Professional Information

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

ORASIL 250 mg Capsules

ORASIL 500 mg Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ORASIL 250

Each capsule contains Amoxicillin Trihydrate equivalent to 250 mg amoxicillin.

Sugar free.

ORASIL 500

Each capsule contains Amoxicillin Trihydrate equivalent to 500 mg amoxicillin.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

ORASIL 250

Maroon / yellow, size "1" hard gelatine capsule filled with white to off white granular powder and imprinted with "A" on maroon cap and "85" on yellow body with black ink.

ORASIL 500

Maroon / yellow, size "0EL" hard gelatine capsule filled with white to off white granular powder and imprinted with "A" on maroon cap and "86" on yellow body with black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ORASIL is indicated for the treatment of mild to moderately severe infections caused by susceptible non-penicillinase-producing organisms:

Amoxicillin therapy should be initiated only if there is microbiological evidence that the causative organism is sensitive to amoxicillin:

- Upper Respiratory tract infections such as sinusitis, pharyngitis, epiglottitis and tonsillitis.
- Lower respiratory tract infections such as acute and chronic bronchitis, lobar and bronchopneumonia.
- Otitis media
- Gastrointestinal infections such as typhoid fever and Salmonella
- Uncomplicated gastroenteritis and enteric fever
- Other infections including Borreliosis (Lyme disease).
- Skin and soft tissue infections.
- Urinary tract infections: cystitis, urethritis, pyelonephritis, bacteriuria in pregnancy.
- As part of combination therapy in established Helicobacter pylori infection, associated with duodenal ulceration.
- Prophylaxis of endocarditis.

4.2 Posology and Method of Administration

The total daily dose as below is administered in divided doses.

The most common regimen is 8 hourly.

The absorption of ORASIL is not affected significantly when taken with food.

Posology

Adults and children over 40 kg:

A total daily dosage of 750 mg to 3 g administered in divided doses.

Maximum recommended dose: 6 g/day in divided doses.

Respiratory tract infections: 500 mg administered 8 hourly.

Lyme disease: 4 g/day in isolated erythema chronicum migrans and 6 g/day in the case of generalised manifestations, both for a minimum of 12 days.

Eradication of Helicobacter pylori: 750 mg - 1 g in combination treatment given 12 hourly for the eradication of established *H. pylori* infection associated with duodenal ulceration for seven days.

Special Populations

Paediatric Population

Children under 40 kg:

20 - 50 mg/kg/day in divided doses.

Maximum recommended dose: 150 mg/kg/day in divided doses.

Lyme disease: 25 - 50 mg/kg/day in isolated erythema chrionicum migrans and 100 mg/kg/day in the case of generalised manifestations, both for a minimum of 12 days.

Elderly:

No adjustment needed: as for adults unless there is evidence of severe renal impairment *(see below)*.

Renal impairment:

Glomerular filtration rate > 30 mŁL/min: No adjustment needed.

Glomerular filtration rate 10 - 30 mŁL/min: Maximum 500 mg 12 hourly.

Glomerular filtration rate <10 mŁL/min: Maximum 500 mg daily.

In patients receiving peritoneal dialysis: Maximum 500 mg daily.

Prophylaxis of Endocarditis

Prophylaxis with alternative antibiotics should be considered if the patient has received penicillin within the previous month or is allergic to penicillin.

For dental, oral or upper respiratory tract procedures:

Prophylaxis for patients undergoing dental extraction, scaling or surgery involving gingival tissues, tonsillectomy, adenoidectomy, bronchoscopy with a rigid bronchoscope and surgical procedures that involve respiratory mucosa.

For patients NOT having a general anaesthetic:

Adults: 2 g orally, 1 hour before the procedure.

Children: 50 mg/kg, 1 hour before the procedure.

Children's dose not to exceed the adult dose.

Method of Administration

For oral administration only.

4.3 Contraindications

Hypersensitivity to amoxicillin, penicillin, any of the cephalosporins or to any of the excipients *(see section 6.1)*.

Amoxicillin as contained in ORASIL is a penicillin and should not be given to patients with a history of hypersensitivity to β-lactam antibiotics (e.g. carbapenem or monobactam). Cross-sensitivity between penicillin and cephalosporin is well documented. Potential cross allergy to other beta-lactams such as cephalosporins should also be taken into account.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy.

Before initiating therapy with ORASIL, careful enquiry should be made concerning previous severe immediate hypersensitivity reactions (such as anaphylaxis) to penicillins, cephalosporins or other beta-lactam products (e.g. carbapenem or monobactam) or other allergens.

If an allergic reaction occurs, ORASIL should be discontinued and the appropriate therapy instituted.

Serious and occasionally fatal hypersensitivity (anaphylactic) 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. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with a cephalosporin.

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction *(see section 4.8).*

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin, as contained in ORASIL *(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.

Serious anaphylactic reactions may require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation, may also be required.

Non-susceptible microorganisms

Amoxicillin is not suitable for the treatment of some types of infections 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 amoxicillin *(see section 5.1)*. 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 ORASIL penetrates into the cerebrospinal fluid in therapeutic quantities and it should, therefore, not be used in the treatment of cerebrospinal infections.

The use of ORASIL may lead to the selection of resistant strains of organisms and sensitivity testing should, therefore, be carried out whenever possible, to demonstrate the appropriateness of therapy *(see Section 4.6)*

Convulsions

Convulsions may occur in patients with impaired renal function or 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)*).

Renal impairment

In patients with renal impairment, the dose should be adjusted according to the degree of impairment *(see section 4.2)*.

Impaired hepatic function:

Changes in liver function tests have been observed in some patients receiving amoxicillin such as in ORASIL.

It should be used with care in patients with evidence of severe hepatic dysfunction.

Transient hepatitis and cholestatic jaundice have been reported.

Skin reactions

The occurrence at the treatment initiation of feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (*see section 4.8)*. This reaction requires amoxicillin discontinuation and contraindicates any subsequent administration.

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

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected beta-lactam antibiotics should be discontinued.

ORASIL should preferably not be used in patients with lymphatic leukaemia and in patients with hyperuricaemia being treated with allopurinol since they are especially susceptible to amoxicillin induced skin rashes.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, the agent should be discontinued and/or appropriate therapy instituted.

Jarisch-Herxheimer reaction

The Jarisch-Herxheimer reaction has been seen following amoxicillin treatment of Lyme disease *(see section 4.8)*. It results directly from the bactericidal activity of amoxicillin on the causative bacteria of Lyme disease, the spirochete Borrelia burgdorferi. Patients should be reassured that this is a common and usually self-limiting consequence of the antibiotic treatment of Lyme disease.

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

Overgrowth of non-susceptible microorganisms

Prolonged use may occasionally result in overgrowth of non-susceptible organisms. Antibiotic-associated colitis and pseudomembranous colitis have been reported with amoxicillin, and may range in severity from mild to life-threatening *(see section 4.8)*. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea or colitis during, or subsequent to, the administration of any antibiotics (this may occur up to

several weeks after cessation of ORASIL therapy). Should prolonged or significant diarrhoea, abdominal cramps, or antibiotic-associated colitis occur, amoxicillin should immediately be discontinued, a physician consulted and appropriate therapy initiated. Antiperistaltic medicinal products are contra-indicated in this situation.

Prolonged therapy

Periodic assessment of organ system functions; including renal, hepatic and haematopoietic function is advisable during prolonged therapy. Elevated liver enzymes and changes in blood counts have been reported *(see section 4.8)*.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur, ORASIL should be discontinued and/or appropriate therapy instituted.

Anticoagulants

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation *(see section 4.5 and 4.8)*.

Crystalluria

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. The presence of high urinary concentrations of ORASIL can cause precipitation of the product in urinary catheters. Therefore, in patients with bladder catheters, a regular check of patency should be maintained *(see section 4.8 and 4.9)*.

Use in Lactation

Amoxicillin is excreted in the milk. Therefore, caution should be exercised when ORASIL is administered to a nursing woman.

Interference with diagnostic tests

Elevated serum and urinary levels of amoxicillin are likely to affect certain laboratory tests. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

It is recommended that when testing for the presence of glucose in urine during amoxicillin treatment, enzymatic glucose oxidase methods should be used.
The presence of amoxicillin may also distort assay results for oestriol in pregnant women.

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.

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin.

Allopurinol

Concurrent administration of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions (see section 4.4).

Digoxin

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

Tetracyclines

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of amoxicillin.

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature, there are cases of increased international normalised ratio in patients maintained on warfarin and prescribed a course of amoxicillin. If coadministration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary *(see sections 4.4 and 4.8)*.

Methotrexate

Serum methotrexate levels should be closely monitored in patients who receive ORASIL and methotrexate simultaneously. Penicillins may reduce the excretion of methotrexate, probably by competition at the common tubular secretion system, causing a potential increase in toxicity.

Oral Contraceptives

ORASIL may decrease the efficacy of oestrogen-containing 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 ORASIL.

ORASIL 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

Concurrent use of ORASIL and oral contraceptives decreases the efficacy of the oral contraceptive. Patients should be strongly advised to use an alternative or additional method of contraception while taking this medicine *(see section 4.5)*.

Pregnancy

The safety of ORASIL in pregnancy has not been established.

Breastfeeding

Amoxicillin is excreted into breast milk in small quantities with the possible risk of sensitisation. Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued. ORASIL should therefore be used with caution when administered to lactating women.

Fertility

There is no data available on the effects of ORASIL on fertility.

4.7 Effects on ability to drive and use machines

ORASIL may cause allergic reactions, dizziness, or convulsions which may influence the ability to drive and use machines *(see section 4.8)*.

ORASIL may have an effect on the 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 summary of adverse reactions

Body System	Undesirable effects		
	Frequent	***Less Frequent***	***Frequency Unknown***
Infections and infestations		*Mucocutaneous candidiasis, Clostridium difficile*	
Blood and lymphatic system disorders [3]		Haemolytic anaemia, Reversible thrombocytopenia, Reversible leucopenia Agranulocytosis Leucopenia (including severe neutropenia or agranulocytosis) Prolongation of bleeding time and prothrombin time *(see section 4.4)* [6]	Thrombocytopenic purpura, Eosinophilia, Jarisch-Herxheimer reaction *(see section 4.4)*
Immune system disorders (see section 4.3 & 4.4) [8]		Serum sickness-like syndrome, Hypersensitivity vasculitis, Anaphylaxis Angioneurotic	

		oedema	
Endocrine disorders	Tiredness and hot flushes.		
Nervous system disorders		Dizziness, Headache Reversible hyperactivity, Convulsions *(see section 4.4)* [9] Hyperkinesia	Aseptic meningitis
Cardiac Disorders			Kounis syndrome *(see section 4.4)*
Gastrointestinal disorders [1]	Diarrhoea, nausea, vomiting, indigestion, abdominal pain and abnormal taste.	Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis (*see section 4.4)*. Black hairy tongue, Gastritis, stomatitis, glossitis, Enterocolitis, mucocutaneous candidiasis, 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 rashes, urticaria, serum sickness-like syndrome	Skin reactions such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal	Purpura, diaphoresis, flushing, petechiae, Linear IgA disease.

		necrolysis, bullous and exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP) *(see section 4.4)*, and drug reaction with eosinophilia and systemic symptoms (DRESS). Erythematous maculopapular rash, Pruritis, Urticaria, Lyell's syndrome, Jarisch-Herxheimer reaction *(see section 4.4)*	
Renal and urinary tract disorders		Interstitial nephritis	Crystalluria (including acute renal injury) *(see sections 4.4 and 4.9)*
Reproductive system and breast disorders	Vaginitis.		

Description of selected adverse reactions

[1] If gastro-intestinal reactions are evident, they may be reduced by taking ORASIL 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.

[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 amoxicillin, 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 are important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose
Symptoms and signs of overdose
Gastrointestinal symptoms (such as nausea, vomiting and diarrhoea) and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed.
Convulsions may occur in patients with impaired renal function or in those receiving high doses (see sections 4.4 and 4.8).
Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water and electrolyte balance.
Amoxicillin can 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.

Mechanism of action

Amoxicillin is a semisynthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.
Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Inherently resistant organisms

Gram-positive aerobes:
Enterococcus faecium
Gram-negative aerobes:
Acinetobacter spp.
Enterobacter spp.
Klebsiella spp.
Pseudomonas spp.
Gram-negative anaerobes:
Bacteroides spp. (many strains of Bacteroides fragilis are resistant).
Others:
Chlamydia spp.
Mycoplasma spp.
Legionella spp.

5.2 Pharmacokinetic Properties

Absorption:

Amoxicillin is rapidly and well absorbed orally. The peak serum level is achieved within 1,5 - 2 hours after oral administration. There is a linear/dose response in peak serum levels after administration.

Amoxicillin is stable in the presence of acidic gastric secretions. 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 amoxicillin. ORASIL may, therefore, be taken with meals.

Distribution:

Approximately 18 % of the total plasma amoxicillin content is protein bound.

Amoxicillin diffuses readily into most body tissues with the exception of the brain and spinal fluid.

Inflammation generally increases the permeability of the meninges to penicillins and this may apply to amoxicillin.

~~Amoxycillin~~ Amoxicillin crosses the placenta and is distributed into breast milk.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose.

Elimination:

The elimination half-life is approximately 1 hour. ~~Amoxycillin~~ Amoxicillin is primarily eliminated via the kidneys. Small amounts of the drug are also excreted in the faeces and bile.

Special Populations

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life, the interval of administration should not exceed twice daily administration

due to immaturity of the renal pathway of elimination. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Gender

Following oral administration of amoxicillin~~/~~ to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of amoxicillin.

Renal impairment

The total serum clearance of amoxicillin decreases proportionately with decreasing renal function (*see sections 4.2 and 4.4*).

Hepatic impairment

Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and toxicity to reproduction and development.

Carcinogenicity studies have not been conducted with amoxicillin.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Cellulose, Microcrystalline

Magnesium Stearate

Capsule shell:

Carmoisine

Iron oxide yellow

Titanium dioxide

Purified Water

Gelatine

Printing black ink:

Shellac

Dehydrated Alcohol
Isopropyl alcohol
Butyl Alcohol
Propylene Glycol
Strong Ammonia solution
Black Iron oxide
Potassium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.
Keep in a cool, dry place.
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

ORASIL 250

White opaque round 500 ml HDPE container with 53 mm neck finish closed with 53 mm – 400 RS closure with induction sealing wad, containing 500 capsules.

ORASIL 500

White opaque round 200 ml HDPE container with 38 mm neck finish closed with 38 mm – 400 RS closure with induction sealing wad, containing 100 capsules.

6.6 Special Precautions for Disposal

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd
Corner Birch Road & Bluegum Avenue,
Anchorville,
Lenasia,
1827
South Africa
Tel: + 2711 056 6999

8. REGISTRATION NUMBER(S)

ORASIL 250: 50/20.1.2/0535

ORASIL 500: 50/20.1.2/0536

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of Registration: 04 May 2021

10. DATE OF REVISION OF THE TEXT

30 May 2025