Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Warfant 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:
Each tablet contains 122.69 mg lactose monohydrate.

For the full list of 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.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

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

Posology

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 stabilized in the therapeutic range it is rarely necessary to alter it.

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

Elderly
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.

Paediatric population
Safety and efficacy of warfarin in children have not been established.
Method of administration
Warfant tablets are for oral administration.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
• Haemorrhagic stroke (see section 4.4 for further details)
• Clinically significant bleeding
• Within 72 hours of major surgery with risk of severe bleeding (for information on other surgery, see section 4.4)
• Within 48 hours postpartum
• Pregnancy (see section 4.6)
• Drugs where interactions may lead to a significantly increased risk of bleeding (see section 4.5)
• Anticoagulation is contraindicated in any physical condition in which the risk of haemorrhage might be greater that the potential clinical benefits of anticoagulation (see also section 4.4).

4.4 Special warnings and precautions for use

Most adverse events reported with warfarin are a result of over anticoagulation therefore it is important that the need for therapy is reviewed on a regular basis and therapy discontinued when no longer required.

If the concomitant use of Miconazole and anticoagulants such as Warfarin is envisaged, the anticoagulant effect should be carefully monitored and titrated (see section 4.5).

Patients should be given a patient-held information booklet ('warfarin card') and informed of symptoms for which they should seek medical attention.

Commencement of therapy

Monitoring

When warfarin is started using a standard dosing regimen the INR should be determined daily or on alternate days in the early days of treatment. Once the INR has stabilized in the target range the INR can be determined at longer intervals.

INR should be monitored more frequently in patients at an increased risk of over coagulation e.g. patients with severe hypertension, liver or renal disease.

Patients for whom adherence may be difficult should be monitored more frequently.

Thrombophilia

Patients with protein C deficiency are at risk of developing skin necrosis when starting warfarin treatment. In patients with protein C deficiency, therapy should be introduced without a loading dose of warfarin even if heparin is given.
Patients with protein S deficiency may also be at risk and it is advisable to introduce warfarin therapy slowly in these circumstances.

Risk of haemorrhage

The most frequently reported adverse effect of all oral anticoagulants is haemorrhage. Warfarin should be given with caution to patients where there is a risk of serious haemorrhage (e.g. concomitant NSAID use, recent ischaemic stroke, bacterial endocarditis, previous gastrointestinal bleeding) (Please see section 4.3).

Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥ 65, highly variable INRs, history of gastrointestinal bleeding, uncontrolled hypertension, cerebrovascular disease, serious heart disease, risk of falling, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs (see section 4.5).

All patients treated with warfarin should have INR monitored regularly. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed on measures to minimise risk of bleeding and to report immediately to physicians signs and symptoms of bleeding.

Checking the INR and reducing or omitting doses depending on INR level is essential, following consultation with anticoagulation services if necessary. If the INR is found to be too high, reduce dose or stop warfarin treatment; sometimes it will be necessary to reverse anticoagulation. INR should be checked within 2–3 days to ensure that it is falling.

Any concomitant anti-platelet drugs should be used with caution due to an increased risk of bleeding.

Haemorrhage

Haemorrhage can indicate an overdose of warfarin has been taken. For advice on treatment of haemorrhage see section 4.9.

Unexpected bleeding at therapeutic levels should always be investigated and INR monitored.

Ischaemic stroke
Anticoagulation following an ischaemic stroke increases the risk of secondary haemorrhage into the infarcted brain. In patients with atrial fibrillation long term treatment with warfarin is beneficial, but the risk of early recurrent embolism is low and therefore a break in treatment after ischaemic stroke is justified. Warfarin treatment should be re-started 2–14 days following ischaemic stroke, depending on the size of the infarct and blood pressure. In patients with large embolic strokes, or uncontrolled hypertension, warfarin treatment should be stopped for 14 days.

Calciphylaxis

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.

Surgery

For surgery where there is no risk of severe bleeding, surgery can be performed with an INR of <2.5. However local recommendations should be taken into consideration.

For surgery where there is a risk of severe bleeding, warfarin should be stopped 3 days prior to surgery.

Where it is necessary to continue anticoagulation e.g. risk of life-threatening thromboembolism, the INR should be reduced to <2.5 and heparin therapy should be started.

If surgery is required and warfarin cannot be stopped 3 days beforehand, anticoagulation should be reversed with low-dose vitamin K.

The timing for re-instating warfarin therapy depends on the risk of post-operative haemorrhage. In most instances warfarin treatment can be re-started as soon as the patient has an oral intake.

Dental Surgery

Warfarin need not be stopped before routine dental surgery, eg, tooth extraction.

Active peptic ulceration

Due to a high risk of bleeding, patients with active peptic ulcers should be treated with caution. Such patients should be reviewed regularly and informed of how to recognise bleeding and what to do in the event of bleeding occurring.

Interactions

Many drugs and foods interact with warfarin and affect the prothrombin time (see section 4.5). Any change to medication, including self-medication with OTC products, warrants increased monitoring of the INR.

Patients should be instructed to inform their doctor before they start to take any additional medications including over the counter medicines, herbal remedies or vitamin preparations.

Thyroid disorders

The rate of warfarin metabolism depends on thyroid status. Therefore patients with hyper- or hypo-thyroidism should be closely monitored on starting warfarin therapy.
Additional circumstances where changes in dose may be required

The following also may exaggerate the effect of warfarin tablets, and necessitate a reduction of dosage:
• Loss of weight
• Acute illness
• Cessation of smoking

The following may reduce the effect of warfarin tablets, and require the dosage to be increased:
• Weight gain
• Diarrhoea
• Vomiting

Anticoagulant-related nephropathy

In patients with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and hematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with a supratherapeutic INR and hematuria (including microscopic).

Other warnings

Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of warfarin are required to achieve the desired anticoagulant effect.

Genetic information

Genetic variability particularly in relation to CYP2C9 and VKORC1 can significantly affect dose requirements for warfarin. If a family association with these polymorphisms is known extra care is warranted.

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

Information on sodium content
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Warfarin has a narrow therapeutic range and care is required with all concomitant therapy. The individual product information for any new concomitant therapy should be consulted for specific guidance on warfarin dose adjustment and therapeutic monitoring. If no information is provided the possibility of an interaction should be considered. Increased monitoring should be considered when commencing any new therapy if there is any doubt as to the extent of interaction.

Miconazole inhibits CYP2C9, caution should be exercised in patients on oral anticoagulants, such as warfarin, and the anticoagulant effect monitored (warfarin dose reduction may be needed).

Pharmacodynamic interactions

Drugs which are contraindicated
Concomitant use of drugs used in the treatment or prophylaxis of thrombosis, or other drugs with adverse effects on haemostasis may increase the pharmacological effect of warfarin, increasing the risk of bleeding.

Fibrinolytic drugs such as streptokinase and alteplase are contraindicated in patients receiving warfarin.

Drugs which should be avoided if possible
The following examples should be avoided, or administered with caution with increased clinical and laboratory monitoring:

- Clopidogrel
- NSAIDs (including aspirin and cox-2 specific NSAIDS)
- Sulfinpyrazone
- Thrombin inhibitors such as bivalirudin, dabigatran
- Dipyridamole
- Unfractionated heparins and heparin derivatives, low molecular weight heparins
- Fondaparinux, rivaroxaban
- Glycoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab
- Prostacyclin
- SSRI and SNRI antidepressants
- Other drugs which inhibit haemostasis, clotting or platelet action

Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. Warfarin may initially be given with a heparin in the initial treatment of thrombosis, until the INR is in the correct range.

Metabolic interactions

Warfarin is a mixture of enantiomers which are metabolised by different CYPP450 cytochromes. R-warfarin is metabolised primarily by CYP1A2 and CYP3A4. S-warfarin is metabolised primarily by CYP2C9. The efficacy of warfarin is affected primarily when the metabolism of S-warfarin is altered.

Drugs that compete as substrates for these cytochromes or inhibit their activity may increase warfarin plasma concentrations and INR, potentially increasing the risk of bleeding. When these drugs are co-administered, warfarin dosage may need to be reduced and the level of monitoring increased.

Conversely, drugs which induce these metabolic pathways may decrease warfarin plasma concentrations and INR, potentially leading to reduced efficacy. When these drugs are co-administered, warfarin dosage may need to be increased and the level of monitoring increased.

There are a small subsets of drugs for which interactions are known; however their clinical effect on the INR is variable. In these cases increased monitoring on starting and stopping therapy is advised.

Care should also be taken when stopping or reducing the dose of a metabolic inhibitor or inducer, once patients are stable on this combination (offset effect).

Listed below are drugs which are known to interact with warfarin in a clinically significant way.

Examples of drugs which potentiate the effect of warfarin
allopurinol, capecitabine, erlotinib, disulfiram, azole antifungals (ketoconazole, fluconazole, miconazole etc),gefitinib, moxifloxacin omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate ,diuretics, oral anti-diabetic agents, anabolic steroids, cimetidine, clofibrate, chloramphenicol, zafirlukast, fibrates, statins (not pravastatin; predominantly associated with fluvastatin)

erythromycin, sulfamethoxazole, metronidazole, levofloxacin
Examples of drugs which antagonise the effect of warfarin
Barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives, rifampicin, azathioprine, phenytoin ,oestrogens, glutethimide, phenazone
Examples of drugs with variable effect
Corticosteroids, nevirapine, ritonavir

Other drug interactions

Broad spectrum antibiotics may potentiate the effect of warfarin by reducing the gut flora which produce vitamin K. Similarly, orlistat may reduce absorption of vitamin K. Cholestyramine and sucralfate potentially decrease absorption of warfarin.

Increased INR has been reported in patients taking glucosamine and warfarin. This combination is not recommended.

Interactions with herbal products

Herbal preparations containing St John's Wort (Hypericum perforatum) must not be used whilst taking warfarin due to a proven risk of decreased plasma concentrations and reduced clinical effects of warfarin.

Many other herbal products have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should generally avoid taking any herbal medicines or food supplements whilst taking warfarin, and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

Alcohol

Acute ingestion of a large amount of alcohol may inhibit the metabolism of warfarin and increase INR. Conversely, chronic heavy alcohol intake may induce the metabolism of warfarin. Moderate alcohol intake can be permitted.

Interactions with food and food supplements

Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. Patients should be advised to avoid cranberry products. Increased supervision and INR monitoring should be considered for any patient taking warfarin and regular cranberry juice.

Limited evidence suggests that grapefruit juice may cause a modest rise in INR in some patients taking warfarin.

Certain foods such as liver, broccoli, Brussels sprouts and green leafy vegetables contain large amounts of vitamin K. Sudden changes in diet can potentially affect control of anticoagulation. Patients should be informed of the need to seek medical advice before undertaking any major changes in diet.

There are limited data on possible drug interactions with glucosamine, but increments in the INR parameter have been reported with oral vitamin K antagonists. Patients treated with oral vitamin K antagonists should therefore be closely monitored at the time of initiation or termination of glucosamine therapy.

Many other food supplements have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should generally avoid taking any food supplements whilst taking warfarin, and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

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.

Laboratory tests

Heparins and danaparoid may prolong the prothrombin time, therefore a sufficient time interval should be allowed after administration before performing the test.

4.6 Fertility, pregnancy and lactation

Pregnancy
Based on human experience warfarin causes congenital malformations and foetal death when administered during pregnancy.

Warfarin is contraindicated in pregnancy especially in the first and third trimester because of the risk of the warfarin embryopathy or 'fetal warfarin syndrome' during first trimester and fatal bleeding and still birth during third trimester of pregnancy . Warfarin is rarely prescribed in the pregnancy and patients should be switched on to other anticoagulants during pregnancy or after conception. Women of child-bearing age who are taking warfarin tablets should use effective contraception during treatment.

Breast-feeding

Warfarin is excreted in breast milk in small amounts. However, at therapeutic doses of warfarin no effects on the breastfeeding child are anticipated. Warfarin can be used during breast-feeding.

Fertility
No data available

4.7 Effects on ability to drive and use machines

Warfarin has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) and not known – cannot be estimated from the available data.

MedDRA system organ class	**Frequency**	**Adverse Reaction**
Infections and infestations	Not known	Fever
Immune system disorders	Not known	Hypersensitivity
Nervous system disorders	Not known	Cerebral haemorrhage; Cerebral subdural haematoma
Vascular disorders	Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Not known	Haemothorax, epistaxis
Gastrointestinal disorders	Not known	Gastrointestinal haemorrhage, rectal haemorrhage, haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena
Hepatobiliary disorders	Not known	Jaundice; hepatic dysfunction
Skin and subcutaneous tissue	Not known	Rash; alopecia; purpura; 'purple toes' syndrome;

disorders		erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis; calciphylaxis
Renal and urinary disorders	Not known	Anticoagulant-relatednephropathy (see section 4.4),haematuria
Investigations	Not known	Unexplained drop in haematocrit; haemoglobin decreased

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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
HPRA Pharmacovigilance,
Website: www.hpra.ie

4.9 Overdose

The benefit of gastric decontamination is uncertain. If the patient presents within 1 hour of ingestion of more than 0.25 mg/kg or more than the patient's therapeutic dose, consider activated charcoal.

In cases of life-threatening haemorrhage
Stop warfarin treatment, give prothrombin complex concentrate (factors II, VII, IX, and X) or (if no concentrate available) fresh frozen plasma. Discuss with local haematologist or National Poisons Information Service, or both.

Non-life threatening haemorrhage
Where anticoagulation can be suspended, give slow intravenous injection of phytomenadione (vitamin K1)

Where rapid re-anticoagulation is desirable (eg, valve replacements) give prothrombin complex concentrate (factors II, VII, IX, and X) or (if no concentrate available) fresh frozen plasma.
Monitor INR to determine when to restart normal therapy. Monitor INR for at least 48 hours post overdose.

For patients on long-term warfarin therapy without major haemorrhage
• INR >8·0, no bleeding or minor bleeding—stop warfarin, and give phytomenadione (vitamin K1)

For patients NOT on long-term anticoagulants without major haemorrhage

Measure the INR (prothrombin time) at presentation and sequentially every 24–48 hours after ingestion depending on the initial dose and initial INR.

• If the INR remains normal for 24–48 hours and there is no evidence of bleeding, there should be no further monitoring necessary.
• Give vitamin K1 (phytomenadione) if:
a) there is no active bleeding and the patient has ingested more than 0·25 mg/kg;

OR

b) the prothrombin time is already significantly prolonged (INR >4·0).

Delay oral vitamin K1 at least 4 hours after any activated charcoal has been given. Repeat INR at 24 hours and consider further vitamin K1.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, Vitamin K antagonists
ATC code: B01AA03
Mechanism of action

Warfarin is a coumarin anti-coagulant. 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

Absorption
Warfarin sodium is readily absorbed from the gastro-intestinal tract. It can also be absorbed through the skin.

Distribution
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.

Biotransformation
Warfarin is metabolised by hepatic microsomal enzymes to inactive metabolites.

Elimination
Inactive metabolites 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 Monohydrate
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.

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.

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road
Citywest Business Park
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0073/139/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 17th October 2010

10 DATE OF REVISION OF THE TEXT

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