SCHEDULING STATUS S4

PROPRIETARY NAME AND DOSAGE FORM

ZITHROMAX® 200 mg/5 ml

Powder for oral suspension

COMPOSITION

ZITHROMAX (azithromycin) is an azalide antibiotic.

ZITHROMAX 200 mg/5 ml powder for oral suspension is a dry blend of azithromycin dihydrate and other excipients which yields on reconstitution with water a suspension containing the equivalent of 200 mg azithromycin per 5 ml.

Inactive excipients:

ZITHROMAX 200mg/5ml powder for oral suspension contains sucrose, sodium phosphate, hydroxypropyl cellulose, xanthan gum, and artificial cherry, creme de vanilla and banana flavouring agents. ZITHROMAX powder for oral suspension is free of other sugars, gluten and azo dyes.

PHARMACOLOGICAL CLASSIFICATION

A20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION

Following oral administration in humans, ZITHROMAX is widely distributed throughout the body; bioavailability is approximately 37 %. The time taken to peak plasma levels is 2 - 3 hours. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days.

Kinetic studies of variable times ranging from hours to days after oral intake have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the drug is highly tissue bound. Concentrations in target tissues such as lung, tonsil and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

In vitro sensitivity does not necessarily imply *in vivo* efficacy. Azithromycin demonstrates activity *in vitro* against a wide range of Gram-positive and Gram-negative bacteria including:

Staphylococcus aureus; Streptococcus pneumoniae, Streptococcus pyogenes (Group A) and other Streptococcus species; *Haemophilus influenzae; Moraxella catarrhalis; Bordetella pertussis; Borrelia burgdorferi; Haemophilus ducreyi; and Chlamydia trachomatis*. Azithromycin also demonstrates *in vitro* activity against *Mycoplasma pneumoniae* and *Treponema pallidum.*

INDICATIONS

Children : 1 year and over (under 45 kg)

ZITHROMAX is indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms.

Adults and children over 45 kg:

ZITHROMAX is indicated for mild to moderate infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis due to *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae* or *Staphylococcus aureus* and pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae;* uncomplicated skin and soft tissue infections; sinusitis due to *Haemophilus influenzae, Streptococcus pneumoniae* or *Staphylococcus aureus;* and as an alternative to first line therapy of pharyngitis/tonsillitis.

CONTRAINDICATIONS

ZITHROMAX is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin or any of the macrolide antibiotics.

Because of the theoretical possibility of ergotism, ZITHROMAX and ergot derivatives should not be co-administered.

Use in hepatic impairment:

As the liver is the principal route of excretion of ZITHROMAX, it should not be used in patients with hepatic disease.

Use during pregnancy and lactation:

The safety and efficacy of ZITHROMAX in pregnancy and lactation have not been established.

WARNINGS and SPECIAL PRECAUTIONS

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.

Pseudomembranous colitis has been reported and may range in severity from mild to life threatening. Therefore it is important to consider this diagnosis in patients with diarrhoea subsequent to administration of ZITHROMAX.

Observation for signs of superinfection with non-susceptible organisms, including fungi, is recommended.

Use in renal impairment:

There are no data regarding ZITHROMAX® usage in patients with renal impairment, thus caution should be exercised when prescribing ZITHROMAX in these patients.

Use in children under 1 year of age:

The safety and efficacy of ZITHROMAX in children less than 1 year have not been established.

INTERACTIONS

Ergot derivatives:

Because of the theoretical possibility of ergotism, ZITHROMAX and ergot derivatives should not be co-administered.

Special administration advised with the following:

Antacids:

In patients receiving ZITHROMAX and antacids, ZITHROMAX should be taken at least 1 hour before or 2 hours after the antacid.

Cimetidine:

A single dose of cimetidine administered 2 hours before ZITHROMAX had no effect on the pharmacokinetics of azithromycin.

No interactions reported with the following:

Carbamazepine:

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite.

Methylprednisolone:

In a pharmacokinetic interaction study in healthy volunteers, ZITHROMAX had no significant effect on the pharmacokinetics of methylprednisolone.

Theophylline:

There is no evidence of any pharmacokinetic interaction when ZITHROMAX and theophylline are co-administered to healthy volunteers.

Zidovudine:

In a preliminary pharmacokinetic study of ZITHROMAX in HIV-positive patients treated with zidovudine, no significant effect on the pharmacokinetic parameters of zidovudine and its glucuronide metabolite was found. The only significant difference in azithromycin kinetics was a shortening of the time to reach maximal concentration when the first and last day levels were compared.

Special precautionary monitoring is advised with the following:

Cyclosporin:

Some of the related macrolide antibiotics interfere with the metabolism of cyclosporin. In the absence of pharmacokinetic studies or clinical data investigating potential interaction between ZITHROMAX and cyclosporin, caution should be exercised before co-administration of these two drugs. If co-administration is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Digoxin:

Some of the macrolide antibiotics have been reported to impair the metabolism of digoxin (in the gut) in some patients. Therefore, in patients receiving concomitant ZITHROMAX, a related azalide antibiotic, and digoxin the possibility of raised digoxin levels should be borne in mind.

Warfarin:

In a pharmacokinetic interaction study, ZITHROMAX did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. ZITHROMAX and warfarin may be co-administered, but monitoring of the prothrombin time should be continued as routinely performed.

Terfenadine:

There have been less frequent reports of an interaction in patients receiving ZITHROMAX and terfenadine where the possibility of such an interaction could not be entirely excluded.

DOSAGE AND DIRECTIONS FOR USE

ZITHROMAX 200 mg/5 ml powder for oral suspension should be administered as a single daily dose

ZITHROMAX suspension should be administered to children using the 5 ml oral dosing syringe or the spoon provided. ZITHROMAX suspension can be taken with food.

Reconstituting instructions for ZITHROMAX 200 mg/5 ml powder for oral suspension for

15 ml and 30 ml bottles:

The table below indicates the volume of water to be used for constitution:

Amount of water to be added	Total deliverable volume (azithromycin content)	Azithromycin concentration after reconstitution
9 ml	15 ml (600 mg)	200 mg/5 ml
15 ml	30 ml (1200 mg)	200 mg/5 ml

Shake well before each use. Oversized bottle provides shake space. Keep tightly closed. After mixing store below 30 °C (no refrigeration required) and discard any unused suspension after 5 days.

Use in children: 1 year and older

The total dose in children is 30 mg/kg which should be given as a single daily dose of 10 mg/kg for 3 days according to the following guidance:

< 15 kg: 10 mg/kg once daily on days 1 - 3.

15 – 25 kg: 200 mg (5 ml) once daily on days 1 - 3.

26 – 35 kg: 300 mg (7,5 ml) once daily on days 1 - 3.

36 – 45 kg: 400 mg (10 ml) once daily on days 1 - 3.

> 45 kg: Dose as per adults (Refer to ZITHROMAX 500 mg Tablets PI).

SIDE EFFECTS

The majority of side effects are gastrointestinal in origin with anorexia, nausea, abdominal discomfort (pain/cramps), flatulence, vomiting and diarrhoea less frequently resulting in dehydration, dyspepsia, constipation and loose stools.

There have been reports of hearing impairment, including hearing loss, deafness and or tinnitus in some patients receiving ZITHROMAX.

Interstitial nephritis and acute renal failure have been reported.

Cases of abnormal liver function including hepatitis and cholestatic jaundice have been reported.

Reductions in neutrophil counts have occasionally been observed.

There have been rare reports of taste disturbances.

Asthenia and parathesia have been reported although a causal relationship may not have been established.

The following side effects have occurred: Chest pain, melena, nephritis, vaginitis, headache, dizziness, convulsions, vertigo, somnolence and fatigue.

Palpitations and arrythmias including ventricular tachycardia have been reported although a causal relationship with ZITHROMAX has not been established.

Allergic reactions including arthralgia, oedema, urticaria, rash, photosensitivity, angioedema and anaphylaxis (less frequently fatal) have occurred. (See Warnings and Special precautions). Less frequently, serious skin reactions including erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis have occurred.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There are no data on overdosage with ZITHROMAX. Typical symptoms of overdosage with macrolide antibiotics include hearing loss, severe nausea, vomiting and diarrhoea. Gastric lavage and general supportive measures are indicated.

IDENTIFICATION

ZITHROMAX 200 mg/5 ml powder for oral suspension is a dry powder which yields on reconstitution with water a cherry/banana flavoured suspension with a slight vanilla odour.

The colour of the powder and reconstituted suspension is white to off-white.

PRESENTATION

ZITHROMAX 200 mg/5 ml powder for oral suspension:

Plastic bottles containing powder to produce 15 ml, or 30 ml reconstituted suspension.

STORAGE INSTRUCTIONS

Store at or below 30 °C. No refrigeration required. Keep out of reach of children. The reconstituted suspension should be stored below 30 °C and any unused suspension discarded after 5 days.

REGISTRATION NUMBER

ZITHROMAX 200 mg/5 ml : 27/20.1.1/0279

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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DATE OF PUBLICATION OF THE PACKAGE INSERT

20 September 1993

NAMIBIA: S2
Reg. No.: 04/20.1.1/1250

BOTSWANA: S2
Reg. No.: BOT9800297

ZIMBABWE: PP
Reg. No.: 92/7.2.5/2684

ZAMBIA:
Reg No.: 120/030