PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

BENZATHINE PENICILLIN 2,4 MG COSPHARM

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for solution for intramuscular injection contains 2,4 Million I.U.

equivalent to approximately 2000 mg Benzathine Benzylpenicillin.

Buffering Agent: Anhydrous Sodium Citrate.

Sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for intramuscular injection.

White or almost white crystalline powder, almost odourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of infections caused by sensitive organisms.

Syphilis.

Prophylactic use:

Prevention of recurrence of rheumatic fever.

4.2 Posology and method of administration

Posology

Adults:

Syphilis: 2,4 Mega Units.

Recurrence of rheumatic fever: 1,2 Mega Units every 3 to 4 weeks.

Children:

Rheumatic fever

600 000 Units every 3 to 4 weeks.

Method of administration

Benzathine Penicillin 2,4 Cospharm should be administered by deep intramuscular injection only.

Reconstitute Benzathine Penicillin 2,4 Cospharm 2,4 Mega Units with 5 ml water for injection.

It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper.

Administer by deep intramuscular injection only. To avoid any inadvertent intravascular administration of Benzathine Penicillin 2,4 Cospharm, aspiration prior to intramuscular injection is advised. The site of injection should be changed if

repeated injections are necessary. The prepared suspension should be shaken well before use and any unused portion discarded. In the treatment of beta-haemolytic streptococcal infections a therapeutic dose must be administered for at least 10 days. The high concentration of suspended Benzathine Penicillin 2,4 Cospharm requires administration at a slow rate, with at least a 20G needle, to prevent blockage of the needle.

Note: If a dosage of 1,2 Mega Units of Benzathine Penicillin is required, it is recommended to reconstitute Benzathine Penicillin 2,4 Cospharm 2,4 Mega Units with 6 ml water for injection.

4.3 Contraindications

- Hypersensitivity to penicillins or any of the excipients listed in section 6.1.

- Babies in the neonatal period born of mothers hypersensitive to penicillins.

Cases of cross-sensitivity to other beta-lactams have been reported. Should not be used in life-threatening conditions e.g., endocarditis, peritonitis or meningitis where very high doses of penicillin is indicated.

Must not be administered intravenously (IV).

4.4 Special warnings and precautions for use

Benzathine Penicillin 2,4 Cospharm should not be used in tissues with reduced perfusion. Before initiating therapy with Benzathine Penicillin 2,4 Cospharm, a careful investigation should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents (see sections 4.3 and 4.8).

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 in atopic individuals. If an allergic reaction occurs, Benzathine Penicillin 2,4 Cospharm must be discontinued and appropriate therapy instituted.

Prior to treatment, a hypersensitivity test should be performed if possible. The patient should be made aware of the possible occurrence of allergic symptoms and of the need to report them.

Caution should be exercised in patients with the following conditions:

- allergic diathesis or bronchial asthma (there is an increased risk of a hypersensitivity reaction);

- renal insufficiency (for dose adjustment, see section 4.2). Care should be taken when high doses are given to patients with renal impairment because of the risk of neurotoxicity or congestive heart failure.

- impaired hepatic function (see section 4.2).

Based on a general principle, particularly in some exposed patients, medical observation should if possible be ensured for at least half an hour after the administration of this antibiotic, as severe immediate allergic reactions may occur even after the first administration.

Beta-lactams are associated with a risk of encephalopathy (confusion, altered levels of consciousness, epilepsy or movement abnormalities), particularly in cases of overdose or impaired renal function.

When treating syphilis, a Jarisch-Herxheimer reaction may occur as a result of the bactericidal action of penicillin on pathogens. Within 2 to 12 hours after administration headaches, fever, sweating, shivering, myalgia, arthralgia, nausea, tachycardia, increased

blood pressure followed by hypotension may occur. These symptoms resolve after 10 to 12 hours. Patients should be informed that this is a usual, transient sequela of antibiotic therapy. Appropriate therapy should be instituted to suppress or attenuate a Jarisch-Herxheimer reaction (see section 4.8).

With long-term treatment (more than a single dose), periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is recommended.

Prolonged use of Benzathine Penicillin 2,4 Cospharm may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for superinfections.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including benzylpenicillin benzathine and may range in severity from mild to life threatening (see section 4.8).

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics.

Should antibiotic-associated colitis occur, Benzathine Penicillin 2,4 Cospharm should be discontinued, a medical practitioner be consulted, and an appropriate therapy initiated.

Anti-peristaltic medicines are contraindicated in this situation.

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

In diseases such as severe pneumonia, empyema, sepsis, meningitis or peritonitis, which require higher serum penicillin levels, alternative treatment such as the water-soluble alkali salt of benzylpenicillin should be considered.

Notes on administering Benzathine Penicillin 2,4 Cospharm:

Painful induration may occur in the event of accidental subcutaneous administration. Ice packs help in such cases.

In the event of inadvertent intravascular injection, Hoigné syndrome may occur (symptoms of shock with mortal fear, confusion, hallucinations, possibly cyanosis, tachycardia and motor disorders, although no circulatory collapse), caused by microemboli of the suspension. The symptoms regress within an hour. If progression is severe, parenteral administration of sedatives is indicated.

In the event of inadvertent intra-arterial injection, particularly in children, serious complications may occur, such as vascular occlusion, thrombosis and gangrene.

Initial signs are pale patches in the skin area of the gluteal region. As a result of high injection pressure, retrograde entry of the injected liquid into the common iliac artery, aorta or spinal arteries may occur.

Repeated injections into a limited area of the muscle tissue, which are associated with long term therapy with depot-penicillins (e.g. in the treatment of syphilis) may induce tissue damage and increased local vascularization. Subsequent injections increase the possibility of penetration of injection substance into the blood, either by direct injection into a blood vessel or caused by the injection pressure itself, or by “rubbing” of the depot. During long term therapy it is therefore recommended to administer each injection a large distance from the preceding injection.

Effect on diagnostic laboratory procedures:

- A positive direct Coombs' test often develops (≥ 1 % to < 10 %) in patients receiving 10 million IU (equivalent to 6 g) benzylpenicillin or more per day. After discontinuation of the penicillin, the direct antiglobulin test may remain positive for 6 to 8 weeks (see section 4.8).

- Determination of urinary protein using precipitation techniques (sulphosalicylic acid, trichloroacetic acid), the Folin-Ciocalteu-Lowry method or the biuret method may lead to false positive results. Urinary protein should therefore be determined by other methods.

- Urinary amino acid determination using the ninhydrin method may likewise lead to false-positive results.

- Penicillins bind to albumin. In electrophoresis methods to determine albumin, pseudobisalbuminaemia may therefore be simulated.

- During therapy with benzylpenicillin benzathine, non-enzymatic urinary glucose detection and urobilinogen detection may exhibit a false positive.

- When determining 17-ketosteroids (using the Zimmermann reaction) in the urine, increased values may occur during therapy with benzylpenicillin benzathine.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per vial of 2.4 Million I.U, i.e. essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of Benzathine Penicillin 2,4 Cospharm is not recommended with:

- bacteriostatic antibiotics: based on the general principle not to combine bactericidal and bacteriostatic antibiotics.

It should only be combined with other antibiotics if a synergistic or an additive effect is to be expected.

Caution should be exercised when co-administering the following:

- probenecid: the administration of probenecid leads to inhibition of the tubular secretion of benzylpenicillin, resulting in an increase in the 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 benzylpenicillin into brain tissue even further.
- methotrexate: when taken at the same time as benzylpenicillin benzathine, the excretion of methotrexate is reduced. This can lead to increased methotrexate toxicity. The combination with methotrexate is not recommended.
- anticoagulants: concomitant use with oral anticoagulants may increase the antivitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the antivitamin K drug adjusted accordingly, both during and after treatment with Benzathine Penicillin 2,4 Cospharm.

4.6 Fertility, pregnancy and lactation

Pregnancy

Benzathine Penicillin 2,4 Cospharm crosses the placenta. 10-30 % of maternal plasma concentrations are found in the foetal circulation. High concentrations are also reached in the amniotic fluid. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Benzathine Penicillin 2,4 Cospharm can be used during pregnancy.

Breastfeeding

Benzathine Penicillin 2,4 Cospharm is excreted in human milk in small amounts. The concentration in maternal milk may reach 2 to 15 % of the mother's serum concentrations. Although no undesirable effects in infants fed on breast milk have been reported to date, consideration must nevertheless be given to the possibility of sensitisation or interference with the intestinal flora. Breast-feeding should be stopped in the case of occurrence of diarrhoea, candidiases or rash in the child. In infants also being fed on baby food, mothers should express and discard breast milk during Benzathine Penicillin 2,4 Cospharm treatment

Breastfeeding can be resumed 24 hours after finishing treatment.

Fertility

No fertility studies have been conducted in humans. Reproductive studies on

mice, rats and rabbits have not revealed any negative effects on fertility. No long-

term fertility studies on laboratory animals are available.

4.7 Effects on ability to drive and use machines

Due to the occurrence of possible serious undesirable effects (e.g. anaphylactic shock with collapse and anaphylactoid reactions, see also section 4.8), Benzathine Penicillin 2,4 Cospharm can have a major influence on the ability to drive and use machines.

4.8 Undesirable effects

Table 2 - Tabulated list of adverse drug reactions

System Organ class	Frequent	Less Frequent	Frequency Unknown
Infections and infestations	Candidiasis		
Blood and lymphatic system disorders		Haemolytic anaemia, Leukopenia Thrombocytopenia, Agranulocytosis	Prolongation of bleeding time and defective platelet function
Immune system disorders		Allergic reactions, Urticaria, Other skin rashes, Angioedema, Erythema multiform, Exfoliative dermatitis, Fever, Arthralgia, Anaphylactic shock with collapse and anaphylactoid reactions (asthma, purpura, gastrointestinal symptoms).	Serum sickness, a generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia can develop within a few hours to several weeks after treatment. Sore mouth, black hairy tongue, Jarisch-Herxheimer reaction.
Nervous system disorders			Convulsions and other signs of central nervous system toxicity
Gastrointestinal disorders	Diarrhoea, Nausea, Stomatitis and glossitis, Vomiting		Pseudomembranous colitis (see section 4.4), heartburn.
Hepatobiliary disorders			Hepatitis, Cholestasis, Increase in liver enzyme values

Renal and urinary disorders		Nephropathy Interstitial nephritis	
General disorders and administration site conditions			Pain at the injection site, Injection site infiltrates, Hoigné syndrome, Nicolau syndrome
Investigations	Positive direct Coombs' test, False-positive urinary protein determination when precipitation techniques are used (Folin- Ciocalteu-Lowry method, biuret method), False-positive urinary amino acid determination (ninhydrin method), Simulation of pseudo bisalbuminaemia when using electrophoresis methods to determine albumin, False-positive nonenzymatic urinary glucose detection and urobilinogen detection, Increased levels		

	when determining 17 ketosteroids in urine (when the Zimmermann reaction is used) (see section 4.4)		

Description of selected adverse reactions

When treating patients with syphilis, a Jarisch-Herxheimer reaction may occur as a result of bacteriolysis, characterised by fever, chills, headache, general and focal symptoms. In patients with dermatomycosis, para-allergic reactions may occur, as common antigenicity may exist between penicillins and dermatophyte metabolites.

In infants, local reactions are possible.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za.

4.9 Overdose

At extremely high doses, penicillins can induce neuromuscular excitability or epileptiform seizures. If overdose is suspected, clinical monitoring and symptomatic measures are indicated. Benzylpenicillin can be haemodialyzed. In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A 20.1.2 Penicillins.

Pharmacotherapeutic group: Antibacterials for systemic use, beta-lactamase sensitive penicillins.

ATC code: J01CE08

Mechanism of action:

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

Resistance

Resistance to benzylpenicillin benzathine can be due to the following mechanisms:

- Inactivation by beta-lactamases: benzylpenicillin benzathine is not beta lactamase-resistant and therefore has no effect against beta-lactamase- producing bacteria(e.g.

staphylococci or gonococci).

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

Pharmacokinetic (PK)/Pharmacodynamic (PD) relationship

Efficacy largely depends on the length of time that the active substance level remains above the minimum inhibitory concentration (MIC) of the pathogen.

Breakpoints

Table 3 - EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints.

Pathogen	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 0,12 mg/l	> 0,12 mg/l
Streptococcus spp. (Groups A, B, C, G)	≤ 0,25 mg/l	> 0,25 mg/l

Streptococcus pneumoniae #	≤ 0,06 mg/l	> 2 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
Non-species-specific breakpoints *	≤ 0,25 mg/l	> 2 mg/l

* Based mainly on serum pharmacokinetics

Infections other than meningitis

The prevalence of acquired resistance in individual species may vary geographically and with time for selected species and local information on the resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Table 4 - Commonly susceptible species.

Aerobic Gram-positive micro-organisms
Streptococcus pyogenes
Streptococcus dysgalactiae subsp. equisimilis ° (Group C & G streptococci)

Streptococci of the “Viridans” group° ^
Other micro-organisms
Treponema pallidum °
° Information derived from published literature, clinical experience and therapeutic guidelines. ^ 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

Following intramuscular administration, benzylpenicillin benzathine is absorbed slowly and converted by hydrolysis to benzylpenicillin. Peak plasma levels are reached 24 hours (children) or 48 hours (adults) post-injection.

Distribution

After intramuscular injection serum levels of benzylpenicillin are sustained:

• 14 days after intramuscular injection of 2,4 Million I.U. a serum level of 0,12 µ g/ml was measured.

The volume of distribution is around 0,3-0,4 l/kg in adults and about 0,75 l/kg in children. Plasma protein binding is approximately 55 %.

Biotransformation and elimination

Elimination largely takes place (50 – 80 %) as unchanged substance via the kidneys (85 – 95 %) and, to a lesser extent, in active form within the bile (about 5 %). The

plasma half-life in adults with healthy kidneys is approximately 30 min.

Kinetics in special patient groups

- *Preterm and newborn infants:* due to the immaturity of kidneys and liver at this age, the serum half-life is up to three hours (and more). The dosing interval must therefore be no shorter than 8 - 12 hours (depending on the degree of maturity).

- *Elderly patients:* elimination processes may also be delayed with advanced age.

The dosage should therefore be adjusted to individual renal function.

5.3 Preclinical safety data

Reproductive studies in mice, rats and rabbits revealed no negative effects on fertility or on the foetus. No long-term studies on laboratory animals are available with regard to carcinogenicity, mutagenicity and fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Buffering Agent: Anhydrous Sodium Citrate.

6.2 Incompatibilities

This medicinal product must not be used with other medicinal products except water for injection.

6.3 Shelf life

36 months.

Following reconstitution, Benzathine Penicillin 2,4 Cospharm, should be used immediately.

6.4 Special precautions for storage

Store at or below 30 °C. Protect from light.

KEEP OUT OF REACH FROM CHILDREN.

6.5 Nature and contents of container

Benzathine Penicillin 2,4 Cospharm is a white or almost white crystalline powder in a 20 ml USP Type III glass vial with a 20 mm Bromo butyl rubber stopper having a 20 mm aluminium flip off seal.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Reconstitution of the suspension for intramuscular injection:

The suspension must be prepared aseptically.

Reconstitute Benzathine Penicillin 2,4 Cospharm with 5 ml water for injection. It is recommended that a needle not larger than 21 gauge is used to reduce fragmentation of the rubber stopper. Administer by deep intramuscular injection only. To avoid any inadvertent intravascular administration of Benzathine Penicillin 2,4 Cospharm, aspiration prior to intramuscular injection is advised. The site of injection should be changed if repeated injections are necessary. The prepared suspension should be shaken well before use and any unused portion discarded. In

the treatment of beta-haemolytic streptococcal infections a therapeutic dose must be administered for at least 10 days. The high concentration of suspended Benzathine Penicillin 2,4 Cospharm requires administration at a slow rate, with at least a 20G needle, to prevent blockage of the needle.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Cospharm Investments (Pty) Ltd.

2 Concourse Crescent

Lonehill

Sandton, 2191

8 REGISTRATION NUMBER

55/20.1.2/0704

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 March 2024

10 DATE OF REVISION OF THE TEXT

To be allocated