**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

BENZATHINE BENZYLPENICILLIN 1.2 MU ANDO Powder for Suspension for Injection

BENZATHINE BENZYLPENICILLIN 2.4 MU ANDO Powder for Suspension for Injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BENZATHINE BENZYLPENICILLIN 1.2 MU ANDO: benzathine benzylpenicillin 989 mg equivalent to benzylpenicillin 1,2 mega.

BENZATHINE BENZYLPENICILLIN 2.4 MU ANDO: benzathine benzylpenicillin 1977,7 mg equivalent to benzylpenicillin 2,4 mega.

Sugar free.

For full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Powder for suspension for injection.

Powder: White to almost white powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of infections caused by organisms sensitive to penicillin.

Streptococcal pharyngitis; syphilis of less than 1 year duration; uncomplicated cases of erysipeloid.

Prophylactic use: recurrence of rheumatic fever.

### 4.2 Posology and method of administration

**Posology**

Adults: Streptococcal pharyngitis, and erysipeloid: 1,2 million units.

Syphilis: 2,4 million units.

Recurrence of rheumatic fever 1,2 million units.

Children: 600 000 units to 1,2 million units.

Should be administered by deep intramuscular injection once a month.

**Method of administration**

**FOR INTRAMUSCULAR USE ONLY.**

**Not for intravenous (IV) use.**

See section 6.6 for preparation of suspension.

**4.3 Contraindications**

Must not be administered to patients who are allergic to penicillin or cephalosporins or to any ingredient of Benzathine Benzylpenicillin Ando listed in section 6.

Babies in the neonatal period born to mothers allergic to penicillin.

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**

**FOR INTRAMUSCULAR USE ONLY.**

Benzathine Benzylpenicillin Ando should not be used in tissues with reduced perfusion.

Before initiating therapy with Benzathine Benzylpenicillin Ando, a careful investigation should be made

concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam medicines (see sections 4.3 and 4.8).

When administered to a patient with penicillin allergy, anaphylactic shock may occur. If an allergic reaction occurs, Benzathine Benzylpenicillin Ando must be discontinued and appropriate therapy instituted. Epinephrine (adrenaline), corticosteroids, antihistamines and appropriate IV fluids should be used to treat anaphylaxis (see section 4.3).

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;
- impaired hepatic function.

Based on a general principle, particularly in some exposed patients, 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.

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 Benzylpenicillin Ando 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 medicines including Benzathine Benzylpenicillin Ando 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 Benzylpenicillin Ando 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 watersoluble alkali salt of benzylpenicillin should be considered.

***Notes on administering Benzathine Benzylpenicillin 1.2 & 2.4 Ando***

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. Disturbances of blood electrolytes may follow the administration of large doses of Benzathine Benzylpenicillin Ando.

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 Benzathine Benzylpenicillin Ando, 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 Benzathine Benzylpenicillin Ando.

*Excipients*

Benzathine Benzylpenicillin Ando powder and solvent for suspension for injection contains phospholipids from the soya lecithin. If you are allergic to peanut or soya, do not use this medicine.

**4.5 Interaction with other medicines and other forms of interaction**

Concomitant administration of Benzathine Benzylpenicillin Ando is not recommended with:

- bacteriostatic *antibiotics*: based on the general principle not to combine bactericidal and 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, 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 Benzylpenicillin Ando.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

Benzathine Benzylpenicillin Ando 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.

Safety and efficacy during pregnancy has not been established.

**Breastfeeding**

Benzathine Benzylpenicillin Ando is excreted in human milk in small amounts. The concentration in maternal milk may reach 2 to 15 % of the mother's serum concentrations.

Safety and efficacy during breastfeeding has not been established.

**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**

Benzathine Benzylpenicillin Ando is not known to affect the ability of a patient to drive or use machines, but the effect on the individual should be known before they attempt to drive or 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 Benzylpenicillin Ando can have a major influence on the ability to drive and use machines.

**4.8 Undesirable effects**

*Summary of the safety profile*

The most frequent and common adverse reactions related to benzylpenicillin benzathine are: candidiasis, diarrhoea, nausea, laboratory investigation changes.

*Table 1 - Tabulated list of adverse drug reactions by MedDRA System Organ Class.*

| **MedDRA System Organ class** | **Frequent** | **Less frequent** | **Frequency unknown** |
|---|---|---|---|
| **Infections and infestations** | Candidiasis | | |
| **Blood and lymphatic system disorders** | | Leukopenia, thrombocytopenia, agranulocytosis | Haemolytic anaemia, neutropenia, prolongation of bleeding time, defective platelet function |
| **Immune system disorders** | Allergic reactions which may include exfoliative dermatitis, other skin rashes, interstitial nephritis and vasculitis, may occur | Angioedema, erythema multiform, arthralgia, anaphylactic shock with collapse and anaphylactoid reactions (asthma, purpura, gastrointestinal) | Serum sickness, a generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia can develop within a few hours to several weeks after starting treatment; superinfection by resistant species, such as pseudomonas or candida, which do not respond to penicillin therapy, may |

| | | | |
|---|---|---|---|
| | | | occur. Some patients with syphilis and other spirochaete infections may have a Jarisch Herxheimer reaction shortly after starting treatment with Benzathine Benzylpenicillin Ando. Symptoms can include fever, chills, headache. and reactions at the site of the lesions. |
| **Gastrointestinal disorders** | Diarrhoea, nausea, stomatitis and glossitis, vomiting | | Heartburn, pseudo-membranous colitis (see section 4.4) |
| **Hepato-biliary disorders** | | | Hepatitis, cholestasis, increases in liver enzyme values |
| **Skin and subcutaneous tissue disorders** | | A sore mouth or tongue and a black hairy tongue | |
| **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),<br><br>False-positive urinary amino acid determination (ninhydrin method),<br><br>Simulation of Pseudobisal buminaemia when using electrophoresis methods to determine albumin,<br><br>False-positive nonenzymatic urinary glucose detection and urobilinogen detection,<br><br>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 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.

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 tumours.

*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. Healthcare 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/Publications/Index/8

**4.9 Overdose**

At extremely high doses, penicillins can induce neuromuscular excitability or epileptiform seizures. If overdose is suspected, supportive treatment and symptomatic measures are indicated. Benzylpenicillin can be haemodialysed.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

A 20.1.2 Penicillins

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

Benzathine penicillin is a narrow spectrum penicillin, sensitive to penicillinase. It is administered by intramuscular injection. A depot is formed from which benzathine penicillin is slowly released and hydrolysed

to benzylpenicillin.

Benzathine penicillin has an antimicrobial action similar to benzylpenicillin. Its use should be restricted to treatment of infections caused by organisms highly sensitive to penicillin because of the relatively low blood concentrations reached.

*Known resistance mechanisms and cross-resistance*

Penicillin resistance can be mediated by alteration of penicillin binding proteins or development of beta-lactamases.

Resistance to penicillin may be associated with cross-resistance to a variety of other beta-lactam antibiotics either due to a shared target site that is altered, or due to a beta-lactamase with a broad range of substance molecules. In addition to this, cross-resistance to unrelated antibiotics can develop due to more than on resistance gene being present on a mobile section of DNA (e.g. plasmid, transposon etc.) resulting in two or more resistance mechanisms being transferred to a new organism at the same time.

**5.2 Pharmacokinetic properties**

Benzylpenicillin sodium BP rapidly appears in the blood following intramuscular injection of water-soluble salts and maximum concentrations are usually reached in 15-30 minutes. Peak plasma concentrations of about 12 mcg/ml have been reported after doses of 600 mg with therapeutic plasma concentrations for most susceptible organisms detectable for about 5 hours. Approximately 60 % of the dose injected is reversibly bound to plasma protein.

In adults with normal renal function the plasma half-life is about 30 minutes. Most of the dose (60-90 %) undergoes renal elimination, 10 % by glomerular filtration and 90 % by tubular secretion. Tubular secretion is inhibited by probenecid, which is sometimes given to increase plasma penicillin concentrations. Biliary elimination of benzylpenicillin sodium BP accounts for only a minor fraction of the dose.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lecithin

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store at or below 30 °C.

### 6.5 Nature and contents of container

Benzathine Benzylpenicillin Ando 1,2 MU: 7 ml clear and transparent, type II (soda-lime) glass mold vials, closed with grey bromination isobutylene isoprene rubber stopper and blue flip-off caps (abbreviated as 7 ml mold vial, butyl rubber stoppers hereafter); then packaged in a transparent PVC tray.

Pack size of 1, 50 or 100 vials. Not all pack sizes may be marketed.

Benzathine Benzylpenicillin Ando 2,4 MU: 12 ml Clear and transparent, type II (soda-lime) glass mold vials, closed with grey bromination isobutylene isoprene rubber stopper and blue flip-off caps (abbreviated as 12 ml mold vial, butyl rubber stoppers hereafter); then packaged in a transparent PVC tray.

Pack size of 1, 50 or 100 vials. Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

*Preparation of suspension:*

Distribute the contents evenly by tapping the vial lightly. Add Water for Injection and shake the vial vigorously.

Within a few minutes the suspension will reach its maximum viscosity and the insoluble penicillin will then be uniformly suspended.

a) 1,2 MU vial: Add 3,5 ml Water for Injection. This will yield a suspension allowing 1,2 mega units in 4 ml to be withdrawn.

b) 2,4 MU vial: Add 7 ml Water for Injection. This will yield a suspension allowing 2,4 mega units in 8 ml to be withdrawn.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Ando Pharma (Pty) Ltd

73 Keurboom Crescent

Plattekloof

Cape Town

7500

## 8. REGISTRATION NUMBER(S)

BENZATHINE BENZYLPENICILLIN 1.2 MU ANDO: 56/20.1.2/0384

BENZATHINE BENZYLPENICILLIN 2.4 MU ANDO: 56/20.1.2/0385

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated by SAHPRA upon approval.

## 10. DATE OF REVISION OF THE TEXT

27 July 2022