1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ZOXIL 250 (capsules)

ZOXIL 500 (capsules)

ZOXIL S (125 mg, powder for suspension)

ZOXIL SF (250 mg, powder for suspension)

2 QUALITIVE AND QUANTITIVE COMPOSITION

ZOXIL 250:

Gelatin capsules containing amoxicillin trihydrate equivalent to 250 mg amoxicillin.

Sugar free.

ZOXIL 500:

Gelatin capsules containing amoxicillin trihydrate equivalent to 500 mg amoxicillin.

Sugar free.

ZOXIL S:

Powder for preparing a fruit-flavoured suspension.

When reconstituted as directed, each 5 ml of the pink suspension contains amoxicillin 125 mg.

Excipients with known effect:

Preservative: Sodium Benzoate 0,295 % *m/m*

Contains sugar: Sucrose 3,002 g

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

ZOXIL SF:

Powder for preparing a fruit-flavoured suspension.

When reconstituted as directed, each 5 ml of the pink suspension contains

amoxicillin 250 mg.

Excipients with known effect:

Preservative: Sodium Benzoate 0,295 % *m/m*

Contains sugar: Sucrose 2,819 g

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

ZOXIL 250:

Dark grey/pink opaque capsules overprinted “ZOXIL 250” in white.

ZOXIL 500:

Dark grey/pink opaque capsules overprinted “ZOXIL 500” in white.

ZOXIL S:

Free-flowing, pink powder. Pink suspension after being reconstituted.

ZOXIL SF:

Free-flowing, pink powder. Pink suspension after being reconstituted.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections caused by non-penicillinase-producing organisms including:

- Upper respiratory tract infections
- Lower respiratory tract infections
- Otitis media
- Typhoid fever
- Upper urinary tract infections
- Lower urinary tract infections
- Skin and soft tissue infections
- Gastro-intestinal tract infections
- Gonorrhoea
- Non-specific urethritis

4.2 Posology and method of administration

Posology

Adults:

- The average adult dose for ZOXIL is 750 mg - 1,5 g/day, but in serious infections up to 6 g daily has been administered.
- 250 mg (1 x 250 mg capsule or 5 ml of 250 mg/5 ml suspension) three times a day.

Special populations

Paediatric population:

- ***Children 2 - 10 years:***

  125 mg (5 ml of 125 mg/5 ml suspension) three times a day.

- ***Children 6 months - 2 years:***

  125 mg (5 ml of 125 mg/5 ml suspension) three times a day.

- ***Infants 0 - 6 months:***

  62,5 mg (2,5 ml of 125 mg/5 ml suspension) three times a day.

- ***Premature infants 1,0 - 2,5 kg:***

  30,0 - 62,5 mg (quarter to half medicine measure of 125 mg/5 ml suspension) once daily for the first 1 - 2 weeks depending on the size and maturity of the infant, thereafter the dose may be given 2 – 3 times daily.

***In severe infections these dosages may be increased.**

Renal impairment:

- Patients with renal insufficiency may possibly require a reduced dose.

During treatment with high doses of ZOXIL, an adequate fluid intake and urinary output must be maintained (*see section 4.4*).

In-dwelling catheters should be checked regularly for potency since at room temperature high urinary concentration of ZOXIL may precipitate out of solution (*see section 4.4*).

Specific dosages:

Indications	**Daily Dosages**		**Duration**
	Adults	**Children**	
Gastro-intestinal tract infections	1 – 2 g	-	4 – 5 days
Acute typhoid fever	4 g -	- 100 mg/kg	14 days 21 days
Gonorrhoea	2 – 3 g	-	Stat

Method of administration

For oral use.

The presence of food does not interfere with the absorption of ZOXIL. ZOXIL may, therefore, be taken with meals.

4.3 Contraindications

- Hypersensitivity to the penicillins or any of the cephalosporins or to any of the excipients listed in section 6.1.
- Amoxicillin as contained in ZOXIL is penicillin and should not be given to patients with a history of hypersensitivity to β-lactam antibiotics (e.g. carbapenem or monobactam). Potential cross allergy to other beta-lactams such as cephalosporins should be taken into account.

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

- Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins.
- Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction *(see section 4.8).*
- Before commencing therapy with any penicillin as contained in ZOXIL, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergies *(see section 4.3*).
- If an allergic reaction occurs, appropriate therapy should be instituted and ZOXIL therapy discontinued.

- Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin *(see section 4.8)*. DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicine intake) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

Skin reactions:

- ZOXIL should be avoided if infectious mononucleosis and glandular fever is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Lymphatic leukaemia:

- ZOXIL should preferably not be used in patients with lymphatic leukaemia, since they are especially susceptible to ampicillin-induced skin rashes.
- The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AEGP). This reaction requires ZOXIL discontinuation and contraindicates any subsequent administration.

Overgrowth of non-susceptible microorganisms:

- Prolonged use may also occasionally result in overgrowth of non-susceptible organisms.
- Antibiotic associated *Pseudomembranous colitis* has been reported. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with ZOXIL use (this may occur up to several weeks after cessation of ZOXIL therapy). If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment with ZOXIL should be discontinued immediately.

- Anti-peristaltic medicines are contraindicated in this situation.

Anticoagulants:

- Prolongation of prothrombin time has been reported rarely in patients receiving ZOXIL. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Hepatic impairment:

- ZOXIL should be used with caution in patients with evidence of hepatic dysfunction.
- Changes in liver function tests have been observed in some patients receiving ZOXIL.
- Transient hepatitis and cholestatic jaundice have been reported.

Renal impairment:

- The dose should be reduced in patients with renal failure.

Prolonged therapy:

- Periodic assessment of renal, hepatic, and haematopoietic functions should be made during prolonged therapy.
- The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur ZOXIL should be discontinued and/or appropriate therapy instituted.

Jarisch-Herxheimer reaction:

- Caution is needed when administering ZOXIL to patients with syphilis, as the Jarisch-Herxheimer reaction may occur in these patients.

Allopurinol:

- ZOXIL should preferably not be used in patients treated with allopurinol since they are especially susceptible to ampicillin-induced skin rashes (*see section 4.5*).

Crystalluria:

- In patients with reduced urine output, crystalluria (including acute renal injury) has been observed. The presence of high urinary concentrations of ZOXIL can cause precipitation of the product in urinary catheters. Therefore, catheters should be visually inspected at intervals. When high doses are administered, adequate fluid intake and urinary output must be maintained *(see section 4.8 and 4.9).*

Convulsions:

- Convulsions may occur in patients with impaired renal function, in those receiving high doses or in patients with predisposing factors (e.g. history of seizures, treated epilepsy or meningeal disorders) (*see section 4.8*).

Non-susceptible microorganisms:

- The use of ZOXIL may lead to the appearance of resistant strains of organisms and sensitivity testing should therefore be carried out wherever possible, to ensure the appropriateness of the therapy.
- ZOXIL is not suitable for the treatment of some types of infection unless the pathogen is already documented and known to be susceptible or there is a very high likelihood that the pathogen would be suitable for treatment with ZOXIL. This particularly applies when considering the treatment of patients with urinary tract infections and severe infections of the ear, nose and throat.
- Amoxicillin, an aminopenicillin, is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of rash if amoxicillin is used (see sub-header ‘Skin reactions’).

There is insufficient evidence at present to show that ZOXIL penetrates into the cerebrospinal fluid in therapeutic quantities and it should, therefore, not be used in the treatment of cerebrospinal infections.

Effects on laboratory tests:

- Since high urine concentrations of amoxicillin as contained in ZOXIL may result in false positive reactions when testing for the presence of glucose in urine, it is recommended that glucose tests based on enzyme-based glucose oxidase reactions be used (*see section 4.5)*.

Oral contraceptives:

- Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated oestriol, oestriol-glucuronide, conjugated oestrone and oestradiol has been noted. This effect may also occur with amoxicillin as contained in ZOXIL.

Oral hormonal contraceptives:

- ZOXIL may reduce the efficacy of oral contraceptives and patients should be warned accordingly *(see section 4.5*).

Use in lactation:

- ZOXIL is excreted in breast milk and should be used with caution when administered to lactating women (*see section 4.6)*.

Sucrose warning for ZOXIL suspension:

- ZOXIL contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.
- Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take ZOXIL.

Important information about excipients of ZOXIL suspension:

- ZOXIL suspension contains 9.45 mg sodium benzoate in each 5 ml. Benzoate salt may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

- This medicine contains less than 1 mmol sodium (23 mg) per ml that is to say essentially 'sodium-free'. The sodium content in ZOXIL suspension must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.

4.5 Interaction with other medicines and other forms of Interaction

Due to amoxicillin's effect on intestinal flora, the absorption of other medicines may be affected.

Allopurinol:

The concomitant administration of allopurinol and ampicillin substantially increases the incidence of skin rashes in patients receiving both medicines as compared to patients receiving ampicillin alone (*see section 4.4)*. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

Digoxin:

- The absorption of concurrently administered digoxin may be increased during treatment with ZOXIL.

Anticoagulants:

- Concomitant administration of ZOXIL and anticoagulants e.g. coumarin may prolong the bleeding time.
- A dose adjustment of anticoagulants may be necessary (*see section 4.4*). If coadministration is necessary, the prothrombin time or internationally normalised ratio should be carefully monitored with the addition or withdrawal of ZOXIL.

Probenecid:

- Probenecid decreases the renal tubular secretion of ZOXIL.
- Concurrent use with ZOXIL may result in increased and prolonged blood concentrations of ZOXIL.

Tetracyclines:

- Tetracyclines and other bacteriostatic medicines may interfere with the bactericidal effects of ZOXIL.

Interaction with Laboratory tests:

- It is recommended that when testing for the presence of glucose in urine during ZOXIL treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of ZOXIL, false positive readings are common with chemical methods (*see section 4.4*).

Methotrexate:

- Interaction between ZOXIL and methotrexate leading to methotrexate toxicity has been reported.
- Serum methotrexate levels should be closely monitored in patients who receive ZOXIL and methotrexate simultaneously (*see section 4.4*). ZOXIL decreases the renal clearance of methotrexate, probably by competition at the common tubular secretion system.

Oral hormonal contraceptives:

- ZOXIL may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

Other forms of interactions:

- Forced diuresis leads to a reduction in blood concentrations by increased elimination of ZOXIL.
- ZOXIL may interfere with protein testing when colorimetric methods are used.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

ZOXIL may reduce the efficacy of oral contraceptives and patients should be warned accordingly (*see section 4.5*).

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

ZOXIL is excreted in breast milk and should be used with caution when administered to lactating women.

4.7 Effects on ability to drive and use machines

ZOXIL may cause allergic reactions, dizziness or convulsions and may thus have an effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision (*see section 4.8*).

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse side effects are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes.

Tabulated list of adverse reactions

Body System	Undesirable effects	
	Less frequent	**Frequency not known**
Infections and Infestations:	*Mucocutaneous candidosis*	
Blood and the lymphatic system disorders [3]:		Haemolytic anaemia, Reversible thrombocytopenia, Thrombocytopenic purpura, Eosinophilia, Reversible leucopenia Agranulocytosis Leucopenia (including severe neutropenia or agranulocytosis) Prolongation of bleeding time and prothrombin time *(see section 4.4)*[6]
Immune system disorders (*see section 4.3 & 4.4*) [8]:	Serum sickness-like syndrome, Hypersensitivity vasculitis, Anaphylaxis Angioneurotic oedema	
Nervous system disorders:	Dizziness, Headache,	Aseptic meningitis

	Reversible hyperactivity, Convulsions *(see section 4.4)*[9] Hyperkinesia	
Cardiac disorders:		Kounis syndrome *(see section 4.4)*
Gastrointestinal disorders [1]:	Diarrhoea, Nausea, Vomiting, Gastritis Stomatitis, Glossitis, Enterocolitis Black hairy tongue, Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (*see section 4.4)*, Tooth discolouration[7]	Drug-induced enterocolitis syndrome *(see section 4.4)*
Hepato-biliary disorders [4]	Hepatitis and cholestatic jaundice	Rises in AST and/or ALT [5]

Skin and subcutaneous tissue disorders [2]	Skin rash, Erythematous maculopapular rash Pruritis, Urticaria, Erythema multiforme Bullous exfoliative dermatitis, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised pustulosis, Lyell's syndrome Acute generalised exanthemous pustulosis (AGEP) (*see section 4.4*), Drug reaction with eosinophilia and systemic symptoms (DRESS), Jarisch-Herxheimer reaction (*see section 4.4*)	Linear IgA disease
Renal and urinary disorders:	Interstitial nephritis	Crystalluria (including acute renal injury) (*see section 4.9*)

[1] If gastro-intestinal reactions are evident, they may be reduced by taking ZOXIL at the start of a meal.

[2] Whenever such reactions occur, treatment should be discontinued.

3 These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1 % of the patients treated with ZOXIL.

[4] The events may be severe and occur predominantly in adult or elderly patients. Signs and symptoms usually occur during or shortly after treatment, but in some cases may not become apparent until several weeks after treatment has ceased.

The hepatic effects are usually reversible. However, in extremely rare circumstances, death has been reported. These have almost always been cases associated with serious underlying disease or concomitant medication.

[5] A moderate rise in Aspartate transaminase (AST) or SGOT and/or Alanine transaminase (ALT) or SGPT has been noted in patients treated with ZOXIL, but the significance of these findings is unknown.

[6] Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

[7] It can be removed by brushing.

[8] Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur. In the event of an anaphylactic reaction, immediate treatment with adrenalin, oxygen, corticosteroids and antihistamines should be initiated.

[9] Convulsions may occur with impaired renal function or in those receiving high doses.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

1.3.1.1 Professional Information for medicines for human use

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

Symptoms:

- Oral administration can cause gastro-intestinal symptoms such as transient diarrhoea, nausea and colic which are dose-related and a result of local irritation and not toxicity.

Treatment:

- If encountered, gastro-intestinal symptoms and disturbances of the fluid and electrolyte balance may be evident.
- They may be treated symptomatically and supportive with attention to the water/electrolyte balance.
- In the absence of an adequate fluid intake and urinary output, crystalluria, in some cases leading to renal failure, is a possibility.
- Amoxicillin may be removed from the circulation by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.20.1.2. Penicillins

Pharmacotherapeutic group: Penicillins with extended spectrum; ATC code: J01CA04

(a) Bacteriology

(i) Spectrum:

Amoxicillin is a penicillinase-susceptible penicillin. Amoxicillin exhibits in vitro, bactericidal activity against a wide range of Gram-negative and Gram-positive organisms including:

Gram-positive bacteria: **Gram-negative bacteria:**

*Staphylococcus aureus (penicillin-sensitive) **

Streptococcus pyogenes

*Streptococcus viridans**

*Streptococcus faecalis**

*Diplococcus pneumoniae**

*Corynebacterium species**

*Clostridium species**

*Bacillus anthracis**

Proteus mirabilis

Brucella species

*Neisseria gonorrhoeae**

Neisseria meningitidis

*Haemophilus influenzae***

Bordetella pertussis

*Escherichia coli**

Salmonella typhi

Salmonella species

Shigella species

* Sensitivity tests must be performed.

** Except type b-strains causing meningitis in children.

(ii) Bactericidal Action:

Amoxicillin exerts a rapid bactericidal activity at normal dosage levels against all susceptible organisms.

(b) Absorption

Amoxicillin is rapidly and well absorbed orally. A single 250 mg oral dose achieves an average peak serum level virtually equal to that achieved by IM injection viz. 5,38 µg/ml oral and 5,6 µg/ml IM. The peak serum level is achieved within 1,5 - 2 hours after oral and 15 minutes after IM or IV (18,2 µg/ml) administration.

After oral administration, there is no significant difference between the peak serum levels in fasting and non-fasting subjects. The presence of food does not interfere with the absorption of ZOXIL. ZOXIL may, therefore, be taken with meals. There is a linear/dose response in peak serum levels after both oral and parenteral administration.

(c) Distribution

(i) Sputum:

The concentration of amoxicillin in sputum does not decrease as occurs with ampicillin as purulence subsides.

(ii) Bile:

ZOXIL is present in bile obtained from a common bile duct drain of a healthy gallbladder, however, biliary levels are lower when the gallbladder is diseased and absent in the presence of biliary tract obstruction.

(iii) Urine:

The average concentration of ZOXIL in urine collected during the first six hours after 250 mg oral dose is 580 µg/ml.

(d) Excretion

(i) Renal:

Approximately 60 % of an oral dose of amoxicillin is excreted unchanged in the active form into the urine within six hours. Approximately 70 % - 80 % of an intramuscular dose and 90 % of an intravenous dose is excreted unchanged in the active form, into the urine within 12 hours.

(ii) Biliary:

A variable percentage of ZOXIL is excreted into the bile.

(e) Probenecid

Even higher ZOXIL serum levels may be achieved after oral administration to patients with normal renal function, by the simultaneous administration of a renal blocking medicine such as probenecid. Probenecid should not be given in the presence of abnormal renal function. No data on the effect of probenecid on parenteral amoxicillin are yet available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ZOXIL 250, ZOXIL 500:

Magnesium stearate

ZOXIL S, ZOXIL SF:

Sucrose

Sodium citrate

Citric acid anhydrous

Sodium benzoate

Disodium edetate

Capsaroma (peppermint)

Lemon flavour

Raspberry flavour

Peach apricot

Spectracol dual FD&C Red No.3 **or**

Idacol FD & C Red No.3 Powder

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ZOXIL 250, ZOXIL 500:

48 months

ZOXIL S, ZOXIL SF:

Dry powder: 24 months

Reconstituted suspension: 7 days or 14 days

Reconstituted suspension: Once reconstituted, ZOXIL S and ZOXIL SF must be used within 7 days kept at 25 ºC or used within 14 days and kept in a refrigerator at 4 ºC.

6.4 Special precautions for storage

ZOXIL 250 and ZOXIL 500:

Store at or below 25 ºC.

Keep the container tightly closed.

Keep in a cool, dry place.

ZOXIL S and ZOXIL SF:

Powder:

Store at or below 25 ºC.

Keep the container tightly closed.

Keep in a cool, dry place.

Reconstituted medicine:

For storage conditions of the reconstituted medicine, see section 6.3.

6.5 Nature and contents of container

ZOXIL 250: White HDPE securitainers with snap on LDPE cap and foam wad containing 15, 100 or 500 x 250 mg amoxicillin capsules.

ZOXIL 500: White HDPE securitainers with snap on LDPE cap and foam wad containing 15 or 100 x 500 mg amoxicillin capsules.

ZOXIL S: Clear glass bottles containing powder for reconstitution to 100 ml of 125 mg/5 ml suspension.

ZOXIL SF: Clear glass bottles containing powder for reconstitution to 100 ml of 250 mg/5 ml suspension.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Viatris South Africa (Pty) Ltd

4 Brewery Street, Isando

Johannesburg,

1609

8 REGISTRATION NUMBER(S)

ZOXIL 250: 28/20.1.2/0124

ZOXIL 500: 28/20.1.2/0125

ZOXIL S: 28/20.1.2/0126

ZOXIL SF: 28/20.1.2/0127

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4 June 1993

10 DATE OF REVISION OF TEXT

20 February 2024