

Part II

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Warfant Tablets 5mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains warfarin sodium clathrate equivalent to 5mg warfarin sodium.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablet

Round pink uncoated tablet, scored and marked 'W5' on one side with company logo on reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For prophylaxis against venous thrombosis and pulmonary embolism, and for use in the treatment of these conditions to prevent their extension. For the prophylaxis of systemic embolisation in patients with rheumatic heart disease and atrial fibrillation.

4.2 Posology and method of administration

Warfant tablets are for oral administration.

Adults: An initial daily dose of 10mg on the first two days. Subsequent daily doses should be adjusted according to the results of the prothrombin time or other appropriate coagulation tests. The single daily maintenance requirement is usually between 5mg and 12mg, but can vary between 2mg and 30mg.

The maintenance dose is omitted if the prothrombin time is excessively prolonged. Once the maintenance dose is stabilised in the therapeutic range it is rarely necessary to alter it.

Doses of warfarin should be given at the same time each day.

Use in elderly patients: The elderly are generally more sensitive to the effects of warfarin and often require a smaller dose on a weight for weight basis than younger patients.

Children: Safety and efficacy of warfarin in children have not been established.

4.3 Contra-indications

Animal studies have shown warfarin to be teratogenic and there have been reports of foetal death and embryopathy associated with its administration during human pregnancy. Warfarin should not be prescribed for pregnant women.

Warfarin should not be given to patients within three days of surgery.

The use in patients known to be hypersensitive to warfarin is contra-indicated.

Herbal preparations containing St. John's Wort (*Hypericum perforatum*) must not be used while taking warfarin due to the risk of decreased plasma concentrations and reduced clinical effects of warfarin (see 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and special precautions for use

There is some evidence that abrupt conclusion or interruption of anticoagulation therapy may lead to complications in the form of relapses or exacerbations of the underlying disease and it is probably wiser to taper off oral anticoagulants when therapy has to be concluded.

Prothrombin times should be determined at least twice weekly for the first two weeks until the results stabilise in the therapeutic range. Subsequent measurements may be made at appropriate intervals, such as every two to three weeks.

When warfarin therapy is first introduced, patients should be told what to do if bleeding occurs.

Warfarin should be given with particular caution to patients with impaired liver or kidney function or in severe hypertension.

Warfarin should be given with particular caution to patients where there is a risk of serious haemorrhage such as haemorrhagic blood dyscrasias, haemophilia, ulcerative disorders, threatened abortion, subacute bacterial endocarditis, in the presence of extensive wounds and after recent surgery to the eye and the central nervous system.

Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of warfarin are required to achieve the desired anticoagulant effect (see also Section 4.5 Interactions).

The anticoagulant effect of warfarin may be increased or decreased by concomitant use of herbal medicines. One such example is the interaction between warfarin and St. John's wort (see also Section 4.5 Interactions with other medicinal products and other forms of interaction).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

Many factors *potentiate* the effect of warfarin:

1. Warfarin in the circulation is firmly bound to plasma protein and will have an increased effect if displaced by other drugs such as diuretics, oral anti-diabetic agents, anti-inflammatory agents and amiodarone.
2. Certain drugs, for example D-thyroxine, potentiate the effects of warfarin by increasing the affinity for the hepatic receptor site.
3. Alcohol may inhibit liver enzymes, leading to a reduced dosage requirement of warfarin.
4. Other drugs which may potentiate the effect of warfarin include anabolic steroids; cimetidine; aspirin and other non-steroidal anti-inflammatory drugs; lipid regulating drugs, including the fibrates, such as clofibrate, and statins, such as simvastatin; sulfinpyrazone; chloral hydrate; some aminoglycoside antibiotics; chloramphenicol; macrolide antibacterials such as erythromycin, clarithromycin or azithromycin; quinolone antibacterials such as ciprofloxacin or nalidixic acid; some anti-fungal drugs, including miconazole; some anti-retroviral agents, such as indinavir or ritonavir (although the effect of the latter on the INR may be variable); antineoplastic drugs, including 5-fluorouracil; selective serotonin reuptake inhibitors (SSRIs), including fluvoxamine and fluoxetine; disulfiram; paracetamol.
5. Renal damage may reduce the rate of excretion of warfarin and thus decrease the dose requirement.
6. Acute illness, weight loss and a decreased intake of vitamin K will exaggerate the response.

Other factors may *decrease* the effect of warfarin:

1. Warfarin is metabolised in the liver by microsomal enzymes. These enzymes are induced by drugs such as barbiturates and phenytoin leading to rapid metabolism of warfarin and necessitating an increased dose.
2. Oestrogens and oral contraceptives increase the concentration of Vitamin K dependent factors. Increased doses of warfarin may therefore be required.
3. Colestyramine may absorb warfarin and thus reduce its effects.
4. Carbamazepine, glutethimide, phenazone, griseofulvin and rifampicin also diminish the effect of warfarin.
5. Weight gain, gastro-intestinal upset and increased intake in Vitamin K will necessitate an increase in maintenance dosage of warfarin.
6. The effect of warfarin and phenprocoumon can be reduced by use of the herbal remedy St. John's wort (*Hypericum Perforatum*). This is due to induction of drug metabolising enzymes by St. John's wort. Herbal preparations containing St. John's wort should therefore not be combined with warfarin. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort. If a patient is already taking St. John's wort check the INR and stop the St. John's wort. Monitor INR closely as this may rise on stopping St. John's wort. The dose of warfarin may need adjusting.

INR alterations, prolongation of bleeding & prothrombin time have been reported in some patients receiving broad spectrum penicillins including co-amoxiclav. These drugs should be used with care in patients on anticoagulant therapy.

Other drugs which may interact with Warfarin include capectabine, gefitinib, moxifloxacin, vitamin K, fluconazole and voriconazole.

Patients receiving warfarin therapy should be educated on and monitored for the potential interaction that occurs with warfarin therapy and high-protein, low-carbohydrate diets.

There is evidence that a wide range of alternative therapy products have the potential to interact with warfarin.

An increased effect of warfarin during concomitant treatment with glucosamine has been reported in post-marketing experience. Therefore, more frequent measurement of the warfarin effect may be considered.

4.6 Pregnancy and lactation

Animal studies have shown warfarin to be teratogenic and there have been reports of foetal death and embryopathy associated with its administration during human pregnancy. Warfarin should not be prescribed for pregnant women.

4.7 Effects on ability to drive and use machines

Nil.

4.8 Undesirable Effects

Side-effects: Bleeding is the most common adverse effect of warfarin therapy and haemorrhage can occur in any tissue or organ. This may be due to over-anticoagulation due to poorly controlled treatment or drug interaction. Bleeding may also occur at therapeutic international normalised ratio (INR) values, in which case the possibility of an underlying condition predisposing to haemorrhage should be investigated. Management of bleeding whilst taking warfarin is discussed in 'Overdose'.

Skin reactions: Purpura and ecchymosis are common in over-anticoagulated patients. Pruritic lesions (macular, papular, vesicular and urticarial) have also been reported. Skin necrosis is a rare but potentially serious effect. It is associated with loading doses of over 10mg, and occurs mainly in obese elderly women, usually within 3 - 5 days of starting treatment.

Leukocytoclastic vasculitis, a primarily cutaneous small vessel vasculitis possibly with systemic involvement may be encountered.

It may be associated with a Protein C or Protein S deficiency. It usually affects fatty tissues (breast, thighs, buttocks) and starts as a localised, painful, erythematous or haemorrhagic lesion which becomes bullous and eventually necrotic. Advice on management usually includes discontinuing the warfarin and administration of vitamin K or fresh frozen plasma, and heparinizing the patient. The 'purple toes' syndrome is also rarely reported.

Other adverse effects that have been reported: Alopecia, diarrhoea, an unexplained fall in the haematocrit, jaundice and hepatic dysfunction, fever, nausea, vomiting and pancreatitis. Hypersensitivity reactions occur extremely rarely. If any of these effects occur, warfarin treatment should normally be stopped immediately.

4.9 Overdosage

Overdosage may cause haemorrhage from any tissue or organ and possible manifestations include haematuria, melaena or spontaneous bruising. Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing warfarin therapy and, if necessary, administering phytonadione (vitamin K₁). If haemorrhage is severe, phytonadione therapy should be accompanied by a more immediate effective treatment such as transfusions of fresh frozen plasma or concentrations of vitamin K-dependent coagulation factors.

Administration of vitamin K₁ may make the patient resistant to oral anticoagulants for some days. For this reason, fresh frozen plasma should be administered to those patients with prosthetic heart valves.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Warfarin is a coumarin anticoagulant. By depressing the hepatic Vitamin K – dependent synthesis of coagulation factors II (prothrombin) VII, IX and X, warfarin can prevent venous thrombosis and embolisation, although it has no direct effect on an established thrombus.

5.2 Pharmacokinetic properties

Warfarin sodium is readily absorbed from the gastro-intestinal tract. It can also be absorbed through the skin. It is extensively bound to plasma proteins and its plasma half life is about 37 hours. It crosses the placenta but does not occur in significant quantities in breast milk. Warfarin is metabolised by hepatic microsomal enzymes to inactivate metabolites which are excreted in urine and stool.

5.3 Preclinical safety data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize Starch
Sodium Starch glycollate (Type A)
Magnesium Stearate
Erythrosine Lake (E127)
Alumina

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Polypropylene container: 5 years
Blister pack: 3 years

6.4 Special precautions for storage

Do not store above 25°C.
Polypropylene container: keep the tablets in the original container in order to protect from light and moisture.

Blister pack: keep the tablets in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Polypropylene securitainer with tamper evident lid.
Pack size: 100 tablets, 500 tablets.

PVC/PVDC/Aluminium Blister Packs.
Pack Size: 28 tablets

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Antigen Pharmaceuticals Ltd.,
Roscrea,
County Tipperary,

8. MARKETING AUTHORIZATION NUMBER

PA 73/139/3

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Date of first authorization: 17th October 1995

Date of last renewal: 17th October 2005

10. DATE OF (PARTIAL) REVISION OF THE TEXT

August 2007