RWANDA FDA
Rwanda Food and Drugs Authority

FOOD AND DRUGS AUTHORIT

SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Fortified Procaine Penicillin for Injection 4mega

Sterile Powder for Injection

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Benzylpenicillin sodium 600 mg
(equivalent to 1.000.000 IU),
Procaine Penicillin 3000 mg
(equivalent to 3.000.000 IU)

<Excipient(s):>

For a full list of excipients, see section 6.1.

3.PHARMACEUTICAL FORM

Sterile Powder for Injection

4.CLINICAL PARTICULARS

4.1Therapeutic indications

Moderately severe to severe infections of the upper respiratory tract, skin and soft-tissue infections, scarlet fever, and erysipelas due to susceptible streptococci (Group A-without bacteremia).
Moderately severe infections of the respiratory tract due to susceptible pneumococci.
Fusospirochetosis (Vincent's gingivitis and pharyngitis). Moderately severe infections of the oropharynx due to susceptible fusiform bacilli and spirochetes.
Syphilis (all stages) due to susceptible Treponema pallidum.
Yaws, Bejel, Pinta due to susceptible organisms.
Fortified Procaine Penicillin is an adjunct to antitoxin for prevention of the carrier stage of diphtheria due to susceptible C. diphtheriae.
Anthrax due to Bacillus anthracis, including inhalational anthrax (post-exposure): to reduce the incidence or progression of the disease following exposure to aerosolized Bacillus anthracis.

4.2Posology and method of administration

Dosage and administration
It is given by I.M. injection only. A suitable amount of Water for Injection is added into the vial before use. 400,000 I.U.-800,000 I.U. each time, once or twice a day.

4.3Method of administration

Fortified Procaine Penicillin may only be administered by deep I.M. injection. Care must be taken to assure that the drug is not injected close to a nerve as this may lead to permanent nerve damage. When treating infants and small children those experienced in the technique should consider

injection into the midlateral aspect of the thigh.

4.4Contraindications

Patients with (a history of) allergy against any penicillin or against Procaine must not be treated with Fortified Procaine Penicillin.

4.5Special warnings and precautions for use

Warnings

Fortified Procaine Penicillin should only be prescribed for the indications listed in this insert.

Anaphylaxis serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of Penicillin hypersensitivity who have 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 anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Pseudomembranous Colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including Penicillin G, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridium. Studies indicate that a toxin produced by Clostridium difficile is one primary cause of antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management of fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against C. difficile colitis.

Procaine Reactions

Immediate toxic reactions to procaine may occur in some individuals, particularly when a large 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.

Precautions for use

Do not inject into or near an artery or nerve.

Injection into or near a nerve may result in permanent neurological damage.

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Penicillin G Procaine Injectable Suspension and other Penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh, and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity, both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

Caution:

1. Before administration skin tests of Procaine and Penicillin should be made. It should not be administrated to patients hypersensitive to Penicillin and Procaine.
2. The suspension prepared by adding a suitable amount of Water for Injection into the vial should be stored below 10℃ and used up within 24 hours.

4.6Interaction with other medicinal products and other forms of interaction

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of Penicillin and concurrent use of these drugs should be avoided.

Concurrent administration of Penicillin and probenecid increases and prolongs serum Penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of Penicillin.

4.8Fertility, pregnancy and lactation

Fertility,Pregnancy

Teratogenic effects—Pregnancy Category B: Reproduction studies performed in the mouse, rat, and

rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. 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.

Lactation

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

4.9Effects on ability to drive and use machines

Not reported

4.10Undesirable effects

Allergic Reactions

Penicillin is a substance of low toxicity but does possess a significant index of sensitization. The following hypersensitivity reactions associated with use of Penicillin have been reported: Skin rashes, ranging from maculopapular eruptions to exfoliative dermatitis; urticaria; serum-sicknesslike reactions, including chills, fever, edema, arthralgia, and prostration. Severe and often fatal anaphylaxis has been reported. As with other treatments for syphilis, the Jarisch-Herxheimer reaction has been reported.

Procaine toxicity manifestations and hypersensitivity reactions have been reported.

Gastrointestinal

Pseudomembranous colitis has been reported with the use of Penicillin G. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

4.11Overdose

Penicillin has the potential to cause neuromuscular hyperirritability or convulsive seizures.

Treatment

Management of overdosage should include monitoring of electrolyte balance, cardiovascular status and renal function. Penicillins are not readily removed by dialysis.

5.PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamic properties

WHO-ATC code: J01CE09, J01CE01

Pharmacotherapeutic group: Combination of penicillin, including beta lactamase inhibitor

Mechanism of action

Benzylpenicillin is a beta-lactam antibiotic and has a bactericidal action against Gram-positive bacteria, Gram-negative cocci, some other Gram-negative bacteria, spirochaetes, and actinomycetes.

It exerts its killing action on growing and dividing bacteria by inhibiting bacterial cell-wall synthesis, although the mechanisms involved are still not precisely understood. Bacterial cell walls are held rigid and protected against osmotic rupture by peptidoglycan. Benzylpenicillin inhibits the final cross-linking stage of peptidoglycan production by binding to and inactivating transpeptidases, penicillin-binding proteins on the inner surface of the bacterial cell membrane. However, it is now realised that other earlier stages in cell-wall synthesis can also be inhibited. Other mechanisms involved include bacterial lysis by the inactivation of endogenous inhibitors of bacterial autolysins. Its action is inhibited by penicillinase and other beta-lactamases that are produced during the growth of certain micro-organisms.

Many Gram-negative organisms are intrinsically resistant by virtue of the inability of benzylpenicillin to penetrate their outer membranes. Intrinsic resistance can also be due to structural differences in the target penicillin-binding proteins. See under Resistance, below, for reference to acquired resistance.

The following pathogenic organisms are usually sensitive to benzylpenicillin: - Gram-positive aerobes and anaerobes including Bacillus anthracis, Clostridium perfringens, Cl. tetani, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae, Listeria monocytogenes, Peptostreptococcus spp., non-beta-lactamase-producing staphylococci, and streptococci including Streptococcus agalactiae (group B), Str. pneumoniae (pneumococci), Str. pyogenes (group A), and some viridans streptococci; enterococci are relatively insensitive. - Gram-negative cocci including Neisseria meningitidis (meningococci) and Neisseria gonorrhoeae (gonococci), although beta-lactamase-producing strains are common.

Gram-negative bacilli including Pasteurella multocida, Streptobacillus moniliformis, and Spirillum minus (or minor); most Gram-negative bacilli, including Pseudomonas spp. and Enterobacteriaceae, are insensitive although some strains of Proteus mirabilis and Escherichia coli may be inhibited by high concentrations of benzylpenicillin.

- Gram-negative anaerobes including Prevotella (non-fragilis Bacteroides) and Fusobacterium spp.
- Other organisms including Actinomyces and the spirochaetes, Borrelia, Leptospira, and Treponema spp.
- Mycobacteria, fungi, mycoplasmas, and rickettsias are not sensitive.

Benzylpenicillin may exhibit synergy with other antimicrobials, particularly the aminoglycosides, and such combinations have been used against enterococci and other relatively insensitive bacteria.

Its activity may be enhanced by clavulanic acid and other beta-lactamase inhibitors, and both enhancement and antagonism have been demonstrated for beta-lactam combinations. Antagonism has been reported to occur with some bacteriostatic drugs, such as chloramphenicol or tetracyclines, that interfere with active bacterial growth necessary for benzylpenicillin to achieve its effect.
Susceptible Gram-positive bacteria acquire resistance to beta lactams mainly through the induction of beta-lactamases, including penicillinases. These enzymes are liberated extracellularly and hydrolyse the beta-lactam ring. This resistance is usually plasmid-mediated and can be transferred from one bacterium to another. Gram-negative bacteria produce beta-lactamases within their cell membranes which may be chromosomally or plasmid-mediated; all Gram-negative species probably contain small amounts of beta-lactamases. Resistance in Gram-negative species may also be due to changes in their outer membrane resulting in the failure of beta lactams to reach their target penicillin-binding proteins. Changes in the binding characteristics of penicillin-binding proteins may also result in resistance in Gram-positive and Gram-negative bacteria.
Most strains of Staphylococcus aureus are now resistant to benzylpenicillin. Streptococcus pneumoniae with reduced susceptibility or complete resistance to benzylpenicillin have increasingly been reported. Strains of Neisseria meningitidis with reduced sensitivity to benzylpenicillin have been identified. Penicillinase-producing Neisseria gonorrhoeae are widespread; reduced sensitivity of gonococci to benzylpenicillin may also result from alterations in penicillin-binding proteins.
Most strains of Haemophilus influenzae and Moraxella catarrhalis (Branhamella catarrhalis) are now resistant.
Some organisms, usually Gram-positive cocci such as staphylococci or streptococci, may develop tolerance and are inhibited but not killed by benzylpenicillin; in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration.

5.2Pharmacokinetic properties

Benzylpenicillin rapidly appears in the blood following intramuscular injection of water-soluble salts, and maximum concentrations are usually reached in 15 to 30 minutes; peak plasma oncentrations of about 12 μg per ml have been reported after single doses of 600 mg.
When given by mouth, benzylpenicillin in inactivated fairly rapidly by the acid gastric secretions and only up to 30% is absorbed, mainly from the duodenum; maximum plasma-penicillin concentrations usually occur in about an hour. In order to attain plasma-penicillin concentrations after oral administration comparable to those following intramuscular injection, up to 5 times as much benzylpenicillin may be necessary. Absorption varies greatly in different individuals and is better in patients with reduced gastric acid production including neonates and the elderly. Food decreases the absorption of Benzylpenicillin and oral doses are best given at least half an hour before or 2 to 3 hours after meal.

Benzylpenicillin is widely distributed at varying concentrations in body tissues and fluids. It appears in pleural, pericardial, peritoneal and synovial fluids but in the absence of inflammation diffuses only to small extent into abcess cavities, avascular areas, the eye, the middle ear, and the cerebrospinal fluid. Inflamed tissue is, however, more rapidly penetrated and, for example, in meningitis higher concentrations of benzylpenicillin are achieved in the CSF. Active transport out of the CSF is reduced by probenecid. In patients with uraemia other organic acids may accumulate in the CSF and compete with Benzylpenicillin for active transport; toxic concentrations of Benzylpenicillin sufficient to cause convulsions can result.

Benzylpenicillin diffuses across the placenta into the foetal circulation, and small amounts appear in the milk of nursing mothers.

The plasma half-life is about 30 minutes although it may be longer in neonates and the elderly because of incomplete renal function. In renal failure the half-life may be increased to about 10 hours. Approximately 60% is reported to be bound to plasma proteins.

Benzylpenicillin is metabolised to a limited extent and the penicilloic acid derivate has been recovered in the urine. Benzylpenicillin is rapidly excreted in the urine, principally by tubular secretion and about 20% of a dose given by mouth appears unchanged in the urine; about 60 to 90% of a dose of aqueous Benzylpenicillin given intramusculary appears in the urine mainly within the first hour. Significant concentrations are achieved in the bile, bit in patients with normal renal function only small amounts are excreted via the bile. Benzylpenicillin is removed by haemodialysis.

Renal tubular secretion is inhibited by probenecid, which sometimes given to increase plasma-penicillin concentration.

When Procaine Penicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin. Peak plasma concentration are produced in 1 to 4 hours, and effective concentrations of benzylpenicillin are usually maintained for 12 to 24 hours. However, plasma concentrations are lower than those following an equivalent dose of benzylpenicillin potassium or sodium.

5.3Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6. 2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Fortified Procaine Penicillin for Injection should not be stored above 30°C. The reconstituted solution should be stored at 2-8°C in a refrigerator and used within 24 hours.

6.5 Nature and contents of container

20ml Type II (soda-lime) glass vial, sealed with Al- cap.

Packs of 50 vials/tray/middle box,12middle boxes/carton.

6.6. Instructions for use and handling

The vials of Fortified Procaine Penicillin for Injection are not suitable for multi-dose use. Any residual solution of Fortified Procaine Penicillin Sodium should be discarded

7.MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

MARKETING AUTHORISATION HOLDERL:Reyoung Pharmaceutical Co., Ltd.

MANUFACTURING SITE ADDRESSES:No.1, Ruiyang Road, Yiyuan County, Shandong Province, China

8. MARKETING AUTHORISATION NUMBER

Lu20160062

9.DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

2016/11/1

10.DATE OF REVISION OF THE TEXT

2024/2/22

11.DOSIMETRY (IF APPLICABLE)

Not applicable

12.INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not applicable

13.DOCUMENT REVISION HISTORY

SN	Date	Version No.	Description of Change (section)
1.	2016-11-01	01	Initial issue
2.	2024.2.22	02	Revised the format of the content according to the

			customer’s requirement