National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

BENZATHINE BENZYLPENICILLIN B.P. 2,400,000 IU

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each Vial contains:
Benzathine Benzylpenicillin BP 24,00,000 UNITS (2.0g)
Buffering Agent: Anhydrous Sodium Citrate USP

3. PHARMACEUTICAL FORM

Powder for injection

4. Clinical particulars

4.1 Therapeutic indications

{Bentarpen} is indicated in adults, adolescents, children and neonates for the treatment and prophylaxis of the following infections caused by pathogens sensitive to penicillin:

For the treatment of:
- erysipelas
- syphilis: early syphilis (primary and secondary)
- latent syphilis (except for neurosyphilis and presence of pathological CSF findings)
- yaws
- pinta

For the prophylaxis of:
- rheumatic fever (chorea, rheumatic carditis)
- poststreptococcal glomerulonephritis
- erysipelas

When using {Bentarpen}, consideration should be given to the general guidelines on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

The dosing recommendations depend on the severity and the type of infection, the age and the hepatorenal function of patients. International guidelines should be considered in addition to national or local guidance for some specific indications (eg syphilis, prophylaxis of rheumatic fever).

Dosage and duration of treatment

General therapy:

Adults and adolescents: 1.2 mio IU once weekly
Children > 30 kg body weight: 1.2 mio IU once weekly
Children < 30 kg body weight: 600,000 IU once weekly
Duration of treatment: single dose
(In streptococcal diseases, a 10-day minimum course of treatment should be observed to avoid secondary diseases. This is generally ensured with a single injection of {Bentarpen} 600,000 IU, {Bentarpen} 1.2 mio IU or {Bentarpen} 2.4 mio IU.)

Treatment of syphilis:

Primary and secondary stage
Adults and adolescents: 1 x 2.4 mio IU
Children: 50,000 IU/kg body weight, however not more than 2.4 mio IU
(If clinical symptoms recur or laboratory findings remain strongly positive, treatment should be repeated.) Duration of treatment: single dose

Late-stage syphilis (latent seropositive syphilis)

Adults and adolescents: 2.4 mio IU once weekly
Children: 50,000 IU/kg body weight, however not more than 2.4 mio IU

Duration of treatment: 3 weeks

Treatment of congenital syphilis: without neurological involvement
Neonates and infants: 1 x 50,000 IU/kg body weight
Duration of treatment: single dose

Treatment of yaws, pinta:
Adults and adolescents: 1 x 1.2 mio IU
Children > 30 kg body weight: 1 x 1.2 mio IU
Children < 30 kg body weight: 1 x 600,000 IU
Duration of treatment: single dose

Prophylaxis of rheumatic fever, poststreptococcal glomerulonephritis and erysipelas:
Adults and adolescents: 1 x 1.2 mio IU every 3-4 weeks
Children > 30 kg body weight: 1 x 1.2 mio IU every 3-4 weeks
Children < 30 kg body weight: 1 x 600,000 IU every 3-4 weeks
Duration of treatment:
a) Without cardiac involvement: at least 5 years, or up to 21 years of age
b) Transient cardiac involvement: at least 10 years, or up to 21 years of age
c) Persistent cardiac involvement: at least 10 years or up to 40 years of age; life-long prophylaxis is sometimes necessary.

Special patient groups
Patients with impaired renal function

Based on creatinine clearance			
Creatinine clearance in ml/min	100-60	50-10	<10
Serum creatinine in mg%	0.8-1.5	1.5-8.0	15
Proportion of the normal daily dose of {Bentarpen}	100%	75%	20-50% (1-3 mio IU/d max.)
Dosage interval	In 1 single administration	In 1 single administration	In 2-3 single administration

Haemodialysis patients
Benzathine-Benzylpenicillin can be removed by hemodialysis. There are no data available on the influence of dialysis on the plasma levels of benzyl penicillin. The decision to treat patients on dialysis with {Bentarpen} needs therefore to be taken on a case by case basis.
Patients with impaired hepatic function
In very severe cases of impaired hepatic and renal function, there may be a delay in the degradation and excretion of penicillins.

4.3 Contraindications
Hypersensitivity to the active substance benzathine Benzylpenicillin, to any of the penicillins, soya, peanut or to any of the excipients

History of a severe immediate hypersensitivity reaction (eg anaphylaxis) to another beta-lactam agent (eg cephalosporin, carbapenem or monobactam)

4.4 Special warnings and precautions for use
{Bentarpen} should not be used in tissues with reduced perfusion. Before initiating therapy with Bentarpen, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents. Serious and occasionally fatal hypersentivity 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, Bentarpen 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):
- In renal insufficiency;
- In impaired hepatic function;

Based on a general principle, in particular in some exposed patients, a medical observation should if possible be ensured for at last half an hour after the administration of this antibiotic, as severe immediate allergic reactions may occur even after the first administration.
When treating syphilis, a Jarisch-Herxheimer reaction may occur as a result of the bactericidal action of penicillin on pathogens. 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.

In long-term treatment (more than 5 days), blood count monitoring and renal function tests are recommended.

Vigilance is required for overgrowth of resistant germs. At the onset of secondary infections, appropriate measures should be taken.

In the event of severe and persistent diarrhoea, antibiotic-associated pseudomembranous colitis (bloody/mucoid, watery diarrhoea, dull, diffuse-to-colicky abdominal pain, fever, occasionally tenesmus) should be considered, which can be life-threatening. In these cases, {Bentarpen} should therefore be discontinued immediately and therapy instituted based on pathogen detection results. Antiperistaltic agents are contraindicated.

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 benzyl penicillin should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of benzathine benzylpenicillin is not recommended with:

Based on the general principle not to combine bactericidal and bacteriostatic antibiotics, {Bentarpen} should not be combined with bacteriostatic antibiotics.

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 probenicid inhibits the penicillin transport from the cerebrospinal fluid, so that the concomitant administration of probenecid reduces the penetration of benzyl penicillin into brain tissue even further.
Methotrexate: when taken at the same time as benzathine benzylpenicillin, 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 anti-vitamin K effect and the risk of bleeding. It is recommended that the International Normalised Ratio (INR) is monitored frequently and the posology of the anti-vitamin K drug adjusted accordingly, both during and after treatment with Bentarpen.

4.6 Pregnancy and Lactation

Pregnancy

Benzathine benzylpenicillin crosses the placenta. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. {Bentarpen} can be used during pregnancy when appropriately indicated and with due consideration of the benefits and risks.

Breast-feeding

Benzathine benzylpenicillin 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, candidosis or rash in the child.

In infants also being fed on baby food, mothers should express and discard breast milk during benzathine benzylpenicillin treatment. Breast-feeding can be resumed upon cessation of treatment 24 hours later.

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

Information not available

4.8 Undesirable effects

The undesirable effects are arranged according to body system and their frequency is categorized as follows:

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
Not known (cannot be estimated from the available data)

Infections and infestations

Common: candidiasis

Blood and lymphatic system disorders

Very rare: haemolytic anaemia, leukopenia, thrombocytopenia, agranulocytosis.

Immune system disorders

Rare: allergic reactions: urticaria, angioedema, erythema multiforme, exfoliative dermatitis, fever, arthralgia, anaphylactic shock with collapse and anaphylactoid reactions (asthma, purpura, gastrointestinal symptoms).

Not known: serum sickness. When treating syphilis, a Jarisch-Herxheimer reaction may occur as a result of bacteriolysis, characterised by fever, chills, general and focal symptoms. In patients with dermatomycosis, para-allergic reactions may occur, as common antigenicity may exist between penicillins and dermatophyte metabolites.

Gastrointestinal disorders

Common: diarrhoea, nausea
Uncommon: stomatitis and glossitis, vomiting
Not known: pseudomembranous colitis.

Hepatobiliary disorders

Not known: hepatitis, cholestasis
Renal and urinary disorders
Rare: nephropathy, interstitial nephritis

General disorders and administration site conditions

Unknown: pain at the injection site, injection site infiltrates
Hoigné- and Nicolau Syndrome

Investigations

Common:

• Positive direct Coombs' test.

• False-positive urinary protein determination when precipitation techniques are used (FolinCiocalteu-Lowry method, biuret method).
• False-positive urinary amino acid determination (ninhydrin method).
• Simulation of pseudobisalbuminaemia when using electrophoresis methods to determine albumin.
• False-positive non-enzymatic urinary glucose detection and urobilinogen detection.
• increased levels when determining 17-ketosteroids in urine (when the Zimmermann reaction is used)

In infants, local reactions are possible.
It cannot be excluded that, in very rare cases and due to the povidone content, povidone may accumulate in the reticuloendothelial system (RES) or local deposits and foreign body granuloma may occur, which may be confused with tumors.

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 haemodialysed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antibacterial for systemic use, beta-lactamase sensitive penicillins.
ATC code: J01CE08

For benzathine benzylpenicillin, 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.

5.2 Pharmacokinetic properties

Pharmacokinetic data issued from the originator Bentarpen dossier are old and information derived from them is limited. However published literature about benzathine benzylpenicillin, clinical experience and therapeutic guidelines can be taken into account.

Absorption

Following intramuscular administration of Bentarpen, the absorption of benzylpenicillin is very slow. Bentarpen is the longest-acting depot penicillin. For many indications, 1-2 injections per month are sufficient. Consequently, the frequency of injections and the resultant local trauma are reduced. Peak plasma levels are reached 24 hours (children) or 48 hours (adults) post-injection.

Distribution

About 55% of the administered dose is plasma protein-bound. When high-dose penicillin therapy is administered, therapeutically effective concentrations are reached even in poorly accessible tissues, such as heart valves, bone, as well as in the cerebrospinal fluid or in empyema, etc. Benzylpenicillin crosses the placenta. 10-30% of maternal plasma concentrations are found in the foetal circulation. High concentrations are also reached in the amniotic fluid. In contrast, transfer into milk is low. The volume of distribution is around 0.3-0.4 l/kg 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 with 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

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Sodium Citrate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months for the date of manufacturing.

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container<and special equipment for use, administration or implantation>

50 vials in printed carton

6.6 Special precautions for disposal <and other handling>

There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

7 <APPLICANT/MANUFACTURER>

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