ZITA Suspension

SCHEDULING STATUS: NS2

PROPRIETARY NAME (AND DOSAGE FORM)
Zita Suspension (powder for oral suspension)

COMPOSITION
Zita Suspension: Powder for oral suspension of azithromycin dihydrate which on reconstitution with water yield a suspension containing the equivalent of 200 mg azithromycin per 5 ml.
Product also contains the following inactive ingredients:
Banana flavour, hydroxypropylcellulose, strawberry flavour, sucrose, trisodium phosphate (anhydrous) and xanthan gum.
Warning: Contains sugar

PHARMACOLOGICAL CLASSIFICATION
A 20.1.1 Broad and medium spectrum antibiotics

PHARMACOLOGICAL ACTION
Pharmacodynamics:
Mechanism of action
Azithromycin is classed as a macrolide antibiotic, like erythromycin. It is a semi-synthetic derivative of erythromycin. Macrolide antibiotics contain a multi-membered lactone ring to which are attached one or more deoxy sugars.

Azithromycin has a 15 membered lactone ring and differs from erythromycin by the addition of a methyl-substituted nitrogen atom into the lactone ring. Azithromycin, like other macrolide antibiotics, is a bacteriostatic agent that inhibits bacterial protein synthesis by binding reversibly to the 50S ribosomal subunits of sensitive organisms.

Pharmacokinetics:
Absorption
Azithromycin administered orally is absorbed rapidly and is distributed widely throughout the body with the exception of the CSF and the brain. The bioavailability is about 37 %. Azithromycin in the tablet dosage form is not reduced by food. Peak plasma concentrations are reached about 2-3 hours after oral administration.

Distribution
Azithromycin is widely distributed throughout the body, including extensive tissue distribution and high drug concentrations within cells (including phagocytes). This result in a much greater concentration of drugs in tissue or secretions compared to simultaneous concentrations in serum.

During pharmacokinetic studies following oral administration, it was seen that there is markedly higher levels in tissue than in plasma (up to 50 times more than the maximum plasma concentration). This indicates that azithromycin is highly tissue bound. Concentrations in target tissue such as prostate, tonsils and lungs are greater than the MIC90 for likely pathogens after a single 500 mg dose.

In vivo, tissue fibroblasts store azithromycin, acting as a natural reservoir. At very low plasma concentrations, azithromycin is 50 % protein bound. At higher concentrations the plasma binding is less.

Metabolism
In the liver, azithromycin undergoes some metabolism to inactive metabolites; however the major route of elimination is biliary excretion. In the urine, only 12 % of azithromycin is excreted unchanged.

Elimination
The elimination half-life is prolonged because of extensive tissue binding and sequestration. The tissue depleted half-life of 2 to 4 days is closely reflected by the plasma terminal elimination half-life.
12 % of azithromycin is excreted unchanged in the urine.

Special populations
Hepatic Impairment
Azithromycin should not be prescribed in patients with liver disease as the liver is the principal route of excretion.
Renal Impairment
Azithromycin should be used with caution in patients with renal impairment as there is no data regarding usage in these patients.

INDICATIONS
Children: 1 year and over (under 45 kg)
Zita Suspension is indicated for pharyngitis/tonsillitis and otitis media caused by susceptible organisms.
Children over 45 kg body weight and adults, including elderly patients:
Zita Suspension 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 pnemoniae or haemophilus influenzae, uncomplicated skin and soft tissue infections, sinusitis due to haemophilus influenzae, streptococcus pneumonia or staphylococcus aureus and as an alternative to first line therapy of pharyngitis/tonsillitis.

CONTRAINDICATIONS
Zita Suspension is contraindicated in patients with a known hypersensitivity to any of the macrolide antibiotics including azithromycin.

There is a theoretical possibility of ergotism when **Zita Suspension** and ergot derivatives are given concomitantly. Co-administration of **Zita Suspension** and ergot derivatives should be avoided.

Use in hepatic Impairment
Azithromycin should not be prescribed in patients with liver disease as the liver is the principal route of excretion.

WARNINGS AND SPECIAL PRECAUTIONS
There have been reports of rare, serious allergic reactions including angioedema and anaphylaxis (rarely fatal). A longer period of observation and treatment may be required with some of these reactions as they may result in recurrent symptoms.
In patients with diarrhoea subsequent to the administration of **Zita Suspension** it is important to consider the diagnosis of pseudomembranous colitis. Cases of mild to life-threatening pseudomembranous colitis have been reported. Investigation for signs of superinfection with organisms that are not susceptible to azithromycin, including fungi, is recommended.
In treatment with other macrolide antibiotics a prolonged cardiac repolarisation and QT interval has been seen, resulting in a risk of developing torsade de pointes and cardiac arrhythmia. In patients who are at risk for prolonged cardiac arrhythmia, the possibility of azithromycin having a similar effect cannot be ruled out.
Use in children under 1 year of age
The safety and efficacy of **Zita Suspension** in children under 1 year have not been established.
Use in renal impairment
In patients with renal impairment, **Zita Suspension** should be used with caution as there is no data regarding the use of this medicine in renal impairment.
Use in hepatic Impairment
Zita Suspension should not be prescribed in patients with liver disease as the liver is the principal route of excretion.
Zita Suspension may aggravate muscle weakness in patients with myasthenia gravis.
Effects on ability to drive and use machines
The potential for dizziness and vertigo, which may occur with the use of **Zita Suspension,** should be taken into account before patients drive or use machines.

INTERACTIONS
Ergot Derivatives
Zita Suspension should not be co-administered with ergot derivatives because in theory there is a possibility of ergotism.
Special precautionary monitoring is advised with the following:
Some macrolides competitively inhibit hepatic cytochrome P450 isoenzymes. This inhibition in hepatic metabolism can result in severe adverse effects. However azithromycin is reported to have little or no effect on hepatic cytochromes and consequently may cause fewer interactions.
There have been rare reports that macrolide antibiotics may cause prolonged QT intervals and should therefore be used with caution with other medicines that are known to have this effect.
It is possible that the use of macrolides in combination with astemizole, cisapride and terfenadine may cause ventricular arrhythmias. For this reason, cisapride should not be used in combination with azithromycin
or any other macrolide.
Cyclosporin
Other macrolides interfere with the metabolism of cyclosporin. There are no pharmacokinetic studies or clinical data to investigate the interaction of azithromycin and cyclosporin. The levels of cyclopsporin should be monitored closely if concomitant usage of these two medicines is necessary. The dosage of cyclosporin should be adjusted if required.

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Digoxin
Some macrolide antibiotics have been known to impair the metabolism of digoxin in the gut. In cases in which digoxin and **Zita Suspension** are given concomitantly, there is a possibility of raised digoxin levels. Digoxin levels should be monitored closely.
Warfarin
Zita Suspension and warfarin may be administered concomitantly but the prothrombin time should be monitored closely.
Special administration is advised with the following:
Antacids
Zita Suspension should be taken at least 1 hour before or 2 hours after an antacid.
Cimetidine
The pharmacokinetics of **Zita Suspension** was not affected by a single dose of cimetidine administered 2 hours before.
No interactions reported with the following:
Carbamazepine
There have been no significant effects seen on the plasma levels of carbamazepine or its metabolite.
Methylprednisolone
It has been noted that **Zita Suspension** has no significant effects on the pharmacokinetics of methylprednisolone.
Theophylline
When **Zita Suspension** and theophylline are co-administered in healthy volunteers there is no evidence of any pharmacokinetic interactions.
Zidovudine
In HIV-positive patients on **Zita Suspension** there was no significant effects on the pharmacokinetics of zidovudine and its glucoronide metabolite. The time taken for maximal concentration of **Zita Suspension** to be reached was shortened.

PREGNANCY AND LACTATION
The safety and efficacy of **Zita Suspension** in pregnancy and lactating women has not been established and therefore the use thereof during pregnancy and lactation is not recommended.
The use of macrolides in breastfeeding may increase the risk of infantile hypertrophic pyloric stenosis.

DOSAGE AND DIRECTIONS FOR USE
Zita Suspension should be administered as a single daily dose.
Zita Suspension should be administered to children using the 5 ml oral dosing syringe. **Zita Suspension** can be taken with food.
Shake well before each use.
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 with **Zita Suspension**

Reconstitution instructions:
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
10 ml	15 ml (600 mg)	200 mg/5 ml
15 ml	30 ml (1200 mg)	200 mg/5 ml

SIDE EFFECTS
Infections and Infestations
Less frequent: Vaginitis, moniliasis.
Blood and the lymphatic system disorders
Less frequent: Neutropenia, thrombocytopenia.
Immune system disorders
Less frequent: Anaphylaxis.
Metabolism and nutrition disorders
Less frequent: Anorexia.
Nervous system disorders
Less frequent: Dizziness, headache, paraesthesia, somnolence, taste perversion, convulsions, hyperactivity, syncope.
Ear and labyrinth disorders
Less frequent: Hearing impairment including hearing loss, deafness, tinnitus, vertigo.
Cardiac disorders
Less frequent: Chest pains, arrhythmias including ventricular tachycardia, palpitations, QT prolongation, torsade de pointes.
Vascular disorders
Less frequent: Hypotension.
Gastrointestinal disorders
Frequent: Abdominal discomfort (pain/cramps), diarrhoea, (rarely resulting in dehydration), nausea.
Less frequent: Constipation, dyspepsia, flatulence, loose stools, vomiting, pseudomembranous colitis, tongue discolouration, melaena, pancreatitis.
Hepato-biliary disorders
Less frequent: Abnormal liver function, hepatitis and cholestatic jaundice, hepatic necrosis and hepatic failure, which have rarely resulted in death.
Skin and subcutaneous tissue disorders
Less frequent: Pruritus, rash, urticaria, allergic reactions, angioedema, oedema, photosensitivity, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Musculoskeletal, connective tissue and bone disorders
Less frequent: Arthralgia.
Renal and urinary disorders
Less frequent: Acute renal failure, interstitial nephritis, nephritis.
General disorders and administrative site conditions
Less frequent: Fatigue, asthenia, malaise.

KNOWN SYMPTOMS OF OVER-DOSAGE AND PARTICULARS OF ITS TREATMENT
There are no data on overdosage with **Zita Suspension**. With macrolide antibiotics, typical symptoms of overdosage include severe nausea, diarrhoea, vomiting, and hearing loss. General support measures and gastric lavage are indicated.

IDENTIFICATION
Zita Suspension 200 mg/5 ml powder for oral suspension is a fine, off white powder with banana/strawberry odour.

PRESENTATION
Zita Suspension is packed in a transparent amber glass type III bottle and polyethylene cap, containing powder to produce 15 ml or 30 ml of reconstituted suspension.

STORAGE INSTRUCTIONS
Store at or below 25 °C in dry place. Protect from light.
The reconstituted suspension should be stored at or below 25 °C, refrigeration is not required.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER
Nam Reg nr: 19/20.1.1/0071

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DATE OF PUBLICATION OF THE PACKAGE INSERT
09 May 2019