AUSTRALIAN PRODUCT INFORMATION

ASPECILLIN VK

phenoxymethylpenicillin tablets

1 NAME OF THE MEDICINE

Phenoxymethylpenicillin (as potassium)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ASPECILLIN VK tablet contains 250 mg or 500 mg of phenoxymethylpenicillin (as potassium) as the active ingredient.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

ASPECILLIN VK 250 mg tablets are bright yellow, smooth, round film coated tablets.

ASPECILLIN VK 500 mg tablets are bright yellow, smooth, film-coated caplet shaped tablets. They are plain on one side and a break bar on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Treatment of mild to moderately severe infections caused by penicillin sensitive staphylococci, pneumococci, gonococci and haemolytic streptococci infections. Therapy should be guided by bacteriological studies, including sensitivity tests, and by clinical response.

For prophylactic use in recurrent streptococcal infections including the prevention of recurrence following rheumatic fever and/or Sydenham's chorea and to prevent bacterial endocarditis in patients with rheumatic fever and/or congenital heart disease who are about to undergo dental or upper respiratory surgery or instrumentation.

Note: oral penicillin should not be used as adjunctive prophylaxis for genitourinary instrumentation or surgery, lower intestinal tract surgery, sigmoidoscopy or childbirth.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

250 mg to 500 mg every four to six hours, preferably one hour before food. The dosage should be determined according to sensitivity of the organisms and severity of the infection.

Prevention of Recurrence Following Rheumatic Fever

250 mg twice a day continuously.

Infants and Small Children

15 mg/kg to 50 mg/kg in three to six divided doses. If not calculated by bodyweight the following dosage schedule may be used:

- Up to 1 year: 60 mg every six hours
- 1 to 5 years: 120 mg every six hours
- 6 to 12 years: 120 to 270 mg every six hours

Renal or Hepatic Impairment

The half-life is greatly extended in these patients.

4.3 CONTRAINDICATIONS

Known hypersensitivity to penicillin and/or cephalosporin.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Risk-benefit should be considered when the following medical problems exist:

History of Sensitivity (allergy to penicillins/cephalosporins)

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or 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 any penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, the drug should be discontinued, and the appropriate therapy instituted. Serious anaphylactoid reactions require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal Disease (pseudomembranous colitis)

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including phenoxymethylpenicillin. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea of colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered.

Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Phenoxymethylpenicillin is not recommended for chronic, severe or deep-seated infections as therapeutic concentrations may not be achieved in the relevant tissues.

Oral administration should not be relied upon to achieve therapeutic levels in some patients with severe illness or with nausea, vomiting, gastric dilation, cardio-spasm or intestinal hypermotility. Occasionally patients will not absorb therapeutic amounts of oral penicillin. Parenteral administration of suitable antibiotics is recommended in these patients.

In a streptococcal infection, therapy should continue for a minimum of ten days. Cultures should be taken following completion of treatment to determine whether Streptococci have been eradicated.

Use of an alternative or additional method of contraception is strongly recommended if an estrogen containing contraceptive is taken concurrently (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

History of Bleeding Disorders

Some penicillins may cause platelet dysfunction and haemorrhage.

Prolonged Use

Prolonged use of penicillins may lead to the development of oral candidiasis.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, phenoxymethylpenicillin should be discontinued immediately and an alternative treatment should be considered.

Use in Hepatic Impairment

The half-life is greatly extended in patients with hepatic impairment.

Use in Renal Impairment

Because most penicillins are excreted through the kidneys, a reduction in dosage, or increase in dosing interval, is recommended in patients with renal function impairment; and the potassium content of high doses of phenoxymethylpenicillin potassium, should be considered in patients with severe renal function impairment.

Use in the Elderly

There are no age specific problems documented with the use of phenoxymethylpenicillin, However, the elderly are more likely to have age-related renal function impairment, which may require dosage adjustment.

Paediatric Use

The half-life of phenoxymethylpenicillin is prolonged in premature infants and neonates up to 3 months of age. Consequently, only three doses a day may be adequate to maintain plasma levels in these infants.

Effects on Laboratory Tests

With Diagnostic Test Results

Glucose, urine: high urinary concentrations of penicillin may produce false positive or elevated test results with copper sulfate tests (Benedict's, Clinitest or Fehling's).

Direct Antiglobulin (Coombs') Tests

False positive results may occur during therapy with any penicillin.

White Blood Cell Count

Leukopenia or neutropenia is associated with the use of all penicillins; the effect is more likely to occur with prolonged therapy and severe hepatic function impairment

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Bacteriostatic drugs may antagonise the effect of penicillin.

Probenecid reduces the tubular excretion of penicillin, thereby increasing concentrations in the blood stream of concomitantly administered penicillin.

Food has a variable effect, generally delaying absorption.

Antacids may reduce absorption of the drug.

When used concurrently with an estrogen containing oral contraceptive, the effectiveness of the oral contraceptive may be decreased because of stimulation of oestrogen metabolism or reduction of enterohepatic circulation of oestrogens, resulting in menstrual irregularities, intermenstrual bleeding and unplanned pregnancies. This interaction may be of greater clinical significance with long-term use of this penicillin; patients should be advised to use an alternative or additional method of contraception while taking this penicillin.

Aminoglycosides: mixing penicillins with aminoglycosides in vitro has resulted in substantial mutual inactivation.

Methotrexate: concurrent use with penicillins has resulted in decreased clearance of methotrexate toxicity; probably due to competition for renal tubular secretion; patients should be closely monitored.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Reproductive studies performed in the mouse, rat and rabbit have revealed no evidence of impaired fertility due to phenoxymethylpenicillin.

Use in Pregnancy

Pregnancy category: A

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, penicillin should be used during pregnancy only if clearly needed.

Use in Lactation

The drug is excreted in breast milk in concentrations lower than plasma levels. As safety to newborn infants has not been established, it is not recommended for breast feeding mothers unless the benefits outweigh any potential risk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most common reactions are nausea, vomiting, epigastric distress, diarrhoea, pruritis ani, black hairy tongue, allergic skin reactions, urticaria and other serum sickness reactions.

The hypersensitivity reactions reported are skin eruptions (macropapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal oedema and anaphylaxis. Fever and eosinophilia may frequently be the only reaction observed.

Haemolytic anaemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are uncommon reactions usually associated with high doses of parenteral penicillin.

Anaphylaxis is a less common reaction.

Skin and Other Subcutaneous Tissue Disorders

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Phenoxymethylpenicillin has low toxicity. However, if there is gross renal impairment, the drug may accumulate in the blood, and the dose should be reduced accordingly.

Treatment

Management of overdose should include monitoring of electrolyte balance, cardiovascular status and renal function. Penicillins are generally not readily removed by dialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Microbiology

Phenoxymethylpenicillin exerts a bactericidal action against penicillin sensitive microorganisms during the stage of active multiplication. It is not active against the penicillinase producing bacteria, which include many strains of staphylococci.

Sensitive organisms include the following:

Gram-positive cocci, e.g. Streptococci (groups A, C, G, H, L and M), and non-penicillinase producing *Staphylococcus pyogenes*.

Gram-positive bacilli, e.g. *Clostridium tetani, Cl. perfrigens*, *Corynebacterium diphtheriae* and *Bacillus anthracis*.

Gram-negative bacteria: some isolates of both *Neisseria meningitidis* and *N. gonorrhoeae* remain sensitive to penicillin while most strains of *Haemophilus influenzae* and *Moraxella catarrhalis* are now resistant. Other aerobic Gram-negative bacilli are highly resistant.

Treponema pallidum is sensitive, but treatment of syphilis with oral penicillins is not recommended.

Susceptibility Test

Dilution or diffusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

A report of "intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinical feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation.

A report of "resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: the prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacology

Phenoxymethylpenicillin produces a bactericidal effect on penicillin sensitive organisms during the stage of active multiplication through inhibition of biosynthesis of cell wall mucopeptides. The antibacterial spectrum of phenoxymethylpenicillin is similar to that of benzyl penicillin, however, it has the advantage of being acid stable and hence better absorbed from the gastrointestinal tract than benzyl penicillin. It is resistant to inactivation by gastric acid. It may be given with meals; however, blood levels are slightly higher when given on an empty stomach. Average blood levels are two to five times higher than the levels following the same dose of oral penicillin G and show much less individual variation.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Usually, up to 60% of the drug is absorbed into the blood stream after oral administration. Absorption is usually rapid and may produce peak serum concentrations within 30 minutes and demonstrable levels are maintained for 4 hours.

Distribution

Penicillin levels are highest in the kidney tissues, with lesser amounts in the liver, skin and intestines. Small amounts are found in other body tissues and the cerebrospinal fluid.

Metabolism

Approximately 80% of phenoxymethylpenicillin is serum protein bound. About 56% of a 500 mg oral dose of the drug is metabolised into inactive metabolite. The oral plasma half-life is about 30 minutes in healthy adults and about 1 to 3 hours in neonates. The half-life is greatly extended in patients with renal or hepatic impairment.

Excretion

About 23 to 36% of the drug is rapidly excreted in the unchanged form in the urine. Bile excretion depends on renal function, being low in normal renal function and high in renal impairment.

The drug is excreted as rapidly as it is absorbed in individuals with normal kidney function; however, recovery of the drug from the urine indicates that only about 25% of the dose given is absorbed, however, in neonates, young infants and individuals with impaired kidney function, excretion is considerably delayed.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of phenoxymethylpenicillin has not been examined.

Carcinogenicity

Long term studies have not been performed in animals.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain calcium hydrogen phosphate dihydrate, magnesium stearate, maize starch, microcrystalline cellulose, Opadry AMB Yellow OY-B-32904 (Proprietary Ingredient: 3024) and Opadry Clear OY-S-29019 (Proprietary Ingredient 3025).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: bottle (HDPE)

Pack size: 25

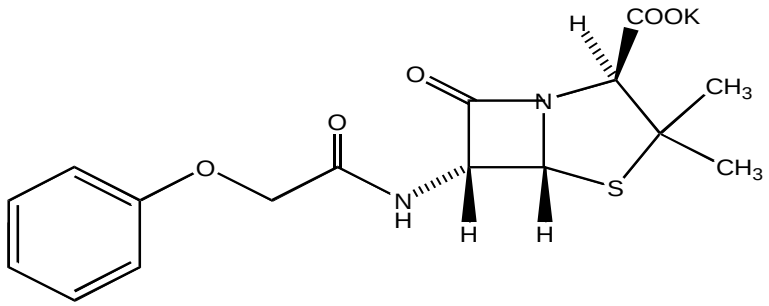
Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



Phenoxymethylpenicillin (or penicillin V) potassium is the potassium salt of the phenoxymethyl analog of penicillin G. It is a white crystalline powder and is soluble in water and polar organic solvents but practically insoluble in vegetable oils and liquid paraffins. Chemical name: potassium (6R)-6-(2-phenoxyacetamido) penicillanate

Molecular formula: $C_{16}H_{17}KN_2O_5S$

Molecular weight: 388.5

CAS Number

132-98-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Mylan Health Pty Ltd

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.mylan.com.au

Phone: 1800 314 527

9 DATE OF FIRST APPROVAL

20/11/2012

10 DATE OF REVISION

15/04/2020

Summary Table of Changes

Section Changed	Summary of New Information
1; 2; 3; 4.1; 4.2; 4.4; 4.5; 4.6; 4.8; 5.1; 5.3; 6.1; 6.4; 6.5; 6.7; 7; 9;	Editorial changes
8	Update to sponsor details following transfer

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