AZITHROMYCIN DIHYDRATE
Zmax One Dose

2 g Extended Release Powder for Oral Suspension
Cherry-Banana Flavored
Antibacterial

1.0 NAME OF THE MEDICINAL PRODUCT

Zmax One Dose

2.0 FORMULATION

Each dose contains azithromycin dihydrate equivalent to 2 g azithromycin base.

3.0 DESCRIPTION

Zmax One Dose (azithromycin dihydrate) extended release powder for oral suspension contains the active ingredient azithromycin (as azithromycin dihydrate), an azalide, a subclass of macrolide antibiotics. Azithromycin has the chemical name (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R)-13-[2,6-dideoxy-3-C-methyl-3-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-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is C\textsubscript{38}H\textsubscript{72}N\textsubscript{2}O\textsubscript{12}, and its molecular weight is 749.0. Azithromycin has the following structural formula:
Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $\text{C}_{38}\text{H}_{72}\text{N}_{2}\text{O}_{12} \cdot 2\text{H}_{2}\text{O}$ and a molecular weight of 785.0.

4.0 PHARMACEUTICAL FORM

Extended release powder for oral suspension.

5.0 CLINICAL PARTICULARS

5.1. Therapeutic Indications

Azithromycin dehydrate extended release powder for oral suspension is indicated for the treatment of susceptible strains of bacteria in mild to moderate respiratory tract infections as follows:

- Acute bacterial exacerbations of chronic bronchitis due to *Haemophilus influenzae*, *Moraxella catarrhalis*, *Haemophilus parainfluenzae* or *Streptococcus pneumoniae*.
- Acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.
- Community acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.
- Pharyngitis/tonsillitis caused by *Streptococcus pyogenes*

5.2 Dosage and Method of Administration

Patients are advised to take Azithromycin dihydrate extended release powder for oral suspension on an empty stomach (at least 1 hour before or 2 hours following a meal) – see section 6.2 Pharmacokinetic Properties.

Use in Adults and Adolescents

The recommended dose for adults and adolescents is a single 2.0 g dose of azithromycin dihydrate extended release powder for oral suspension.
In the Phase 3 program, no patient vomited within five minutes of dosing Zmax. In the event that a patient vomits within five minutes of administration, the healthcare provider should consider additional antibiotic treatment since there would be minimal absorption of azithromycin. Since insufficient data exist on absorption of azithromycin if a patient vomits between five and 60 minutes following administration, alternative therapy should be considered. Neither a second dose of Zmax nor alternative treatment is warranted if vomiting occurs ≥ 60 minutes following administration in patients with normal gastric emptying time.

Use in Children

Azithromycin dihydrate extended release powder is not recommended for children of 12 years or younger.

Use in Elderly

No dose adjustment is necessary in elderly patients requiring azithromycin therapy (see section 6.2 Pharmacokinetic Properties).

Use in Patients with Renal Impairment

No dosage adjustment is recommended for patients with mild-to-moderate renal impairment (GFR 10-80 ml/min). Caution should be exercised when Azithromycin dihydrate extended release powder for oral suspension is administered to patients with severe renal impairment (GFR <10 ml/min).

Use in Patients with Hepatic Impairment

The pharmacokinetics of azithromycin in patients with hepatic impairment have not been established for azithromycin dihydrate extended release powder for oral suspension. Based on studies with immediate release-formulations, no dosage adjustment is recommended for patients with mild to moderate hepatic impairment. Azithromycin should be used with caution in patients with severe hepatic impairment.

5.3 Contraindications

Hypersensitivity to azithromycin, erythromycin or any macrolide or ketolide antibiotic.
Hypersensitivity to any excipients, i.e. glycerol dibehenate, poloxamers, sucrose, sodium phosphate tribasic anhydrous, magnesium hydroxide, hydroxypropylcellulose, xanthan gum, colloidal anhydrous silica, titanium oxide, artificial cherry flavor and artificial banana flavor.

5.4 Special Warnings and Precautions for Use

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

Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with severe hepatic disease (see section 6.2 Pharmacokinetic Properties).

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see section 6.2 Pharmacokinetic Properties).

In patients receiving ergot derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

As with any antibiotic preparation, observation for signs of superinfection with nonsusceptible organisms, including fungi is recommended.

Prolonged cardiac repolarization and QT interval, which has been associated with a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk of cardiac arrhythmia.

Azithromycin dihydrate extended release powder for oral suspension contain 19.36 g of sucrose.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Azithromycin dihydrate extended release powder for oral suspension contain 148 mg of sodium.

5.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Caution is warranted when azithromycin is administered to patients taking other medicinal products with the potential to prolong QT interval (see section 5.4 Special Warnings and Precautions for Use).

Antacids: Co-administration of azithromycin dihydrate extended release powder for oral suspension with a single 20 ml dose of co-magaldrox did not affect the rate and extent of azithromycin absorption.

All other drug interaction studies for azithromycin dihydrate extended release powder for oral suspension were performed with immediate-release formulations providing comparable total azithromycin exposure (dosing regimes ranging from 500 mg to 1200 mg).

Cetirizine: In healthy volunteers, co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine): Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

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

Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin
increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

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

Ergot: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 5.4 Special Warnings and Precautions for Use).

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

**Atorvastatin:** Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

**Carbamazepine:** In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

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

**Coumarin-Type Oral Anticoagulants:** In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

**Cyclosporin:** In a pharmacokinetic study of 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
cyclosporin, the resulting cyclosporin $C_{\text{max}}$ and AUC$_{0-5}$ were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

**Efavirenz:** Co-administration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

**Fluconazole:** Co-administration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, however, a clinically insignificant decrease in $C_{\text{max}}$ (18%) of azithromycin was observed.

**Indinavir:** Co-administration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

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

**Midazolam:** In healthy volunteers, co-administration of azithromycin 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:** Studies conducted with immediate release azithromycin indicate that co-administration of nelfinavir at steady-state results in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known side effects of azithromycin is warranted.

**Rifabutin:** Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment with azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8 Undesirable Effects).
Sildenafil: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and Cmax, of sildenafil or its major circulating metabolite.

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

Theophylline: There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam: In 14 healthy volunteers, co-administration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole: Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin 1200 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.

5.6 Pregnancy and Lactation

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women.

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

There are no data on secretion in breast milk. Azithromycin should be used in breast-feeding mothers only where adequate alternatives are not available.
5.7 Effects on Ability to Drive and Use Machines

There is no evidence to suggest that azithromycin may affect a patient’s ability to drive or operate machinery.

5.8 Undesirable Effects

During phase III clinical studies, 23% of adult subjects receiving azithromycin dihydrate extended release powder for oral suspension experienced treatment-related adverse reactions. The majority (69%) had gastrointestinal reactions, such as diarrhea/loose stools, nausea, abdominal pain, or vomiting. Most gastrointestinal events were mild-to-moderate in severity, and for 68% of these subjects the symptoms resolved within 2 days.

Treatment-related adverse events observed during phase III clinical studies with azithromycin dihydrate extended release powder for oral suspension are listed below according to the standard system organ class of MedDRA. Adverse events are ranked using the following convention: very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); and rare (>1/10,000, <1/1,000).

Infections and Infestations

*Uncommon*: vaginitis and oral candidiasis

Nervous System Disorders

*Common*: headache  
*Uncommon*: dizziness and dysgeusia

Ear and Labyrinth Disorders

*Rare*: vertigo

Cardiac Disorders:

*Rare*: palpitations

Gastrointestinal Disorders

*Very common*: diarrhea
*Common*: nausea, abdominal pain and vomiting
*Uncommon*: loose stools, flatulence, dyspepsia, gastritis and constipation
Skin and Subcutaneous Tissue Disorders

*Uncommon:* rash and pruritus
*Rare:* urticaria

General Disorders and Administration Site Conditions

*Uncommon:* asthenia and chest pain

In subjects with normal baseline values, the following clinically significant laboratory abnormalities (irrespective of drug relationship) were reported in azithromycin dihydrate extended release powder for oral suspension clinical trials.

Blood and Lymphatic System Disorders

*Uncommon:* leukopenia and neutropenia

Investigations

*Common:* reduced lymphocyte count, increased eosinophil count and reduced blood bicarbonate

*Uncommon:* elevated blood bilirubin, elevated aspartate aminotransferase, elevated alanine aminotransferase, elevated blood urea, elevated creatinine and alterations in blood potassium. Where follow up was provided, changes in laboratory tests appeared to be reversible.

5.9 Overdose

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

6.0 PHARMACOLOGICAL PROPERTIES

6.1 Pharmacodynamic Properties

Antibacterial agent, macrolides
ATC-code: J01F A10
Mode of Action

The mode of action of azithromycin is inhibition of bacterial protein synthesis by binding to the 50S ribosomal subunits and preventing translocation of peptides, without affecting polynucleotide synthesis.

Mechanism of Resistance

There are two predominant resistance determinants in clinical isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes*: mef and erm. Mef encodes an efflux pump that mediates resistance to 14- and 15-membered macrolides only. Mef has also been described in a variety of other species. The erm gene encodes a 23S-rRNA methyltransferase that adds methyl groups to adenine 2058 of the 23S rRNA (E. coli rRNA numbering system).

The methylated nucleotide is in domain V and has been found to interact with lincosamides and streptogramin B, in addition to macrolides, resulting in a phenotype known as MLSb resistance. Erm(B) and erm(A) are found in clinical isolates of *S. pneumoniae* and *S.pyogenes*.

The AcrAB-TolC pump in *Haemophilus influenzae* is responsible for the innate higher levels of MIC values to macrolides. In clinical isolates, mutations in 23S rRNA, specifically in nucleotides 2057-2059 or 2611 in domain V, or mutations in ribosomal proteins L4 or L22 are rare.

Breakpoints

The recommended MIC breakpoints (µg/ml) for azithromycin (recommendation of the NCCLS) are:

*Haemophilus* spp.: S ≤ 4 with no recommendation for resistance breakpoint*  
*Streptococci* including *S. pneumoniae* and *S. pyogenes*: S ≤ 0.5, R ≥ 2.

*The current absence of data on resistant strains precludes defining any category other than susceptible. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.
Antibacterial Spectrum

The susceptibility of bacterial species to azithromycin is shown in the table below.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly Susceptible Species  Resistance Levels¹

Aerobic Gram-positive bacteria:

* Staphylococcus aureus, Streptococcus agalactiae, Streptococci (Groups C, F, G) and Viridans group streptococci.

Aerobic Gram-negative bacteria:

* Bordetella pertussis, Haemophilus ducreyi, Haemophilus influenzae*, Haemophilus parainfluenzae*, Legionella pneumophila, Moraxella catarrhalis* and Neisseria gonorrhoeae.

Other:

* Chlamydia pneumoniae*, Chlamydia trachomatis, Mycoplasma pneumoniae* and Ureaplasma urealyticum.

Species for which acquired resistance may be a problem

Aerobic Gram-positive bacteria:

* Streptococcus pneumoniae* 13%
* Streptococcus pyogenes* 10% - 14%

Note: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains.

Inherently Resistant Organisms

Enterobacteriaceae

Pseudomonas

*Species for which efficacy has been demonstrated in clinical trials
Species with natural intermediate susceptibility

¹Resistance levels reflect recent published survey values.
6.2 Pharmacokinetic Properties

Azithromycin dihydrate extended release powder for oral suspension are a modified release formulation, which provides a full course of antibacterial therapy in a single oral dose. Data from separate pharmacokinetic studies in healthy adult subjects indicate that higher peak serum concentration (C\text{\text{max}}) and greater systemic exposure (AUC) of azithromycin are achieved on the day of dosing following a single dose of azithromycin dihydrate extended release powder for oral suspension compared to dosing with conventional immediate-release formulations.

Absorption

Azithromycin dihydrate extended release powder for oral suspension are formulated to release azithromycin slowly in the small intestine.

The relative bioavailability of azithromycin dihydrate extended release powder for oral suspension compared to azithromycin sachet formulation is 83%. Peak serum concentrations are achieved approximately 2.5 hours later.

Effect of Co-administration of Meals

When a 2.0 g dose of azithromycin dihydrate extended release powder for oral suspension was administered to healthy subjects following a high-fat meal, peak serum concentration and systemic exposure increased (115% and 23% respectively). Following a standard meal in healthy subjects, peak serum concentration was increased by 119% but systemic exposure was not affected.

Results from clinical studies suggest that azithromycin dihydrate extended release powder for oral suspension are better tolerated when administered in a fasted state.

Distribution

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

Azithromycin concentrations are higher in tissues than in plasma and serum. The extensive distribution of drugs to tissues may be
relevant to clinical activity. The antimicrobial activity of azithromycin is pH related and appears to be reduced with decreasing pH. Hence, high tissue concentrations should not be interpreted as being quantitatively related to clinical efficacy.

**Metabolism**

The majority of systemically available azithromycin is excreted unchanged in the bile. *In vitro* and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

**Elimination**

Serum azithromycin concentrations following a single 2.0 g dose of azithromycin dihydrate extended release powder for oral suspension declined in a polyphasic pattern with a terminal elimination half-life of 59 hours. The prolonged terminal half-life is thought to be due to an enlarged apparent volume of distribution.

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.

**Pharmacokinetics in Special Patient Groups**

**Renal Impairment**

The pharmacokinetics of azithromycin in subjects with mild-to-moderate renal impairment (GFR 10 – 80 ml/min) were not affected following a single 1 g dose of immediate release azithromycin. Statistically significant differences in AUC 0-120 (8.8 mg × hr/ml vs. 11.7 mg × hr/ml), C_{max} (1.0 mg/ml vs. 1.6 mg/ml) and CLr (2.3 ml/min/kg vs. 0.2 ml/min/kg) were observed between the group with severe renal impairment (GFR < 10 ml/min) and the group with normal renal function.

**Hepatic Impairment**

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. The urinary clearance of azithromycin appears to increase in these patients, perhaps to compensate for reduced hepatic clearance.
Elderly

Elderly volunteers (>65 years) had slightly higher AUC values than in young volunteers (<40 years) after a 5-day regimen, but these are not considered clinically significant, and hence no dose adjustment is recommended.

6.3 Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and for humans is unknown.

7.0 PHARMACEUTICAL PARTICULARS

7.1. Incompatibilities

Not applicable.

7.2. Shelf-life

See expiry date on the product label for the dry granules. Reconstituted suspension should be consumed within 12 hours.

7.3. Special Precautions for Storage

Before reconstitution: Do not store above 30°C. Keep container tightly closed.

7.4. Nature and Contents of Container

Azithromycin dihydrate extended release powder for oral suspension (Zmax One Dose) for adults is supplied in bottles containing 2.0 g of azithromycin (as dihydrate) and is constituted with 60 mL of water.

The drug product is packaged in high density polyethylene (HDPE) bottles with a child resistant closure, sealed in a foil pouch.
A polypropylene dosing cup is provided to measure water for constitution.

7.5 Instructions for Use and Handling

Instructions for Pharmacist:

Reconstitution: Add 60 mL water and replace cap. Shake well.

Patient Instructions:

Keep the container tightly closed. After reconstitution, store between 15-25°C. Do not refrigerate or freeze.

Use the prepared suspension within 12 hours. Shake well before use.

Drink the entire contents of the bottle.

7.6 CAUTION:

Food, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

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