Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Kopen Sugar Free 250mg/5ml Powder for Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of Oral Solution contains 250mg of Phenoxymethylpenicillin as Phenoxymethylpenicillin Potassium.

Excipients with known effect

Sorbitol
The 250mg/5ml solution contains 800.00 mg of sorbitol in each 5 ml dose.

Sodium Benzoate (E211)
Each 5ml of Oral Solution contains 16mg of Sodium benzoate (E 211).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Oral Solution.
A pale yellow granular powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For use in treatment of infections caused by susceptible staphylococci, pneumococci, gonococci, and haemolytic streptococci.

Phenoxymethylpenicillin is also indicated for
- Prophylaxis of pneumococcal infection (e.g. in asplenia and in patients with sickle cell disease).

- Prophylaxis of rheumatic fever.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults: 250mg to 500mg every six hours depending on the severity of the condition.

The elderly: as for adults

Renal Impairment: Reduced dosage if renal function is markedly impaired.

Prophylactic use:
- Pneumococcal infection (e.g. asplenia)

Adults: 500mg every 12 hours
Children 6 - 12 years: 250mg every 12 hours
Children <5 years: 125mg every 12 hours

- Rheumatic fever

250 mg twice daily is recommended for long-term prophylaxis of rheumatic fever.

Children
Infants (up to 1 year): 62.5 mg every six hours. The total daily dose is 250mg in divided doses.
Children 1 - 5 years: 125mg 6 hourly
Children 6 - 12 years: 250mg 6 hourly

Method of Administration
For instructions on reconstitution on the medicinal product before administration, see section 6.6.

For oral administration only
Ideally, each dose should be given half an hour before (or at least three hours after) a meal.

To avoid late complications (rheumatic fever), infections with β-haemolytic streptococci should be treated for 10 days.

The treatment of acute otitis media with penicillin V should be limited to five days. However, 5-10 days treatment may be recommended in patients with potential for complications.

4.3 Contraindications

Phenoxymethylpenicillin is contraindicated in patients known to be hypersensitive to Penicillin, including ampicillin, and should be used with caution in patients with known histories of allergy or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Before initiation of penicillin therapy, careful enquiry should be made concerning previous hypersensitivity reaction to penicillin, cephalosporins or other drugs. Fatal anaphylaxis has been observed with oral penicillin.

Patients suffering from severe gastrointestinal impairments accompanied by vomiting and diarrhoea should not be treated with penicillin V, because sufficient absorption is not ensured. (In those cases a parenteral administration is recommended, e.g. with benzyl penicillin or another adequate antibiotic).
Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Administer with caution in the presence of markedly impaired renal function, as safe dosage may be lower than that recommended.

In patients undergoing long-term penicillin V treatment the complete and differential blood count, as well as the liver and kidney function, should be monitored.

Prolonged use of an antibiotic may result in the development of superinfection due to organisms resistant to that anti-infective including Pseudomonas and Candida. If superinfection occurs, appropriate measures should be taken.

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of penicillins. These are serious and potentially life-threatening cutaneous conditions. Patients should be advised of the signs and symptoms of SJS and TEN (e.g., progressive skin rash often with blisters or mucosal lesions) and instructed to discontinue use immediately and seek urgent medical attention.

Information about excipients:

Sorbitol:
Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Sodium benzoate:
Increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue). Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in new-born babies (up to 4 weeks old).

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per 5 ml dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Aminoglycosides: Neomycin may reduce the absorption of phenoxymethylpenicillin.

Bacteriostatic antibacterials: Bacteriostatic antibacterials such as Chloramphenicol, Erythromycin and Tetracyclines have been reported to antagonise the bactericidal activity of penicillins and concomitant use is not recommended.

Guar Gum: Reduces the absorption of phenoxymethylpenicillin.

Methotrexate: Use of phenoxymethylpenicillin while taking methotrexate can cause reduced excretion of methotrexate thereby increasing the risk of toxicity.

Probenecid: Reduces excretion of phenoxymethylpenicillin by blocking renal tubular secretion.

Laboratory tests: Non enzymatic methods of detecting glucose in the urine may show false positive results during treatment with phenoxymethylpenicillin. Phenoxymethylpenicillin may also interfere with tests for urobilinogen

4.6 Fertility, pregnancy and lactation

Pregnancy:
The product should not be used during pregnancy unless considered essential by the physician.
There are no or a limited amount of data from the use of Phenoxymethylpenicillin in pregnant women. As a precautionary measure, it is preferable to avoid the use of Phenoxymethylpenicillin during pregnancy.

Lactation:
The product is excreted in breast milk, presenting the risk of candidiasis and also of central nervous system toxicity due to prematurity of the blood brain barrier. There is a theoretical possibility of later sensitisation.

4.7 Effects on ability to drive and use machines

None known

4.8 Undesirable effects

The most common reactions to oral penicillin are gastrointestinal effects and hypersensitivity reactions. Hypersensitivity reactions of all intensities - to the point of anaphylactic shock- have also been observed after oral penicillin use. Severe anaphylactoid reactions, which occur significantly less often after oral administration of penicillin than after intravenous or intramuscular administration, may necessitate appropriate emergency management.

The following convention has been utilised for the classification of undesirable effects:-
Very common ($\geq$1/10), Common ($\geq$1/100, <1/10), Uncommon ($\geq$1/1000, <1/100), Rare ($\geq$1/10,000, <1/1000), Very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic disorders:
Very rare: Changes in blood counts, including, thrombocytopenia, granulocytopenia, agranulocytosis, neutropenia, leucopenia, eosinophilia, pancytopenia and haemolytic anaemia. These changes are reversible on discontinuation. Coagulation disorders have also been reported.

Metabolism and Nutrition Disorders
Very common: Loss of appetite

Gastrointestinal disorders:

Common: Gastric discomfort, flatulence, nausea, vomiting, abdominal pain, diarrhoea, glossitis, stomatitis. These disorders are usually light and abate during or at the latest
after discontinuing treatment.
Uncommon: Sore mouth and black hairy tongue (discolouration of tongue)
Rare: Dry mouth
Very rare: tooth discolouration.

Hepatobiliary disorders:
Rare: Transiently raised liver enzymes
Very Rare: Hepatitis, cholestatic jaundice.

Skin and subcutaneous tissue disorders:
Common: exanthema
Rare: Toxic epidermal necrolysis, allergic vasculitis, exfoliative dermatitis.
Very Rare: Severe skin reactions such as Stevens-Johnson syndrome

Immune disorders:
Common: Allergic reactions (typically manifest as skin reactions). Urticarial, erythematous or morbilliform rash, pruritus may occur.
Very rare: Serious allergic reactions including drug fever, arthralgia, eosinophilia, angioneurotic oedema, laryngeal oedema, bronchospasm, tachycardia, dyspnoea, serum sickness, allergic vasculitis and dropping of blood pressure up to life threatening shock.

Frequently fever and eosinophilia will be the only manifestations of penicillin hypersensitivity.

Infections and infestations:
Very Rare: a pseudomembranous enterocolitis may occur, mostly caused by Clostridium difficile,

Nervous system disorders:
Rare: Taste alteration
Not Known: Central nervous system toxicity has been reported (especially with high doses or in severe renal impairment); paraesthesia may occur with prolonged use.

Renal and urinary disorders:
Very Rare: Interstitial nephritis.

Investigations:
Rare: blood pressure decreased

Reporting of suspected adverse reactions
Reporting suspected adverse reactionsafter authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

Symptoms: A large oral overdose of penicillin may cause nausea, vomiting, stomach pain, diarrhoea, and rarely, major motor seizures. If other symptoms are present, consider the possibility of an allergic reaction. Hyperkalaemia may result from over dosage, particularly in patients with renal insufficiency.

Management: No specific antidote is known. Symptomatic and supportive therapy is recommended. Activated charcoal with a cathartic, such as sorbitol may hasten drug elimination. Penicillin may be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J01CE02

Phenoxymethylpenicillin is a beta-lactamase sensitive natural penicillin.

Mechanism of Action:
Phenoxymethylpenicillin acts through interference with the final stage of synthesis of the bacterial cell wall. The action depends on its ability to bind certain membrane-bound proteins, (penicillin-binding proteins or PBPs) that are located beneath the cell wall. These proteins are involved in maintaining cell wall structure, in cell wall synthesis and in cell division, and appear to possess transpeptidase and carboxypeptidase activity.

Bacterial surface enzymes called autolysins also appear to be involved in the lethal effect of penicillins, particularly for gram-positive bacteria. In gram-negative bacilli osmotic rupture of cells may occur when the cell wall is weakened. Phenoxymethylpenicillin can also produce morphological changes in vitro including the formation of long filaments or abnormally shaped cells. Bacteria that are not growing or dividing are generally not killed by phenoxymethylpenicillin.

Mechanism(s) of Resistance:
Phenoxymethylpenicillin is inhibited by penicillinase and other beta-lactamases that are produced by certain micro-organisms. The incidence of beta-lactamase producing organisms is increasing.

EUCAST clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens are:

EUCAST Species-related breakpoints (Susceptible≤ /Resistant>) Units: mg/L	
Staphylococcus	≤0.12/>0.12
Streptococcus A, B, C, G	≤0.25/>0.25
S. pneumoniae	≤0.5/>2

Staphylococci: Most staphylococci are penicillinase-producers. Penicillinase-producing strains are resistant. The benzylpenicillin breakpoint (shown) will mostly, but not unequivocally, separate beta-lactamase producers from non-producers.

Streptococci: Strains with MIC values above the S/I breakpoint are very rare or not yet reported. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant. Streptococci groups A, B, C and G do not produce beta-lactamase. The addition of a beta-lactamase inhibitor does not add clinical benefit.

Streptococcus pneumoniae: For phenoxymethylpenicillin, report S. pneumoniae with benzylpenicillin MICs above 0.06 mg/L resistant.

5.2 Pharmacokinetic properties

Absorption: Rapidly but incompletely absorbed after oral administration; calcium and potassium salts are better absorbed than the free acid. Absorption appears to be reduced in patients with coeliac disease. Absorption appears to be more rapid in fasting than non-fasting subjects.

Blood concentration: After an oral dose of 125mg, peak serum concentration of 200 to 700ng/ml are attained in 2 hours. After an oral dose of 500mg, peak serum concentrations reach 2 to 5ug/ml in 2 to 4 hours.

Half life: Biological half life - about 30 minutes.

Distribution: Widely distributed throughout the body and enters pleural and ascitic fluids and also in cerebrospinal fluid when the meninges are inflamed; Phenoxymethylpenicillin crosses the placenta and is secreted in the milk; (protein binding 50 to 80% bound plasma proteins).

Metabolic reactions: Hydroxylation may occur.

Excretion: 20% to 35% of an oral dose is excreted in the urine in 24 hours.

5.3 Preclinical safety data

Not Applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Benzoate (E211)
Saccharin Sodium
Trusil Orange Flavour
Quinoline yellow (E104)
Sorbitol (E420)
Ammonium Glycyrrhizate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened container: 2 years
Reconstituted oral solution: 7 days.

6.4 Special precautions for storage

Unconstituted powder: Store below 25°C. Store bottle in the original carton. Keep the bottle tightly closed in order to protect from moisture.

Reconstituted oral solution: Store at 2°C - 8°C (in a refrigerator). Store in the original container. Keep the bottle tightly closed.

6.5 Nature and contents of container

Natural high density polyethylene bottle 150ml with white cap with a blue TE band containing 100ml of oral solution on reconstitution.
Natural high density polyethylene bottle 150ml with a child resistant /tamper evident cap containing 100 ml of oral Solution on reconstitution
5ml spoon (Biesterfield, Hugo Meding Cat. No. 7229) comprised of polypropylene with CE mark.
Or
5 ml opaque polystyrene spoon

6.6 Special precautions for disposal and other handling

Powder for Oral Solution: To prepare add 84ml of water.
Shake until all powder is in solution.
The reconstituted oral solution is a yellow solution with an orange odour and flavour.
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Athlone Pharmaceuticals Limited
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1 Burlington Road
Dublin 4
D04 C5Y6
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1418/014/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 April 1988

Date of last renewal: 11 April 2008

10 DATE OF REVISION OF THE TEXT

April 2024