1. NAME OF THE MEDICINAL PRODUCT

PENILEVEL 600,000 I.U. powder and solvent for injectable solution
PENILEVEL 1,000,000 I.U. powder and solvent for injectable solution
PENILEVEL 2,000,000 I.U. powder and solvent for injectable solution
PENILEVEL 5,000,000 I.U. powder and solvent for injectable solution
PENILEVEL 10,000,000 I.U. powder and solvent for injectable solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PENILEVEL 600,000 I.U. contains 600,000 I.U. of Benzylpenicillin sodium.
Each vial of PENILEVEL 1,000,000 I.U. contains 1,000,000 I.U. of Benzylpenicillin sodium.
Each vial of PENILEVEL 2,000,000 I.U. contains 2,000,000 I.U. of Benzylpenicillin sodium.
Each vial of PENILEVEL 5,000,000 I.U. contains 5,000,000 I.U. of Benzylpenicillin sodium.
Each vial of PENILEVEL 10,000,000 I.U. contains 10,000,000 I.U. of Benzylpenicillin sodium.

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for injectable solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

- Infections produced by gram-positive micro-organisms such as: pneumonia, pleurisy and pneumococcal meningitis.
- Tonsillitis, pharyngitis, swollen tonsils, otitis media, acute sinusitis, scarlet fever, pneumonia, pulmonary abscess, puerperal fever, septicaemia and streptococcal endocarditis.
- Bronchopneumonia, osteomyelitis, septicaemia, empyema, pulmonary abscess, acute enterocolitis septic miscarriage, non-acute endocarditis and meningitis caused by staphylococcus that does not produce penicillinase.
- Gonorrhoea and its gonococcal genitourinary complications.
- Meningococcal meningitis, gaseous gangrene, diphtheria and tetanus.
- Stomatitis, Vincent's angina caused by spirochetes, actinomycosis produced by actinomycetes and syphilis produced by treponema pallidum.
- As a prophylactic in fully established indications

4.2. Posology and method of administration

Posology
Adults
- Generally injected intramuscularly: The usual therapeutic does is 1,000,000 I.U. every 6 hours.
- Intravenously: The usual therapeutic dose is 1,000,000 I.U. every 4 hours.
- In physiological saline for infusion: The usual therapeutic does is 10-100 millions of I.U. daily.

Children
- The dose varies according to age and body weight. In general, the correct dose will be calculated by taking into consideration that the above dosages are for an adult of 60 kg.

Method of administration
Dissolve the powder from the vial with the solvent from the ampoule until obtaining a solution

PENILEVEL can be administered intramuscularly or intravenously, directly or via dilution in perfusion solutions.

To administer PENILEVEL intravenously it is appropriate to adjust the concentration of the injectable to up to 1,000,000 I.U. per 4 mL, diluting if necessary, with sterile apyrogenic water, and inject slowly.

To administer PENILEVEL in perfusion solutions, the correct dilution is around 10,000,000 I.U. per 100 mL of physiological saline

The solubility of PENILEVEL allows it to reach concentrations in the order of 1,000,000 I.U. per mL.

4.3. Contraindications

Hypersensitivity to the active substance, penicillins and derivatives (cephalosporins) or to any of the excipients listed in section 6.1.

4.4. Special warnings and precautions for use

The appearance of any type of allergic manifestation supposes the interruption of the treatment.

No exclusively geriatric symptoms have been described for the use of penicillins. Nevertheless, these patients are more prone to suffer renal dysfunction depending on their age and it might be necessary to adjust the dose in patients receiving penicillin.

The risk/benefit ratio must be evaluated in the following clinical situations:
- General allergy, History of sensitivity to multiple allergens.
- Renal dysfunction. It is recommended to reduce the dose or increase the dose interval in patients with renal dysfunction.

4.5. Interaction with other medicinal products and other forms of interaction

Interactions with other medicinal products:
- The “in vitro” mixing of penicillins and aminoglycosides have given rise to a substantial mutual inhibition. If administered simultaneously with this antibacterial group, they must be administered at least an hour apart.
- The bacteriostatic drugs (tetracycline, chloramphenicol, sulphonamides) can interfere with the bactericidal properties of the penicillins.
- The penicillins may reduce the effect of oral contraceptives, probably due to the reduction in enteropathic circulation of the oestrogens. Although the interaction is weak, the patients should

be advised to use an additional or alternative method of contraception during treatment with penicillins.
- The simultaneous use with methotrexate boosts its toxicity by reducing its renal tubular secretion. The patients must be monitored, it may be necessary to increase the dose of calcium folinate and administer both for longer periods.
- The simultaneous use with probenecid reduces the renal secretion of the penicillins, giving rise to an increase and prolongation of its serum concentration, lengthening its elimination high life and increasing the risk of toxicity.

Interferences with diagnosis:
- Blood:
  - False protein increase with turbidimetric methods that use sulfosalicylic, trichloroacetic, acetic or nitric acids.
  - Positive Coombs test (anti-globulin) in 3% of patients.
- Urine:
  - False protein increase with turbidimetric methods that use sulfosalicylic, trichloroacetic, acetic or nitric acids.
  - High penicillin concentrations in urine can give false high results for the determination of glucose in urine when using tests with copper sulphate. No interference is produced with enzymatic tests.
  - False increase of 17-ketosteroids with the method of Noryberski and the colour reaction of Zimmerman.
  - False increase of delta aminolevulinic acid with the method of Mauzerall and Granick.
  - Reduction in the urinary excretion of aminohippuric acid and of sulfone phthalein.

4.6. Pregnancy and lactation

Category B during pregnancy. Studies performed in animals have shown no signs of fertility alteration or harm to the foetus. There are no suitable or controlled studies in humans. No problems for the foetus have been described with the use of penicillins in mothers during the gestation period; however, the risk/benefit ratio should be evaluated at all times for its use during this period.

The data from a limited number of risk pregnancies have shown no adverse reactions of Benzylpenicillin sodium on the pregnancy or the health of the foetus or new-born. To date there is no additional relevant epidemiological data. Studies in animals do not show any direct or indirect harmful effects on pregnancy, embryonic/foetal development, birth or post-natal development (See section 5.3)
Care must be taken when prescribing to pregnant women.

Use during lactation. The penicillins are distributed to breast milk, some at low concentrations. Although no significant problems have been described in humans, the use of penicillin in lactating mothers could give rise to sensitisation, diarrhoea, candidiasis and cutaneous rash in the breast fed baby.

4.7. Effects on ability to drive and use machines

PENILEVEL has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

The undesirable effects are listed in decreasing order of severity within each frequency interval,

Frequent (≥1/100 to <1/10).
Rare (≥1/1,000 to <1/100).

- Frequent:
  Allergic alteration (exanthematous eruptions, pruritus, serum sickness, Jarisch-Herxheimer reaction; exceptionally anaphylactic reactions).
- Rare:
  Blood alterations: eosinophilia, neutropenia, leucopoenia, thrombocytopenia, haemolytic anaemia.

Intramuscular administration can provoke local pain, sensitivity or swelling/ hardening at the site of injection. The frequency of appearance has not been determined.

Treatment should be suspended in the case of hematuria, anaphylactic reaction, extensive exanthematous eruptions and convulsive crisis.

4.9. Overdose

Severe anaphylactic reactions require immediate urgent treatment, consisting of parenteral epinephrine, oxygen, intravenous corticosteroids and assisted respiration.

There is no specific antidote for the treatment of overdose, the treatment of penicillin overdose must be symptomatic and of maintenance. Haemodialysis can help to eliminate penicillins from the blood.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactamase sensitive penicillins, ATC code: J01CE.

Benzylpenicillin sodium is a bactericidal antibiotic of the beta-lactamase family. It acts during the period of bacterial growth, inhibiting the biosynthesis of the mucopeptide of the cell wall.

5.2. Pharmacokinetic properties

Absorption
After intramuscular administration, maximum concentrations of Benzylpenicillin sodium are reached after 15-30 minutes and are detectable for 3-4 hours.

Distribution
It is widely distributed throughout the tissues of the organism, especially if they are inflamed. A small proportion crosses the haemato-encephalic barrier and, in much greater quantity, the placenta barrier. It reaches therapeutic levels in the foetus and the amniotic liquid, also passing into breast milk. It binds to the plasma proteins at a proportion of 50-65%.

Elimination
25% of the dose administered is metabolised, most of it being eliminated in the urine, with 75% of the dose unmodified. Around 60% or more of the dose is eliminated in the urine, in the first 6 hours after administration. In adults, the elimination half-life is of 30-45 minutes.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.
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6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Water for injection.

6.2. Incompatibilities

None have been described.

6.3. Shelf life

5 years.

Once diluted, administer immediately.

6.4. Special precautions for storage

Does not require special storage conditions.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5. Nature and contents of the container

Case with a type II glass vial with butyl stopper containing powder for solution and glass ampoule containing water for injection.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling.

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

LABORATORIOS ERN, S.A.
Pedro IV, 499 -
08020 Barcelona, Spain

8. MARKETING AUTHORISATION NUMBER(S)

E.N.33.579	PENILEVEL 600,000 I.U.
E.N.33.580	PENILEVEL 1,000,000 I.U.
43.504	PENILEVEL 2,000,000 I.U.
41.245	PENILEVEL 5,000,000 I.U.
48.882	PENILEVEL 10,000,000 I.U.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation

01/03/1960	PENILEVEL 600,000 I.U.
01/03/1960	PENILEVEL 1,000,000 I.U.
01/11/1966	PENILEVEL 2,000,000 I.U.
01/07/1965	PENILEVEL 5,000,000 I.U.
01/02/1970	PENILEVEL 10,000,000 I.U.

10. DATE OF REVISION OF THE TEXT

Month/year