PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAMES (and dosage forms):

APEN 500 (capsules)

APEN S (suspension)

COMPOSITION:

Ampicillin trihydrate B.P. and Cloxacillin sodium B.P. available as:

APEN 500: Gelatin capsule containing the equivalent of 250 mg ampicillin and 250 mg cloxacillin.

Sugar free.

Excipients: magnesium stearate, gelatin, yellow iron oxide, black iron oxide, titanium dioxide, indigotine, erythrosine, red iron oxide.

APEN S: Powder for preparing a fruit-flavoured suspension. When dispensed as directed each 5 ml of the suspension contains the equivalent of 125 mg ampicillin and 125 mg cloxacillin.

Excipients: saccharin sodium (dried), monoammonium glycyrrhizinate, disodium edetate, sodium citrate (dried), simethicone, menthol dry flavour, tutti-frutti dry flavour, blood orange dry flavour.

Each 5 ml contains sucrose 3,6 g.

The powder contains 0,13 % m/m sodium benzoate B.P. as a preservative.

PHARMACOLOGICAL CLASSIFICATION:

A.20.1.2 Penicillins

PHARMACOLOGICAL ACTION:

Ampicillin is an aminopenicillin with a broad spectrum of activity. It is bactericidal in action and its spectrum includes gram-negative and gram-positive organisms. Cloxacillin is an isoxazolyl penicillin and bactericidal in action. It is resistant to penicillinase produced by staphylococcus. Its antibacterial spectrum includes penicillinase- and non-penicillinase-producing Staphylococcus.

Bacteriology:

Ampicillin/cloxacillin exhibits *in vivo* and *in vitro* bactericidal activity against some Gram-positive and Gram-negative organisms.

***In vitro* sensitivity does not necessarily imply *in vivo* efficacy.**

Pharmacokinetics:

Absorption:

Both ampicillin and cloxacillin are acid stable and well absorbed orally, giving peak serum levels two hours after dosing. As there is a linear dose/response in

peak serum levels after oral administration of both components, doubling the dose virtually doubles the peak serum levels.

Excretion:

Both components are excreted primarily by the kidneys by glomerular filtration and tubular secretion.

Severe renal impairment markedly prolongs the persistence of ampicillin in the plasma. Peritoneal dialysis is ineffective in removing ampicillin from the blood, but haemodialysis removes about 40 % of the body store in about 7 hours. Cloxacillin is not removed by haemodialysis.

Bile: Bile concentrations of ampicillin/cloxacillin vary from 3 to 48 times the serum concentration, according to the condition of the biliary tract.

Probenecid:

Higher ampicillin/cloxacillin serum levels can be achieved in patients with normal renal function by the concurrent administration of a renal blocking agent such as probenecid. In adults, a dose of 500 mg of probenecid four times daily will result in 1,5 - 2 fold increase in ampicillin/cloxacillin serum levels.

INDICATIONS:

APEN 500 and **APEN S** are indicated for infections caused by susceptible organisms.

CONTRA-INDICATIONS:

APEN 500 and **APEN S** should not be given to:

- Patients known to be hypersensitive or allergic to penicillins or cephalosporins as cross-sensitivity has been reported (see **WARNINGS**).
- Babies in the neonatal period, born to mothers hypersensitive to ampicillin.
- **APEN 500** and **APEN S** are not recommended for chronic or severe infections such as infective endocarditis, meningitis or syphilis.
- Safety in pregnancy and lactation has not been established (see **PREGNANCY AND LACTATION**).
- Ocular administration.

WARNINGS:

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

- Bleeding disorders, history of carnitine deficiency.
- Congestive heart failure (CHF) or hypertension.
- Cystic fibrosis.
- Gastrointestinal disease or history thereof, especially antibiotic-associated colitis.
- Infectious mononucleosis.
- Renal function impairment.

Because of the variability in intestinal absorption of cloxacillin-containing products, oral administration is not a suitable substitute for the parenteral route in treatment of severe infections.

Use with caution in patients with a known history of allergy.

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on ampicillin/cloxacillin therapy. Before initiating therapy with **APEN 500** and **APEN S**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity that have experienced severe reactions when treated with cephalosporins.

If an allergic reaction occurs, **APEN 500** and **APEN S** should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine), oxygen, intravenous corticosteroids, antihistamines and airway management, including intubation.

APEN 500 and **APEN S** should be discontinued if a skin rash occurs. **APEN 500** and **APEN S** contain ampicillin and should preferably be avoided if infectious mononucleosis, lymphatic leukaemia or possibly HIV infection is suspected and also in patients receiving allopurinol treatment, because of an increased risk of rashes associated with these conditions, following the administration of **APEN 500** and **APEN S.**

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported.

Increases in the INR have been reported in patients receiving **APEN 500** and **APEN S**.
Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Care should be taken when high doses of **APEN 500** and **APEN S** are given to patients with renal impairment (due to the risk of neurotoxicity) or congestive heart failure.

In the presence of impaired renal function large doses of **APEN 500** and **APEN S** (e.g. more than 8 g per day in an adult) may cause cerebral irritation, convulsions and coma.

Children with renal insufficiency may require a reduced dosage of **APEN 500** and **APEN S**.

Periodic assessment of organ function, including renal, hepatic and haematopoietic functions, is advisable during prolonged therapy.

APEN 500 and **APEN S** contain sodium, therefore disturbances in blood electrolyte may follow administration of large doses.

When high doses are administered, adequate fluid intake and urinary output must be maintained.

Sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.

APEN 500 and **APEN S** may reduce the efficacy of oral contraceptives, and patients should be warned accordingly to use alternative or additional measures of contraception.

INTERACTIONS:

APEN 500 and **APEN S** may also interact with bacteriostatic antibacterials such as chloramphenicol and tetracyclines and may be incompatible *in vitro* with other medicines, including a number of other antibacterials.

Concurrent use of **APEN 500** and **APEN S** with ACE inhibitors, potassium-sparing diuretics, potassium-containing medications or potassium supplements may promote serum potassium accumulation with possible resultant hyperkalaemia, especially in patients with renal insufficiency, concurrent administration with ACE inhibitors may result in hyperkalaemia since reduction of aldosterone production induced by ACE inhibitors may lead to elevation of serum potassium.

Concurrent use of medication with an antiplatelet function with **APEN 500** and **APEN S** may increase the risk of haemorrhage due to additive inhibition of platelet aggregation. In addition, hypoprothrombinaemia induced by large doses of salicylates, and the gastrointestinal ulcerative or haemorrhagic potential of NSAIDs or salicylates may also increase the risk of haemorrhage when these medications are used concurrently with **APEN 500** and **APEN S**.

Patients receiving anticoagulants, heparin or thrombolytic agents may experience a prolonged INR and bleeding following treatment with **APEN 500** and **APEN S**.

APEN 500 and **APEN S** may reduce the efficacy of oral contraceptives (see **WARNINGS**).

The concomitant administration of allopurinol and **APEN 500** and **APEN S** substantially increases the incidence of skin rashes in patients receiving both

agents as compared to patients receiving ampicillin alone. This is especially so for hyperuricemic patients. It is not known whether this potentiation of rashes is due to allopurinol or the hyperuricaemia present in these patients.

No information is available about the concurrent use of **APEN 500** and **APEN S** and alcohol. However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram-like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with **APEN 500** and **APEN S.**

It is recommended that when testing for the presence of glucose in urine during **APEN 500** and **APEN S**, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of penicllins such as **APEN 500** and **APEN S**, false positive or falsely elevated readings are common with chemical methods such as copper sulphate.

APEN 500 and **APEN S** may also interfere with some diagnostic tests such as direct antiglobulin (Coombs') test, and some tests for urinary or serum proteins. **APEN 500** and **APEN S** may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.

The effects of methotrexate may be enhanced by **APEN 500** and **APEN S.**

PREGNANCY AND LACTATION:

Safety of **APEN** in pregnancy and lactation has not been established.

APEN crosses the placenta.

Use in lactation:

Small amounts of **APEN 500** and **APEN S** are distributed into breast milk. The use of **APEN 500** and **APEN S** by breast-feeding mothers may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant.

DOSAGE AND DIRECTIONS FOR USE:

The average adult dosage for **APEN** is 2 - 4 g per day.

In severe infections, dosages may be safely increased.

Adults and children over 10 years:

500 mg – 1 g (1 - 2 x 500 mg capsules) every 6 hours.

Children 2 - 10 years:

250 – 500 mg (5 - 10 ml of 250 mg/5 ml suspension) every 6 hours. (The dosage should correspond to a daily dosage of 50 – 150 mg/kg).

Children up to 2 years:

250 mg (5 ml of 250 mg/5 ml suspension) every 6 hours).

Note:

(1) Best results are obtained if dosages are administered half to one hour prior to meals or at least two hours after meals.

(2) Patients with renal insufficiency may require a reduced dosage.

Instructions to reconstitute:

To reconstitute to 100 ml, add 57 ml water, invert bottle and shake until all powder is dispersed. Once reconstituted the **APEN S** should be used within 7 days, if stored in a cool place (below 25 ºC), or 14 days if stored in a refrigerator (5 ºC). Shake the bottle well before each dose (see **STORAGE INSTRUCTIONS**).

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

The side effects are listed below by body system and organ class.

The most frequently reported adverse effects are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, abnormal taste, headache, dizziness, tiredness and hot flushes.

Hypersensitivity reactions:

Frequent: Skin rashes such as erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis and bullous and exfoliative dermatitis and other skin rashes.

Less frequent: Severe allergic reactions including angioedema, anaphylaxis, serum sicknes and vasculitis (see **WARNINGS**).

Frequency unknown: Generalised sensitivity reaction with urticaria, fever, joint pains and eosinophilia can develop within a few hours to several weeks after starting treatment, interstitial nephritis.

Infections and infestations:

Less frequent:

Superinfections by resistant species such as Pseudomonas or Candida may occur.

Blood and the lymphatic system disorders:

Frequency unknown: Haemolytic anaemia, leucopenia and granulocytopenia, agranylocytosis, thrombocytopenia, coagulation disorders such as prolongation of bleeding time, and defective platelet function have been reported in patients receiving prolonged high dosages of **APEN 500** and **APEN S**.

Disturbances of blood electrolytes may follow administration of large doses due to the sodium content (see **WARNINGS**).

Investigations:

Frequency unknown: Hypokalaemia, hypernatraemia.

Disturbances of blood electrolytes may follow administration of large doses of **APEN 500** and **APEN S** and may interfere with some diagnostic tests (see **INTERACTIONS**).

Nervous system disorders:

Frequency unknown: Hyperkinesia, dizziness and convulsions may occur; paraesthesia can occur following long-term administration.

Gastro-intestinal disorders:

Frequent: Nausea, vomiting and diarrhoea.

Frequency unknown: Stomatitis, glossitis, black hairy tongue as well as heartburn.

Mucocutaneous candidiasis and antibiotic-associated colitis including pseudomembranous colitis and haemorrhagic colitis.

Hepato-biliary disorders:

Frequency unknown: A moderate rise in liver enzymes (aspartate transaminse (AST) and/or alanine transaminase (ALT) values has been noted, but the significance of this is unclear, hepatitis and cholestatic jaundice.

Skin and subcutaneous tissue disorders:

Frequency unknown: Skin sensitisation may occur. (Avoid contact of skin with **APEN 500** and **APEN S**). Also refer to **Hypersensitivity** reactions above.

Renal and urinary disorders:

Frequency unknown: Crystalluria. (See **WARNINGS** and **Special precautions**.)

Special precautions:

When high doses are administered, adequate fluid intake and urinary output must be maintained.

Dosage should be adjusted in patients with renal impairment (see **DOSAGE AND DIRECTIONS FOR USE**).

There have been rare reports of paraesthesia following long-term administration.

The sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take **APEN S.**

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF IT'S TREATMENT:

Overdosage with **APEN 500** and **APEN S** is usually asymptomatic.

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident and symptoms of water and electrolyte imbalance should be treated symptomatically.

Adequate fluid intake and urinary output must be maintained to minimize the possibility of crystalluria.

The ampicillin content in the **APEN 500** and **APEN S** may be removed from the circulation by haemodialysis but not the cloxacillin.

Peritoneal dialysis is not effective in the removal of ampicillin content. Treatment is symptomatic and supportive (see **SIDE EFFECTS AND SPECIAL PRECAUTIONS**).

IDENTIFICATION:

APEN 500: Grey/Aubergine capsules imprinted “APEN 500”.

APEN S: Free-flowing off-white powder. Ivory coloured suspension.

PRESENTATION:

APEN 500: Glass bottles containing 20 or 100 capsules.

APEN S: Glass bottles containing powder for the reconstitution of 100 ml of suspension.

STORAGE INSTRUCTIONS:

Containers of **APEN** should be kept tightly closed in a cool, dry place at or below 25 °C. Once reconstituted **APEN S** should be used within 7 days, if stored in a cool place at or below 25 °C, or 14 days if stored in a refrigerator (5 °C).

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

APEN 500: 27/20.1.2/0108

APEN S: 27/20.1.2/0109

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Viatris South Africa (Pty) Ltd

4 Brewery Street,

Isando

Johannesburg,

1609

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