APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

AURO AMOXICLAV 375 mg (Tablet)

AURO AMOXICLAV 625 mg (Tablet)

AURO AMOXICLAV 1 000 mg (Tablet)

COMPOSITION:

AURO AMOXICLAV 375 mg:

Each film-coated tablet contains Amoxicillin Trihydrate equivalent to 250 mg Amoxicillin, and Potassium Clavulanate equivalent to 125 mg Clavulanic acid.

AURO AMOXICLAV 625 mg:

Each film-coated tablet contains Amoxicillin Trihydrate equivalent to 500 mg Amoxicillin, and Potassium Clavulanate equivalent to 125 mg Clavulanic acid.

AURO AMOXICLAV 1 000 mg:

Each film-coated tablet contains Amoxicillin Trihydrate equivalent to 875 mg Amoxicillin, and Potassium Clavulanate equivalent to 125 mg Clavulanic acid.

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.) The clavulanic acid component has very little bactericidal action.

Pharmacokinetics:

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. Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation. 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 incubation 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.

AURO AMOXICLAV 1000 mg should not be used in patients with a glomerular filtration rate of less than 30 ml/minute.

Special Precautions:

Caution is needed when administering amoxicillin 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.

The sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.

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 leukaemia 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 Administration).**

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 and appropriateness of therapy.

INTERACTIONS:

Probenecid decreases the renal tubular secretion of amoxicillin, but does not affect clavulanic acid excretion. Concurrent use with **AURO AMOXICLAV** may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

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

The concomitant administration of allopurinol and ampicillin 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 amoxicillin by nursing mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant.

DOSAGE AND DIRECTIONS FOR USE:

For Oral Formulations:

Tablets should be taken immediately before a meal.

Dosages:

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.

Adults:

The adult dose of **AURO AMOXICLAV** is one **AURO AMOXICLAV 375 mg** tablet every eight hours at the start of a meal. For more severe infections and infection of the respiratory tract, the dose should be one **AURO AMOXICLAV 625 mg** tablet every eight hours at the start of a meal, or one **AURO AMOXICLAV 1000 mg** tablet every 12 hours at the start of a meal.

Since **AURO AMOXICLAV 375 mg, 625 mg and 1000 mg** tablets contain the same amount of clavulanic acid (125 mg as the potassium salt) two **AURO AMOXICLAV 325 mg** tablets are not equivalent to one **AURO AMOXICLAV 625 mg** tablet, and two **AURO AMOXICLAV 625 mg** tablets are not equivalent to one **AURO AMOXICLAV 1000 mg.** Therefore, two **AURO AMOXICLAV 375 mg** tablets should not be substituted for one **AURO AMOXICLAV 625 mg** tablet or two **AURO AMOXICLAV 625 mg** tablets for one **AURO AMOXICLAV 1 000 mg** tablet for the treatment of more severe infections.

Impaired renal function:

Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increases in patients with renal failure. Therefore, the dose may need to be reduced or the interval extended.

Dosage adjustments are based on the maximum recommended level of amoxicillin. The following schedule is proposed:

AURO AMOXICLAV 375 mg, 625 mg:

Mild impairment (creatinine clearance greater than 30 ml/minute): no change in dosage.

Moderate impairment (creatinine clearance 10 to 30 ml/minute): 1 tablet every 12 hours.

Severe impairment (creatinine clearance less than 10 ml/minute): half a tablet every 12 hours.

AURO AMOXICLAV 1 000 mg should not be used in patients with glomerular filtration rate of less than 30 ml/minute.

Haemodialysis decreases serum concentrations of both amoxicillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

Dosage Guide:

Amoxicillin-Sensitive Organisms

Product	Upper Respiratory Tract Infection	Lower Respiratory Tract Infection	Urinary Tract Infection	Skin & Soft Tissue infections
AURO-AMOXICLAV 375 mg	1 Tablet 8 hourly	—	1 Tablet 8 hourly	1 Tablet 8 hourly
AURO-AMOXICLAV 625 mg	1 Tablet 8 hourly	1 Tablet 8 hourly	1 Tablet 8 hourly	1 Tablet 8 hourly
AURO-AMOXICLAV 1 000 mg	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly

Amoxicillin-Resistant Organisms

Product	Upper Respiratory Tract Infection (Otitis media)	Lower Respiratory Tract Infection (Bronchitis)	Urinary Test infection	Skin & Soft Tissue infections
AURO-AMOXICLAV 375 mg	—	—	1 Tablet 8 hourly	1 Tablet 8 hourly
AURO-AMOXICLAV 625 mg	1 Tablet 8 hourly	1 Tablet 8 hourly	1 Tablet 8 hourly	1 Tablet 8 hourly
AURO-AMOXICLAV 1 000 mg	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly

Children:

The dose of **AURO AMOXICLAV** in children is 25 - 50 mg/kg/day of the 4 parts amoxicillin, 1 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.

SIDE EFFECTS:

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

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 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, urticaria, serum sickness-like syndrome, erythema

multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

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: Interstitial nephritis, hypersensitivity vasculitis, bullous exfoliative dermatitis

Gastrointestinal disorders:

Frequent: Nausea, vomiting, diarrhoea,

Less frequent: glossitis, black 'hairy' tongue, mucocutaneous candidiasis

The following side effects have been reported and frequencies are unknown: gastritis, stomatitis, enterocolitis, and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis).

If gastro-intestinal reactions are evident, they may be reduced by taking **AURO AMOXICLAV** at the start of a meal.

Hepato-biliary disorders:

Less frequent: Hepatitis, cholestatic jaundice

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.**

Renal and urinary disorders:

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

Blood and the lymphatic system disorders:

Less frequent: reversible leucopenia

The following side effects have been reported and frequencies are unknown: Haemolytic anaemia, prolongations of bleeding time and prothrombin time, reversible thrombocytopenia, *thrombocytopenic purpura, eosinophilia, agranulocytosis.

These reactions are usually reversible on discontinuation of therapy and are believed to be

hypersensitivity phenomena. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

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, dizziness.

General disorders and administration site disorders:

The following side effects have been reported and frequencies are unknown: Superficial tooth discolouration, especially with the suspension and chewable tablet formulations.

It can usually be removed by brushing.

Investigations

A moderate raise in Aspartate transaminase (AST) and/or Alanine transaminase (ALT) has been noted in patients treated with **AURO AMOXICLAV**, but the significance of these findings is unknown.

A slight thrombocytosis was noted in less than 1 % of the patients treated with **AURO AMOXICLAV**.

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 375 mg:

White oval shaped film coated tablets, debossed with 'A' on one side and '63' on the other side.

AURO AMOXICLAV 625 mg

White oval shaped film coated tablets, debossed with 'A' on one side and '64' on the other side.

AURO AMOXICLAV 1000 mg:

White coloured, capsule shaped, film coated tablets, debossed with 'A' on one side and with a score line in between '6' and '5' on the other side.

PRESENTATION:

AURO AMOXICLAV 375 mg:

Tablets are packed in 25 micron Polyamide / 45 micron Aluminium foil / 60 micron PVC film (width 138 mm) as the forming material and 25 micron Printed Aluminium foil (width 138 mm) as the lidding material. Each blister contains 5 tablets.

Pack size: 15's: Each carton contains 3 blisters of 5 tablets each.

Pack size: 100's: Each carton contains 20 blisters of 5 tablets each.

AURO AMOXICLAV 625 mg:

Tablets are packed in 25 micron Polyamide / 45 micron Aluminium foil / 60 micron PVC film (width 138 mm) as the forming material and 25 micron Printed Aluminium foil (width 138 mm) as the lidding material. Each blister contains 5 tablets.

Pack size: 15's: Each carton contains 3 blisters of 5 tablets each.

AURO AMOXICLAV 1 000 mg:

1. Tablets are packed in 25 micron Polyamide / 45 micron Aluminium foil / 60 micron PVC film (width 138 mm) as the forming material and 25 micron Printed Aluminium foil (width 138 mm) as the lidding material. Each blister contains 5 tablets.

Pack size: 10's: Each carton contains 2 blisters of 5 tablets each.

2. Tablets are packed in printed 40 micron Aluminium foil laminated with 150-gauge poly on one side and plain 40 micron Aluminium foil laminated with 150-gauge poly on other side. Each strip contains 10 tablets.

Pack size: 10's: One strip pack containing tablets.

STORAGE INSTRUCTIONS:

Store at or below 30 °C. Do not remove blister from carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

AURO AMOXICLAV 375 mg: 41/20.1.2/0535

AURO AMOXICLAV 625 mg: 41/20.1.2/0536

AURO AMOXICLAV 1 000 mg 41/20.1.2/0537

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

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