Summary of Product Characteristics

1. Name of the finished pharmaceutical product

Benzathine benzylpenicillin for injection 2.4MIU

2. Qualitative and quantitative composition

Each vial contains Benzathine benzylpenicillin 2.4MIU.

3. Pharmaceutical form

Powder for injection

4. Clinical particulars

4.1 Therapeutical Indications:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of penicillin G benzathine and other antibacterial drugs, penicillin G benzathine should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Intramuscular penicillin G benzathine is indicated in the treatment of infections due to penicillin-G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine:

Mild-to-moderate infections of the upper-respiratory tract due to susceptible streptococci.

Venereal infections—Syphilis, yaws, bejel, and pinta.

Medical Conditions in which Penicillin G Benzathine Therapy is indicated as Prophylaxis:

Rheumatic fever and/or chorea—Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as follow-up prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

4.2 Posology and method of administration

Benzathine benzylpenicillin is given by deep intramuscular injection.

Benzathine benzylpenicillin 900 mg is equivalent to about 720 mg of benzylpenicillin (1.2 million units).

For early syphilis, a single dose of benzathine benzylpenicillin 1.8 g by deep intramuscular injection is given, usually as 2 injections at separate sites. In late syphilis, 1.8 g is given at weekly intervals for 3 consecutive weeks. Benzathine benzylpenicillin is not usually recommended for the treatment of neurosyphilis because of reports of inadequate penetration into the CSF.

Infants up to 2 years of age may be given a single intramuscular dose of 37.5 mg/kg for the treatment of congenital syphilis, provided there is no evidence of infection in the CSF.

For the treatment of other treponemal infections, such as yaws, pinta, and endemic syphilis (bejel), a single intramuscular dose of benzathine benzylpenicillin 900 mg is given; a dose of 450 mg may be used in children.

For streptococcal pharyngitis and the primary prevention of rheumatic fever, the adult dose is a single intramuscular injection of 900 mg; children under 30 kg may be given 225 to 675 mg.

To prevent recurrences of acute rheumatic fever, 900 mg is given intramuscularly every 3 or 4

weeks to adults; a dose of 450 mg has been used for children under 30 kg.

4.3 Contraindications

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication

4.4 Special warnings and precautions for use

Penicillin G benzathine 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 and/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 Penicillin G Benzathine, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. if an allergic reaction occurs, Penicillin G Benzathine 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.

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

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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.

Precautions

General

Prescribing Penicillin G Benzathine 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 a development of drug-resistant bacteria.

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intra-arterial administration, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

Information for Patients

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop

watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including Penicillin G Benzathine should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Penicillin G Benzathine is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Penicillin G Benzathine or other antibacterial drugs in the future.

Laboratory Tests

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

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 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.

4.6 Pregnancy and Nursing women

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.

Nursing Mothers

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine is administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been conducted with this drug.

Pediatric Use

Geriatric Use

Clinical studies of penicillin G benzathine 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, and it

may be useful to monitor renal function.

4.7 Effects on ability to drive and use machines

Not reported.

4.8 Undesirable effects

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

As with other treatments for syphilis, the Jarisch-Herxheimer reaction has been reported.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia, and prostration); and anaphylaxis including shock and death. Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. (See WARNINGS section.)

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of penicillin G benzathine:

Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache.

Cardiovascular: Cardiac arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism; vasodilation; vasovagal reaction; cerebrovascular accident; syncope.

Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.

Hemic and Lymphatic: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, edema, hemorrhage, cellulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer. Neurovascular reactions including warmth, vasospasm, pallor, mottling, gangrene, numbness of the extremities, cyanosis of the extremities, and neurovascular damage.

Metabolic: Elevated BUN, creatinine, and SGOT.

Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.

Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transverse myelitis; seizures; coma. A syndrome manifested by a variety of CNS symptoms such as severe agitation with confusion, visual and auditory hallucinations, and a fear of impending death (Hoigne's syndrome), has been reported after administration of penicillin G procaine and, less commonly, after injection of the combination of penicillin G benzathine and penicillin G procaine. Other symptoms associated with this syndrome, such as psychosis,

seizures, dizziness, tinnitus, cyanosis, palpitations, tachycardia, and/or abnormal perception in taste, also may occur.
Respiratory: Hypoxia; apnea; dyspnea.
Skin: Diaphoresis.
Special Senses: Blurred vision; blindness.
Urogenital: Neurogenic bladder; hematuria; proteinuria; renal failure; impotence; priapism

4.9 Overdose

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Benzylpenicillin exerts a bactericidal action against penicillin sensitive microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide. It is not active against the penicillinase-producing bacteria which include many strains of Staphylococci. The following in-vitro data are available but the clinical significance is unknown. Benzylpenicillin exerts high in vitro activity against Staphylococci (except penicillinase-producing strains), Streptococci (Groups A, C, G, H, L and M) and Pneumococci. Other organisms sensitive to benzylpenicillin are: Neisseria gonorrhoea, Corynebacterium diphtheria, Bacillus anthracis, Clostridia spp, Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes and Leptospira spp. Treponema pallidum is extremely sensitive to the bactericidal action of benzylpenicillin.

5.2 Pharmacokinetic properties

When benzathine benzylpenicillin is given by intramuscular injection, it forms a depot from which it is slowly released and hydrolysed to benzylpenicillin.
Peak plasma concentrations are produced in about 24 hours and are lower than those after an equivalent dose of benzylpenicillin potassium or sodium. However, depending on the dose, benzylpenicillin is usually detectable in plasma for up to 4 weeks (but see below).
Distribution into the CSF is reported to be poor. Due to the slow absorption from the site of injection, benzylpenicillin has been detected in the urine for up to 12 weeks after a single dose.
Benzathine benzylpenicillin is relatively stable in the presence of gastric juice, but absorption from the gas-trointestinal tract is variable. Plasma concentrations of benzylpenicillin after an oral dose are lower than those from the same dose of a soluble penicillin; peak con-centrations are also produced less rapidly, but may persist for longer.
Plasma concentrations.
Benzathine benzylpenicillin has been given every 4 weeks for secondary prophylaxis against rheumatic fever, although some advocate giving it every 3 weeks
to ensure adequate plasma concentrations of benzylpenicillin.
Typical concentrations achieved after a single intramuscular injection of benzathine benzylpenicillin 900 mg have been cited as about 100, 20, and 2 nanograms/mL on days 1, 14, and 32 respectively. In one study1 adequate concentrations (defined as 20 nanograms or more per mL) were seen in more than 80% of serum samples at 3 weeks, but in only 36% at 4 weeks. In a further study, 2 in which single doses of 900 mg, 1.35 g and 1.8 g were compared, it appeared that doses higher than the 900mg dose of benzathine benzylpenicillin usually recommended might

prolong the duration of protective plasma concentrations of ben-zylpenicillin (defined as above 25 nanograms/mL) and improve the efficacy of dosing every 4 weeks for prophylaxis against
rheumatic fever.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store in a cool & dry place below 30°C.

KEEP OUT OF THE REACH OF CHILDREN

6.5 Presentation:

12ml molded vial, 1vial+10ml WFI/tray/box
or
12ml molded vial, 50vials/tray/box

7. Marketing authorisation holder

B&O PHARM
ZAC de la Masquère - 500 rue de l'Hers - 31750 ESCALQUENS France

Manufacturer

Reyoung Pharmaceutical Co., Ltd.
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09/2020.