SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT
PENIBRIN® 500 mg
PENIBRIN® 1 g
PENIBRIN® 2 g

Powder for Solution for Injection/Infusion
For I.M. or I.V. Injection

QUALITATIVE AND QUANTITATIVE COMPOSITION
Penibrin 500 mg*:*
One vial contains 531.4 mg of ampicillin sodium (equivalent to 500 mg ampicillin).
Penibrin 1 g:
One vial contains 1063 mg of ampicillin sodium (equivalent to 1000 mg ampicillin).
Penibrin 2 g:
One vial contains 2126 mg of ampicillin sodium (equivalent to 2000 mg ampicillin).

1. INDICATIONS AND USAGE

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.

2. 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 body weight 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 I.V. administration for at least 3 days and continuing with the I.M. route every 3-4 hours.

Children
A daily dosage of 150-200 mg/kg body weight is recommended, starting with I.V. administration for at least 3 days and continuing with the I.M. 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) I.M. 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) I.M. therapy.

Special precautions for disposal and other handling

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

For single use only.

<u>Intramuscular Use</u>

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.

<u>Intravenous Use</u>

Penibrin 500 mg
- Solution for I.V. administration:
  Dissolve the contents of the 500 mg vial in 5 ml solvent (water for injections).
- Solution for I.V. 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 I.V. administration:
  Dissolve the contents of the 1 g vial in 5 ml solvent (water for injections).
- Solution for I.V. 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 I.V. administration:
  Dissolve the contents of the 2 g vial in 10 ml solvent (water for injections).
- Solution for I.V. 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.

3. DOSAGE FORMS AND STRENGTHS

Powder for solution for injection/infusion.
White to cream-tinged powder.

Penibrin 500 mg*:*
One vial contains 531.4 mg of ampicillin sodium (equivalent to 500 mg ampicillin).
Penibrin 1 g:
One vial contains 1063 mg of ampicillin sodium (equivalent to 1000 mg ampicillin).
Penibrin 2 g*:*
One vial contains 2126 mg of ampicillin sodium (equivalent to 2000 mg ampicillin).

4. CONTRAINDICATIONS

- Hypersensitivity to the active substance
- A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

5. WARNINGS AND PRECAUTIONS

WARNINGS
Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and 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, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all

antibacterial agents, including ampicillin for injection, and may range in severity from mild diarrhea 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 diarrhea following antibiotic 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 antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

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

A high percentage (43 to 100 percent) of patients with infectious mononucleosis who receive ampicillin develop a skin rash. 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. Therefore, the administration of ampicillin is not recommended in patients with mononucleosis. It is not known whether these patients are truly allergic to ampicillin.

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.

Information for Patients
Patients should be counseled that antibacterial drugs 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, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may: (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ampicillin or other antibacterial drugs in the future.

Diarrhea 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
As with any potent drug, periodic assessment of organ system function, including renal, hepatic, and hematopoietic, should be made during prolonged therapy.
Transient elevation of serum transaminase has been observed following administration of ampicillin. The significance of this finding is not known.

Excipient with known effect:
Penibrin 500 mg: Each vial contains approximately 33 mg sodium.
Penibrin 1 g: Each vial contains approximately 66 mg sodium.
Penibrin 2 g: Each vial contains approximately 132 mg sodium.

6. DRUG INTERACTIONS

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of skin rashes 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.

Drug/Laboratory Test Interactions
With high urine concentrations of ampicillin, 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 (such as Clinistix or Tes-Tape) be used.

7. USE IN SPECIFIC POPULATIONS

Pregnancy
Reproduction studies have been performed in laboratory animals at doses several times the human dose and have revealed no evidence of adverse effects due to ampicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery
Oral ampicillin-class antibiotics are poorly absorbed during labor. Studies in guinea pig showed that intravenous administration of ampicillin slightly decreased the uterine tone and frequency of contractions, but moderately increased the height and duration of contractions. However, it is not known whether use of these drugs in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers
Ampicillin is excreted in trace amounts in human milk. Therefore, caution should be exercised when ampicillin-class antibiotics are administered to a nursing woman.

Pediatric Use
Guidelines for the administration of these drugs to children, including neonates are presented in **DOSAGE AND ADMINISTRATION** section.

8. ADVERSE REACTIONS

As with other penicillins, it may be expected that untoward reactions will be essentially limited to sensitivity phenomena. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and in those with a history of allergy, asthma, hay fever, or urticaria.

The following adverse reactions have been reported as associated with the use of ampicillin:

Gastrointestinal
Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, enterocolitis, pseudomembranous colitis, and diarrhea. (These reactions are usually associated with oral dosage forms.)

Hypersensitivity Reactions
Skin rashes and urticaria have been reported frequently. A few cases of exfoliative dermatitis and erythema multiforme have been reported. Linear IgA bullous dermatosis has been reported. Anaphylaxis is the most serious reaction experienced and has usually been associated with the parenteral dosage form.

Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, ampicillin should be discontinued, unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to ampicillin therapy. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen, and intravenous steroids.

Liver– A moderate rise in serum glutamic oxaloacetic transaminase (SGOT) has been noted, particularly in infants, but the significance of this finding is unknown. Mild transitory SGOT elevations have been observed in individuals receiving larger (two to four times) than usual and oft-repeated intramuscular injections. Evidence indicates that glutamic oxaloacetic transaminase (GOT) is released at the site of intramuscular injection of ampicillin sodium and that the presence of increased amounts of this enzyme in the blood does not necessarily indicate liver involvement.

Hemic and Lymphatic Systems– Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, and agranulocytosis have been reported during therapy with the penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

Central Nervous System – Seizures

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il.

9. OVERDOSAGE

In cases of overdose, 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 peritoneal dialysis.

10. DESCRIPTION

Ampicillin for injection, USP the monosodium salt of [2S-[2α,5α,6β(S*)]]-6-[(aminophenylacetyl)amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2carboxylic acid, is a synthetic penicillin. It is an antibacterial agent with a broad spectrum of bactericidal activity against both penicillin-susceptible Gram-positive organisms and many common Gram-negative pathogens.
Ampicillin for injection, USP is a white to cream-tinged, crystalline powder. The reconstituted solution is clear, colorless and free from visible particulates.

Each vial of ampicillin for injection, USP contains ampicillin sodium equivalent to 125 mg, 250 mg, 500 mg, 1 gram or 2 grams ampicillin. Ampicillin for injection, USP contains 65.8 mg [2.9 mEq] sodium per gram ampicillin.

It has the following molecular structure:

The molecular formula is C16H18N3NaO4S, and the molecular weight is 371.39. The pH range of the reconstituted solution is 8 to 10.

11.CLINICAL PHARMACOLOGY

Ampicillin diffuses readily into most body tissues and fluids. However, penetration into the cerebrospinal fluid and brain occurs only when the meninges are inflamed. Ampicillin is excreted largely unchanged in the urine and its excretion can be delayed by concurrent administration of probenecid. Due to maturational changes in renal function, ampicillin half-life decreases as postmenstrual age (a sum of gestational age and postnatal age) increases for infants with postnatal age of less than 28 days.
The active form appears in the bile in higher concentrations than those found in serum. Ampicillin is the least serum-bound of all the penicillins, averaging about 20% compared to approximately 60 to 90% for other penicillins. Ampicillin is well-tolerated by most patients and has been given in doses of 2 grams daily for many weeks without adverse reactions.

Microbiology
While *in vitro* studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the **INDICATIONS AND USAGE** section has not been demonstrated.

Antibacterial Activity
The following bacteria have been shown in *in vitro* studies to be susceptible to ampicillin for injection:
Gram-positive Bacteria
Hemolytic and nonhemolytic *streptococci*
Streptococcus pneumoniae
Nonpenicillinase-producing *staphylococci*
Clostridium spp.
B. anthracis
Listeria monocytogenes
Most strains of *enterococci*.

Gram-negative Bacteria
H. influenzae
N. gonorrhoeae
N. meningitidis
Proteus mirabilis
Many strains of *Salmonella*, *Shigella*, and *E. coli.*
Ampicillin does not resist destruction by penicillinase.

12. NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis
No long-term animal studies have been conducted with this drug.

13. HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Penibrin 500 mg: One vial contains 531.4 mg of ampicillin sodium (equivalent to 500 mg ampicillin).

Penibrin 1 g: One vial contains 1063 mg of ampicillin sodium (equivalent to 1000 mg ampicillin).

Penibrin 2 g: One vial contains 2126 mg of ampicillin sodium (equivalent to 2000 mg ampicillin).

Incompatibilities
Ampicillin solutions should always be administered separately, unless compatibility with other infusion solutions or medicines has been established.
This medicinal product must not be mixed with other solutions except those mentioned in section **DOSAGE AND ADMINISTRATION**.
Ampicillin solutions should not be mixed with aminoglycosides, metronidazole and injectable tetracycline derivatives such as oxytetracycline, rolitetracycline and doxycycline. Visual signs of incompatibility are precipitation, clouding and discoloration.

Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf-life after preparation of the ready-to-use solution
Use only clear solutions prepared immediately before application.
Any unused solution, remaining after reconstitution, must be discarded.

Special precautions for storage

Store below 25°C.
For storage conditions after reconstitution of the medicinal product, see section 13.

Nature and contents of container

Glass vial with halogenated butyl rubber stopper.
Pack sizes: 1 vial, 10 vials or 25 vials.

Not all pack sizes may be marketed.

Special precautions for disposal

The solutions should always be prepared freshly before use and checked for clarity. Use only clear solutions for injection or infusion! Do not use solutions with cloudiness or precipitation. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

14. LICENCE HOLDER AND MANUFACTURER

Licence holder:
Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv, 6944020

Manufacturer:
Sandoz GmbH,
BIOCHEMIESTRASSE 10
A-6250 Kundl, Austria.

15. REGISTRATION NUMBERS:

Penibrin 500: 115.63.22419
Penibrin 1 g: 032.41.22422
Penibrin 2 g: 102.72.27337

The leaflet was revised in May 2025 according to MoH guidelines.