1.3.1.1.2 PROPOSED CLEAN PROFESSIONAL INFORMATION (clean)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AMOXICLAV 125-31,25 mg/5 ml AURO(Powder for oral Suspension)

AMOXICLAV 250-62,5 mg/5 ml AURO (Powder for oral Suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMOXICLAV 125-31,25 mg/5 ml AURO:

Each 5 ml (After reconstitution) contains: Amoxicillin Trihydrate Ph.Eur, equivalent to Amoxicillin 125 mg and Potassium Clavulanate Ph.Eur. equivalent to Clavulanic acid 31.25 mg

AMOXICLAV 250-62,5 mg/5 ml AURO:

Each 5 ml (After reconstitution) contains: Amoxicillin Trihydrate Ph.Eur. equivalent to Amoxicillin 250

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AMOXICLAV AURO 125-31.25 mg/5 ml:

White to off white granular powder forming a white to off white suspension with a strawberry flavour on constitution with water.

AURO-AMOXICLAV 250-62,5 mg/5 ml:

White to off white granular powder forming a white to off white suspension with a strawberry flavour on constitution with water.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMOXICLAV AURO formulations are indicated for the treatment of infections caused by amoxicillin resistant organisms producing beta-lactamases sensitive to clavulanic acid:

Upper respiratory tract infections, such as sinusitis, recurrent otitis media, tonsillitis.

Lower respiratory tract infections, such as bronchitis and bronchopneumonia.

Genito-urinary tract infections, such as cystitis, urethritis, pyelonephritis.

Skin and soft tissue infections.

AMOXICLAV AURO formulations will also be effective in the treatment of infections caused by amoxicillin sensitive organisms at the appropriate amoxicillin dosage since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

4.2 Posology and method of administration

Directions for reconstitution:

AMOXICLAV 125-31,25 mg/5 ml AURO:

For reconstitution to 100 ml, add 92 ml water, invert the bottle and shake well until all the powder is dispersed.

AMOXICLAV AURO 250-62,5 mg/5 ml:

For reconstitution to 100 ml, add 90 ml water, invert the bottle and shake well until all the powder is dispersed.

AMOXICLAV AURO suspension may be taken immediately before a meal.

Dosage:

General Information: For infections caused by amoxicillin sensitive organisms the dosage is that approved for amoxicillin as the clavulanic acid component does not contribute to the therapeutic effect.

Children:

The dose of **AMOXICLAV AURO** in children is 25-50 mg/kg/day of the 4 parts amoxicillin, I part clavulanic acid preparations (which corresponds to a daily dosage of the equivalent of 20-

40 mg/kg of amoxicillin and 5-10 mg/kg of clavulanic acid) to be taken in divided doses every eight hours, at the start of a meal.

Dosage Guide:

Amoxicillin-Sensitive Organisms

Product	Upper Respiratory Tract Infections	Lower Respiratory Tract Infections	Urinary Tract Infections	Skin & Soft Tissue Infections
AMOXICLAV AURO 125-31.25 mg/5 ml (9-18 kg)	5-10 ml * 8 hourly	5-10 ml * 8 hourly	5-10 ml * 8 hourly	5-10 ml * 8 hourly
AMOXICLAV AURO 250-62.5 mg/5 ml (18-37 kg)	5 ml * 8 hourly	5 ml * 8 hourly	5 ml * 8 hourly	5 ml * 8 hourly

Amoxicillin-Resistant Organisms

Product	Upper Respiratory Tract Infections (Otitis media)	Lower Respiratory Tract Infections (Bronchitis)	Urinary Tract Infections	Skin & Soft Tissue Infections
AMOXICLAV AURO 125-31.25 mg/5 ml	5-10 ml ^ 8 hourly	5-10 ml * 8 hourly	5-10 ml * 8 hourly	5-10 ml * 8 hourly

(9-18 kg)				
AMOXICLAV AURO 250-62.5 mg/5 ml (18-37 kg)	5-10 ml ^ 8 hourly	5-10 ml * 8 hourly	5-10 ml * 8 hourly	5-10 ml * 8 hourly

* To correspond to a dosage of 25-50 mg/kg/day.

^ To correspond to a dosage of 50 mg/kg/day.

4.3 Contraindications

Hypersensitivity to penicillins or to cephalosporins. Cross-sensitivity between penicillins and cephalosporins is well documented.

AMOXICLAV AURO is contra-indicated in patients with a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients on penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). Before initiating therapy with **AMOXICLAV AURO**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens (see section 4.3 and 4.8). 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 cephalosporins.

If an allergic reaction occurs, **AMOXICLAV AURO** should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management, including intubation may also be required.

AMOXICLAV AURO 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.

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported.
Prolongation of prothrombin time has been reported rarely in patients receiving **AMOXICLAV AURO**. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Periodic assessment of organ function, including renal, hepatic and haematopoietic functions, is advisable during prolonged therapy.

Transient hepatitis and cholestatic jaundice has been reported. **AMOXICLAV AURO** should be used with caution in patients with evidence of hepatic dysfunction.

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

When high doses are administered, adequate fluid intake and urinary output must be maintained.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function, is advisable during prolonged therapy. Since **AMOXICLAV AURO** contains amoxicillin, an aminopenicillin, it 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. **AMOXICLAV AURO** should be given with caution to patients with lymphatic leukemia 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 (usually involving *Aerobacter, Pseudomonas* or *Candida),* the agent should be discontinued and/or appropriate therapy instituted.

Impaired hepatic function:
Changes in liver function tests have been observed in some patients receiving **AMOXICLAV AURO**. It should be used with care in patients with evidence of severe hepatic dysfunction.

Impaired renal function:
In patients with moderate or severe renal impairment **AMOXICLAV AURO** dosage should be adjusted.
(See section 4.2).
Use in Lactation:
Amoxicillin is excreted in the milk; there is no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when **AMOXICLAV AURO** is administered to a nursing woman.

The use of **AMOXICLAV AURO** 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.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after medicine use) 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.

In patients with reduced urine output, crystalluria (including acute renal injury) 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. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

4.5 Interaction with other medicines and other forms of interaction

AMOXICLAV AURO may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

The concomitant administration of allopurinol and **AMOXICLAV AURO** substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricaemia present in these patients.

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

Methotrexate:

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

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 but not clavulanic acid.

Interaction with Laboratory tests:

It is recommended that when testing for the presence of glucose in urine during **AMOXICLAV AURO** treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of **AMOXICLAV AURO** in pregnancy has not been established.

Breastfeeding

Amoxicillin is distributed into breast milk. Although significant problems in humans have not been documented, the use of **AMOXICLAV AURO** by breast feeding mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering **AMOXICLAV AURO** at the start of a meal. In addition, as these symptoms are especially related to the potassium clavulanate component, where these gastrointestinal symptoms occur and a higher concentration of amoxicillin is required, consideration should be given to administering the additional amoxicillin separately.

The following adverse reactions have been reported and may occur with **AMOXICLAV AURO:**

b. Tabulated list of adverse reactions

System Organ Class	Frequency	Side effects
Infections and infestations	Less frequent.	Mucocutaneous candidiasis
Blood and the lymphatic system	Less frequent.	Reversible thrombocytopenia, thrombocytopenic purpura and reversible leucopenia, thrombocytosis, prolongation of bleeding time and prothrombin time, haemolytic anaemia,

		eosinophilia and agranulocytosis
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 **AMOXICLAV AURO**. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.		
Immune system disorders	Less frequent:	Serum sickness-like syndrome, hypersensitivity vasculitis, angioneurotic oedema, anaphylaxis
Nervous system disorders	Frequent:	Headache.
	Less frequent	Convulsions[1,] reversible hyperactivity and dizziness.
	Frequency not known	Aseptic meningitis

	[1.]Convulsions may occur with impaired renal function or in those receiving high doses.	
Cardiac disorders:	Frequency not known	Kounis syndrome (see section 4.4)
Vascular disorders	Frequency not known	Hot flushes.
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea
	Less frequent	Glossitis, indigestion, enterocolitis, antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) and abnormal taste, superficial tooth discolouration[1.]
	Frequency not known	Abdominal pain, gastritis, stomatitis, black ‘hairy’ tongue, Drug-induced enterocolitis syndrome (DIES)

	[1.]Superficial tooth discolouration has been reported especially with the suspension formulations.It can usually be removed by brushing. If gastrointestinal reactions are evident, they may be reduced by taking **AMOXICLAV AURO** at the start of a meal.	
Hepato-biliary disorders	Less frequent	Hepatitis and cholestatic jaundice, a moderate raise in aspartate transaminase (AST) and/or alanine transaminase (ALT)
	The events may be severe, and occur predominantly in adults 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. **Hepato-biliary disorders** **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.	
Skin and subcutaneous tissue disorders	Less frequent	Skin rashes, pruritus urticaria, erythema multiforme, Stevens-Johnson syndrome toxic epidermal necrolysis
	Frequency not known	Bullous exfoliative dermatitis, Linear IgA disease
	Whenever such reactions occur, **AMOXICLAV AURO** should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (section 4.4).	
Renal and urinary disorders	Frequency not known	Crystalluria, interstitial nephritis
Reproductive system and breast disorders	Frequency not known	Vaginitis
General disorders and administrative site conditions disorders:	*Less frequent*	Tiredness.

4.9 Overdose

Overdosage with amoxicillin is usually asymptomatic. However, gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4). Adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria.

Amoxicillin may be removed from the circulation by haemodialysis. The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

PHARMACOLOGICAL CLASSIFICATION

A 20.1.2 Penicillins

5.1 Pharmacodynamic properties

AMOXICLAV AURO is a combination of amoxicillin and clavulanic acid.

Amoxicillin is a semisynthetic beta-lactamase-susceptible penicillin, which has *in vitro* bactericidal activity against a broad spectrum of non beta-lactamase-producing Gram positive, and Gram negative organisms. The spectrum of activity does not include those organisms that produce beta-lactamases, namely resistant staphylococci, and all strains of *Pseudomonas, Klebsiella* and *Enterobacter.*

Clavulanic acid has been shown *in vitro* to be an irreversible inhibitor of beta-lactamases produced by:

Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Haemophilus influenzae, Neisseria gonorrhoea and *Bacteroides fragilis.* Clavulanic acid does not inactivate the chromosomally mediated (Sykes Type 1 Cephalosporinase) beta-lactamases produced by *Acinetobacter* species, *Citrobacter* species, *Enterobacter,* Indole

positive *Proteus, Providencia* species and *Serratia marcescens. In vitro* the formulation showed synergism against amoxicillin-resistant organisms, with no evidence of antagonism and the activity was not reduced in the presence of serum.

(In vitro activity does not necessarily imply *in vivo* efficacy.)

5.2 Pharmacokinetic properties

Absorption:

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1 - 2 hours after administration. There is a linear dose response in peak serum levels.

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither is adversely affected by the presence of food in the stomach.

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.

Excretion:

The elimination half-life of amoxicillin is approximately 1 hour. Small amounts of amoxicillin are also excreted in the faeces and bile.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Aspartame

Hypromellose

Silica colloidal anhydrous

Silicon dioxide,

Strawberry guarana flavour

Succinic acid

Silicon dioxide (Syloid)

Xanthum gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Dry powder: 18 months

Reconstituted suspension: 7 days

6.4 Special precautions for storage

Store at or below 30 °C. Protect from moisture.

STORAGE FOR RECONSTITUTED SUSPENSION:

Reconstituted Suspension should be kept in a refrigerator (2 — 8°C) and used within 7 days.

Do not freeze.

6.5 Nature and contents of container

AMOXICLAV 125-31,25 mg/5 ml AURO:

One 150 ml heavy weight HDPE translucent, round bottle closed with a screw cap packed in a printed carton with a package insert.

(100 ml of suspension after reconstitution)

One 200 ml Amber coloured, round glass bottle closed with a screw cap packed in a printed carton with a package insert.

(100 ml of solution after reconstitution).

AMOXICLAV 205-62,5 mg/5 ml AURO:

One 150 ml heavy weight HDPE translucent, white opaque round bottle closed with a screw

cap packed in a printed carton with a package insert.

(100 ml of suspension after reconstitution).

One 200 ml Amber coloured, round glass bottle closed with a screw cap packed in a printed

carton with a package insert.

(100 ml of solution after reconstitution)

7. HOLDER OF CERTIFICATE OF REGISTRATION

Aurogen South Africa (Pty) Ltd

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8. REGISTRATION NUMBER

AMOXICLAV 125-31,25 mg/5 ml AURO: 41/20.1.2/0963

AMOXICLAV 250-62,5 mg/5 ml AURO: 41/20.1.2/0964

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 April 2009.

10. DATE OF REVISION OF TEXT

16 September 2025.