SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Apsin VK.
Phenoxy methylpenicillin 250 mg / 5 ml Oral Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains 275 mg of Phenoxy methylpenicillin potassium equivalent to phenoxy methylpenicillin 250 mg.

Excipients with known effect

Apsin VK contains 57.8 g of sucrose. Each 5 ml of the reconstituted solution will contain 2.89 g of sucrose.

Apsin VK contains 28.5 mg potassium per dose, it also contains Sunset yellow (E110) and Ponceau 4R (E124).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Phenoxy methyl penicillin is a bactericidal agent active against many penicillin sensitive organisms in vitro. These include streptococci (groups A, C and G), pneumococci, many staphylococci (not beta-lactamase producers), Corynbacterium diptheriae, Bacillus anthracis, Actinomyces bovis, Streptobacillus moniliformis, Listeria monocytogenes, Treponema species, Clostridium species and Leptospira.
The potassium salt of phenoxyhylpenicillin is used in the management of infections caused by the above organisms where adequate blood levels of phenoxyhylpenicillin may be expected from oral treatment and where toxicity from the infection is unlikely to hinder absorption due to abnormal gastrointestinal motility, nausea etc. In practice this means the management of mild and moderate infections due to presumptive streptococcal infections where phenoxyhylpenicillin remains one of the drugs of first choice for all infections outside the CNS.

Phenoxyhylpenicillin may also be used orally following suitable sensitivity studies for the treatment of mild to moderate infections due to other organisms. It is most suitable for pneumococcal (respiratory tract infections), streptococcal infections (skin and soft tissues) and infections such as Vincent's angina (gingival and pharyngeal infections) due to fusospirochaetosis. In more severe infections and those infections due to Treponema species, it is more usual to use long-acting parenteral formulations of penicillin G.

Prophylactic Use:
Phenoxyhylpenicillin may be used prophylactically in:

- Prevention of infection in patients with an absent or dysfunctional spleen (and in association with pneumococcal and other immunisations).
- The specific streptococcal syndrome of rheumatic fever, which can lead to cardiac valvular damage and rheumatic heart disease and/or chorea.

### 4.2 Posology and method of administration

**Posology**

Phenoxyhylpenicillin 125 mg / 5ml Oral Solution should be given in divided doses (4 times a day) and should be taken at least 30 minutes before or 2 hours after food.

<table>
<thead>
<tr>
<th>Adults (including the elderly) and children over 12 years:</th>
<th>250mg - 500mg every six hours, upto 1g every six hours depending on the severity of the infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic use</td>
<td>250mg twice daily is recommended for long term prophylaxis of rheumatic fever</td>
</tr>
<tr>
<td>Children:</td>
<td></td>
</tr>
<tr>
<td>Infants (up to 1 year)</td>
<td>62.5mg every six hours</td>
</tr>
<tr>
<td>1-5 years</td>
<td>125mg every six hours</td>
</tr>
<tr>
<td>6-12 years</td>
<td>250mg every six hours</td>
</tr>
</tbody>
</table>
The last dose of the day may be doubled to avoid disturbing the sleeping pattern.

Elderly: The recommended dosage for adults should be used unless there is renal impairment.

**Patients with Renal Impairment**

Reduce dose if renal function is markedly impaired.

In patients with beta-haemolytic streptococcal infection it is usual to continue treatment at the full dosage for 10 days in order to minimise the occurrence of secondary complications such as acute nephritis, scarlet fever and rheumatic fever and post-treatment cultures should be taken to confirm the eradication of pathogenic bacteria.

**Prophylactic Use:**
For the prevention of infection in patients with an absent or dysfunctional spleen (and in association with pneumococcal and other immunisations) the usual dosage is 250 - 500 mg twice daily (250 mg twice daily in children aged 6-12 years, 125 mg twice daily in children under 5 years). The duration of prophylaxis is at the discretion of the physician. This may be lifelong, but is especially important in the first two years after splenectomy, for all children aged up to 16, and when there is underlying impaired immune function.

Where phenoxymethylpenicillin is being used for the long-term prophylaxis of patients with rheumatic fever, the usual adult dose is 250 mg twice daily with infants and childrens’ dosage in proportion.

**Method of Administration**

For oral administration

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

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

Phenoxymethylpenicillin is contraindicated in patients known to be hypersensitive to Penicillin and should be used with caution in patients with known histories of allergy.
Phenoxymethylpenicillin should not be used in chronic or deep seated infections such as subacute bacterial endocarditis, meningitis or syphilis nor in patients with hypersensitivity to penicillins or cephalosporins.

4.4 Special warnings and precautions for use

All degrees of hypersensitivity including fatal anaphylaxis have been seen following the use of oral penicillins. These reactions are more likely to occur in individuals with a history of sensitivity to penicillins, cephalosporins and allergens.

Special care must be taken when using phenoxymethylpenicillin in patients with a history of allergy or atopy as they are more likely to develop hypersensitivity reactions. Because of this problem the penicillins should not be used for trivial infections or where they are likely to be inactive e.g. in viral infections such as the common cold.

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

Streptococcal infections should be treated for a minimum of 10 days, and post therapy cultures should be performed to confirm the eradication of the organisms.

It should be noted that each 125 mg dose contains about 1/3 mmol of potassium. Such a quantity is normally insignificant unless total renal failure has occurred requiring constant monitoring of plasma potassium and potassium consumption when intake with

Apsin VK at higher doses may become significant. However, phenoxymethylpenicillin is excreted in the urine mainly unchanged leading to relatively high urinary levels. Consequently, in severe renal impairment, the dose of Apsin VK should be reduced and plasma samples monitored to maintain adequate but normal therapeutic levels (not more than 5 unit/ml, about 3 mg/l) of phenoxymethylpenicillin with appropriately spaced and reduced doses. In anuria single loading doses after each dialysis session are all that are normally required and the associated potassium load will normally be acceptable.

Prolonged use of antibiotics of all types promotes the overgrowth of non-susceptible organisms to that antibiotic. This may lead to super-infection with a non-susceptible organism such as a fungi. If super infection occurs, appropriate measures should be taken.

Occasionally patients do not absorb normal therapeutic doses of orally administered penicillin and this may be a cause of therapeutic failure. This is more likely in patients with a severe illness or infection or who are suffering from nausea, vomiting, gastric stasis/dilatation, cardiospasm or with gastrointestinal hypermotility.
Sucrose:
This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth.

Potassium:
To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

E110 & E124:
This product contains Ponceau 4R (E124) and Sunset yellow (E110) which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Neomycin may reduce the absorption of phenoxymerthylpenicillin.

Guar gum may slow the speed of absorption of phenoxymerthylpenicillin.

Concomitant use of uricosuric drugs (e.g. probenecid) reduces the excretion of phenoxymerthylpenicillin resulting in increased plasma levels.

Combined use of phenoxymerthylpenicillin and oral anticoagulants (e.g. warfarin) may prolong prothrombin time and interfere with anticoagulant control.

Phenoxymerthylpenicillin may reduce the excretion of methotrexate causing an increased risk of toxicity.

Certain bacteriostatic antibiotics such as Chloramphenicol, Erythromycin and Tetracyclines have been reported to antagonise the bactericidal activity of penicillins and concomitant use is not recommended.

Excretion of penicillins reduced by sulfinpyrazone.

Penicillins may inactivate oral typhoid vaccine if ingested concomitantly.

4.6 Fertility, pregnancy and lactation

Although both laboratory and clinical studies have shown no evidence of problems it is wise to exercise caution when prescribing for pregnant or nursing mothers.
Pregnancy

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.

Breast-feeding
Phenoxymethylpenicillin metabolites are excreted in human milk to such an extent that effects on breastfed newborns are likely.

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. 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.

Blood and lymphatic disorders:
There have been very rare (<1/10,000) reports of changes in blood counts, including, thrombocytopenia, neutropenia, leucopenia, eosinophilia and haemolytic anaemia. Coagulation disorders (including prolongation of bleeding time and defective platelet function) have also been reported.

Gastrointestinal disorders:
Nausea, vomiting, abdominal pain, diarrhoea are common (≥1/100 to <1/10). Sore mouth and black hairy tongue (discolouration of tongue) has been reported rarely (≥1/10,000 to <1/1,000).

Hepatobiliary disorders:
Hepatitis and cholestatic jaundice have been reported very rarely (<1/10,000).

Immune disorders:
Allergic reactions may commonly occur (≥1/100 to <1/10) and typically manifest as skin reactions (See Skin and subcutaneous disorders). Severe allergic reactions causing angioedema, laryngeal oedema and anaphylaxis have been reported rarely (≥1/10,000 to <1/1,000).

Serum sickness-like reactions are characterised by fever, chills, arthralgia and oedema.

Infections and infestations:
Pseudomembranous colitis has rarely (≥1/10,000 to <1/1,000) been reported.

Nervous system disorders:
Central nervous system toxicity including convulsions has been reported (especially with high doses or in severe renal impairment); paraesthesia may occur with prolonged use.

Neuropathy is an infrequent reaction and is usually associated with high doses of parenteral penicillin.

Renal and urinary disorders:
Interstitial nephritis has occurred in very rare cases (<1/10,000).

Nephropathy is an infrequent reaction and is usually associated with high doses of parenteral penicillin.

Skin and subcutaneous disorders
Urticarial, erythematous or mobilliform rash and pruritus occur commonly (≥1/100 to <1/10) while exfoliative dermatitis occurs rarely (≥1/10,000 to <1/1,000).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after 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 yellow card scheme at www.mhra.gov.uk/yellowcard.

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 overdosage, particularly for patients with renal insufficiency and serum potassium may need to be monitored.

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

ATC Code: JO1C E02
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.

PK/PD relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for phenoxymethylpenicillin.

Mechanism(s) of Resistance:

Phenoxymethylpenicillin is inhibited by penicillinase and other beta-lactamases that are produced by certain microorganisms. The incidence of beta-lactamase producing organisms is increasing.

Mechanisms of resistance

The two main mechanisms of resistance to phenoxymethylpenicillin are:

• Inactivation by bacterial penicillinases and other beta-lactamases

• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance.

EUCAST clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens (version 1.0 22.11.210) are:

The susceptibility of streptococci Groups A, C and G and Staphylococcus aureus to phenoxymethylpenicillin is inferred from the susceptibility to benzylpenicillin.

<table>
<thead>
<tr>
<th>EUCAST Species-related breakpoints (Susceptible&lt;Resistant&gt;) Units: mg/L</th>
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</thead>
<tbody>
<tr>
<td>Staphylococcus</td>
</tr>
<tr>
<td>Streptococcus A, C, G</td>
</tr>
<tr>
<td>S. pneumoniae</td>
</tr>
</tbody>
</table>

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.

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

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Expert advice should be sought as necessary when the local prevalence of resistance is such that the utility of the agent in at least some types of infection is questionable.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus A, C, G</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
</tr>
</tbody>
</table>

### 5.2 Pharmacokinetic properties

Phenoxymethylpenicillin is absorbed well from the gastro-intestinal tract, but incompletely and to an unpredictable extent. It may be better absorbed after food.

**Absorption**: Rapidly but incompletely absorbed after oral administration (about 60% of an oral dose is absorbed). 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.

After an oral dose of 500mg, peak serum concentrations reach 3 to 5 microgram/ml in 30 to 60 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).

**Biotransformation**

Hydroxylation may occur.
Elimination
20% to 35% of an oral dose is excreted in the urine in 24 hours.

Biological half-life is about 30’ minutes, increased to about 4 hours in severe renal impairment.

5.3 Preclinical Safety Data

Preclinical information has not been included because the safety profile of phenoxymethylpenicillin has been established after many years of clinical use. Please refer to section 4.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Saccharin sodium
Orange flavouring
Sunset yellow (E110)
Ponceau 4R (E124).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

This product has a registered shelf life of 36 months. The shelf life after reconstitution is 7 days.

6.4 Special Precautions for Storage

Store granules in a dry place below 20°C.

6.5 Nature and Contents of Container

150 ml clear Winchester bottles with screw caps containing 100ml of product.
6.6 Special precautions for disposal and other handling

To reconstitute: Loosen granules, add 60ml water and shake well.

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

TEVA UK Limited
Brampton Road, Hampden Park
Eastbourne, East Sussex, BN22 9AG

8 MARKETING AUTHORISATION NUMBER(S)

PL 00289/5279R

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

10/08/2016