Applicant: Aurogen South Africa (Pty) LTD
Product Name: AURO AMPICILLIN 500 mg/ 1000 mg
Dosage form and strength: INJECTION 500 mg/ 1000 mg

PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

AURO AMPICILLIN INJECTION 500 mg (Powder for injection)

AURO AMPICILLIN INJECTION 1000 mg (Powder for injection)

COMPOSITION:

AURO AMPICILLIN INJECTION 500 mg is available in vials containing the equivalent of 500 mg ampicillin as ampicillin sodium, presented as a powder for reconstitution. Sugar free.

AURO AMPICILLIN INJECTION 1000 mg is available in vials containing the equivalent of 1000 mg ampicillin as ampicillin sodium, presented as a powder for reconstitution. Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION:

Ampicillin for injection has *in vitro* bactericidal activity against a broad spectrum of non-penicillinase-producing gram-positive and gram-negative organisms. Ampicillin inhibits the bacterial cell wall from forming, by specifically inhibiting the activity of transpeptidase enzymes, which catalyse cross-linkage of the glycopeptide polymer unit that forms the cell wall.

In vitro sensitivity does not necessarily imply in vivo efficacy.

Pharmacokinetics:

Intramuscular injection of 0,5 or 1 g of sodium ampicillin yields peak plasma concentrations of about 7 or 10 micrograms per ml, respectively, at 1 hour; these decline exponentially, with a half-time of approximately 80 minutes. Severe renal impairment markedly prolongs the persistence of ampicillin in the plasma. Peritoneal dialysis is ineffective in removing ampicillin from the blood, but haemodialysis removes about 40 % of the body store in about 7 hours. Adjustment of the dose of ampicillin is

required in the presence of renal dysfunction. Ampicillin appears in the bile, undergoes enterohepatic circulation, and is excreted in appreciable quantities in the faeces.

Ampicillin is metabolised to some extent to penicilloic acid which is excreted in the urine.

Renal clearance of ampicillin occurs partly by glomerular filtration and partly by tubular secretion. Following parenteral administration about 60 to 80 % is excreted in the urine within 6 hours. Ampicillin is removed by haemodialysis. High concentrations are reached in the bile; it undergoes enterohepatic recycling and some is excreted in the faeces. Ampicillin is widely distributed and therapeutic concentrations can be achieved in ascitic, pleural, and joint fluids. It crosses the placenta into the foetal circulation and small amounts are distributed into breast milk. There is little diffusion into the CSF except when the meninges are inflamed. About 20 % is bound to plasma proteins and the plasma half-life is about 1 to 1,5 hours. The half-life may be increased in neonates and the elderly; in renal impairment half-lives of 7 to 20 hours have been reported.

INDICATIONS:

AURO AMPICILLIN INJECTION is indicated for the treatment of bacterial infections caused by non-penicillinase- producing ampicillin-sensitive organisms. **AURO AMPICILLIN INJECTION** is effective in conditions caused by:

- Gram-positive non-penicillinase producing staphylococci, haemolytic and non-haemolytic streptococci, *Diplococcus pneumoniae, Clostridium species* and *Streptococcus faecalis.*
- Gram-negative cocci *Neisseria species*.,*H.influenzae, E.coli, Proteus mirabilis* and many strains of brucellae, *Salmonellae* and *Shigellae*.

Parenteral usage is indicated where oral dosage is inappropriate.

CONTRA-INDICATIONS:

AURO AMPICILLIN INJECTION should not be given to:

- Patients known to be hypersensitive or allergic to penicillins or cephalosporins (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).
- Babies in the neonatal period, born to mothers hypersensitive to ampicillin.
- Safety in pregnancy and lactation has not been established (see "**PREGNANCY AND LACTATION"**).

Applicant: Aurogen South Africa (Pty) LTD
Product Name: AURO AMPICILLIN 500 mg/ 1000 mg
Dosage form and strength: INJECTION 500 mg/ 1000 mg

WARNINGS AND SPECIAL PRECAUTIONS:

Serious and occasionally fatal hypersensitivity (severe anaphylactic) reactions have been reported in patients on ampicillin/penicillin therapy. Before initiating therapy with **AURO AMPICILLIN INJECTION,** careful enquiry should be made concerning previous hypersensitivity or allergic reactions to penicillins, cephalosporins or other allergies.

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 that have experienced severe reactions when treated with cephalosporins. Resuscitative equipment should be available when **AURO AMPICILLIN INJECTION** is to be administered, and patients should be observed for at least one hour after administration of **AURO AMPICILLIN INJECTION**. If an allergic reaction occurs, **AURO AMPICILLIN INJECTION** should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine), oxygen, intravenous steroids, anti-histamines and airway management, including intubation.

Use with caution in patients with known history of allergy. Caution is needed when administering **AURO AMPICILLIN INJECTION** to patients with syphilis as the Jarisch- Herxheimer reaction may occur shortly after commencing treatment in these patients. This reaction, which manifests in fever, chills, headache and reactions at the site of the lesion, may be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

AURO AMPICILLIN INJECTION should be discontinued if a skin rash occurs. It should preferably be avoided if infectious mononucleosis, lymphatic leukemia or possibly HIV infection is suspected and also in patients receiving allopurinol treatment, because of an increased risk of rashes associated with these conditions, following the administration of **AURO AMPICILLIN INJECTION**.

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

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported. Increases in the INR have been reported in patients receiving **AURO AMPICILLIN INJECTION**. 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.

AURO AMPICILLIN INJECTION should not be mixed in the same syringe or administration set with aminoglycosides such as gentamycin, as substantial inactivation of the aminoglycosides may result, or with other beta-lactam antibacterials such as cephalosporins, as substantial mutual inactivation may result. If these groups of antibacterials are to be administered concurrently, they should be administered in separate sites, at least 1 hour apart.

The meningococcal carrier state is not eliminated by **AURO AMPICILLIN INJECTION** therapy.

Sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary. Do not add to containers of infusions containing dextrose. It may be piggybacked via the same administration set. Caution is required when administering **AURO AMPICILLIN INJECTION** 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. Dosage should be adjusted in patients with renal impairment.

There have been rare reports of paraesthesia following long-term administration.

The use of lignocaine together with AURO AMPICILLIN INJECTION should be considered only when administering an intramuscular injection, and must not be given intravenously.

Effects on ability to drive and use machines:

AURO AMPICILLIN INJECTION may cause drowsiness and dizziness. Patients should be advised to exercise caution until you know how the medicine affects them.

INTERACTIONS:

AURO AMPICILLIN INJECTION should not be mixed in the same syringe or administration set with aminoglycosides such as gentamycin, as substantial inactivation of the aminoglycosides may result, or with other beta-lactam antibacterials such as cephalosporins, as substantial mutual inactivation may result. If these groups of antibacterials are to be administered concurrently, they should be administered at separate sites, at least 1 hour apart (see **"WARNINGS AND SPECIAL PRECAUTIONS"**).

AURO AMPICILLIN INJECTION markedly decreases the clearance of methotrexate given intravenously for the treatment of neoplasms, which may result in toxicity. Patients should be closely

monitored; and leucovorin doses may need to be increased and administered for longer periods of time. Concurrent use of **AURO AMPICILLIN INJECTION** with ACE inhibitors, potassium-sparing diuretics, potassium- containing medications or potassium supplements may promote serum potassium accumulation with possible resultant hyperkalaemia, especially in patients with renal insufficiency; concurrent administration with ACE inhibitors may result in hyperkalaemia since reduction of aldosterone production induced by ACE inhibitors may lead to elevation of serum potassium. Concurrent use of medication with an antiplatelet function with **AURO AMPICILLIN INJECTION** may increase the risk of haemorrhage due to additive inhibition of platelet aggregation. In addition, hypoprothrombinaemia induced by large doses of salicylates, and the gastrointestinal ulcerative or haemorrhagic potential of NSAIDs or salicylates may also increase the risk of haemorrhage when these medications are used concurrently with **AURO AMPICILLIN INJECTION**.
Patients receiving anticoagulants, heparin or thrombolytic agents may experience a prolonged INR and bleeding following treatment with **AURO AMPICILLIN INJECTION**.
AURO AMPICILLIN INJECTION may reduce the efficacy of oral contraceptives and patients should be warned accordingly to use alternative or additional measures of contraception.
The concomitant administration of allopurinol and **AURO AMPICILLIN INJECTION** substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving ampicillin alone. This is especially so for hyperuricemic patients. It is not known whether this potentiation of rashes is due to allopurinol or the hyperuricaemia present in these patients.
No information is available about the concurrent use of **AURO AMPICILLIN INJECTION** and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram- like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with **AURO AMPICILLIN INJECTION**.
It is recommended that when testing for the presence of glucose in urine during treatment with **AURO AMPICILLIN INJECTION**, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of penicillins such as **AURO AMPICILLIN INJECTION**, false positive or falsely elevated readings are common with chemical methods such as copper sulphate. An increase in INR has been associated with intravenous administration of some penicillins such as **AURO AMPICILLIN INJECTION**.

Applicant: Aurogen South Africa (Pty) LTD
Product Name: AURO AMPICILLIN 500 mg/ 1000 mg
Dosage form and strength: INJECTION 500 mg/ 1000 mg

PREGNANCY AND LACTATION:

Safety in pregnancy and lactation has not been established.

Animal studies with **AURO AMPICILLIN INJECTION** have shown no teratogenic effects.

Use in lactation:

Small amounts of **AURO AMPICILLIN INJECTION** is distributed into breast milk. The use of **AURO AMPICILLIN INJECTION** by breast-feeding mothers may lead to sensitization, diarrhoea, candidiasis and skin rash in the infant.

DOSAGE AND DIRECTIONS FOR USE:

Recommended Adult Dosage:

Adults (including elderly patients): 500 - 1000 mg 4 - 6 times a day intravenously for as long as IV therapy is required.

Meningitis: 2 g six-hourly intravenously. (Children.s dosage: 150 mg/kg daily intravenously in 4 divided doses). In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose must be administered for at least 10 days.

The above dosages may be increased in particularly severe infections.

Children < 20 kg:

10 - 25 mg/kg 6 hourly.

Children ≥ 20 kg:

Adult dose.

Meningitis or severe infections:

50 mg/kg 6 hourly.

Neonates:

5 mg/kg/dose (meningitis: 100 mg/kg/dose) 12 hourly in the first week of life, and then 8 hourly. Then 1 - 3 mg/kg/dose 6 hourly.

Administration:

Intramuscular: 500 mg, 1 g - add 1,5 to 2,0 ml Water for Injections.

Intravenous: Dissolve the contents of a vial in the specified volume of Water for Injections: 500 mg -

10,0 ml; 1 g - 20,0 to 30,0 ml. The intravenous dose is given by slow injection (3 - 4 minutes) but may also be added to infusion fluids or be injected, suitably diluted, into the drip tube over 3 - 4 minutes - refer to table under “Stability”.

Intraperitoneal: Dialysis: 50 mg per litre of dialysate.

Therapeutic: Dissolve 500 mg in 5 to 10 ml Water for Injections.

Intrapleural: Dissolve 500 mg in 5 to 10 ml Water for Injections.

Intra-Articular: 50 - 100 mg/ml of Water for Injections or 0,5 % lignocaine hydrochloride to make up to volume of 2,5 ml.

Sub-Conjunctival: Dissolve 100 mg in 0,5 ml Water for Injections.

Topical: Sprinkle 500 mg to 1 g dry powder extraperitoneally before closure and suturing.

Stability and Injectable solution: Only freshly prepared solutions should be used (see “**Reconstitution and storage instructions”**).

Compatibility:

Intravenous infusion : AURO AMPICILLIN INJECTION is compatible with the following intravenous fluids, but solutions must be used within the periods shown below.

Table: Period of stability of AURO AMPICILLIN INJECTION intravenous infusion solutions at room temperature.

Normal Saline	6 - 8 hours
5 % Dextrose	1 hour
Dextrose saline	1 hour
Ringer’s solution	6 - 8 hours
1,4 % Sodium bicarbonate	4 hours

AURO AMPICILLIN INJECTION should not be added to infusion bottles containing Dextran 40 Injection but may be injected into the drip tubing of such an infusion.

Blood and Plasma: A dilute solution (i.e. 500 mg dissolved in 20 ml Water for Injections) should be injected slowly into the drip tubing rather than added to the infusion bottle.

Applicant: Aurogen South Africa (Pty) LTD
Product Name: AURO AMPICILLIN 500 mg/ 1000 mg
Dosage form and strength: INJECTION 500 mg/ 1000 mg

Reconstitution and storage instructions:

Reconstitute the powder using a suitable sterile diluent.

When prepared for intramuscular or direct intravenous injection, **AURO AMPICILLIN INJECTION** should be administered immediately after reconstitution.

Do not freeze.

NB: AURO AMPICILLIN INJECTION VIALS ARE NOT SUITABLE FOR MULTIDOSE USE.

SIDE-EFFECTS:

Hypersensitivity reactions:

If any hypersensitivity reaction occurs, treatment should be discontinued immediately.

Less frequent:

Severe allergic reactions including angioneurotic oedema, anaphylaxis, serum sickness and vasculitis have been reported. Skin rashes such as erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis and bullous and exfoliative dermatitis and other skin rashes have been reported.

A generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia can develop within a few hours to several weeks after starting treatment.

Interstitial nephritis can occur.

Infections and infestations:

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

Caution is needed when administering **AURO AMPICILLIN INJECTION** to patients with syphilis as the Jarisch- Herxheimer reaction may occur shortly after commencing treatment in these patients. This reaction, which manifests in fever, chills, headache and reactions at the site of the lesion, may be

dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

Superinfection by resistant species such as pseudomonas or candida, which do not respond to therapy with **AURO AMPICILLIN INJECTION** may occur.

Blood and the lymphatic system disorders:

Less frequent:

Leucopenia, thrombocytopenia, and coagulation disorders such as prolongation of bleeding time and defective platelet function have been reported in patients receiving prolonged high dosage of parenteral benzylpenicillin sodium such as **AURO AMPICILLIN INJECTION**, e.g. in subacute bacterial endocarditis.

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

Haemolytic anaemia, granulocytopenia and agranulocytosis have been reported in patients receiving prolonged high dosage of parenteral benzylpenicillin sodium such as **AURO AMPICILLIN INJECTION**, e.g. in subacute bacterial endocarditis.

Disturbances of blood electrolytes may follow administration of large doses of **AURO AMPICILLIN INJECTION**.

Haematological parameters should be monitored during prolonged and high dose therapy.

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

Investigations:

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

Disturbances of blood electrolytes may follow administration of large doses of **AURO AMPICILLIN INJECTION**

and may interfere with some diagnostic tests, such as those for urinary glucose using copper sulphate, direct anti- globulin (Coombs.) tests, and some tests for urinary or serum proteins. **AURO AMPICILLIN INJECTION** may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.

Metabolism and nutrition disorders:

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

Nervous system disorders:

Less frequent:

Convulsions.

Intrathecal administration of **AURO AMPICILLIN INJECTION** is not used, since it may precipitate convulsions when given by this route.

Convulsions and other signs of toxicity to the central nervous system may occur particularly with intravenous administration, in those receiving high doses or in patients with impaired renal function or renal failure.

There have been rare reports of paraesthesia following long-term administration.

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

Hyperkinesia and dizziness may occur.

Gastrointestinal disorders:

Frequent:

Nausea, vomiting and diarrhoea.

Less frequent:

Antibiotic-associated colitis (pseudomembranous colitis) has been reported.

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

Stomatitis, glossitis, black hairy tongue and heartburn have been reported.

Mucocutaneous candidiasis and antibiotic-associated colitis (haemorrhagic colitis) has been reported.

Hepato-billiary disorders:

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

A moderate rise in liver enzyme (aspartate transaminase (AST) and/or alanine transaminase (ALT) values has been noted, but the significance of this is unclear. Hepatitis and cholestatic jaundice have been reported.

Skin and subcutaneous tissue disorders:

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

Contact with **AURO AMPICILLIN INJECTION** should be avoided since skin sensitisation may occur.

Renal and urinary disorders:

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

Crystalluria has been reported. When high doses are administered, adequate fluid intake and urinary output must be maintained. Dosage should be adjusted in patients with renal impairment.

Massive doses of sodium penicillins such as **AURO AMPICILLIN INJECTION** may cause hypokalaemia and sometimes hypernatraemia. Use of a potassium sparing diuretic may be helpful.

Care should be taken when high doses of **AURO AMPICILLIN INJECTION** are given to patients with renal impairment (due to the risk of neurotoxicity) or congestive heart failure. In the presence of impaired renal function large doses of **AURO AMPICILLIN INJECTION** (e.g. more than 8 g per day in an adult) may cause cerebral irritation, convulsions and coma. Renal systems should be monitored during prolonged and high dose therapy.

Applicant: Aurogen South Africa (Pty) LTD
Product Name: AURO AMPICILLIN 500 mg/ 1000 mg
Dosage form and strength: INJECTION 500 mg/ 1000 mg

General disorders and administration site conditions:

The use of lignocaine or benzyl alcohol together with AURO AMPICILLIN INJECTION must be used only when administering an intramuscular injection, and not given intravenously.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdosage with ampicillins such as **AURO AMPICILLIN INJECTION** is usually asymptomatic. 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 crystalluria.

AURO AMPICILLIN INJECTION may be removed from the circulation by haemodialysis. Peritoneal dialysis is not effective in the removal thereof. Treatment is symptomatic and supportive (see **"SIDE EFFECTS"**).

IDENTIFICATION:

AURO AMPICILLIN INJECTION 500 mg:

White to off white crystalline powder filled in 7.5 ml tubular vial, stoppered with 20 mm grey colour bromo butyl rubber stopper and sealed with 20 mm dark green colour PP disc.

AURO AMPICILLIN INJECTION 1000 mg:

White to off white crystalline powder filled in 7.5 ml tubular vial, stoppered with 20 mm grey colour bromo butyl rubber stopper and sealed with 20 mm dark blue colour PP disc.

PRESENTATION:

AURO AMPICILLIN INJECTION 500 mg:

7.5 ml clear transparent tubular glass vial fitted with a 20 mm grey colour bromo butyl rubber stopper and sealed with a 20 mm dark green colour PP disc.

AURO AMPICILLIN INJECTION 1000 mg:

Applicant: Aurogen South Africa (Pty) LTD
Product Name: AURO AMPICILLIN 500 mg/ 1000 mg
Dosage form and strength: INJECTION 500 mg/ 1000 mg

7.5 ml clear transparent tubular glass vial fitted with a 20 mm grey colour bromo butyl rubber stopper and sealed with a 20 mm dark blue colour PP disc.

Pack size:

1. Single vial packed in a printed carton with a package insert.
2. 10 Vials packed in a plain E-fluted box with partition and pack insert.
3. 50 Vials packed in a plain E-fluted box with partition and pack insert.
4. 100 Vials packed in a plain E-fluted box with partition and pack insert.

STORAGE INSTRUCTIONS:

Store at or below 30 °C in a dry place.

Protect from light.

When prepared for intramuscular or direct intravenous injection **AURO AMPICILLIN INJECTION** should be administered immediately after reconstitution.

Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

Discard any unused portion(s).

REGISTRATION NUMBER:

Auro Ampicillin Injection 500 mg: 41/20.1.2/0122

Auro Ampicillin Injection 1000 mg: 41/20.1.2/0123

Applicant: Aurogen South Africa (Pty) LTD
Product Name: AURO AMPICILLIN 500 mg/ 1000 mg
Dosage form and strength: INJECTION 500 mg/ 1000 mg

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

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building No.1, First Floor,

53 Phillip Engelbrecht Avenue, Meyersdal Ext. 12,

Johannesburg,1448,

South Africa.

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

02 February 2022