SUMMARY OF PRODUCT CHARACTERISTICS

Penicillin G Sodium 5 MU
Penicillin G Sodium 10 MU

Powder for solution for I.V. or I.M. injection

1. NAME OF THE MEDICINAL PRODUCT

Penicillin G Sodium 5 MU
Penicillin G Sodium 10 MU

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Penicillin G Sodium 5 MU:
Each vail contains 2.994 g benzylpenicillin sodium, corresponding to 5,000,000 IU.

Sodium content: 8.42 mmol or 193 mg sodium

Penicillin G Sodium 10 MU:
Each vail contains 5.988 g benzylpenicillin sodium, corresponding to 10,000,000 IU.

Sodium content: 16.84 mmol or 386 mg sodium

3. PHARMACEUTICAL FORM

White to off-white powder for solution for injection.

pH after reconstitution: 5.5 — 7.5

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Infections due to penicillin - sensitive microorganisms.

4.2. Posology and method of administration

Parenteral drug products should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.
Penicillin G should preferably be administered by intramuscular injection. However when large doses are required, it may be advisable to administer Penicillin G by means of a continuous intravenous drip.

Severe infections
A minimum of 5 MU daily is recommended for the treatment of severe infections due to susceptible strains of Streptococci, Pneumococci and Staphylococci (bacteremia, empyema, severe pneumonia, pericarditis, endocarditis, meningitis and other severe infections).

Anthrax
A minimum of 5 MU/ day in divided doses, until cure is achieved.

Actinomycosis
1-6 MU/ day for cervicofacial cases.
10-20 MU/ day for thoracic and abdominal disease.

Clostridial infections
20 MU per day (as adjunctive therapy to antitoxin).

Diphtheria
For prevention of the carrier state, 0.3-0.4 MU/ day in divided doses for 10-12 days.

Erysipeloid Endocarditis
2-20 MU/ day for 4-6 weeks.

Fusospirochetal Infections
5-10 MU/ day.

Gram-negative Bacteremia
20-80 MU/ day.

Listeria infections
In adults with meningitis, 15-20 MU/ day for 2 weeks.
In adults with endocarditis, 15-20 MU/ day for 4 weeks.
In neonates, 0.5-1.0 MU/ day.

Pasteurella infections
In bacteremia and meningitis: 4-6 MU/ day for 2 weeks.

Rat-bite fever
12-15 MU daily for 3-4 weeks.

Gonorrheal endocarditis and arthritis
A minimum of 5 MU daily.

Syphilis
Penicillin G may be used in the treatment of acquired and congenital syphilis but, because of the necessity of frequent dosage, hospitalization is recommended.
Dosage and duration of therapy is determined by the age of the patient and the stage of the disease.

Meningococcal Meningitis
1-2 MU intramuscularly every 2 hours, or continuous intravenous drip of 20-30 MU/ day.

4.3. Contraindications

- Hypersensitivity to the active substance
- History of hypersensitivity to penicillin
- History of severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporin monobactam, carbapenem)

4.4. Special warnings and precautions for use

In cases of cephalosporin hypersensitivity, a cross allergy is possible (frequency according to the literature is 5-10%).

Prior to treatment, a hypersensitivity test should be carried out Patients should be informed about the possible occurrence of a hypersensitivity reaction. Particular caution is required in patients with allergic diathesis or bronchial asthma. After administering the medication, patients should be observed for 30 minutes, and an adrenaline solution should be ready for injection in the event of an emergency. If an allergic reaction occurs, treatment must be discontinued and, if necessary, symptomatic treatment instituted..

Severe cutaneous adverse reactions (SCAR), including Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with beta-lactam antibiotics (including penicillins) treatment (see section 4.8).

Benzylpenicillin is contraindicated in patients who are hypersensitive to penicillins. Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to benzylpenicillin (see section 4.3). Benzylpenicillin should be used with caution in patients with a history of non-severe hypersensitivity reactions to any other beta-lactam antibiotics (e.g. cephalosporins or carbapenems) and not at all in patients with history of severe hypersensitivity reactions. If a severe allergic reaction or SCAR occurs during treatment with benzylpenicillin, treatment with the medicinal product should be discontinued and appropriate measures taken

Caution should be exercised in patients with the following conditions:

- allergic diathesis (urticaria or hay fever) or asthma (increased risk of hypersensitivity reactions)
- severe heart conditions or severe electrolyte disturbances of any other origin(attention should be paid to electrolyte intake in this patient group, especially potassium intake)
- renal insufficiency
- liver damage
- epilepsy, cerebral oedema or meningitis (increased risk of seizures, especially with high dose administration (> 20 mega IU) of penicillin G-Sodium; see section 4.8)
- existing mononucleosis (increased risk of skin rash)
- when treating co-infections in patients with acute lymphatic leukemia (increased risk of skin reactions)
- dermatomycoses (para-allergic reactions are possible as there may be common antigenicity between penicillins and metabolic products of dermatophytes; see section 4.8).

In rare cases, prolongation of the prothrombin time has been reported in patients receiving penicillins. Appropriate monitoring should be performed when anticoagulants are co-administered. Adjustment of the oral anticoagulant dose may be necessary to obtain the desired degree of anticoagulation (see sections 4.5 and 4.8).

It should be remembered that the absorption of Penicillin G-Sodium is delayed after intramuscular administration in patients with diabetes (see section 5.2).

In venereal diseases, dark-field examinations should be performed before the start of therapy if co-existing syphilis is suspected. Serological tests for monitoring purposes should also be performed for at least 4 months.

In long-term therapy, vigilance is required for the possible occurrence of an overgrowth of resistant organisms.. If secondary infections occur, appropriate measures should be taken.

If severe, persistent diarrhea occurs, antibiotic- associated pseudomembranous colitis should be considered (mucohaemorrhagic, watery diarrhoea; dull, diffuse to colicky abdominal pain; fever; occasionally tenesmus), which may be life-threatening. In these cases, Penicillin G-sodium must therefore be discontinued immediately i and treatment based on the identification of the pathogen initiated. . Preparations that inhibit peristalsis are contraindicated.

When treating Lyme borreliosis or syphilis, a Jarisch-Herxheimer reaction may occur as a result of the bactericidal action of penicillin on the pathogens, which is characterized by fever, chills, general symptoms and focal symptoms (mostly 2 to 12 hours after the initial dose). Patients should be informed that this is a usual transient sequela of antibiotic therapy. For the suppression or alleviation of a Jarisch-Herxheimer reaction (see section 4.8), appropriate therapy should be instituted.

For conditions such as severe pneumonia, empyema, sepsis, meningitis or peritonitis, which require higher serum penicillin levels, treatment with the water-soluble alkali salt of benzylpenicillin should be instituted.

If neurological involvement cannot be excluded in patients with congenital syphilis, forms of penicillin reaching a higher level in cerebrospinal fluid should be used.

Severe local reactions can occur with intramuscular administration to infants. If possible, intravenous therapy should be performed.

When intravenously administering very high doses (above 10 MU/ day), the administration site should be alternated every other day to avoid superinfections and thrombophlebitis.

Due to possible electrolyte disturbances, Penicillin G-Sodium should be administered slowly with infusions of more than 10 MU and, due to the possibility of seizure reactions, when administering more than 20 MU risk (see section 4.8).

In prolonged treatment (more than 5 days) with high penicillin doses, monitoring of the electrolyte balance, s, blood count monitoring and renal function tests are recommended.

Effect on diagnostic laboratory procedures:

- A positive direct Coomb's test often develops (≥ 1% to < 10%) in patients receiving 10 million IU (equivalent to 6 g) of benzylpenicillin or more per day. Upon discontinuation of the penicillin, the direct antiglobulin test may still remain positive for 6 to 8 weeks (see sections 4.5 and 4.8).
- Determination of urinary protein using the precipitation techniques (sulphosalicylic acid, trichloroacetic acid), the Folin-Ciocalteu-Lowry method or the Biuret method may lead to false positive results. Caution should therefore be exercised when interpreting the results of such tests in patients receiving Penicillin G-Sodium. Protein determination with test strips is not affected.
- Equally, urinary amino acid determination using the ninhydrin method may lead to false positive results.
- Penicillins bind to albumin. In electrophoresis methods to determine albumin, pseudobisalbuminemia may thereby be simulated.
- During therapy with Penicillin G-Sodium, non-enzymatic urinary glucose detection and urobilinogen detection may prove false-positive. Enzymatic urine glucose tests should be used in patients on therapy with Penicillin G-Sodium, as these are not affected by this interaction.
- When determining 17-ketosteroids (using the Zimmermann reaction), in urine, increased values may occur during therapy with Penicillin G-Sodium.

This medicinal product contains 39 mg sodium per 1MU dose, equivalent to 2% of the WHO

recommended maximum daily dietary intake of 2 g sodium for an adult.
Penicillin G Sodium is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

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

Concomitant administration of Penicillin G -Sodium is not recommended with:
Based on the general principle not to combine bactericidal and bacteriostatic antibiotics, Penicillin G-Sodium should not be combined with bacteriostatic antibiotics.

Mixed injections or infusions: To avoid undesirable chemical reactions, administration of mixed injections or infusions or of admixtures with solutions that contain carbohydrates such as glucose, should be avoided (see section 6.2).

Caution is required when co-administering with:
Probenecid: Administration of probenecid leads to an inhibition of the tubular secretion of benzylpenicillin, resulting in an increase in serum concentration and prolongation of the elimination half-life. Furthermore probenecid inhibits the penicillin transport from the cerebrospinal fluid, so that the concomitant administration of probenecid reduces the penetration of benzyl penicillin into brain tissue even further.

, Anti-inflammatories, antirheumatics and antipyretics: When co- administering Penicillin G-Sodium with anti-inflammatories, antirheumatics or antipyretics: (especially indomethacin, phenylbutazone, salicylates at high doses), it should be pointed out that excretion is competitively inhibited , resulting in an increase in serum concentration and prolongation of the elimination half-life.

Digoxin: In patients treated on digoxin treatment, Penicillin G-Sodium should only be used with caution, as there is a risk of bradycardia as a result of interactions.

Methotrexate: When taken at the same time as Penicillin G-Sodium, the excretion of methotrexate is reduced. This can lead to increased methotrexate toxicity. Concomitant use of methotrexate and penicillin should be avoided if possible. If concomitant use is unavoidable, a reduction in the methotrexate dose should be considered and methotrexate serum levels should be monitored. The patient should be monitored for possible additional adverse reactions of methotrexate, including leukopenia, thrombocytopenia and skin suppuration.

Oral anticoagulants: Oral anticoagulants and penicillin antibiotics have been used extensively in practice without interactions. However, in the literature there are reports of an increased number of patients who experienced a bleeding event when they were prescribed acenocoumarol or warfarin at the same time as penicillin. If concomitant use is required, the prothrombin time or other suitable coagulation parameters should be carefully monitored upon co- administration or discontinuation of penicillin. Furthermore, an adjustment of the oral anticoagulant dose may be necessary (see sections 4.4 and 4.8).

Synergism between antibiotics:
Penicillin G-Sodium should only be given in combination with other antibiotics if a synergistic or at least an additive effect is anticipated. In general, the individual components of a combination must be given at the full effective dose. (exception if synergism is proven, the dose of the more toxic combination partner can be reduced).

If duly indicated, it should, in particular, be remembered that Penicillin G-Sodium can be combined with the following bactericidal antibiotics:

- Isoxazolyl penicillins (e.g. flucloxacillin and other narrow-spectrum beta lactams)
- aminopenicillins
- aminoglycosides

The above-mentioned penicillins are given by slow intravenous injection prior to the Penicillin G-Sodium infusion. Wherever possible, aminoglycosides should be given separately via the intramuscular route.

4.6. Fertility, pregnancy and lactation

Pregnancy
Benzylpenicillin crosses the placenta. 1-2 hours after administration, concentrations corresponding to those in maternal serum are reached in fetal serum. studies in animal have shown no indications of direct or indirect health effects with regard to reproductive toxicity.

Penicillin G-Sodium may be used in pregnancy if duly indicated and after consideration of the benefits and risks.

Penicillin G-Sodium is not indicated during pregnancy for the treatment of syphilis.

Breast-feeding
Small amounts of penicillins appear in breast milk.
Although no undesirable effects have been reported in breast-fed infants to date, the possibility of sensitization or an adverse effect on the intestinal flora must nevertheless be considered.
In infants also fed on baby food, mothers should express and discard breast milk during treatment with Penicillin G-Sodium treatment. Breast-feeding can be resumed 24 hours after the cessation treatment.
Fertility
No studies have been performed to investigate the effects of Penicillin G-Sodium on fertility.

4.7. Effects on ability to drive and use machines

Generally, Penicillin G-Sodium effect has no influence on the ability to concentrate and react.. Due to the occurrence of possible serious undesirable effects (e.g. anaphylactic shock with collapse and anaphylactoid reactions, see also section 4.8), Penicillin G-Sodium can have an influence on the ability to drive and use machines.

4.8. Undesirable effects

Undesirable effects are ranked according to body system and frequency according to the following classification:

Very common (≥1/10)
Common (≥1/100to <1/10)
Uncommon (≥1/1,000to <1/100)
Rare (≥1/10,000to <1/1,000)
Very rare (<1/10,000)

Not known (cannot be estimated from available data)

Blood and lymphatic system disorders
Very rare:
Eosinophilia, leukopenia, neutropenia, granulocytopenia, agranulocytosis, pancytopenia, hemolytic anemia, coagulation disorders
not known:
Prolongation of the bleeding time and prothrombin time, thrombocytopenia (see section 4.4)

Immune system disorders
Uncommon:
Allergic reactions: urticaria, erythema multiforme, exfoliative dermatitis, fever arthralgia, anaphylaxis or anaphylactoid reactions (asthma, purpura, gastrointestinal symptoms). Para-allergic reactions may occur in patients with dermatomycoses, as there may be common antigenic between penicillins and metabolic products of dermatophytes.
Not known:
Serum sickness, Jarisch-Herxheimer reaction in association with spirochete infections (syphilis and Lyme disease), angioedema

Metabolism and nutrition disorders
Rare:
Electrolyte imbalances may occur upon rapid infusion of more than 10 MU.

Nervous system disorders
Rare:
Neuropathy. Convulsive reactions may occur upon infusion of high doses (in adults more than 20 MU); this should be particularly borne in mind in patients with severely impaired renal function, epilepsy, meningitis, cerebral oedema or during cardiopulmonary bypass.

Not known :
Metabolic encephalopathy

Gastrointestinal disorders
Uncommon:
Stomatitis, glossitis, black hairy tongue (lingua villosa nigra), nausea, vomiting
If diarrhea develops during treatment, the possibility of pseudomembranous colitis should be considered (see section 4.4).

Rare :
Diarrhoea caused by Clostridium *difficile*

Hepato biliary disorders
Not known:
Hepatitis, cholestasis

Skin and subcutaneous tissue disorders
Not known: pemphigoid, Acute generalised exanthematous pustulosis (AGEP), Pruritus, Maculo papular rash, Rash morbilliform, Erythema.

Renal and urinary disorders
Rare:
Nephropathy (after intravenous administration of more than 10 MU Penicillin G-Sodium), albuminuria, cylindruria and hematuria
Oliguria or anuria which can rarely occur during high-dose penicillin therapy generally disappears within 48 hours upon discontinuation of treatment. Diuresis can also be stimulated with 10% mannitol solution.

General disorders and administration site conditions
Rare:
Severe local reactions during intramuscular administration to infants.

Investigations
Common:

- Positive direct Coomb's test
- False-positive urinary protein determination using precipitation techniques (Folin-Ciocalteu-Lowry method, Biuret method)
- False-positive urinary amino acid determination (ninhydrin method)
- falsification of pseudobisalbuminemia when using electrophoresis methods to determine albumin.
- False-positive non-enzymatic urinary glucose detection and urobilinogen detection
- increased values when determining of 17-ketosteroids in urine (using the Zimmermann reaction) (see section 4.5)

Description of selected adverse reactions
Severe cutaneous adverse reactions SCARs (Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis) have been reported with beta-lactam antibiotics, including penicillins (see section 4.4).

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. 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/

4.9. Overdose

increased neuromuscular hyperexcitability or susceptibility to cerebral seizures can be anticipated in the event of an overdose . Countermeasures: Discontinuation, clinical surveillance and symptomatic treatment if required. Penicillin G-Sodium can be hemodialysed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group
Benzylpenicillin (Penicillin G) is a semi-synthetic, beta-lactamase-sensitive, beta-lactam antibiotic.

ATC code: J01CE01

Mechanism of action
The For benzylpenicillin, the mechanism of action is based on inhibition of bacterial cell wall synthesis (during the growth phase) through a blockade of penicillin-binding proteins (PBPs) such as transpeptidases. This results in a bactericidal action.

pharmacokinetic /pharmacodynamic relationship
Efficacy largely depends on the length of time that the active substance level remains above the pathogen`s MIC.

Resistance mechanisms
Resistance to benzylpenicillin may be due to the following mechanisms:
- Inactivation by beta-lactamases: Benzylpenicillin is sensitive to beta-lactamase and is therefore inactive against beta-lactamase-producing bacteria (e.g. staphylococci or gonococci).

- Reduced affinity of PBPs for benzylpenicillin: The acquired resistance in pneumococci and a few other streptococci to benzylpenicillin is due to modifications of existing PBPs as a result of a mutation. However, the formation of an additional PBP with reduced affinity for benzylpenicillin is responsible for resistance in methicillin (oxacillin)-resistant staphylococci .
- In Gram-negative bacteria, inadequate penetration of benzylpenicillin through the outer cell wall can lead to an insufficient inhibition of PBPs.
- Benzylpenicillin can be actively transported from the cell by efflux pumps. .
  Benzylpenicillin is partially or completely cross-resistant to other penicillins and cephalosporins.

Breakpoints

Testing of benzylpenicillin is performed using the standard dilution series. results are evaluated on the basis of breakpoints for benzylpenicillin. The following minimum inhibitory concentrations have been established for susceptible and resistant germs:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints (version 10.0)

PATHOGEN	SUSCEPTIBLE	RESISTANT
Staphylococcus aureus	≤ 0.125 mg/L	> 0.125 mg/L
Streptococcus spp. **(Groups A, B, C, G)**	≤ 0.25 mg/L	> 0.25 mg/L
Streptococcus pneumoniae (indications other than meningitis)	≤ 0.06 mg/L	> 2 mg/L
Streptococcus pneumoniae (meningitis)	≤ 0.06 mg/L	> 0.06 mg/L
Streptococci of the "viridans" group	≤ 0.25 mg/L	> 2 mg/L
Neisseria meningitidis	≤ 0.06 mg/L	> 0.25 mg/L
Neisseria gonorrhoeae	≤ 0.06 mg/L	> 1 mg/L
Gram-negative anaerobes	≤ 0.25 mg/L	> 0.5 mg/L
Gram-positive anaerobes	≤ 0.25 mg/L	> 0.5 mg/L
Listeria monocytogenes	≤ 1 mg/L	> 1 mg/L
Pasteurella multocida	≤ 0.5 mg/L	> 0.5 mg/L
Corynebacterium spp.	≤ 0.125 mg/L	> 0.125 mg/L
Aerococcus sanguinicola and	≤ 0.125 mg/L	> 0.125 mg/L
Kingella kingae	≤ 0.03 mg/L	> 0.03 mg/L
PK/PD (Non-species related) breakpoints *	≤ 0.25 mg/L	> 2 mg/L

Prevalence of acquired resistance

The prevalence of acquired resistance in individual species may vary geographically and over time. Thus, local information on the resistance situation is required, particularly for the adequate treatment of severe infections. If based on the local resistance situation, the efficacy of benzylpenicillin is questionable, expert therapeutic advice should be sought. Particularly in cases of serious infection or unsuccessful therapy, a, microbiological diagnosis should be sought, with the detection of the pathogen and its susceptibility to benzylpenicillin.

Prevalence of acquired resistance based on data from the past 5 years from national resistance monitoring projects and studies (version: April 2019):

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Actinomyces israeli °
Corynebacterium diphtheriae °
Erysipelothrix rhusiopathiae °
Gardnerella vaginalis °
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Streptococcus dysgalactiae subsp. *equisimilis* (group C & G streptococci)
Streptococci of the “viridians” group ° ^

Aerobic Gram-negative micro-organisms
Borrelia burgdorferi°
Eikenella corrodens ° $
Haemophilus influenzae ° $
Neisseria meningitidis °
Anaerobic micro-organisms
Clostridium perfringens °
Clostridium tetani °
Fusobacterium spp. °
Peptoniphilus spp. °
Peptostreptococcus spp. °
Veillonella parvula °
Other micro-organisms
Treponema pallidum °
Species in which acquired resistance may pose a problem during use
Aerobic Gram-positive micro-organisms
Enterococcus faecalis $
Staphylococcus aureus +
Staphylococcus epidermidis +
Staphylococcus haemolyticus +
Staphylococcus hominis +
Aerobic Gram-negative micro-organisms
Neisseria gonorrhoeae $
Naturally resistant species
Aerobic Gram-positive micro-organisms
Enterococcus faecium
Nocardia asteroides
Aerobic Gram-negative micro-organisms
All *Enterobacterales species*
Legionella pneumophila
Moraxella catarrhalis
Pseudomonas aeruginosa
Anaerobic micro-organisms
Bacteroides spp.
Other micro-organisms
Chlamydia spp.
Chlamydophila spp.
Mycoplasma spp.

° At the time of the publishing of the table, no current data were available. . Susceptibility is assumed in the primary literature, standard works and therapeutic recommendations.

$ The natural susceptibility of most isolates is within the intermediate range.

+ In at least one region, the resistance rate is over 50%.

^ Collective name for a heterogeneous group of streptococci species. The resistance rate can vary depending on the streptococci species present.

5.2. Pharmacokinetic properties

Absorption

Benzylpenicillin is not acid-stable and can therefore only be administered parenterally The alkali salts of benzylpenicillin are rapidly and completely absorbed after IM. injection.
Peak plasma levels of 150-200 1U/mL are reached 15 - 30 min. after IM. injection of 10 MU of Penicillin G-Sodium. After a short infusion (30 min.), peak levels of up to 500 IU/mL may be reached. About 55% of the administered dose is bound to plasma proteins.

Distribution

When administering high-dose penicillin therapy, therapeutically effective concentrations are reached even in poorly accessible tissues such as cardiac valves, bone, cerebrospinal fluid or empyema, etc.
Benzylpenicillin crosses the placenta. 10-30% of maternal plasma concentrations are found in the fetal circulation. High concentrations are also attained in the amniotic fluid. On the other hand, passage into breast milk is low. The volume of distribution is about 0.3-0.4 l/kg; in children, about 0.75 l/kg. Plasma protein binding is approximately 55%.

Biotransformation and elimination
Elimination occurs largely (50–80%) as unchanged substance via the kidneys (85–95%) and, to a lesser degree, in active form with the bile (approximately 5%).
The plasma half-life is approximately 30 minutes in adults with healthy kidneys.

Kinetics of special patient groups
- *Diabetics* Absorption from the intramuscular depot is likely to be delayed in diabetics. .
- *Pre-term and newborn infants:* Due to the immaturity of the kidney and liver at this age, the serum half-life can be up to three hours (or more). The dosing interval should therefore be no less than 8–12 hours (depending on maturity).
- *Elderly: Equally,* elimination processes may be delayed with advanced age; the dosage should therefore be adjusted to renal function in each individual case.

5.3. Preclinical safety data

Reproduction studies in mice, rats and rabbits have shown no negative effects on fertility or on the fetuses. There are no long-term studies available in laboratory animals with regard to carcinogenesis, mutagenesis or fertility.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

None.

6.2. Incompatibilities

The contents of the vial should only be used in a solution with water for injections, 5% glucose solution or 0.9% sodium chloride, in order to avoid incompatibilities.

In order to avoid undesirable chemical reactions or undesirable effects, the already dissolved vials should not be mixed with other mixed injections or infusions (e.g. Ringer's lactate solution, etc.).
Oxidising and reducing substances, alcohol, glycerol, macrogols and other hydroxy-compounds can inactivate benzylpenicillin.
Benzylpenicillin solutions are most stable in the pH range of 6–7 (optimum at pH 6.8).
Benzylpenicillin is incompatible in solution with the following:
- cimetidine
- cytarabine
- chlorpromazine hydrochloride
- dopamine hydrochloride
- heparin
- hydroxyzine hydrochloride
- lactate
- lincomycin hydrochloride
- metaraminol
- sodium hydrogen carbonate

- oxytetracycline
- pentobarbital
- tetracycline hydrochloride
- thiopental sodium
- vancomycin

Benzylpenicillin is not compatible with vitamin B complex and ascorbic acid in mixed solutions.

6.3. Shelf life

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C

For reconstituted product used for IM injection in-use storage times and conditions are 48 hours at 2°C to 8°C and 8 hours below 25 °C.

For the diluted product used for IV Injection/Infusion in-use storage times and conditions are 24 hours at 2°C to 8°C and 4 hours below 25 °C.

6.4. Special precautions for storage

Store below 25 °C.

For in-use storage times and conditions, refer to section 6.3

6.5. Nature and contents of container

Type III glass vials with halogenated butyl rubber stopper.

Pack sizes:
Penicillin G Sodium 5 MU dry powder vial:
1, 10 and 25 vials (with a volume of 15 mL).
Penicillin G Sodium 10 MU dry powder vial:
1, 10 and 25 vials (with a volume of 30 mL).

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other instructions for handling

Reconstitution
Constitute as follows:
Penicillin G Sodium 5 MU: add 3.5 ml Water for Injection to provide a concentration of 1 MU/ml.
Penicillin G Sodium 10 MU: add 7 ml Water for Injection to provide a concentration of 1 MU/ml.

Preparation for IV infusion solution:
Penicillin G sodium 5 MU: dissolve in 50 ml Water for Injection.
Penicillin G sodium 10 MU: dissolve in 100 ml Water for Injection.

If this ratio is observed, an approximately isotonic solution is obtained.

The product should be used immediately after dissolution.

This medicinal product is for single use only

Reconstitution and dissolution should take place in controlled and validated aseptic conditions.

7. LICENCE HOLDER AND MANUFACTURER

License Holder
Teva Israel Ltd ,124 Dvora HaNevi'a St, Tel Aviv, Israel

Manufacturer
Sandoz GmbH, Kundl, Austria

8. REGISTRATION NUMBERS
Penicillin G Sodium 5 MU: 024.73.21066
Penicillin G Sodium 10 MU: 137.28.21065

This leaflet was revised in May 2023 according to MOHs guidelines.