1.3.1 Product Information for Health Professionals

Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

FORTIFIED PROCAINE PENICIILIN FOR INJECTION 4 MEGA

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)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for injection in 20 ml glass vials.

Description: White, crystalline powder

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Procaine Penicillin is a salt of Benzylpenicillin which is almost insoluble in water. After administration by i.m. injection it forms a depot at the injection site, from which Benzylpenicillin is released slowly.

This leads to lower plasma drug concentrations which last longer than after injection of Benzylpenicillin, thus allowing treatment of moderately severe infections with one single injection per day. Due to the Benzylpenicillin Sodium added rather high initial plasma drug levels are achieved rapidly after i.m. injection.

The released Penicillin G is an antibiotic with (bactericidal) antimicrobial activity against many Gram-positive bacteria (including listeria, Corynebacterion diphtheriae, clostridia, pneumococci) and some Gram-negative cocci (including gonococci and meningococci) and against some spirochaetes and actinomyces. It is inactivated by penicillinase, an enzyme produced by many "penicillin-resistant" bacteria, such as "resistant" staphylococci.

Fortified Procaine Penicillin is used (like Procaine Penicillin) in the treatment of a variety of moderately severe infections due to susceptible organisms, including: infections of the respiratory tract (bronchitis, pneumonia); skin infections such as erysipelas; lymphadenitis and lymphangitis; gonorrhoea; acute pelvic inflammatory disease; (congenital) syphilis; (cutaneous) anthrax.

NOTE: When selecting antibiotics for the prevention of bacterial endocarditis, the physician or dentist should read the full joint statement of the American Heart Association and the American Dental Association.

4.2. Posology and method of administration

Dosage varies with type and severity of infection. The following dosage recommendations can therefore only be used as guidelines:

Adults: (0,6-) 1-1,5 (-4) million IU daily in 1-2 divided doses by deep i.m. injection.

Children: 30.000-100.000 IU/kg daily in 1-2 divided doses by deep i.m. injection.

Duration of treatment depends on indication and clinical course. Textbooks of medicine should be consulted in specific situations as there are many differing dosage regimens for specific diseases. Some of the most important dosage recommendations concern:

- congenital syphilis: 50,000 IU/kg daily i.m. for 2 weeks;

- early syphilis (less than one year´s duration)

in adults:1.2 million IU once daily i.m. for 10 consecutive days;

- acute uncomplicated gonorrhoea: 4.8 million IU i.m. accompanied by 1 g Probenecid orally. This regimen cannot provide a 100% cure rate but it is quite effective in situations where patients´ compliance cannot be assured otherwise;

- anthrax (cutaneous): 0.6-1.2 million IU i.m. daily.

Important: 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.

4.3 Contraindications

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

4.4 Special warnings and 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.

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 penicillin. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or 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 penicillin, cephalosporins or other allergens. If an allergic reaction occurs, procaine penicillin should be discontinued and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Care is necessary if very high doses of penicillins are given, especially if renal function is poor, because of the risk of neurotoxicity. The intrathecal route should be avoided. Renal, hepatic, and haematological status should be monitored during prolonged and high-dose therapy. Because of the Jarisch-Herxheimer reaction, care is also necessary when treating patients with spirochaete infections, particularly syphilis.

Penicillins may interfere with some diagnostic tests such as those for urinary glucose using copper sulfate, direct antiglobulin (Coombs') tests, and some tests for urinary or serum proteins. Penicillins may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.

Concurrent administration of Probenecid leads to a reduced urinary excretion of Penicillin G. This brings about an increased drug serum level. The combination of Procaine Penicillin and Probenecid (adults: 1 g once daily; children 2-5 years: 250 mg once daily; children > 5 years: 500 mg once daily) can be helpful in situations where high initial drug levels are required.

4.5 Interaction 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 Probenicid leads to a reduced urinary excretion of Penicillin G. This brings about an increased drug serum level. The combination of Procaine Penicillin and probenicid (adults: 1 g once daily; children 2 - 5 years: 250 mg once daily, children > 5 years: 500 mg once daily) can be helpful in situations, where high initial drug levels are required.

Studies using procaine penicillin, ampicillin or carbeacillin indicate that penicillins can interfere with urinary glucose determinations using cupric sulphate (e.g. Benedicts' solution, Clinitest). In high concentrations, penicillins can cause false positive results in these tests for urinary glucose. Glucose oxidase tests for urinary glucose (e.g. Clinistix, Tes-tape) are reportedly not affected by the presence of penicillins.

4.6 Pregnancy and lactation

Safety for use in pregnancy has not been established. Fortified Procaine Penicillin G, like other penicillins, the cephalosporins and erythromycin is one of the antibiotics of first choice during all stages of pregnancy.

Pregnancy

Teratogenic Effects: Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to Benzylpenicillin. 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 Benzylpenicillin is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

None.

4.8 Undesirable effects

Allergic reactions against penicillins are occasionally dramatic. Acute hypersensitivity reactions typically begin within 1-30 minutes after administration of the drug. They are more frequent after injection than after peroral administration: Tingling sensation in the feet, face or mouth and sweating followed by a general flush are early signs of anaphylaxy.

This may proceed to a "lump in the throat" airway obstruction and cardiovascular shock may follow. Appropriate and immediate treatment is imperative. This may comprise administration of Epinephrine, i.v. fluids (plasma expanders) and vasopressor drugs. Patients should be placed in a recumbent position with their feet elevated. Antihistamins and corticosteroids may help shorten the course of reaction.

Some patients with syphillis may experience a Jarisch-Herxheimer reaction (with headache, fever, chills and generalized malaise) shortly after starting treatment with penicillin.

Pain at the injection site is quite common. When doses are repeated, rotate the injection side. Injection of Procaine Penicillin directly into a blood vessel may lead to signs of neurotoxicity (nausea, anxiety, tinnitus and convulsions).

4.9 Overdose

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

5.1 Pharmacodynamics properties

WHO-ATC code: J01CR01

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.

5.2 Pharmacokinetic 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 concentrations 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.

5.3. Preclinical 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

Sodium Citrate Anhydrous, Citric Acid Anhydrous, Sodium Carboxymethyl Cellulose

6.2. Incompatibility

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.

Like other antibiotics, penicillin G sodium may occasionally reduce the efficacy of oral contraceptives.

6.3. Shelf life

36 months (or 3 years)

6.4. Special precautions for storage

Store protected from moisture, freezing and excessive heat at a temperature not exceeding 25°C.

6.5. Nature and content of container

1. GLASS VIAL

Clear, colourless 20 ml glass vials Type III with grey rubber closure and additional sealed with aluminium cap and a label printed in 3 color (PANTONE® 233 C, Cool Gray 2 C, Black) TROGE® layout.

2, MID-BOX FOR 50 VIALS

Three color printed (PANTONE® Pink 233C, Cool Gray 2C, Black) cardboard box in TROGE® layout.

6.6 Special precautions for disposal and other handling

Unused medicine or its waste should be wasted as required by the relevant local authority.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

NA

9. DATA ON FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

NA

10. DATE OF (PARTIAL) REVISION OF THE TEXT

August 2018