PROFESSIONAL INFORMATION (CLEAN)

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

AURO-AMOXICLAV 125-31.25 mg/5 ml (Powder for oral Suspension)

AURO-AMOXICLAV 250-62.5 mg/5 ml (Powder for oral Suspension)

COMPOSITION

AURO-AMOXICLAV 125-31.25 mg/5 ml:

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

AURO-AMOXICLAV 250-62.5 mg/5 ml:

Each 5 ml (After reconstitution) contains: Amoxicillin Trihydrate Ph.Eur. equivalent to Amoxicillin 250 mg and Potassium Clavulanate Ph.Eur. equivalent to Clavulanic acid 62.5 mg

PHARMACOLOGICAL CLASSIFICATION

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION

AURO-AMOXICLAV 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.)

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.

INDICATIONS

AURO-AMOXICLAV 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.

AURO-AMOXICLAV 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.

CONTRA-INDICATIONS

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

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

WARNINGS AND SPECIAL PRECAUTIONS

Warnings

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with **AURO-AMOXICLAV**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. 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, **AURO-AMOXICLAV** 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.

AURO-AMOXICLAV 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 **AURO-AMOXICLAV**. 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. **AURO-AMOXICLAV** should be used with caution in patients with evidence of hepatic dysfunction.

Special Precautions:
Caution is needed when administering **AURO-AMOXICLAV** 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 **AURO-AMOXICLAV** 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. **AURO-AMOXICLAV** 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 **AURO-AMOXICLAV**. 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 **AURO-AMOXICLAV** dosage should be adjusted.

(See **DOSAGE AND DIRECTIONS FOR USE**).

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 **AURO-AMOXICLAV** is administered to a nursing woman.

The use of **AURO-AMOXICLAV** 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.

INTERACTIONS

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

The concomitant administration of allopurinol and **AURO-AMOXICLAV** 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.

Interaction with Laboratory tests:

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

PREGNANCY AND LACTATION

Use in Pregnancy:

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

Use in Lactation:

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

DOSAGE AND DIRECTIONS FOR USE

Directions for reconstitution:

AURO-AMOXICLAV 125-31.25 mg/5 ml:

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

AURO-AMOXICLAV 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.

AURO-AMOXICLAV 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 **AURO-AMOXICLAV** 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**
AURO-AMOXICLAV 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
AURO-AMOXICLAV 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**

AURO-AMOXICLAV 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
AURO-AMOXICLAV 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.

SIDE EFFECTS

The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering **AURO-AMOXICLAV** 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 **AURO-AMOXICLAV:**

Immune system disorders:

Less frequent:

Skin rashes, pruritus and urticaria, serum sickness-like syndrome, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported. Whenever such reactions occur, **AURO-AMOXICLAV** should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see **WARNINGS AND SPECIAL PRECAUTIONS**).

The following side effects have been reported and frequencies are unknown:

Hypersensitivity vasculitis and bullous exfoliative dermatitis. Whenever such reactions occur, **AURO-AMOXICLAV** should be discontinued.

Interstitial nephritis can occur.

Gastrointestinal disorders:

Frequent:

Nausea, vomiting, diarrhoea

Less frequent:

Glossitis

The following side effects have been reported and frequencies are unknown:

Indigestion, abdominal pain, gastritis, stomatitis, black 'hairy' tongue, enterocolitis, mucocutaneous candidiasis and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) and abnormal taste. 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 **AURO-AMOXICLAV** at the start of a meal.

Hepato-biliary disorders:

Less frequent:

Hepatitis and cholestatic jaundice have been reported. 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. **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.**

A moderate raise in aspartate transaminase (AST) and/or alanine transaminase (ALT) has been noted in patients treated with **AURO-AMOXICLAV**.

Renal and urinary disorders:

The following side effects have been reported and frequencies are unknown:

Crystalluria.

Reproductive system and breast disorders:

The following side effects have been reported and frequencies are unknown:

Vaginitis.

Blood and the lymphatic system disorders:

Less frequent:

Reversible thrombocytopenia, thrombocytopenic purpura and reversible leucopenia have been reported. 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 **AURO-AMOXICLAV**. Prolongation of bleeding time and prothrombin time have also been reported less frequently. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

The following side effects have been reported and frequencies are unknown:

Haemolytic anaemia, eosinophilia and agranulocytosis have been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Nervous system disorders:

Frequent:

Headache.

Less frequent:

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

The following side effects have been reported and frequencies are unknown:

Reversible hyperactivity and dizziness.

Vascular disorders:

The following side effects have been reported and frequencies are unknown:

Hot flushes.

General disorders and administrative site conditions:

Less frequent:

Tiredness.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

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.

IDENTIFICATION

AURO-AMOXICLAV 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.

PRESENTATION

AURO-AMOXICLAV 125-31.25 mg/5 ml:

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).

AURO-AMOXICLAV 250-62.5 mg/5 ml:

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)

STORAGE INSTRUCTIONS

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.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

AURO-AMOXICLAV 125-31.25 mg/5 ml: 41/20.1.2/0963

AURO-AMOXICLAV 250-62.5 mg/5 ml: 41/20.1.2/0964

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

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