SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
DEVAPEN 800 IU Powder For Solution For IM Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial contains
Active substance:
125 mg Potassium penicillin G, equivalent to 200.000 IU/Vial and
600 mg Procaine penicillin G, equivalent to 600.000 IU/Vial

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

3. PHARMACEUTICAL FORM
Vial containing powder for injection
White-light yellow, free-flowing powder with characteristic odor.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
DEVAPEN is used for the treatment of serious infections caused by penicillin G-susceptible microorganisms.

4.2 Posology and method of administration
Posology/frequency and duration of administration:
Due to its short half-life, Penicillin G is administered in divided doses, usually every 4-6 hours with the exception of meningococcal meningitis/septicemia, i.e., every 2 hours.
If doses are divided and administered every 12 hours or in longer intervals, proper amount should be chosen for the desired blood levels. Dosage depends on the severity and nature of the infection, degree of pathogen sensitivity to penicillin and patient's response to the treatment.

It is especially important that the pathogen should be isolated as soon as possible. Concomitant use with another anti-bacterial drug may be necessary.

For most acute infections, treatment should be continued for at least 48 to 72 hours after the patient becomes asymptomatic. Antibiotic therapy for Group A ß-hemolytic streptococcal infections should be maintained for at least 10 days to reduce the risk of rheumatic fever.

Usual doses are as follows if not otherwise recommended:

Serious infections due to susceptible strains of streptococci (including S. pneumoniae) -septicemia, empyema, pneumonia, pericarditis, endocarditis and meningitis:	12 to 24 million units/day depending on the infection and its severity administered in equally divided doses every 4-6 h.
Serious infections due to susceptible strains of staphylococci - septicemia, empyema, pneumonia, pericarditis, endocarditis and meningitis	5 to 24 million units/day depending on the infection and its severity administered in equally divided doses every 4-6 h.
Anthrax	Minimum of 8 million units/day in divided doses every 6 h. Higher doses may be required depending on susceptibility of organism.

Actinomycosis Cervicofacial disease Thoracic and abdominal disease	 1 to 6 million units/day 10 to 20 million units/day
Clostridial infections Botulism (adjunctive therapy to antitoxin) Gas gangrene (debridement and/or surgery as indicated) Tetanus (adjunctive therapy to human tetanus immune globulin)	20 million units/day
Diphtheria (adjunctive therapy to antitoxin and for the prevention of the carrier state)	2 to 3 million units/day in divided doses for 10-12 days
Erysipelothrix endocarditis	12 to 20 million units/day for 4-6 weeks
Fusospirochetosis (severe infections of the oropharynx [Vincent's], lower respiratory tract and genital area)	5 to 10 million units/day
Gram negative bacillus infections (*E. coli, E. aerogenes, A. faecalis, Salmonella, Shigella and Proteus mirabilis*), bacteremia	20 to 80 million units/day
Listeria infections Meningitis Endocarditis	 15 to 20 million units/day for 2 weeks 15 to 20 million units/day for 4 weeks
Pasteurella infections including bacteremia and meningitis	4 to 6 million units/day for 2 weeks
Haverhill fever; Rat-bite fever (*Spirillum minus* or *Streptobacillus moniliformis)*	12 to 20 million units/day for 3-4 weeks
Disseminated gonococcal infections, such as meningitis endocarditis, arthritis, etc., caused by penicillin - susceptible organisms	10 million units/day; duration depends on the type of infection
Syphilis (neurosyphilis)	The dosage and duration of treatment are determined by the patient's age and the stage of the disease. Hospitalization of the patient is recommended.
Meningococcal meningitis and/or septicemia	24 million units/day as 2 million units every 2 h

For prophylaxis against bacterial endocarditis in patients with congenital heart disease, rheumatic or other acquired valvular heart disease when undergoing dental procedures and surgical procedures of the upper respiratory tract, use a combined parenteral-oral regimen. 1.000.000 units of aqueous crystalline penicillin G (30,000 units/kg in children) intramuscularly, mixed with 600,000 units procaine penicillin G (600,000 units for children) should be given ½ to 1 hour before the procedure.

Method of administration:
The intramuscular route is the preferred route of administration for penicillin solution prepared at required concentrations.
Do not inject into or near to an artery or nerve. Injection into or near a nerve may result in permanent neurological damage.
Parenteral products should be visually inspected prior to application for particulate matter or discoloration.

Additional information on special populations
Renal/Hepatic impairment:
Penicillin G is relatively nontoxic, and dosage adjustments are generally required only in cases of severe renal impairment. The recommended dosage regimens are as follows:

- Creatinine clearance <10 ml/min/1.73 m^2: Administer a full loading dose (see recommended dosages above) followed by one-half of the loading dose every 8 to 10 hours.
- Uremic patients with creatinine clearance >10 ml/min/1.73 m^2: Administer a full loading dose (see recommended dosages above) followed by one-half of the loading dose every 4 to 5 hours.
- Additional dosage modifications should be made in patients with hepatic disease and renal impairment.

Pediatric population:
Incompletely developed renal function in newborns may delay elimination of penicillin. Therefore, appropriate reductions in the dosage and frequency of administration should be made in these patients.
All newborns treated with penicillins should be monitored closely for clinical and laboratory evidences of toxic adverse effects.
Pediatric doses are generally determined on a weight basis and should be calculated for each patient individually.
This product should not be administered to patients requiring less than 1 million units per dose.

Recommended doses are:

Indication	**Dosage**
Serious infections such as pneumonia and endocarditis caused by sensitive streptococcus (including *S. pneumoniae*) and meningococcus.	150.000 units/kg/day divided in equal doses every 4 to 6 h; duration depends on infecting organism and type of infection.
Meningitis caused by susceptible strains of pneumococcus and meningococcus	250,000 units/kg/day divided in equal doses every 4 h for 7 to 14 days depending on the infecting organism (maximum dose of 12 to 20 million units/day
Disseminated gonococcal infections (penicillin susceptible strains)	Weight less than 45 kg:
Arthritis	100,000 IU/kg/day in 4 equally divided doses for 7 to 10 days
Meningitis	250,000 IU/kg/day in equal doses every 4 h for 10 to 14 days
Endocarditis	250,000 IU/kg/day in equal doses every 4 h for 4 weeks
Arthritis, meningitis, endocarditis	Weight 45 kg or greater: 10 million IU/day in 4 equally divided doses with the duration of therapy depending on the type of infection
Syphilis after the newborn period (congenital and neurosyphilis)	200,000 to 300,000 IU/kg/day (administered as 50,000 IU/kg every 4 to 6 h) for 10 to 14 days
Diphtheria (adjunctive therapy to antitoxin and for prevention of the carrier state)	150,000 to 250,000 IU/kg/day in equal doses every 6 h for 7 to 10 days
Rat-bite fever; Haverhill fever (with endocarditis caused by S. moniliformis)	150,000 to 250,000 IU/kg/day in equal doses every 4 h for 4 weeks

Neonates are administered for 500.000-1.000.000 IU/day in Listeria infections (*L. monocytogenes*).

Geriatric population:
Clinical studies of Penicillin G did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. It may be useful to monitor renal function.

4.3 Contraindications

- Hypersensitivity to penicillin and its derivatives.
- For flu and cold as it is not effective in treating viral infections.
- As a precaution, to patients with anamnesis of sensitivity to multiple allergens.

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity reactions have been reported in patients on penicillin therapy. This situation is more frequent following parenteral therapy compared to oral therapy. To prevent these signs, anamnesis of the patient should be carefully taken into consideration; careful inquiry should be made containing whether the patient has tendency of allergic diseases or sensitivity to penicillin, cephalosporin and other allergens. In addition, it should be taken into consideration that patients with no sign in anamnesis may also, even if seldom, show the above mentioned hypersensitivity signs. Renal and hematopoietic functions should be controlled periodically, especially for the patients administered for high dose and patients with a prolonged penicillin treatment.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Penicillin, and may range in severity from mild diarrhea to fatal colitis.

It is important to consider possibility of pseudomembranous colitis in patients who present with diarrhea following antibiotic usage. Careful medical history is necessary since Pseudomembranous colitis may occur over 2 months after the administration of antibiotics.

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.

It should be taken into consideration that nonsusceptible microorganisms including fungi may grow during long term treatment. If superinfection occurs, appropriate measures should be taken.

Prescribing Penicillin G Potassium 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.

All cases of penicillin treated syphilis should receive adequate follow-up including clinical and serological examinations.

If an allergic reaction occurs, penicillin G should be discontinued immediately and appropriate therapy instituted. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroid, and airway management, including intubation, should

also be administered as indicated.

Erythema, wheal, flare, or eruption indicates procaine sensitivity. This sensitivity should be treated by the usual methods, including barbiturates. Penicilin G procaine preparations should not be used. Antihistaminics appear beneficial in treatment of procaine reactions.

Procaine Reactions
Immediate toxic reactions to procaine may occur in some individuals, particularly when a large and single dose is administered (4.8 million units). These reactions may be manifested by mental disturbances, including anxiety, confusion, agitation, depression, weakness, seizures, hallucinations, combativeness, and expressed "fear of impending death." The reactions noted in carefully controlled studies occurred in approximately one in 500 patients who received large doses of Penicillin G Procaine. Reactions are transient, lasting from 15 to 30 minutes.

This medicinal product contains less potassium than 1 mmol (39 mg) in each dose; i.e. essentially ‘potassium- free’.

Laboratory interactions:
After treatment with penicillin G, false-positive reactions for glucose in the urine may occur with Benedict’s solution, Fehling’s solution or Clinitest tablet. Such interactions do not occur in enzyme-based tests such as Clinistix and Tes-Tape.
Penicillin G has been associated with pseudoproteinuria by some test methods.

4.5 Interaction with other medicinal products and other forms of interaction
Bacteriostatic antibacterials (i.e., chloramphenicol, erythromycins, sulfonamides or tetracyclines) may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Penicillin blood levels may be prolonged by concurrent administration of probenecid which blocks the renal tubular secretion of penicillins.
Other drugs may compete with Penicillin G for renal tubular secretion and thus prolong the half-life of penicillin. These drugs include: aspirin, phenylbutazone, sulfonamides, indomethacin, thiazide diuretics, furosemide and ethacrynic acid.

If used with oral contraceptives, unexpected pregnancy may occur. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

When used with methotrexate, it may decrease the elimination of methotrexate and thus increase the risk of methotrexate toxicity.

Additional information on special populations:
There is no data.

Pediatric population:
There is no data.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy category: B

Women of child bearing potential/Birth control (Contraception)
Penicillin G interacts with the orally taken contraceptive drugs. Thus, an alternative, efficient and safe birth control method should be applied during treatment period.

Pregnancy
Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Breast-feeding
Penicillins are excreted in human milk. Caution should be exercised when penicillins are administered to a nursing woman.

Fertility
Reproduction studies performed in animals have revealed no evidence of impaired fertility.

4.7 Effects on ability to drive and use machines
There is no data.

4.8 Undesirable effects
Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1.000, <1/100), rare (≥1/10.000, <1/1.000), very rare (<1/10.000), unknown (cannot be estimated from available data).

Blood and lymphatic system disorders
Common: drug induced eosinophilia
Unknown: Reactions include neutropenia, which resolves after penicillin therapy is discontinued; Coombs-positive hemolytic anemia, an uncommon reaction, occurs in patients treated with intravenous penicillin G in doses greater than 10 million units/day and who have previously received large doses of the drug; and with large doses of penicillin, a bleeding diathesis can occur secondary to platelet dysfunction.

Immune system diseases
Unknown: The reported incidence of allergic reactions to all penicillins ranges from 0.7 to 10% in different studies. Sensitization is usually the result of previous treatment with penicillin, but some individuals have had immediate reactions when first treated. In such cases, it is postulated that prior exposure to penicillin may have occurred via trace amounts present in milk or vaccines.

2 types of allergic reactions to penicillin are noted clinically – Immediate and delayed.
Immediate reactions usually occur within 20 minutes of administration and range in severity from urticaria and pruritus to angioneurotic edema, laryngospasm, bronchospasm, hypotension, vascular collapse and death. Such immediate anaphylactic reactions are very rare and usually occur after parenteral therapy, but a few cases of anaphylaxis have been reported following oral therapy.
Another type of immediate reaction, an accelerated reaction, may occur between 20 minutes and 48 hours after administration and may include urticaria, pruritus, fever and, occasionally, laryngeal edema.
Delayed reactions to penicillin therapy usually occur within 1-2 weeks after initiation of therapy. Manifestations include serum sickness-like symptoms, i.e., fever, malaise, urticaria, myalgia,

arthralgia, abdominal pain and various skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis.
Contact dermatitis has been observed in individuals who prepare penicillin solutions.

The Jarisch-Herxheimer reaction is a systemic reaction, that may occur after the initiation of penicillin therapy in patients with syphilis or other spirochetal infections (i.e., Lyme disease and Relapsing fever). The reaction begins one to two hours after initiation of therapy and disappears within 12 to 24 hours. It is characterized by fever, chills, myalgias, headache, exacerbation of cutaneous lesions, tachycardia, hyperventilation, vasodilation with flushing and mild hypotension. The pathogenesis of the Herxheimer reaction may be due to the release from the spirochetes of heat-stable pyrogen.

Metabolism and nutrition disorders
Penicillin G Potassium, (1 million units contains 1.68 mEq of potassium ion) may cause serious and sometimes fatal hyperkalemia, when given intravenously in large doses.

Nervous system disorders
Unknown: Neurotoxic reactions including hyperreflexia, myoclonic twitches, seizures and coma have been reported following the administration of massive intravenous doses, and are more likely in patients with impaired renal function.

Gastrointestinal system disorders
Unknown: Pseudomembranous colitis has been reported with the onset occurring during or after penicillin G treatment. Nausea, vomiting, stomatitis, black or hairy tongue, and other symptoms of gastrointestinal irritation may occur, especially during oral therapy.

Renal and urinary tract disorders
Unknown: Renal tubular damage and interstitial nephritis have been associated with large intravenous doses of penicillin G. Manifestations of this reaction may include fever, rash, eosinophilia, proteinuria, eosinophiluria, hematuria and a rise in serum urea nitrogen. Discontinuation of penicillin G results in resolution in the majority of patients.

General disorders and administration site disorders:
Unknown: Phlebitis and thrombophlebitis may occur, and pain at the injection site has been reported with intravenous administration.

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 via the national reporting system.

4.9 Overdose
Risk of acute overdose, either accidental or deliberate, is not expected with injectable penicillins. However, neurological adverse reactions including convulsions, agitation, confusion, asterixis, hallucinations, stupor, coma, multifocal myoclonus, seizures and encephalopathy may occur with the attainment of high CSF levels of ß-lactams. Hyperkalemia may develop. Overdose may be seen especially in patients with renal failure.
In cases of overdose, discontinue medication, treat symptomatically, and institute supportive measures as required. Potassium penicillin G may be removed from the body by hemodialysis, although the degree of effectiveness of this procedure is questionable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Penicillins, Beta-lactamase sensitive penicillins
ATC Code: J01CE01

Penicillin G is bactericidal against penicillin-susceptible microorganisms during the stage of active multiplication. It acts by inhibiting biosynthesis of cell-wall mucopeptide. It is not effective against the penicillinase-producing bacteria, which include many strains of staphylococci.

Penicillin G is very effective *in vitro* against staphylococci (except penicillinase-producing strains), streptococci (groups A, B, C, G, H, L and M), pneumococci and *Neisseria meningitidis*.
Other organisms susceptible *in vitro* to penicillin G are *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Bacillus anthracis*, *Clostridium*, *Actinomyces species*, *Spirillum minus*, *Streptobacillus moniliformis*, *Listeria monocytogenes*, and *Leptospira*. *Treponema pallidum* is extremely susceptible.
Some species of gram-negative bacilli are susceptible to very high intravenous doses of penicillin G; including some strains of *Escherichia coli*, *Proteus mirabilis*, *Salmonella* and *Shigella*, *Enterobacter aerogenes* and *Alcaligenes faecalis*. Penicillin G is no longer considered a drug of choice for infections caused by these organisms.

5.2 Pharmacokinetic properties

General characteristics

Absorption:
Penicillin G is rapidly absorbed following both intramuscular and subcutaneous injection.

Distribution:
Penicillin G is distributed to most areas of the body including lung, liver, kidneys, muscle, bone and placenta. In the presence of inflammation, levels of penicillin in abscesses, middle ear, pleural, peritoneal and synovial fluids are sufficient to inhibit most susceptible bacteria. Penetration into the eye, brain, cerebrospinal fluid (CSF) or prostate is poor in the absence of inflammation. With inflamed meninges, the penetration of penicillin G into the CSF improves, such that the CSF/serum ratio is 2 to 6%. Inflammation also enhances its penetration into the pericardial fluid. Penicillin G is actively secreted into the bile and resulting in levels at least 10 times those achieved simultaneously in serum. Penicillin G penetrates poorly into human polymorphonuclear leukocytes.

Biotransformation:
Between 15-30 % of an IM penicillin G is metabolized in liver to its inactive derivatives.

Elimination:
The clearance of penicillin G in normal individuals is predominantly via the kidney. It is mainly excreted in the urine undergoes tubular secretion. It is the result of glomerular filtration and active tubular transport.
In patients with normal renal function, the elimination half-life of Penicillin G is 20-30 minutes.
58-85% of the total dose of 300.000 IU is excreted in the urine within 5-hour period. For this reason, high and frequent doses are required to maintain the elevated serum levels desirable in treating certain severe infections in individuals with normal kidney function. In neonates and young infants, and in individuals with impaired kidney function, excretion is considerably delayed. The serum half-life of penicillin G correlates inversely with age and clearance of creatinine and ranges from 3.2 hours in infants 0 to 6 days of age to 1.4 hours in infants 14 days of age or older.

Small amount of drug is excreted in feces, bile and breast milk.
Although Procaine penicillin G reaches lower serum concentrations, it is more efficient when compared with sodium and potassium forms. It reaches to peak level within 1-4 hours following administration and remains detectable for up to 5-7 days.

Linearity/Non-linearity:
A linear relationship, including the lowest range of renal function, is found between the serum elimination rate constant and renal function as measured by creatinine clearance.

5.3 Preclinical safety data
Long-term animal studies on carcinogenicity, mutagenicity and fertility have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None.

6.2 Incompatibilities
None

6.3 Shelf life
48 months

6.4 Special precautions for storage
Store at room temperature below 25°C.
Reconstituted product should be used immediately.

6.5 Nature and contents of container
Colorless type III glass vial with rubber stopper and aluminum flip-off cap and colorless, Type I glass ampoule with ring containing 2 ml water for injection.
Each carton box contains 1 vial and 1 diluent ampoule.

6.6 Special precautions for disposal and other handling
Injectable dry powder is reconstituted with diluent. It should be administered immediately after reconstitution.
Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

91/32

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 15.07.1968
Date of last renewal : 03.10.2011

10. DATE OF REVISION OF THE TEXT