone marrow transplants);
- Digoxin (used for treatment of heart problem);
- Colchicine (used for treatment of gout);
- Nelfinavir (used for treatment of HIV infections);
- Ergotamine and ergot derivatives (used for migraine treatment). Ergotamine and ergot derivatives should not be used with pms-AZITHROMYCIN.

Some medicines may affect how well pms-AZITHROMYCIN works. Check with your doctor before starting any new prescription or over-the-counter medicines, including natural/herbal remedies or antacids, while on pms-AZITHROMYCIN.

How to take pms-AZITHROMYCIN:

- Although you may feel better early in treatment, pms-AZITHROMYCIN should be taken exactly as directed.
- Misuse or overuse of pms-AZITHROMYCIN could lead to the growth of bacteria that will not be killed by pms-AZITHROMYCIN (resistance). This means that pms-AZITHROMYCIN may not work for you in the future.
- Do not share your medicine.
- pms-AZITHROMYCIN can be taken with or without food.

Usual adult dose:
If your doctor prescribes pms-AZITHROMYCIN 250 mg tablets for 3 days for treatment of bronchitis:

Days 1 through 3: Take two tablets each day.

If your doctor prescribes the 5-day pms-AZITHROMYCIN 250 mg tablets for 5 days for treatment of respiratory tract infections or certain types of skin infections:

Day 1: Take 2 tablets once.
Days 2 through 5: Take 1 tablet daily.

If your doctor prescribes pms-AZITHROMYCIN 250 mg tablets for 1 day for treatment of genital ulcers or non-gonococcal urethritis and cervicitis:

Day 1: Take four tablets once.

If your doctor prescribes pms-AZITHROMYCIN 250 mg tablets for 1 day for treatment of gonococcal urethritis and cervicitis:

Day 1: Take eight tablets once.

If your doctor prescribes pms-AZITHROMYCIN 600 mg tablets for prevention of Mycobacterium avium complex (MAC) disease:

Take two tablets once weekly.

Overdose:

If you think you, or a person you are caring for, have taken too much pms-AZITHROMYCIN, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed Dose:

If you forget to take a dose, call your pharmacist or doctor. Do not double dose.

What are possible side effects from using pms-AZITHROMYCIN?

These are not all the possible side effects you may have when taking pms-AZITHROMYCIN. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Diarrhea/loose stools
- Stomach pain
- Nausea and vomiting
- Headache

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
***Clostridioides difficile* colitis (bowel inflammation):** severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness			✓
UNCOMMON			
Abnormal heart rhythm: feel your heart beating in your chest, abnormal heartbeat, dizziness or feeling faint			✓
Severe allergic reaction: trouble breathing, swelling of the face, mouth, throat, neck, severe skin rash or blisters			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Liver disorder: abdominal pain, nausea, vomiting, yellowing of skin and eyes, dark urine			✓
Myasthenia gravis: muscle weakness, drooping eyelid, vision changes, difficulty chewing and swallowing, trouble breathing		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store pms-AZITHROMYCIN at room temperature between 15°C and 30°C

Keep pms-AZITHROMYCIN and all medicines out of the reach and sight of children.

If you want more information about pms-AZITHROMYCIN:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.pharmascience.com, or by calling 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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