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Physician's Package Insert

עלון לרופא

PENIBRIN®

פניברין®

Powder for Solution for Injection

להזרקה לתוך השריר או לתוך הוריד

Composition

Each vial contains:

Active Ingredient

Ampicillin

500 mg, 1 g or 2 g

(as sodium salt)

Contains the sodium equivalent per vial as follows: Penibrin 500 mg: 1.431 mmol sodium, Penibrin 1 g: 2.862 mmol sodium, Penibrin 2 g: 5.723 mmol sodium

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: beta-lactam antibiotics, penicillins with extended spectrum.

ATC code: J01CA01

Ampicillin is a bactericidal broad-spectrum penicillin of the aminopenicillin group. Like other penicillins and cephalosporins, its mechanism of action is based on inhibition of cell wall synthesis.

EUCAST (The European Committee on Antimicrobial Susceptibility Testing) breakpoints:

Staphylococci, streptococci, *M. catarrhalis* and *H. influenzae* are normally considered to be susceptible at ≤ 1 mg/L and resistant at ≥ 2 mg/L, whilst *Enterobacteriaceae* and *Pseudomonas* spp. are considered to be susceptible at ≤ 8 mg/L and resistant at ≥ 16 mg/L.

Ampicillin - spectrum of activity:

The prevalence of resistance may vary geographically and with time for selected species. The information presented represents only an approximate guideline on the likelihood whether or not microorganisms may be susceptible to ampicillin.

Susceptible

Escherichia coli, *Proteus mirabilis*, *Salmonella* spp., *Shigella* spp., *Haemophilus influenzae*, *Bordetella pertussis*, Group A, B, C, G, H, L and M streptococci, *Streptococcus pneumoniae*, Group D streptococci (enterococci), Non-penicillinase-producing staphylococci, *Neisseria* spp., *Brucella* spp., *Erysipelothrix rhusiopathiae*, *Corynebacteria*, *Bacillus anthracis*, *Actinomycetes*, *Streptobacilli*, *Spirillum minus*, *Pasteurella multocida*, *Listeria* spp.

Organisms of the order *Spirochaetales* (e.g. *Leptospira* spp., *Treponema* spp., *Borrelia* spp. and other *Spirochaeta* spp.)

Anaerobes (e.g. peptococci, peptostreptococci, *Clostridium* spp., fusobacteria)

Resistant

Bacteroides fragilis, *Klebsiella*, *Enterobacter*, *Proteus vulgaris*, *Proteus rettgeri* and *morganii*, *Pseudomonas aeruginosa*, *Serratia marcescens*.

Beta-lactamase-(penicillinase)-producing staphylococci.

Pharmacokinetic properties

Absorption

Peak serum levels are reached within approximately 1 hour following I.M. administration.

Distribution

Diffusion into tissue and body fluids, including inflammatory exudates, is good. In patients with inflamed meninges, diffusion into cerebrospinal fluid is adequate for therapeutic purposes. In patients with normal liver function, high concentrations are reached in the bile. Ampicillin crosses the placenta and is excreted into breast milk. Plasma protein binding is low (about 15%).

Elimination

Ampicillin is mainly eliminated from the body via the kidneys, with a half-life of 1 to 2 hours. A large part (approximately 70%) of the administered dose is found in the urine in a therapeutically active form.

In cases of oliguria, the half-life may be prolonged to up to 8-20 hours. Half-life is also prolonged in neonates (2-4 hours).

Ampicillin is removed from the body by haemodialysis but not by peritoneal dialysis.

Indications

Penibrin injection is recommended in serious infections when prompt, effective levels of the antibiotic must reach the site of infection. Such infections include meningitis, subacute bacterial endocarditis, peritonitis, septicemia, severe forms of chronic bronchitis, osteomyelitis, pneumonia and pyelonephritis due to susceptible organisms.

Contraindications

Known hypersensitivity to ampicillin.

Proved and suspected hypersensitivity to β -lactam antibiotics, e.g. penicillins and cephalosporins.

Concomitant use of ampicillin in patients with infectious mononucleosis (glandular fever), cytomegalovirus infection or lymphatic leukaemia should be avoided, as skin reactions may occur more frequently in such cases.

Babies born to mothers with a history of hypersensitivity to penicillin.

History of jaundice or impaired liver function due to ampicillin use.

Warnings

Concomitant use of ampicillin in patients with infectious mononucleosis (glandular fever), cytomegalovirus infection or lymphatic leukaemia should be avoided, as the occurrence of skin reactions is more common in such cases.

Before the start of treatment with ampicillin, a careful history of previous hypersensitivity reactions to penicillins or cephalosporins should be taken. The possibility of a cross-allergy (10% – 15%) with cephalosporins should be considered.

Special care should be taken in patients with an allergic diathesis or bronchial asthma and patients with mycosis.

The patient should be informed about the possibility of allergic reactions and of the need to report these.

If an immediate-type allergy occurs (e.g. urticaria, anaphylaxis), therapy should be discontinued and the patient treated with the usual agents, such as adrenaline, antihistamines and corticosteroids.

Serious and occasionally even fatal hypersensitivity (anaphylactoid) reactions due to penicillin therapy have been reported. These reactions are more likely to occur in individuals with a history of hypersensitivity to penicillin and/or a history of sensitivity to multiple allergens.

There have been reports of individuals with a history of penicillin hypersensitivity who experienced severe reactions when treated with cephalosporins. Before initiating therapy with any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine, oxygen, intravenous steroids, and airway management including intubation.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin-class antibiotics should not be administered to patients with mononucleosis.

Administration of antibiotics alone for the treatment of cholangitis and cholecystitis is suitable only in milder cases without severe cholestasis.

Vigilance is required for a possible overgrowth of resistant organisms or fungi in long-term therapy. In the case of infusions, the administration site should be changed every 48 hours. If secondary infections occur, appropriate measures should be taken.

Common antigenicity may exist between dermatophytes and penicillin. As a result, reactions similar to those occurring after renewed contact cannot be excluded in patients with mycosis, even after the initial administration of penicillin.

In the event of severe and persistent diarrhoea, antibiotic-associated pseudomembranous colitis should be considered (mucohaemorrhagic, watery diarrhoea, dull, diffuse to colicky abdominal pain, fever, occasionally tenesmus), which can be life-threatening. In these cases, Ampicillin must be discontinued immediately and treatment instituted on the basis of pathogen detection tests. Preparations that inhibit peristalsis are contraindicated.

In patients with impaired renal function, the excretion of ampicillin is delayed; depending on the degree of functional impairment, it may be necessary to reduce the maximum daily dose.

Liver function tests are recommended in long-term treatment with high doses, as well as urine tests and kidney function tests in cases of pre-existing renal damage or if skin conditions occur. Blood count monitoring is indicated to detect antibody-induced reactions of the haematopoietic system, especially haemolytic anaemia.

Fertility, pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of ampicillin on pregnancy or on the health of the foetus/newborn child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Due to the limited experience in humans, ampicillin should not be used unless strictly indicated, after consideration of the benefits and risks.

Breast-feeding

Ampicillin is excreted in human milk. Diarrhoea and colonisation of the mucous membranes by yeast-like fungi may therefore occur in the breast-fed infant, so that breast-feeding may have to be discontinued. The possibility of sensitisation should be considered.

However, ampicillin may be used during breast-feeding after due consideration of the benefits and risks.

Fertility

No data are available with regard to effects on fertility.

Use in Infants

Penicillins are excreted largely unchanged by the kidney. Because of incompletely developed renal function in infants, the rate of elimination will be slow. Use caution in administering to newborns and evaluate organ system function frequently.

Adverse Reactions

Undesirable effects are categorized according to body system and frequency, based on the following classification system:

Very common ($\geq 1/10$)

Common ($\geq 1/100$; $< 1/10$)

Uncommon ($\geq 1/1,000$; $< 1/100$)

Rare ($\geq 1/10,000$; $< 1/1,000$)

Very rare ($< 1/10,000$)

Not known (cannot be estimated from the available data)

Within each frequency grouping undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Uncommon: Chronic and repeated use may lead to superinfection with resistant organisms or yeast-like fungi.

Blood and lymphatic system disorders

Very rare: myelosuppression, blood dyscrasias, e.g. thrombocytopenia, agranulocytosis, leukopenia and eosinophilia.

Anemia, pancytopenia, prolongation of the bleeding and prothrombin time.

These phenomena are generally reversible upon discontinuation.

Immune system disorders

Rare: drug fever, Lyell's syndrome, laryngeal oedema, serum sickness, allergic vasculitis, haemolytic anaemia, Stevens-Johnson syndrome

Very rare: anaphylactic reactions

Not known: when treating abdominal typhoid, leptospirosis or during syphilis treatment, a Jarisch-Herxheimer reaction may occur as a result of bacteriolysis.

Nervous system disorders

Rare: dizziness, headache.

Not known: at very high serum ampicillin concentrations, which may be due to factors such as impaired renal function or the use of very high doses, states of central nervous excitation, myoclonus and seizures may occur.

Gastrointestinal disorders

Uncommon: gastrointestinal disorders (nausea, vomiting, diarrhea, stomach ache, meteorism) usually subside during therapy and do not necessitate discontinuation. Normalization of the intestinal flora is expected to occur approximately 3-5 days following cessation of treatment. If diarrhea occurs during treatment, the possibility of pseudomembranous colitis should be considered (see also "Special warnings and precautions for use").

Not known: As with other penicillins, glossitis and stomatitis may occur.

Dry mouth, impaired sense of taste.

Hepatobiliary disorders

Rare: as with other beta-lactam antibiotics, hepatitis and cholestatic jaundice have been rarely observed.

Very rare: A transient rise in transaminases is possible.

Skin and subcutaneous tissue disorders

Very common: skin reactions manifesting in the form of pruritus, skin redness with sensation of heat (rash) and hives.

Common: the typical "ampicillin" exanthem is mostly morbilliform/maculopapular and appears after 8 - 10 days on first-time use; with repeated use, it occurs on day 2 to 3. The exanthem generally subsides within a few days, even with a continuation of the therapy.

Exanthemata seem to occur more often than normal in the presence of viral infections, renal insufficiency or at doses above 6 g/day.

Very rare: angioedema (hypersensitivity reaction), exfoliative dermatitis and erythema multiforme.

Musculoskeletal and connective tissue disorders

Very rare: arthralgia.

Renal and urinary disorders

Rare: crystalluria (with high-dose I.V. administration)

Very rare: interstitial nephritis.

General disorders and administration site conditions

Very rare: fever.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Israeli Ministry of Health on: <http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il>

Precautions

In the treatment of group A β -hemolytic streptococcal infections, penicillin therapy should be continued for at least 10 days to help prevent the occurrence of acute rheumatic fever or glomerulonephritis. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

As with any potent drug, periodic assessment of renal, hepatic and hematopoietic functions should be made during prolonged therapy. This is particularly important in infants including prematures and neonates.

The possibility of superinfection with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfection occurs, appropriate therapy should be instituted. In the case of infusions, the site of administration should be changed every 48 hours.

Ampicillin should be used with caution in patients with renal (ampicillin excretion is delayed) or hepatic function impairment.

Ampicillin should also be used with caution in patients with gastrointestinal disease or history of gastrointestinal disease, especially ulcerative colitis, regional enteritis or antibiotic-associated colitis since penicillins may cause pseudo-membranous colitis.

In the event of severe and persistent diarrhea, the possibility of antibiotic-associated *pseudomembranous colitis*, which can be life-threatening, should be considered (mucohaemorrhagic, watery diarrhea, dull, diffuse to colicky abdominal pain, fever, occasionally tenesmus). In these cases, ampicillin should be discontinued immediately and treatment should be instituted, based on the results of pathogen detection tests. Preparations that inhibit peristalsis are contraindicated.

Ampicillin has no influence on the ability to drive and use machines.

Drug Interactions

Since penicillins such as ampicillin are active only against proliferating organisms, they should not be combined with bacteriostatic antibiotics. If warranted by the antibiogram, combination with other bactericidal antibiotics (cephalosporins, aminoglycosides) is possible.

Penicillins/Chloramphenicol/Erythromycin/Tetracyclines /Sulfonamides: Since bacteriostatic drugs may interfere with the bactericidal effect of penicillin in the treatment of meningitis or other situations where a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

Ampicillin/Allopurinol: The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes (exanthem) in patients receiving both drugs, as compared to patients receiving ampicillin alone.

It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients.

Ampicillin/Atenolol: Ampicillin may reduce the urinary excretion of atenolol.

Penicillins/Probenecid: Concomitant administration of probenecid leads to increased and prolonged plasma concentrations due to an inhibition of the renal elimination. Probenecid can therefore lead to a reduction in the tissue distribution and diffusion of ampicillin.

Ampicillin/Coumarin: If coumarin-type anticoagulants are co-administered, the susceptibility to bleeding may be increased. There have been reports of a prolongation of the prothrombin time in patients who have received ampicillin. Adequate monitoring should be performed when co-prescribing ampicillin and anticoagulants; the dose of orally administered anticoagulants may also need to be adjusted.

Ampicillin/Methotrexate: Ampicillin can inhibit the excretion of methotrexate and thereby enhance the undesirable effects of methotrexate. Methotrexate blood levels should be monitored.

Ampicillin/Digoxin: During ampicillin therapy, the absorption of co-administered digoxin may be increased.

Ampicillin/Oral Typhoid Vaccine: The efficacy of an oral typhoid vaccine may be reduced when ampicillin is co-administered.

Diagnostic Interference

Ampicillin might interfere with the determination of urinary amino acids by paper chromatography.

Treatment with penicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest, Benedict's Solution or Fehling's Solution, but not with tests based on enzymatic glucose oxidase reactions such as Clinistix or Testape.

Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone, and estradiol have been noted.

The urobilinogen detection test may be impaired.

Effects on ability to drive and use machines

Based on experience to date, ampicillin has no influence on the ability to concentrate and react. However, undesirable effects can lead to risks when engaging in the above activities. This applies particularly in combination with alcohol.

Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproduction toxicity, genotoxicity and carcinogenic potential.

Traditional *in vitro* test methods and animal studies showed no evidence of any teratogenic or mutagenic potential for ampicillin. However, systematic preclinical long-term studies on carcinogenesis, mutagenicity and impaired fertility, conducted according to the latest criteria have not been performed on ampicillin.

Dosage and Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.

The recommended dosages are given below:

In stubborn, severe infections, a higher dosage may be administered.

Adults

250-500 mg every 6 hours, by intramuscular or intravenous injection.

Gonorrhea

2 doses of 500 mg spaced 12 hours apart. Treatment may be repeated if necessary.

Children

12.5 mg/kg bodyweight every 6 hours, by intramuscular or intravenous injection.

Note: Larger doses may be required for stubborn or severe infections. The children's dosage is intended for individuals whose weight will not cause a dosage to be calculated greater than that recommended for adults.

*Septicemia**Adults:*

A daily dosage of 8-14 g is recommended, starting with IV administration for at least 3 days and continuing with the IM route every 3-4 hours.

Children

A daily dosage of 150-200 mg/kg body weight is recommended, starting with IV administration for at least 3 days and continuing with the IM route every 3-4 hours.

*Bacterial Meningitis caused by N. Meningitidis or H. Influenzae**Adults*

A few adults have been treated with doses ranging from 8-14 g daily. Treatment was initiated with intravenous drip therapy for at least 3 days, and continued with frequent (every 3-4 hours) IM therapy.

Children

Children have been treated with doses of 150-200 mg/kg body weight/ day. Treatment was initiated with intravenous drip therapy for at least 3 days, and continued with frequent (every 3-4 hours) IM therapy.

Special precautions for disposal and other handling

Make sure that dispersal is complete. **Use only clear solutions prepared immediately before application. Any unused solution, remaining after reconstitution, must be discarded.**

For single use only.

Intramuscular Use

Use Water for Injections for reconstitution to provide a solution with a concentration of 250 mg/ml, as follows:

- 1.8 ml for the 500 mg vial.
- 3.5 ml for the 1 g vial.
- 6.8 ml for the 2 g vial.

*Intravenous Use***Penibrin 500 mg**

- Solution for IV administration:

dissolve the contents of the 500 mg vial in 5 ml solvent (water for injections).

- Solution for IV infusion:

dissolve the contents of the 500 mg vial in 5 ml solvent (water for injections).
The prepared solution can be mixed with any amount of isotonic NaCl 0.9% solution.

Penibrin 1 g

- Solution for IV administration:
dissolve the contents of the 1 g vial in 5 ml solvent (water for injections).
- Solution for IV infusion:
dissolve the contents of the 1 g vial in 5 ml solvent (water for injections). The prepared solution can be mixed with any amount of isotonic NaCl 0.9% solution.

Penibrin 2 g

- Solution for IV administration:
dissolve the contents of the 2 g vial in 10 ml solvent (water for injections).
- Solution for IV infusion:
dissolve the contents of the 2 g vial in 10 ml solvent (water for injections). The prepared solution can be mixed with any amount of isotonic NaCl 0.9% solution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Caution: For direct intravenous administration, the solution should be injected slowly over a period of 3-5 minutes for doses up to 500 mg and over a period of 10-15 minutes for larger doses. More rapid administration may result in convulsive seizures. The infusion should last between 15 and 20 minutes.

Intravenous Drip Infusion

Isotonic 0.9% Sodium Chloride Injection appears to be a suitable diluent for the intravenous infusion. Reconstitute as directed above prior to diluting with any amount of Isotonic 0.9% Sodium Chloride Injection and infuse over 15 to 20 minutes.

Overdosage

In the event of overdosage with aminopenicillins, urological symptoms - such as haematuria and crystalluria, haemorrhagic cystitis, interstitial nephritis, oliguria, hyperkalemia and/or renal impairment - have occurred in isolated cases, which were reversible without permanent sequelae. The risk of experiencing these undesirable effects is increased in patients with severely impaired renal function, epilepsy and meningitis.

If high concentrations are reached in the cerebrospinal fluid, neurological symptoms including seizures may occur.

In the event of overdosage, careful monitoring of vital signs and symptomatic treatment of any symptoms that occur are indicated. There is no specific antidote. Ampicillin can be removed from the circulation by haemodialysis.

In case of overdosage, discontinue medication, treat symptomatically, and institute supportive measures as required. In patients with renal function impairment, ampicillin-class antibiotics can be removed by hemodialysis but not by peritoneal dialysis.

Pharmaceutical Precautions

Prior to reconstitution, Penibrin vials should be stored below 25°C

Solutions for injections should be freshly prepared.

If Penibrin is prescribed concurrently with an aminoglycoside the two antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside can occur under these conditions.

Drug Reg. No.: 500 mg 115 63 22419 00
 1 g: 032 41 22422 00
 2 g: 102 72 27337 00

Manufacturer

Sandoz GmbH
 Kundl, Austria

Licence Holder

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Marketed by:

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