PACKAGE INSERT FOR

CIPLA-WARFARIN 1 mg (Tablets)

CIPLA-WARFARIN 3 mg (Tablets)

CIPLA-WARFARIN 5 mg (Tablets)

SCHEDULING STATUS:

S4

PROPRIETARY NAME (AND DOSAGE FORM):

CIPLA-WARFARIN 1 mg (Tablets)

CIPLA-WARFARIN 3 mg (Tablets)

CIPLA-WARFARIN 5 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.

CIPLA-WARFARIN 5 mg: Each tablet contains warfarin sodium clathrate equivalent to 5 mg warfarin sodium.

PHARMACOLOGICAL CLASSIFICATION:

A 8.2 Anticoagulants.

PHARMACOLOGICAL ACTION:

Warfarin is a member of the coumarin-type anticoagulants. It acts in the liver, where it inhibits the synthesis of Vitamin K dependent coagulation factors. The resultant *in vivo* effects include the sequential depression of Factors VII, IX, X and II and the anticoagulant factors protein C and S.

Pharmacokinetics:

Warfarin is well absorbed orally. Maximum plasma concentrations are reached within 2 - 8 hours. Plasma protein binding is high (approximately 99 % binds to albumin). Warfarin has an average half-life of 40 hours (range from 20 to 60 hours). The duration of action ranges from 2 to 5 days. The rate of absorption from the gastrointestinal tract is decreased when taken with food. Warfarin is metabolised in the liver and kidneys. Inactive metabolites are excreted in the urine and stool. The volume of distribution of warfarin is approximately 0.14 L/kg.

INDICATIONS:

CIPLA-WARFARIN is indicated for:

- the prevention and management of deep vein thrombosis.
- the prevention and management of pulmonary embolism.
- the prevention of thromboembolism in: atrial fibrillation, prosthetic heart valves and postmyocardial infarction.
- the treatment of transient ischaemic attacks.

CONTRA-INDICATIONS:

CIPLA-WARFARIN should not be used in patients with:

- Known hypersensitivity to warfarin or other coumarins.
- Bleeding disorders, including haemophilia or leukemia.
- Peptic ulceration or other bleeding gastrointestinal disorders.
- Bleeding from respiratory or genitourinary tract.
- Large open wounds, including surgical wounds, or surgery involving large exposed raw surfaces.
- Infective endocarditis, pericarditis or pericardial effusion.
- Impaired liver- or renal function.
- Hypertension.
- Cerebrovascular bleeding, cerebral or aortic aneurysm.
- Recent or contemplated neuro- or ophthalmic surgery.
- Polyarthritis.
- Vitamin C deficiency.
- Major regional block anaesthesia.
- Lack of co-operation.

CIPLA-WARFARIN is also contra-indicated under the following conditions:

- Where there are insufficient laboratory facilities.
- Pregnancy and in breastfeeding mothers (see **"PREGNANCY AND LACTATION"**).
- Threatened abortion.
- Children < 18 years, as safety has not been established.

WARNINGS:

Abrupt cessation of **CIPLA-WARFARIN** therapy is not advisable. If modification of therapy is required, the dose should be tapered over 3 - 4 weeks. The elderly, patients with vitamin K deficiency and patients with hyperthyroidism require special care.

Each patient's dosage should be individualised and assessed periodically by means of prothrombin time determinations (see **"DOSAGE AND DIRECTIONS FOR USE"**).
The management of patients undergoing dental procedures or elective surgery requires close liaison between doctors, surgeons and dentists. Dosage adjustments may be necessary.

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

- dietary deficiency over prolonged periods.
- infections or disturbances of intestinal flora, candidiasis, antibiotic therapy.
- diabetes, vasculitis, polycythaemia vera, allergic or anaphylactic disorders.

Non-steroidal anti-inflammatory medicines should not be used with **CIPLA-WARFARIN.**

INTERACTIONS:

A wide variety of drug interactions involving different mechanisms may occur, resulting in the augmentation or reduction of the anticoagulant properties of **CIPLA-WARFARIN.** Some interacting medicines do so by more than one mechanism, resulting in unpredictable effects. Possible mechanisms of drug interactions include:

- displacement from plasma protein (albumin) binding sites.

- altering the metabolism of **CIPLA-WARFARIN** by hepatic microsomal enzyme inhibition or induction.
- interference with absorption or metabolism of either **CIPLA-WARFARIN** or vitamin K.
- additional anticoagulant effects by medicines which inhibit platelet function.

Medicines that augment the anticoagulant effect of CIPLA-WARFARIN include:
Amiodarone, anabolic steroids, aspirin and other NSAIDS, cimetidine, clofibrate, disulfiram, phenylbutazone and other pyrazolones, sulphinpyrazone, sulphonamides, sulphonylurea-type antidiabetic agents and thyroid hormones and acute or chronic ingestion of alcohol with liver impairment.

Medicines that reduce the anticoagulant effect of CIPLA-WARFARIN include:
Barbiturates, glutethimide, rifampicin and vitamin K which is a specific antagonist. Chronic ingestion of alcohol, without liver impairment.

Medicines that may augment the anticoagulant effect of CIPLA-WARFARIN include:
Alcohol, allopurinol, aminoglycosides, chloral hydrate, chloramphenicol, danazol, dextropropoxyphene, diazoxide, erythromycin, glucagon, metronidazole, miconazole, phenytoin, quinidine, triclofos and vitamin E.

Medicines that may reduce the anticoagulant effect of CIPLA-WARFARIN include:
Carbamazepine, cholestyramine, glucocorticoids, griseofulvin and oral contraceptives (oestrogens).

Certain herbal medicines augment the anticoagulant properties of **CIPLA-WARFARIN.**

PREGNANCY AND LACTATION:

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

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.

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:

Each patient's sensitivity towards warfarin therapy, as indicated by the prothrombin time (PT) or international normalised ratio (INR), should predict the dosage of **CIPLA-WARFARIN** for that person.

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

Satisfactory levels of PT or INR for maintenance vary with different conditions and the risk of thromboembolism.

INR 2.0 - 2.5 (PT ratio 1.3 - 1.5)

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

INR 2.0 - 3.0 (PT ratio 1.3 - I.6)

Prophylaxis of deep vein thrombosis (DVT) in:

- hip surgery;
- fractured femur operations.

Prevention of thromboembolism in:

- atrial fibrillation;
- mitral stenosis with embolism;
- myocardial infarction;
- tissue prosthetic heart valves.

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

INR 3.0 - 4.5 (PT ratio 1.6 - 2.0)

Pulmonary embolism.

Recurrent DVT.

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 from 10 - 15 mg per day for 3 days.

Maintenance doses range from 2.5 mg to 10 mg per day.

Doses should be administered at the same time each day.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-Effects:

The major risk of **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.

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 must be thoroughly instructed about their medication, the importance of patient compliance and given advice on possible lifestyle modifications. The possibility of medicine interactions must also be explained. The need for dosage adjustments prior to elective surgery or in women contemplating pregnancy should be discussed (see **"PREGNANCY AND LACTATION"**). Patients should carry an anticoagulant alert card or other proof that they are on anticoagulant treatment.

Prothrombin time may be increased by:

Collagen disease, carcinoma, congestive heart failure, diarrhoea, hepatic disorders, infectious hepatitis, jaundice, fever, poor nutritional state.

Prothrombin time may be decreased by:

Diabetes mellitus, hyperlipidaemia, hypothyroidism, oedema and hereditary resistance to warfarin therapy.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Excessive haemorrhage may occur:

- In the event of an excessively long PT or INR or if there is minor bleeding, omission of one or more doses of warfarin may be sufficient to return levels to the therapeutic range.
- In the event of non-significant bleeding, small doses of oral vitamin K (1 - 5 mg) may be sufficient.

- In the event of serious bleeding, treatment 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.

CIPLA-WARFARIN 5 mg: Light pink coloured, circular, flat, bevelled tablets with a breakline on one side. 'W' and '5' 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.

CIPLA-WARFARIN 5 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 at or below 25°C. Protect from light.

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

CIPLA-WARFARIN 1 mg: 41/8.2/0120

CIPLA-WARFARIN 3 mg: 41/8.2/0121

CIPLA-WARFARIN 5 mg: A38/8.2/0422

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

CIPLA MEDPRO (PTY) LTD.

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