CIPLA-WARFARIN 1 mg (Tablets)

CIPLA-WARFARIN 3 mg (Tablets)

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-WARFARIN 1 mg (Tablets)

CIPLA-WARFARIN 3 mg (Tablets)

COMPOSITION:

CIPLA-WARFARIN 1 mg: Each tablet contains warfarin sodium clathrate equivalent to 1 mg warfarin sodium.

CIPLA-WARFARIN 3 mg: Each tablet contains warfarin sodium clathrate equivalent to 3 mg warfarin sodium.

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants.

PHARMACOLOGICAL ACTION:

Warfarin is a coumarin-type anticoagulant and acts by inhibiting synthesis of Vitamin K dependent coagulation factors in the liver. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X and II and the anticoagulant factors protein C and S.

Pharmacokinetics:

Absorption is essentially complete and maximal plasma concentrations are reached in 2 to 8 hours. Approximately 99 % is bound to albumin in the plasma. The half-life ranges from 20 to 60 hours with a mean of 40 hours. The duration of action is 2 to 5 days. Food in the gastrointestinal tract can decrease the rate of absorption. Warfarin is transformed to inactive metabolites by the liver and kidneys and these are excreted in the urine and faeces. The volume of distribution of warfarin is approximately 0.14 liter/kilogram.

INDICATIONS:

CIPLA-WARFARIN is used in:

The prevention and management of deep vein thrombosis and pulmonary embolism.

Prevention of thromboembolism in:

- Artrial fibrillation,
- Prosthetic heart valves,
- Post-myocardial infarction.

In the treatment of transient ischaemic attacks.

CONTRAINDICATIONS:

CIPLA-WARFARIN is contraindicated in patients with:

- Known hypersensitivity to warfarin or similar products;
- Haemorrhagic states;
- Peptic ulcers or other gastrointestinal disease involving bleeding;
- Conditions involving bleeding from respiratory or genitourinary tract;
- Severe wounds (including surgical);
- Infective endocarditis;
- Impaired liver function;
- Impaired kidney function;
- Hypertension;
- Cerebrovascular haemorrhage;
- Aneurysm - cerebral, aortic;
- Pericarditis, pericardial effusion;
- Neuro- or ophthalmic surgery - recent or contemplated;
- Surgery involving large exposed raw surfaces;
- Polyarthritis;
- Vitamin C deficiency;
- Major regional block anaesthesia;
- Inadequate laboratory facilities or lack of patient co-operation;
- Threatened abortion;
- Safety in children younger than 18 years has not been established;
- Pregnancy and lactation (see "**PREGNANCY AND LACTATION**").

WARNINGS:

Abrupt cessation of **CIPLA-WARFARIN** therapy is not recommended. The dose should be tapered over three to four weeks.

Special care is required in the elderly, in patients with Vitamin K deficiency and in patients with hyperthyroidism.

Dosage should be individualised for each patient and periodic determinations of prothrombin time should be done (see **"DOSAGE AND DIRECTIONS FOR USE"**).

The management of patients who undergo dental and surgical procedures requires close liaison between doctors, surgeons and dentists. An adjustment of dosage may be necessary.

CIPLA-WARFARIN should be used with caution in patients with:

- prolonged dietary deficiency;
- infectious diseases or disturbances of intestinal flora, sprue, antibiotic therapy;
- polycythaemia vera, vasculitis, severe diabetes, allergic or anaphylactic disorders.

Non-steroidal anti-inflammatory agents, including aspirin, should not be used with **CIPLA-WARFARIN**.

INTERACTIONS:

A wide variety may occur, increasing or diminishing the anticoagulant response with different mechanisms involved. Some agents interact by more than one mechanism, therefore the net effect may be unpredictable.

Mechanisms of interaction include:

* displacement from albumin binding sites.

* altering metabolism of **CIPLA-WARFARIN** by inhibition or induction of hepatic

microsomal enzymes.

* interference with absorption or metabolism of **CIPLA-WARFARIN** or vitamin K.

* additional anticoagulant effects by agents that inhibit platelet function.

Agents that enhance the anticoagulant effect of CIPLA-WARFARIN:

Sulphonamides, sulphonylurea-type antidiabetic agents, clofibrate, cimetidine, phenylbutazone and other pyrazolones, anabolic steroids, sulphinpyrazone, aspirin and other NSAIDS, thyroid hormones, disulfiram and amiodarone, alcohol (acute or chronic ingestion with liver impairment).

Agents that diminish the anticoagulant effect of CIPLA-WARFARIN:

Barbiturates, rifampicin and glutethimide. Vitamin K is a specific antagonist. Alcohol (chronic ingestion without liver impairment).

Agents that may enhance the anticoagulant effect of CIPLA-WARFARIN:

Allopurinol, danazol, diazoxide, metronidazole, aminoglycosides, alcohol, miconazole, triclofos, chloral hydrate, chloramphenicol, phenytoin, erythromycin, quinidine, dextropropoxyphene, Vitamin E and glucagon.

Agents that may diminish the anticoagulant effect of CIPLA-WARFARIN:

Oral contraceptives (oestrogens), carbamazepine, griseofulvin, glucocorticoids and cholestyramine.

Certain herbal products enhance the anticoagulant effect of **CIPLA-WARFARIN**.

PREGNANCY AND LACTATION:

CIPLA-WARFARIN should be avoided in pregnancy and lactation as it is a recognised teratogen (see "CONTRAINDICATIONS").

Pregnancy:

When **CIPLA-WARFARIN** is given in the first trimester of pregnancy it can cause the foetal warfarin syndrome. CNS or warfarin embryopathy abnormalities may develop following use in any trimester but appear most likely after use in the second trimester. Spontaneous abortion and stillbirth have been reported.

Lactation:

CIPLA-WARFARIN is distributed into milk only in its active form; studies in infants who are breast-fed while their mothers were taking **CIPLA-WARFARIN** did not find any effect on prothrombin time, however, breast-fed infants (especially neonates) are very sensitive to oral anticoagulants because of the low concentrations of vitamin K in breast milk.

DOSAGE AND DIRECTIONS FOR USE:

The administration and dosage of **CIPLA-WARFARIN** must be individualised for each patient according to the patient's sensitivity as indicated by the prothrombin time (PT) or international normalised ratio (INR).

PT measurements should be carried out before treatment, on the 2nd and 3rd days of treatment and then on alternate days until the maintenance dose is established. Thereafter

the patient should be monitored monthly. Satisfactory levels of PT or INR for maintenance vary with the condition treated and the risk of thromboembolism.

INR 2.0 - 2.5 (PT ratio 1.3 - 1.5)

Prophylaxis of deep vein thrombosis (DVT), including surgery in high risk patients.

INR 2.0 - 3.0 (PT ratio 1.3 - 1.5)

Prophylaxis of deep vein thrombosis (DVT) in hip surgery and fractured femur operations.

Prevention of thromboembolism in myocardial infarction, mitral stenosis with embolism, atrial fibrillation, tissue prosthetic heart valves.

Treatment of DVT, pulmonary embolism, transient ischaemic attacks, systemic embolism.

INR 3.0 - 4.5 (PT ratio 1.5 - 2.0)

Recurrent DVT and pulmonary embolism.

Arterial disease including myocardial infarction.

Mechanical prosthetic heart valves.

The correlation between the INR and the PT ratio is based on thromboplastin with an International Sensitivity Index of 2.3.

Initial doses are usually within the range of 10 - 15 mg daily for 3 days. Maintenance doses range from 2.5 -10 mg daily.

Doses should be given at the same time each day.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The major risk from **CIPLA-WARFARIN** therapy is of haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia.

Body as a whole:

Less Frequent: Alopecia, fever.

Gastrointestinal System Disorders:

Less Frequent: Diarrhoea, nausea, vomiting, bloated stomach or gas, loss of appetite, stomach cramps or pain.

Cardiovascular System Disorders:

None Reported.

Haematological and Lymphatic System Disorders:

Less Frequent: Haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia, leucopenia and granulocytosis.

Metabolic Disorders:

Less Frequent: Inhibits vitamin K synthesis, lipid emboli, including systemic atheroemboli and cholesterol emboli.

Musculoskeletal System Disorders:

Less Frequent: Increased risk of oesteoporotic fracture due to vitamin K deficiency. Patients on long-term **CIPLA-WARFARIN** treatment may be at increased risk.

Skin and Appendages Disorders:

Less Frequent: Hypersensitivity reactions and skin reactions. Purple toe syndrome – a reversible, sometimes painful, bluish discolouration (due to cholesterol embolisation) of the toes may occur. Skin necrosis may occur. **CIPLA-WARFARIN** appears to precipitate the syndrome of venous limb gangrene, spreading rapidly and requiring disfiguring debridement or occasionally amputation. Sores, ulcers or white spots in the mouth or throat.

Urogenital System Disorders:

Less Frequent: Renal damage with resultant oedema and proteinuria, with difficulty in urination.

Hepatic System Disorders:

Less Frequent: Hepatotoxicity, usually asymptomatic and seen on laboratory results, dark urine and jaundice. Hepatic injury resolved on withdrawal of **CIPLA-WARFARIN**.

Special Precautions:

Patients should be given detailed instructions concerning their medication, the importance of compliance and advice concerning modification of their lifestyle if necessary. The possibility of interactions should be explained. The need for modification of therapy before elective operative procedures or in women contemplating pregnancy should be discussed (see "**PREGNANCY AND LACTATION**"). Patients should carry an anticoagulant card or other proof that they are on anticoagulants.

The following factors may be responsible for an increase in prothrombin time: Carcinoma, collagen disease, congestive heart failure, diarrhoea, elevated temperature, hepatic disorders, infectious hepatitis, jaundice, poor nutritional state.

The following factors may be responsible for a decrease in prothrombin time: Diabetes mellitus, oedema, hereditary resistance to warfarin therapy, hyperlipidaemia, hypothyroidism.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Excessive bleeding may occur.

If an excessively long PT or INR occurs or there is minor bleeding, omission of one or several doses of **CIPLA-WARFARIN** may be sufficient to return levels to the therapeutic range.

If non-significant bleeding occurs, small doses of Vitamin K (1 - 5 mg) orally may suffice.

Serious bleeding may be treated with Vitamin K (20 - 40 mg) by slow intravenous administration together with replacement of clotting factors.

IDENTIFICATION:

CIPLA-WARFARIN 1 mg: Light brown coloured, circular, flat, bevelled tablets with a breakline on one side. 'W' and '1' engraved on breakline side and plain on the other side of tablet.

CIPLA-WARFARIN 3 mg: Light blue coloured, circular, flat, bevelled tablets with a breakline on one side. 'W' and '3' engraved on breakline side and plain on the other side of tablet.

PRESENTATION:

CIPLA-WARFARIN 1 mg: Supplied in white, opaque PVC/PVDC and aluminium foil blister strips of 10 tablets, packed in 30's, 60's or 100's in a carton.

CIPLA-WARFARIN 3 mg: Supplied in white, opaque PVC/PVDC and aluminium foil blister strips of 10 tablets, packed in 30's, 60's or 100's in a carton.

STORAGE INSTRUCTIONS:

Store below 25°C.

Keep the blisters in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

To be allocated.

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

CIPLA MEDPRO (PTY) LTD.

Rosen Heights

Pasita Street

Rosen Park, Bellville

7530, R.S.A.

DATE OF PUBLICATION OF THIS PACKAGE INSERT: