# NEW ZEALAND DATA SHEET

# CILICAINE® VK

## 1. Product Name

Cilicaine VK, 250 mg and 500 mg capsules

## 2. Qualitative and Quantitative Composition

Each CILICAINE VK 250mg capsules contains 250mg phenoxymethylpenicillin (as potassium) also known as penicillin V.

Each CILICAINE VK 500mg capsules contains 500mg phenoxymethylpenicillin (as potassium) also known as penicillin V.

For the full list of excipients see section 6.1

## 3. Pharmaceutical Form

CILICAINE VK 250 mg capsule: Opaque maroon body and cap, size 2.

CILICAINE VK 500 mg capsule: Opaque maroon body and cap, size 0.

## 4. Clinical Particulars

### *4.1 Therapeutic indications*

When oral therapy is required in the treatment of mild to moderately severe infections due to penicillin sensitive organisms. 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 complications of childbirth.

Official guidelines for the suitable use of antibacterial agents should be taken into consideration.

### *4.2 Dose and method of administration*

**Adults**

250mg to 500mg every four to six hours. The dosage should be determined according to sensitivity of the organisms and severity of the infection.

Prevention of recurrence following rheumatic fever: 250mg twice a day continuously.

### General information regarding dosage administration

To avoid complications (rheumatic fever), infections caused by beta haemolysed streptococci are to be treated for 10 days.

PK / PD data suggest that administration three times a day provides an increased clinical effect and is therefore always recommended for serious infections such as pneumonia and erysipelas, and at least in the initial stage of other infections (see Section 5.1).

### Method of administration

Phenoxymethylpenicillin should ideally be taken on an empty stomach (1 hour before or 2 hours after meals) to ensure maximum absorption,

## *4.3 Contraindications*

Hypersensitivity to the active substance phenoxymethylpenicillin potassium, to other penicillins and/or cephalosporin, or a hypersensitivity to any of the excipients listed in section 6.1.

## *4.4 Special warnings and precautions for use*

### 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. Cross-sensitivity between penicillin and cephalosporin can occur. If an allergic reaction occurs, the medicine 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 medicine discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Therefore, patients with diarrhoea should be closely monitored.

Caution should be exercised when using this in patients who have allergic diseases or bronchial asthma.

If the patient develops an allergic reaction, the treatment should be discontinued immediately, and treatment with adrenaline, antihistamines and corticosteroids should be initiated.

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

Agents 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 oestrogen containing contraceptive is taken concurrently (see Interactions below).

### History of bleeding disorders

Some penicillins may cause platelet dysfunction and haemorrhage.

### Renal function 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. The half-life is greatly extended in these patients.

### Prolonged use

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

### Carcinogenicity

Long term studies have not been performed in animals

### Genotoxicity

The genotoxic potential of phenoxymethylpenicillin has not been examined.

### Use in children

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.

### Use in 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 with severe renal function impairment.

### Hepatic impairment

The half-life is greatly extended in these patients.

### Laboratory value alterations

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 Interaction with other medicines and other forms of interaction*

Bacteriostatic agents 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 medicine.

When used concurrently with an oestrogen-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 causing an increase in methotrexate toxicity; probably due to competition for renal tubular secretion; patients should be closely monitored.

## *4.6 Fertility, pregnancy and lactation*

### Pregnancy

Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the foetus. There are, however, no adequate and well controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the foetus can be excluded. Because animal reproduction studies are not always predictive of human response, penicillin should be used during pregnancy only if clearly needed.

### Breast-feeding

The medicine 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.

### Fertility

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

No data available for effect on human fertility.

## *4.7 Effects on ability to drive and use machines*

***Phenoxymethylpenicillin has no or negligible influence on the ability to drive and use machines. Patients should take precautions until they know how this medicine affects them.4.8 Undesirable effects***

The most common reactions to oral penicillin are nausea and minor gastrointestinal disorders with loose stools and hypersensitivity reactions. Although hypersensitivity reactions have been reported much less frequently after oral than after parenteral therapy, it should be remembered that all forms of hypersensitivity, including fatal anaphylaxis have been observed with oral penicillin.

Adverse reactions, which have been associated with phenoxymethylpenicillin, are given below, listed by system organ class and frequency. Frequency are defined as: very common (>1/10), common (>1/100) and <1/10), uncommon (>1/1 000 and < 1/100), rare (>1/10 000 and < 1/1000) and very rare <1/10 000) and not known (cannot be estimated from the available data).

| **System Organ Class** | **Frequency** | **Adverse event** |
|---|---|---|
| Blood and lymphatic disorders | Very rare | Changes in blood counts, (including, thrombocytopenia, neutropenia, leucopenia, eosinophilia and haemolytic anaemia), Coagulation disorders (including prolongation of bleeding time and defective platelet function) |
| Immune System disorders | Common | Allergic reactions may commonly occur and typically manifest as skin reactions (See Skin and subcutaneous tissue disorders) |
| | Rare | Anaphylactic reaction, Severe allergic reactions causing angioedema, laryngeal oedema and anaphylaxis |
| | Not known | Hypersensitivity<br><br>Serum sickness-like reactions are characterised by fever, chills, arthralgia and oedema |
| Gastrointestinal disorders | Common | Nausea, vomiting, abdominal pain and diarrhoea |
| | Uncommon | Sore mouth and black hairy tongue (discolouration of tongue) |
| | Rare | Superficial discolouration of the teeth. (usually the discolouration can be removed by teeth brushing.) |
| | Not known | Pseudomembranous colitis |
| Hepatobiliary disorders | Very rare | Hepatitis and cholestatic jaundice |
| Skin and subcutaneous tissue disorders | Common | Urticarial, erythematous or morbilliform rash pruritus, rash |
| | Rare | exfoliative dermatitis |
| | Unknown | Diaphoresis, Severe cutaneous adverse reactions (SCAR), including 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. |
| Infections and infestations | Uncommon | Pseudomembranous colitis |

| System Organ Class | Frequency | Adverse event |
|---|---|---|
| Nervous system disorders | Unknown | Central nervous system toxicity including convulsions (especially with high doses or in severe renal impairment); paraesthesia may occur with prolonged use.<br><br>Neuropathy is usually associated with high doses of parenteral penicillin. |
| Renal and urinary disorders | Uncommon | Nephropathy is usually associated with high doses of parenteral penicillin. |
| | Very rare | Interstitial nephritis |

**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 professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

## *4.9 Overdose*

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

**Symptoms:**

An overdose of penicillin may cause nausea, vomiting, diarrhoea, electrolyte imbalance, anaphylactic reaction etc.

**Treatment**

Symptomatic therapy should be given. In case of anaphylaxis, treatment with adrenaline, antihistamines and corticosteroids should be initiated. Management of overdose should include monitoring of electrolyte balance, cardiovascular status and renal function. Penicillins are generally not readily removed by dialysis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

# 5. Pharmacological Properties

## *5.1 Pharmacodynamic properties*

Pharmacotherapeutic group: Beta-lactamse sensitive penicillins ATC Code: J01CE02

Phenoxymethylpenicillin (penicillin V) exerts a bactericidal action against penicillin sensitive micro-organisms during the stage of active multiplication by inhibiting the cell-wall sythesis. It is not active against the penicillinase producing bacteria, which include many strains of staphylococci.

The penicillin binds to and inhibits the enzymes (transpeptidases), which are responsible for linking-up the pentapeptides which are one of the building blocks of the bacteria´s cell walls. When under the influence of penicillin, the bacteria´s cell walls will be increasing weakened during the growth phase. They will be unable to divide and will swell up until they finally burst and die.

Phenoxymethylpenicillin produces a bacterial 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.Available knowledge of pharmacokinetics and pharmacodynamics indicates that for beta lactam antibiotics, the effect is primarily dependent on the time period for which the free antibiotic concentration in serum is above the minimum inhibitory concentration of the relevant bacterium (T>MIC). Based on this knowledge, shorter dosage intervals should be considered for maximal clinical effect.

| | |
|---|---|
| Sensitive | Gram-positive cocci, Streptococci (groups A, C, G, H, L and M), and non-penicillinase producing Staphylococcus pyogenes and pneumococci<br><br>Gram-positive bacilli: Clostridium tetani, Cl. Perfrigens, Corynebacterium diphtheriae and Bacillus anthracis.<br><br>Gram-negative bacteria, both Neisseria meningitidis and N. gonorrhoeae are sensitive to a degree<br><br>Treponema pallidum is sensitive, (but treatment of syphilis with oral penicillins is not recommended.)<br><br>Corynebacterium diphteriae<br>Pasteurella multocida<br>Peptococci<br>Peptostreptococci<br>Actinomyces<br>Fusobacteria<br>Capnocytophaga canimorsus<br>Borellia burgdorferi<br>Borellia vincenti |
| Intermediary | Haemophilus influenzae |
| Resistant | Aerobic Gram-negative bacilli are highly resistant.<br><br>Staphylococci<br>Enterococci<br>Moraxella catarrhalis<br>Gram negative intestinal bacteria<br>Pseudomonas<br>Legionella<br>Bacteroides fragilis<br>Clostridium difficile<br>Mycoplasma<br>Chlamydia |

Pneumococcal resistance can occur (1-10%).
For Haemophilus influenzae, resistance is common (> 10%).
Non-beta-lactamase-producing H. influenzae can be treated with high doses of phenoxymethylpenicillin.

Beta lactamase-producing bacteria are resistant, this applies to most of the staphylococcal strains as well as Moraxella catarrhalis. Mycoplasma and Chlamydia are resistant.

Resistance mechanisms: Resistance can occur due to bacterial synthesis of a large number of beta-lactamases that hydrolyse the penicillin. Several of these can be inhibited with clavulanic acid. Additionally, resistance can occur due to production of altered penicillin-binding proteins (PBP). Resistance is often plasmid-mediated.

Cross-resistance occurs within the beta lactam group (penicillins and cephalosporins).

Penicillin-resistant pneumococci are not uncommon in certain parts of the rest of Europe.

If infection is due to penicillinase-forming staphylococci, or if this is suspected, a penicillinase-stable penicillin should be chosen.

Resistance varies geographically and information on local resistance conditions should be obtained from a local microbiological laboratory.

## *5.2 Pharmacokinetic properties*

### Absorption

Phenoxymethylpenicillin potassium is water soluble and oxygen-stable and is absorbed up to approx. 60%. Absorption is usually rapid and may produce peak serum concentrations within 30 minutes and demonstrable levels are maintained for 4 hours. After one-time doses of 800 mg administered to adults on a fasting stomach, and after 0.5-1 hours have elapsed, maximum serum concentrations of about 10 mg./ml on average are achieved. At the same time, the consumption of food results in a reduced degree of absorption and a lower maximal serum concentration. The biological half-life in serum is approx. 30 minutes, and the protein binding rate is about 80%. Phenoxymethylpenicillin is excreted mainly in the urine, where 30-50% of an administered dose can be detected in antibacterially active form within 8 hours.

### Distribution

The concentration is high in well-vascularized tissues, e.g. kidneys, lung, skin and mucous membranes with lesser amounts in the liver, skin and intestines. Small amounts are found in all other body tissues and the cerebrospinal fluid.Therapeutic serum concentration should be 5-20 times the MIC value of the particular bacterium, i.e. 2-2.4 micrograms/ml by infections caused by common penicillin-sensitive bacteria.

### Metabolism

About 56% of a 500mg oral dose of the medicine is metabolised into inactive metabolite

Hepatic.

### Elimination

Approx. 30% of the administered dose is excreted as an active form via the kidneys. Bile excretion depends on renal function, being low in normal renal function and high in renal impairment. 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.

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

## *5.3 Preclinical safety data*

No data available

# 6. Pharmaceutical Particulars

## *6.1 List of excipients*

Cilicaine VK capsules also contain:

- Magnesium Stearate.
- Titanium Dioxide
- Iron Oxide Red,
- Gelatin,

Contains sulfites

## *6.2 Incompatibilities*

Not applicable

## *6.3 Shelf life*

3 years.

## *6.4 Special precautions for storage*

Store at or below 25°C.

## *6.5 Nature and contents of container*

PVC/PVA/PVDC/Al blisters. Pack sizes of 25 or 50 capsules.

Not all pack sizes may be marketed.

## *6.6 Special precautions for disposal*

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

# 7. Medicines Schedule

Prescription Medicine

# 8. Sponsor Details

Viatris Ltd
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Ellerslie
AUCKLAND
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Telephone 0800 168 169

# 9. Date of First Approval

16 March 2000

# 10. Date of Revision of the Text

21 November 2022

## *Summary table of changes*

| Section | Summary of new information |
|---|---|
| 2, 4.2, 4.8, 5.1, 5.2 | Minor editorial changes |
| 4.1 | Addition of statement to refer to Official guidelines for the suitable use of antibacterial agents should be taken into consideration. |
| 4.2 | Updated information on timing with food<br><br>Addition of general information section regarding dosage administration |
| 4.3 | Inclusion of hypersensitivity to phenoxymethylpenicillin potassium or any excipients of the product |
| 4.4 | Addition of cross-sensitivity between penicillin and cephalosporin<br><br>Addition of warning to monitor patients with diarrhoea<br><br>Addition of caution when using in patients who have allergic diseases or bronchial asthma. If the patient develops an allergic reaction, the treatment should be discontinued immediately, and treatment with adrenaline, antihistamines and corticosteroids should be initiated. |
| 4.6 | Addition of statement No data available for effect on human fertility |
| 4.7 | Addition of Phenoxymethylpenicillin has no or negligible influence on the ability to drive and use machines.<br><br>Patients should take precautions until they know how this medicine affects them. |
| 4.8 | Adverse events tabulated<br><br>Undated statement about most common reactions |
| 4.9 | Addition of section on Symptoms and updated Treatment section |
| 5.1 | Updated section on mechanism of action, rearrangement of section information.<br><br>Addition of Sensitivity table and data and moving previous information into the table<br><br>Additional information on resistance |
| 5.2 | Additional information on Absorption, distribution, metabolism and elimination. Arrangement of previous data into these sections |
| 10 | Updated date of revision of text |