PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S4**

1 NAME OF THE MEDICINE

AMPICILLIN 250 mg FRESENIUS (powder for solution for injection/infusion)

AMPICILLIN 500 mg FRESENIUS (powder for solution for injection/infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AMPICILLIN 250 mg INJECTION

Each vial contains ampicillin sodium equivalent to ampicillin 250 mg.

AMPICILLIN 500 mg INJECTION

Each vial contains ampicillin sodium equivalent to ampicillin 500 mg.

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A white powder in sealed vials.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

AMPICILLIN FRESENIUS is effective in conditions caused by the Gram-positive non-penicillinase producing Staphylococci, haemolytic and non-haemolytic streptococci, *Diplococcus pneumoniae, Clostridia sp*. and *Streptococcus faecalis*. Also the Gram-negative cocci *Neisseria* sp., *H. influenzae, E. coli, Proteus mirabilis* and many strains of Brucellae, Salmonellae and Shigellae. Parenteral usage is indicated where oral dosage is inappropriate.

4.2 Posology and method of administration

Posology

The usual dose for adults is 500 mg six-hourly. In severe infections this dose may be given up to 6 times in one day.

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose must be administered for at least 10 days.

Meningitis: 2 g six-hourly intravenously. (Children's dosage: 150 mg/kg daily intravenously in 4 divided doses).

The above dosages may be increased in particularly severe infections.

Paediatric population

The recommended intravenous and intramuscular dosages for children are ¼ to ¾ of the adult dose and are increased in relation to the age from infants to 15 years.

Children < 20 kg:

10 - 25 mg/kg six-hourly.

Children ≥ 20 kg:

Adult dose.

Meningitis or severe infections:

50 mg/kg six-hourly.

Neonates:

5 mg/kg/dose (meningitis: 100 mg/kg/day 12 hourly in the first week of life, and then eight-hourly. Then 1 - 3 g/kg/day six-hourly.

Method of administration

Intramuscular Use:

250 mg, 500 mg - add 1,5 to 2,0 mL water for injection.

Direct Intravenous Use:

Dissolve the contents of a vial in the specified volume of water for injection.

250 mg - 5,0 mL; 500 mg - 10,0 mL

If AMPICILLIN 250 mg FRESENIUS or AMPICILLIN 500 mg FRESENIUS is administered, administration should be by slow injection over a period of 3-4 minutes.

CAUTION: More rapid administration may result in convulsive seizures.

Intravenous Drip:

Reconstitute as directed above (Direct Intravenous Use) prior to diluting with Intravenous solution. Stability studies on ampicillin sodium at several concentrations in various intravenous solutions indicate the drug will lose less than 10 % activity at the temperatures noted for the time periods stated (see Table 1).

Intrathecal:

Intrathecal administration is not recommended, because it is a potent convulsant when given by this route.

Infants 0 to 2 years, 5 to 10 mg daily - dissolve in 0,5 mL.

*Single injection daily.

Children 2 to 12 years, 10 to 20 mg daily - dissolve in 0,5 to 1 mL.

*Single injection daily.

Adults up to 40 mg daily - dissolve in up to 2 mL.

*Single injection daily.

*(Only sterile solutions should be used i.e. water for injection, sterile normal saline or cerebrospinal fluid [CSF]).

Intraperitoneal:

Dialysis: 50 mg per litre of dialysate.

Therapeutic: Dissolve 500 mg in 5 to 10 mL water for injection

Intrapleural:

Dissolve 500 mg in 5 to 10 mL water for injection

Intra-articular:

50 - 100 mg/mL of water for injection or 0,5 lignocaine (lidocaine) hydrochloride to make up to volume of 2,5 mL.

Topical:

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

Stability and compatibility:

Injectable solution: Only freshly prepared solution should be used.

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

Table 1: Period of stability of AMPICILLIN FRESENIUS intravenous infusion solutions at room temperature

Normal saline	6 - 8 hours
5 % Dextrose	1 hour
Dextrose saline	1 hour
M/6 Sodium lactate	4 hours
Ringer's solution	6 - 8 hours
1,4 % Sodium bicarbonate	4 hours

AMPICILLIN FRESENIUS 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 injection) should be injected slowly into the drip tubing rather than added to the infusion bottle.

4.3 Contraindications

AMPICILLIN FRESENIUS should not be given to:

- patients known to be hypersensitive to penicillin or cephalosporins (see section 4.4)
- babies in the neonatal period, born to mothers hypersensitive to ampicillin
- Ocular administration

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Before initiating therapy with AMPICILLIN FRESENIUS, careful enquiries should be made concerning previous hypersensitivity or allergic reactions to penicillins, cephalosporins or other allergies. (see section 4.3). When administered to a patient with penicillin sensitivity, anaphylactic shock may occur. Cases of cross-sensitivity with cephalosporins and other penicillins have been reported.

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 FRESENIUS is to be administered, and patients should be observed for at least one hour after administration of AMPICILLIN FRESENIUS**.**

If an allergic reaction occurs, AMPICILLIN FRESENIUS should be discontinued and the appropriate therapy instituted.

SERIOUS ANAPHYLACTIC REACTIONS MAY REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH ADRENALINE (EPINEPHRINE), OXYGEN, INTRAVENOUS STREOIDS, ANTIHISTAMINES AND AIRWAY MANAGEMENT, INCLUDING INTUBATION SHOULD BE ADMINISTERED AS INDICATED. USE WITH CAUTION IN PATIENTS WITH KNOWN HISTORY OF ALLERGY.

Jarisch-Herxheimer reaction

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 optic atrophy.

Antibiotic associated diarrhoea and Clostridium difficile associated diarrhoea (CDAD)

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including AMPICILLIN FRESENIUS and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibacterial drug use.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Allergic skin reactions

A high percentage (43 to 100 percent) of patients with infectious mononucleosis develop a skin rash when treated with ampicillin, such as AMPICILLIN FRESENIUS. Typically, the rash appears 7 to 10 days after the start of oral ampicillin therapy and remains for a few days to a week after the drug is discontinued. In most cases, the rash is maculopapular, pruritic and generalized. Skin testing for hypersensitivity may be advisable before AMPICILLIN FRESENIUS is used in patients who have had penicillin rashes.
AMPICILLIN FRESENIUS should be discontinued if a skin rash occurs.

Ampicillin should preferably not be given to patients with infectious mononucleosis, lymphatic leukaemia, HIV infection and patients receiving allopurinol treatment because of an increased risk of developing skin rashes.

Neutropenia

Neutropenia has been widely reported in patients given high doses of beta lactam antibiotics, such as AMPICILLIN FRESENIUS, particularly in patients treated for 10 days or more. Monitoring of the leucocyte count is recommended during long-term treatment with high doses.

Renal impairment

Care should be taken when high doses are given to patients with renal impairment (because of the risk of neurotoxicity) or congestive heart failure. Renal and haematological systems should be monitored during prolonged and high dose therapy.

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

Electrolyte disturbance should be monitored when high doses are given due to the sodium content of AMPICILLIN FRESENIUS.

Hepatic impairment

Hepatitis and cholestatic jaundice have been reported less frequently with many penicillins. Hepatic status 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. Do not add to containers of infusions containing dextrose. It may be piggybacked via the same administration set.

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

Prolonged use may result in overgrowth of non-susceptible organisms. The medicine should be discontinued and specific or supportive therapy instituted.

Pseudomembranous enterocolitis has been reported.

Increases in the International Normalized Ratio (INR) have been reported in patients receiving AMPICILLIN FRESENIUS. 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.

AMPICILLIN FRESENIUS should not be mixed in the same syringe or administration set with aminoglycosides such as gentamycin, or with other beta-lactam antibacterials such as cephalosporins.

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

General

The possibility of superinfections with mycotic organisms or bacterial pathogens should be kept in mind during therapy. In such cases, discontinue the medication and substitute appropriate treatment.

Prescribing ampicillin for injection in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

Intrathecal administration is not recommended, because it is a potent convulsant when given by this route.

Information for Patients

Patients should be counselled that antibacterial medicines including ampicillin should only be used to treat bacterial Infections. They do not treat viral infections (e.g. the common cold).

When ampicillin is prescribed to treat a bacterial Infection, patients should be told that

although it is common to feel better early in the course of therapy, diarrhoea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (With or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests

Transient elevation of serum transaminase has been observed following administration of ampicillin. Assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during prolonged therapy.
The significance of this finding is not known.

Medicine/Laboratory Test Interactions

False positive glucose reactions may occur if Clinitest, Benedict's Solution, or Fehling's Solution are used.
Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be used.

4.5 Interaction with other medicines and other forms of interaction

Allopurinol

The concomitant administration of allopurinol and AMPICILLIN FRESENIUS substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving ampicillin alone. (see section 4.4) This is especially so for hyperuricaemic patients. It is not known whether this potentiation of rashes is due to allopurinol or the hyperuricaemia present in these patients.

Antibiotics

AMPICILLIN FRESENIUS 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.

Anticoagulants

Concurrent use of medication with an antiplatelet function with AMPICILLIN FRESENIUS may increase the risk of haemorrhage due to additive inhibition of platelet aggregation. (see section 4.4) 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 FRESENIUS. Patients receiving anticoagulants, heparin or thrombolytic agents may experience a prolonged INR and bleeding following treatment with AMPICILLIN FRESENIUS.

Oral contraceptives

AMPICILLIN FRESENIUS may decrease the efficacy of oestrogen-containing oral contraceptives.

Cytotoxic medicines

AMPICILLIN FRESENIUS 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.

Potassium levels

Concurrent use of AMPICILLIN FRESENIUS 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.

Interference with diagnostic tests

It is recommended that when testing for the presence of glucose in urine during treatment with AMPICILLIN FRESENIUS, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of penicillins such as AMPICILLIN FRESENIUS, 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 AMPICILLIN FRESENIUS.

Alcohol

No information is available about the concurrent use of AMPICILLIN FRESENIUS 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 FRESENIUS.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Breastfeeding

Safety in lactation has not been established.

Small amounts of AMPICILLIN FRESENIUS are distributed into breast milk. The use of AMPICILLIN FRESENIUS by breast-feeding mothers may lead to sensitization, diarrhoea,

candidiasis and skin rash in the infant.

4.7 Effects on ability to drive and use machines

No information available.

4.8 Undesirable effects

Summary of the safety profile (see also section 4.4).

Side effects are usually mild, transitory and infrequent and are similar to those found with other penicillins, however the administration of high doses to children may cause cerebral irritation and convulsions.

Hypersensitivity reactions:

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

Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effect**
Blood and lymphatic system disorders	Less frequent	Eosinophilia, leucopenia, thrombocytopenia, coagulation disorders
	Unknown	Haemolytic anaemia, granulocytopenia, agranulocytosis, disturbances of blood electrolytes
Hepatobiliary disorders	Unknown	Elevated Aspartate Transaminase (AST) levels, Elevated Alanine Transaminase (ALT) levels, hepatitis, cholestatic jaundice
Immune system disorders	Less frequent	Hypersensitivity, serum sickness
Infections and infestations	Unknown	Jarisch- Herxheimer resulting in fever, chills, headache and reactions at site of lesion
	Unknown	Superinfection (by resistant species such as pseudomonas or candida)

Investigations	Unknown	Disturbances of blood electrolytes, disturbance of diagnostic tests (urinary glucose using copper sulphate tests, direct anti-globulin-Coombs tests, urinary/serum protein tests, Guthrie tests for phenylketonuria)
Gastrointestinal disorders	Frequent	Nausea, vomiting, diarrhoea
	Less frequent	Antibiotic-associated colitis (pseudomembranous colitis)
	Unknown	Stomatitis, glossitis, black hairy tongue, sore mouth or tongue, pruritis ani, heartburn, mucocutaneous candidiasis, antibiotic-associated colitis (haemorrhagic colitis)
General disorders and administration site conditions	Less frequent	Fever, joint pains
Metabolism and nutrition disorders	Unknown	Electrolyte disturbances
Nervous system disorders	Less frequent	Convulsions, paraesthesia
	Unknown	Hyperkinesia, dizziness
Renal and urinary disorders	Less Frequent	Interstitial nephritis
	Unknown	Crystalluria, hypokalaemia, hypernatraemia, neurotoxicity, cerebral irritation, convulsions, coma
Skin and subcutaneous tissue disorders	Less frequent	Angioneurotic oedema, anaphylaxis
	Less frequent	Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous, exfoliative dermatitis, skin rash, pruritus, urticaria, purpura, erythema multiforme
Vascular disorders	Less	Vasculitis

	frequent	

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 Overdose

See section 4.8 for possible symptoms of overdosage.

In patients with renal impairment, because serum levels increase, dosage may be reduced if required. Should a serious allergic reaction occur, AMPICILLIN FRESENIUS should be discontinued and the patient treated specifically (antihistamines, pressor amines or corticosteroids).

Treatment is symptomatic and supportive.

Overdosage with ampicillins such as AMPICILLIN FRESENIUS 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.

AMPICILLIN FRESENIUS may be removed from the circulation by haemodialysis. Peritoneal dialysis is not effective in the removal thereof.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class of medicine: A.20.1.2. Penicillins

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* ACTIVITY.

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-life 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

No known excipients.

6.2 Incompatibilities

See Section 4.2.

6.3 Shelf life

Powder for Solution for injection

A shelf-life of 36 months is applicable when the products are stored at or below 30 °C in Glass vials.

Diluted Solution for injection

A shelf- life of 24 hours is applicable for the Concentrate for Solution for Infusion when stored at 2 °C to 8 °C (refrigerated condition) and 6 hours when stored at temperature 25 °C ± 2 °C and 30 °C ± 2 °C.

6.4 Special precautions for storage

Stored at or below 30 °C.

Protect from light.

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

Do not freeze.

Discard any unused portion(s).

6.5 Nature and contents of container

Vials of sterile white powder containing 250 mg or 500 mg ampicillin as ampicillin sodium,

packed in containers of 10 and 100.

The container closure system consists of clear glass vial type II, which after filling with the powder for injection/ infusion is closed with an elastomeric stopper.

The elastomeric stopper is an integral part of the closure for sterile and pyrogen-free parenteral powders for injection or infusion. The stopper comes into direct contact with the powder for injection or infusion. Besides closing the vial, it has the function to provide a seat for a hypodermic needle.

For the purpose of protecting the stopper surface from contamination and sealing the rubber stopper, an aluminium flip-off cap is used. It is not exposed to the powder. The cap is provided with a plastic lid as a safety device.

The container closure system guarantees a safe package of the drug product regarding tightness and protection from microbial contamination.

6.6 Special precautions for disposal and other handling

Reconstitution and storage instructions:

Reconstitute the powder using a suitable sterile diluent.

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

Do not freeze.

NB: AMPICILLIN FRESENIUS VIALS ARE NOT SUITABLE FOR MULTIDOSE USE

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

AMPICILLIN 250 mg FRESENIUS: H/20.1.2/25

AMPICILLIN 500 mg FRESENIUS: H/20.1.2/26

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 September 1975

10 DATE OF REVISION OF THE TEXT

04 September 2024