SCHEDULING STATUS: S4

1. NAME OF MEDICINE

AMPICILLIN 250 INJECTION UNIMED

AMPICILLIN 500 INJECTION UNIMED

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

AMPICILLIN 250 INJECTION UNIMED

Each vial contains: Ampicillin sodium BP equivalent to ampicillin anhydrous 250 mg.

AMPICILLIN 500 INJECTION UNIMED

Each vial contains: Ampicillin sodium BP equivalent to ampicillin anhydrous 500 mg.

Excipients: None.

Sugar free

3. PHARMACEUTICAL FORM

AMPICILLIN 250 INJECTION UNIMED:

White to off-white crystalline, odourless, hygroscopic powder in a 5 ml clear glass USP type III vial sealed with a grey butyl rubber plug and tear off golden yellow aluminium seal.

AMPICILLIN 500 INJECTION UNIMED:

White to off-white crystalline, odourless, hygroscopic powder in a 5 ml clear glass USP type III vial sealed with a grey butyl rubber plug and tear off silver aluminium seal.

After reconstitution, a clear, colourless to pale yellow solution, free from visible particles is formed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMPICILLIN INJECTION UNIMED (ampicillin) is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Infections of the genitourinary tract caused by *E coli*, *P. mirabilis* and *enterococci*.

Respiratory tract and ENT infections e.g. pharyngitis, tonsillitis, sinusitis, laryngitis, otitis media, bronchitis, pneumonia caused by various bacteria including non-penicillinase-producing *H. influenzae*, *staphylococci*, and *streptococci* including *Streptococcus pneumoniae*.

Infections of the gastro-intestinal tract *caused by Shigella, S. typhosa and other Salmonella*, *E. coli*, *P. mirabilis*, and *enterococci*.

Meningitis - *N. meningitidis* (after confirmation by sensitivity testing).

Miscellaneous infections e.g. Septicaemia, endocarditis and biliary tract infections. Skin and soft tissue infections, bacteremia and as an adjunct in the treatment of sepsis caused by Gram-negative bacteria.

4.2 Posology and method of administration

Dosage varies with the type and the severity of the infection, renal function, and age. Doses for children should not exceed doses recommended for adults.

Parenteral administration is reserved for severe infections that cannot be treated by oral ampicillin.

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 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.

Renal impairment

Dosage should be adjusted in patients with renal impairment.

Method of administration

DIRECTIONS FOR USE OF PARENTERAL AMPICILLIN INJECTION UNIMED:

Use only freshly-prepared solutions.

Intramuscular use: Dissolve 250 mg or 500 mg in 1 to 2 ml of sterile water for injection and withdraw the entire contents.

Direct intravenous injection: Dissolve 250 mg or 500 mg in 5 to 10 ml of sterile water for injection. Administer the dose by slow injection over a period of 3 to 5 minutes.

Intravenous drip: Stability studies on ampicillin sodium at concentration of 2 mg/ml and 30 mg/ml in various intravenous solutions indicate that the medicine will lose less than 10 % activity at room temperature (25 °C) for the time periods stated below:

Isotonic sodium chloride: 8 hours

5 % Dextrose in water: 4 hours

10 % Invert sugar in water: 4 hours

M/6 Sodium lactate solution (in concentration of 30 mg/ml): 8 hours

4.3 Contraindications

— AMPICILLIN INJECTION UNIMED is contraindicated in individuals with a history of a previous hypersensitivity reaction to any of the pencillins, such as ampicillin in AMPICILLIN INJECTION UNIMED**.**

— Patients allergic to cephalosporins or cephamycins may be allergic to penicillins, such as ampicillin in AMPICILLIN INJECTION UNIMED also.

— It is contraindicated in babies born of hypersensitive mothers in the neonatal period.

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity (severe anaphylactic) reactions have been reported in patients on ampicillin/penicillin therapy. Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). Careful history of sensitivity to allergens, including previous hypersensitivity reactions to penicillins and cephalosporins should be taken before instituting therapy with AMPICILLIN INJECTION UNIMED.

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 AMPICILLIN INJECTION UNIMED is to be administered, and patients should be observed for at least one hour after administration of AMPICILLIN INJECTION UNIMED. If an allergic reaction occurs, AMPICILLIN INJECTION UNIMED 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.

Care should be taken when treating patients with syphilis, as the Jarisch-Herxheimer reaction may occur shortly after starting treatment. This reaction, manifesting as fever, chills, headache and reactions at the site of the lesion, can be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

AMPICILLIN INJECTION UNIMED should be discontinued if any 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 AMPICILLIN INJECTION UNIMED.

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

In prolonged therapy, and particularly with high dosage regimens, periodic evaluation of the renal, hepatic and hematopoietic systems is recommended. Care should be taken when high doses are given to patients with renal impairment (because of the risk of neurotoxicity) or

congestive heart failure. Dosage should be adjusted in patients with renal impairment (see section 4.2).

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported. It may range in severity from mild to life threatening. Increases in the INR have been reported in patients receiving AMPICILLIN INJECTION UNIMED. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. There have been rare reports of paraesthesia following long-term administration.

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

Paediatric use

Pencillins are excreted primarily unchanged by the kidney; therefore, the incompletely developed renal function in neonates and young infants will delay the excretion of ampicillin in AMPICILLIN INJECTION UNIMED. Administration to neonates and young infants should be limited to the lowest dosage compatible with an effective therapeutic regimen.

AMPICILLIN INJECTION UNIMED contains sodium

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

AMPICILLIN 250 INJECTION UNIMED: This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

AMPICILLIN 500 INJECTION UNIMED: This medicinal product contains 30,96 mg sodium per 500 mg vial, equivalent to 1.55 % of WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with other medicines and other forms

AMPICILLIN INJECTION UNIMED 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.

AMPICILLIN INJECTION UNIMED 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.

Probenecid may decrease renal tubular secretion of ampicillin resulting in increased blood levels and/or ampicillin toxicity.

AMPICILLIN INJECTION UNIMED may decrease the efficacy of oral contraceptives and increased breakthrough bleeding may occur.

Allopurinol increases possibility of skin rash, particularly in hyperuricemic patients, when AMPICILLIN INJECTION UNIMED is given concurrently. 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 AMPICILLIN INJECTION UNIMED 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 AMPICILLIN INJECTION UNIMED.

Chloramphenicol, erythromycin, sulfonamides, or tetracycline may interfere with the bactericidal effect of AMPICILLIN INJECTION UNIMED.

After treatment with AMPICILLIN INJECTION UNIMED, a false-positive reaction for glucose in the urine may occur with copper sulfate tests but not with enzyme based tests. Due to the high urinary concentrations of penicillins such as AMPICILLIN INJECTION UNIMED, false positive or falsely elevated readings are common with chemical methods such as copper sulphate.

Concurrent use of AMPICILLIN INJECTION UNIMED 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 AMPICILLIN INJECTION UNIMED 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 AMPICILLIN INJECTION UNIMED.

Patients receiving anticoagulants, heparin or thrombolytic agents may experience a prolonged INR and bleeding following treatment with AMPICILLIN INJECTION UNIMED.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy and lactation has not been established.

Animal reproduction studies with ampicillin as in AMPICILLIN INJECTION UNIMED have failed to demonstrate a risk to the foetus. There are no adequate and well controlled studies in pregnant women.

Lactation

Ampicillin-class antibiotics are excreted in milk. AMPICILLIN INJECTION UNIMED use by nursing mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash of infants. Use with caution when administered to lactating women.

Fertility

No fertility data is available.

4.7 Effects on ability to drive and use machines

Adverse effects on the ability to drive or operate machinery have not been observed.

Caution is advised for patients not to drive or use machines, until their individual susceptibility to the effects of AMPICILLIN INJECTION UNIMED is known.

4.8 Undesirable effects

Table 1: Tabulated list of adverse reactions		
System Organ Class	**Adverse reactions**	**Frequency**
Infections and infestations	Superinfection	Frequency unknown
Blood and Lymphatic system disorders**	Anaemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and granulocytopenia have been reported. Coagulation disorders such as prolongation of bleeding time and defective platelet function.	Less frequent
	Haemolytic anaemia, agranulocytosis	Frequency unknown
Immune system disorders*	Anaphylaxis, angioneurotic oedema, serum sickness and vasculitis.	Less frequent
	Jarisch- Herxheimer reaction (see section 4.4)	Frequency unknown
Renal and urinary disorders	Interstitial nephritis	Less frequent
	Crystalluria (including acute renal injury)	Frequency unknown
Nervous system disorders	Convulsions, paraesthesia	Less frequent
	Hyperkinesia and dizziness	Frequency unknown

Gastrointestinal disorders	Nausea, vomiting, diarrhoea	Frequent
	Antibiotic-associated colitis (pseudomembranous colitis)	Less frequent
	Stomatitis, glossitis, black hairy tongue and heartburn. Mucocutaneous candidiasis and antibiotic-associated colitis (haemorrhagic colitis)	Frequency unknown
Hepatobiliary disorders	A moderate rise in liver enzymes (AST and ALT). Hepatitis and cholestatic jaundice.	Frequency unknown
Skin and subcutaneous tissue disorders***	Skin rashes are most common side effects and are erythematous, pruritic and maculopapular. The rash which usually does not develop within the first week of therapy, may cover the entire body including the sole, palms, and oral mucosa.	Frequent
	Other hypersensitivity reactions that have been reported are skin rash, urticaria, erythema multiforme and an occasional case of exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis.	Less frequent

	Linear IgA disease	Frequency unknown
Cardiac Disorders	Kounis Syndrome	Frequency unknown
General disorders and administration site conditions	Other adverse reactions that have been reported with the use of AMPICILLIN INJECTION UNIMED are laryngeal stridor and high fever.	Less frequent
Investigations	Disturbances of blood electrolytes may follow administration of large doses of AMPICILLIN INJECTION UNIMED 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. AMPICILLIN INJECTION UNIMED may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.	Frequency unknown

***** A generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia can develop within a few hours to several weeks after starting treatment. If hypersensitivity reaction occurs, treatment should be discontinued immediately.

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is 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 Overdosage

In the event of overdosage, medicine should be discontinued and symptomatic and supportive measures should be instituted as required.

Overdosage with ampicillins such as AMPICILLIN INJECTION UNIMED 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. In patients with renal function impairment, ampicillin-class antibiotics can be removed by haemodialysis but not by peritoneal dialysis. Treatment is symptomatic and supportive).

5. PHARMACOLOGICAL PROPERTIES

A 20.1.2 Penicillins

5.1 Pharmacodynamic properties

A semi-synthetic aminopenicillin with an *in vitro* bactericidal action against a broad spectrum of non-penicillinase producing gram-positive and gram-negative pathogens.
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.

The following organisms are resistant to ampicillin: *Enterobacter*, *Pseudomonas*, *Klebsiella*, *Serratia*, *Acinetobacter* and indole-positive *Proteus.*

5.2 Pharmacokinetic properties

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 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

AMPICILLIN INJECTION UNIMED vials are not suitable for multidose use.

Do not add to containers of infusions containing dextrose. It may be piggybacked via the same administration set.

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.

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

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C, protected from moisture.

Use the prepared solution immediately.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

AMPICILLIN 250 INJECTION UNIMED: Carton containing 5, 50 or 100 clear glass USP type III vials.

AMPICILLIN 500 INJECTION UNIMED: Carton containing 5, 50 or 100 clear glass USP type III vials.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution: see section 4.2

7. HOLDER OF CERTIFICATE OF REGISTRATION

UNIMED HEALTHCARE (PTY) LTD

Corner Birch Road and Bluegum Avenue,

Anchorville,

Lenasia, 1827,

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Tel: +27 11 056 6999

8. REGISTRATION NUMBERS:

AMPICILLIN 250 INJECTION UNIMED: 30/20.1.2/0247

AMPICILLIN 500 INJECTION UNIMED: 30/20.1.2/0248

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

AMPICILLIN 250 INJECTION UNIMED: 21 June 1996

AMPICILLIN 250 INJECTION UNIMED: 21 June 1996

10. DATE OF REVISION OF TEXT

11 March 2025