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Before you contact this company: often several companies will market medicines with the same active ingredient. Please check that this is the correct company before contacting them. **Why?**

Summary of Product Characteristics last updated on the eMC: 11/10/2010

Warfarin 3 mg Tablets

1. NAME OF THE MEDICINAL PRODUCT

Warfarin 3 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 3.0 mg of Warfarin sodium.

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet.

Warfarin tablets are presented as flat bevelled edged, blue tablets engraved with company logo or plain on one side and with a breakline and A324 on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prophylaxis of systemic embolism in rheumatic heart disease and atrial fibrillation. Prophylaxis and treatment of venous thrombosis and pulmonary embolism. Transient cerebral ischaemic attacks. Prophylaxis of thromboembolism after insertion of prosthetic heart valve.

4.2 Posology and method of administration

Route of administration : Oral

Adults

Whenever possible, base-line prothrombin time should be determined before the initial dose is given. An initial loading dose for warfarin is usually in the order of 0.45 - 0.50 mg/kg for adults, tailored to individual requirements for the desired degree of anticoagulant effect. The maintenance dose is usually started after 48 hours and depends upon the prothrombin time - reported as international normalised ratio (INR). Currently recommmended ranges of therapeutic anticoagulation are the following:

- prophylaxis of deep-vein thrombosis including surgery in high risk patients (INR 2 -2.5)
- prophylaxis in hip surgery and fractured femur operations, treatment of deep vein thrombosis, pulmonary and systemic embolism, prevention of venous thromo-embolism in myocardial infarction, transient ischaemic attacks, mitral stenosis with embolism, tissue prosthetic heart valves. (INR 2 - 3)
- Recurrent deep-vein thrombosis and pulmonary embolism, mechanical prosthetic heart valves, arterial disease including myocardial infarction. (INR 3 - 4.5)

The daily maintenance dose, taken at the same time each day, is usually between 5 mg and 12 mg, but can vary between 2 mg and 30 mg. In the early days of treatment, INR should be determined daily or on alternate days. Then, depending on response, determinations should be at longer intervals and then, up to every 8 weeks.

ELDERLY

The elderly may be more susceptible to the effects of warfarin, resulting in increased risk of haemorrhage. Lower maintenance doses, weight for weight, than those usually recommended for adults may be required for these patients.

CHILDREN

Infants, especially neonates, may be more sensitive to the effects of anticoagulants in general, due to vitamin K deficiency.

Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. It is not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin should be advised to avoid this drink unless the health benefits are considered to outweigh any risks. Increased medical supervision and INR monitoring should be considered for any patient taking warfarin and a regular intake of cranberry juice.

It is not known whether other cranberry products, such as capsules or concentrates, might also interact with warfarin. Therefore similar caution should be observed with these products.

4.3 Contraindications

- Known hypersensitivity to warfarin or to any of the excipients
- 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 (first and third trimesters, see section 4.6).
- Drugs where interactions may lead to a significantly increased risk of bleeding (see section 4.5)

Pregnancy, hypersensitivity to warfarin, within 3 days of surgery, bacterial endocarditis, severe renal or hepatic disease, actual or potential haemorrhagic conditions (eg haemophilia, hypertension, gastrointestinal ulceration, threatened abortion).

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.

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).

Risk factors for bleeding include high intensity of anticoagulation (INR>4.0), age $\geq$ 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 minimize 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 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.

Surgery

For surgery where there is no risk of severe bleeding, surgery can be performed with an INR of <2.5.

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 e.g. 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

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.

Changes in the patients clinical status, especially associated with intercurrent illness, or liver disease will require more frequent INR monitoring. Renal damage may reduce the excretion rate of warfarin and decrease the dose requirement. Weight loss and decreased intake of vitamin K will enhance warfarin effects while weight gain, increased intake of vitamin K and gastrointestinal upset will necessitate a higher maintenance dose.

More frequent monitoring is necessary if any new medication, including non-prescription medication is added to or withdrawn from the regimen of a patient stabilised on warfarin, or if the dose of a concurrently used medication is changed. The patient should carry identification to show that they are taking an anticoagulant and inform all physicians, pharmacists and dentists that such a medication is being used.

If any symptoms of bleeding occur the patient should contact their doctor immediately.

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

Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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 contra-indicated 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 metabolized by different CYP P450 cytochromes. R-warfarin is metabolized primarily by CYP1A2 and CYP3A4. S-warfarin is metabolized 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 subset of drugs for which interactions are known however the 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 etc) omeprazole, ,paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate zafirlukast, fibrates, statins (not pravastatin, predominantly associated with fluvastatin) erythromycin, sulfamethoxazole, metronidazole
Examples of drugs which antagonise the effect of warfarin
Barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives rifampicin, azathioprine, phenytoin
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. Cholestyamine 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.

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.

Laboratory tests

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

Warfarin interacts with many other medications. Not all interactions have been identified. Some drugs may interact by more than one mechanism and in several cases, both increased and decreased anticoagulation have been reported for the same interacting substance. Care is required when any medication is added to or withdrawn from patients on anticoagulant therapy. Patient monitoring should be more frequent in such cases.

Drugs which may potentiate the effect of warfarin include the following:

- sulfinpyrazone, sulphonamides, phenylbutazone, erythromycin, cimetidine primarily by hepatic microsomal enzyme inhibitions.
- Antiarrhythmics - amiodarone, propafenone, quinidine.
- Non-steriodal anti-inflammatory agents including diflunisal, mefenamic acid, flurbiprofen, piroxicam, sulindac, phenylbutazone, azapropazone, dextropropoxyphene, indometacin and possibly others (azapropazone markedly enhances anticoagulant effect).
- Anabolic steroids - stanozolol, oxymetholone and others.
- Antidepressants - amitriptyline, nortriptyline, paroxetine, fluvoxamine.
- Antidiabetics – tolbutamide, metformin, glucagons.
- Antibacterials - some cephalosporins, chloramphenicol, ciprofloxacin, co-trimoxazole, erythromycin, metronidazole and possibly nalidixic acid, neomycin, norfloxacin, tetracyclines, other broad spectrum antibiotics such as ampicillin and trimethoprim.
- Antifungals - miconazole, fluconazole, itraconazole, ketoconazole.
- Antivirals – neviapine, ritonavir
- Cytotoxics – etoposide, ifosfamide, sorafenib, fluorouracil
- Others – paracetamol, omeprazole, thyroxine, simvastatin, danazol, flutamide, tamoxifen, disulfiram, clofibrate, allopurinol, clopidogrel, entacapone, glucosamine, levamisole, sitaxentan, testosterone.
- Alcohol - large amounts or chronic ingestion
- Other drugs which are potentially hepatoxic.

Drugs which may inhibit the effect of warfarin include the following:

- Aminoglutethimide, Barbiturates, Rifampicin, Gluthetimide
- Antiepileptics - Carbamazepine, Primidone primarily by hepatic microsomal enzyme induction.
- Others - oral contraceptives, griseofulvin, vitamin k (enteral feeds), acitretin,
- Cytotoxics – azathioprine, mercaptopurine, mitotane,
- Sucralfate - impairs warfarin absorption.
- The effect of warfarin can be reduced by concomitant use of the herbal remedy St John's wort (Hypericum perforatum)

Drugs which have been reported to both potentiate and inhibit warfarin effects include phenytoin, corticosteroids, ACTH and colestyramine.

Drugs which increase risk of bleeding due to their antiplatelet effects include diflunisal salicylates, dipyridamole, phenylbutazone and erlotinib. Salicylates, diflunisal and phenylbutazone also have additional detrimental effects on the gastrointestinal mucosa (e.g erosion).

Because warfarin is metabolised by CYP2C9, patients who are receiving treatment with imatinib and require anticoagulation should receive low-molecular-weight or standard heparin instead of warfarin.

Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. It is not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin should be advised to avoid this drink unless the health benefits are considered to outweigh any risks. Increased medical supervision and INR monitoring should be considered for any patient taking warfarin and a regular intake of cranberry juice.

It is not known whether other cranberry products, such as capsules or concentrates, might also interact with warfarin. Therefore similar caution should be observed with these products.

4.6 Pregnancy and lactation

Pregnancy

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

Warfarin is contraindicated in pregnancy in the first and third trimester.

Women of child-bearing age who are taking Warfarin Tablets should use effective contraception during treatment.

Lactation

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

PREGNANCY

Oral anticoagulants cross the placenta and should not be used during pregnancy. Congenital malformations have been reported in infants born to mothers taking these agents during pregnancy. The critical period of exposure is the 6th to 9th week of gestation. Also, during the second and third trimesters foetal or neonatal haemorrhage, foetal death in utero and increased risk of maternal haemorrhage have been reported. If the mother's condition necessitates anticoagulation, heparin should be used from the start of the 6th gestational week through the end of the 12th week, and again at term, in order to lessen risk of adverse outcome to the mother and foetus.

Women of child bearing age who are receiving anticoagulant therapy should be cautioned about the possible complications of pregnancy.

LACTATION

Warfarin is excreted into breast milk in extremely small quantities and is therefore considered compatible with breast-feeding.

4.7 Effects on ability to drive and use machines

None Known

4.8 Undesirable effects

MedDRA system organ class	**Adverse Reaction**
Infections and infestations	Fever
Immune system disorders	Hypersensitivity
Nervous system disorders	Cerebral haemorrhage; Cerebral subdural haematoma
Vascular disorders	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Haemothorax, epistaxis
Gastrointestinal disorders	Gastroinestinal haemorrhage, rectal haemorrhage, haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena

Hepatobiliary disorders	Jaundice; hepatic dysfunction
Skin and subcutaneous disorders	Rash; alopecia; purpura; 'purple toes' syndrome; erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis
Renal and Urinary disorders	Haematuria
Investigations	Unexplained drop in haematocrit; haemoglobin decreased

Haemorrhage is the major risk with warfarin. If therapy is well controlled, bleeding is rare. The occurrence of gastrointestinal haemorrhage during anticoagulant therapy, particularly if prothrombin time is within therapeutic range, may indicate the presence of an underlying haemorrhagic occult lesion which requires further investigation.

Other adverse effects of Warfarin which have been reported included agranulocytosis, leukopenia, diarrhoea, gastrointestinal irritation, "purple toes" syndrome (painful, blue-purple coloured toes), Hypersensitivity, skin rashes, jaundice and hepatic dysfunction, acute adrenal insufficiency, renal damage with resultant oedema and proteinuria, mouth ulcers and alopecia. Purpura, fever, nausea and vomiting, pancreatitis, epistaxis and haemothorax have also been observed and indicate that Warfarin should be discontinued immediately.

Haemorrhagic necrosis has been reported rarely during anticoagulant therapy. When it occurs, fatty tissues are most often affected. Concurrent use of heparin during the first five to seven days of anti-coagulant therapy may decrease the risk of tissue necrosis. At the first sign of necrosis (an erythematous swollen patch) administration of vitamin K may prevent the development of ecchymosis and infarction.

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 (50 g for adults; 1g/kg for children)

In cases of life-threatening haemorrhage

Stop warfarin treatment, give prothrombin complex concentrate (factors II, VII, IX, and X) 30–50 units/kg *or* (if no concentrate available) fresh frozen plasma 15 mL/kg. 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 K_1) 10–20 mg for adults (250 micrograms/kg for a child);

Where rapid re-anticoagulation is desirable (e.g. valve replacements) give prothrombin complex concentrate (factors II, VII, IX, and X) 30–50 units/kg *or* (if no concentrate available) fresh frozen plasma 15 mL/kg.

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 K_1) 0.5-1 mg for adults, 0.015-0.030 mg/kg (15-30 micrograms/kg) for children by slow intravenous injection or 5 mg by mouth (for partial reversal of anticoagulation give smaller oral doses of phytomenadione e.g. 0.5–2.5 mg using the intravenous preparation orally); repeat dose of phytomenadione if INR still too high after 24 hours. Large doses of phytomenadione may completely reverse the effects of warfarin and make re-establishment of anticoagulation difficult.

• INR 6.0–8.0, no bleeding or minor bleeding—stop warfarin, restart when INR < 5.0

• INR < 6.0 but more than 0.5 units above target value—reduce dose or stop warfarin, restart when INR < 5.0

For patients NOT on long term anticoagulants without major heamorrhage

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 K_1 (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).

The adult dose of vitamin K_1 is 10-20 mg orally (250 micrograms/kg body weight for a child). Delay oral vitamin K_1 at least 4 hours after any activated charcoal has been given. Repeat INR at 24 hours and consider further vitamin K_1.

Abnormal bleeding is the main sign of Warfarin overdose and may be manifested by blood in the stools, haematuria, melaena, petechiae, excessive menstrual bleeding, excessive bruising or persistent oozing from superficial injuries.

In life-threatening haemorrhage, vitamin K1 (phytomenadione) 5 - 10 mg should be given by slow intravenous injection and a concentrate of factors II, IX and X, with factor VII concentrate if available. If concentrate is unavailable, fresh frozen plasma (about 1 litre for an adult) should be infused, though this may not be as effective. Infusions should be monitored carefully to avoid precipitating pulmonary oedema in patients with heart disease or the elderly.

Less severe haemorrhage can be controlled by temporarily withdrawing Warfarin doses and, if necessary, giving Vitamin K1 0.5 mg - 2 mg by slow intravenous injection.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: B01A A03

Group: Antithrombotic agents – Vitamin K antagonists

Warfarin is a synthetic 4-hydroxycoumarin derivative which acts by preventing the formation of active procoagulation factors II, VII, IX and X in the liver by inhibiting the Vitamin K- mediated gamma-carboxylation of precursor proteins. Full therapeutic activity is not achieved until circulating coagulation factors have been removed by normal catabolism. This occurs at different rates for each factor, with factor VII having the shortest half-life. Warfarin has no direct thrombolytic effect, though it may limit the extension of existing thrombi.

5.2 Pharmacokinetic properties

Warfarin is almost completely absorbed from the gastro-intestinal tract with its rate, but not extent of absorption decreased by food. Peak plasma concentrations are reached within 2-8 hours. Peak therapeutic effect, which must await catabolism of circulating coagulation factors, is not achieved for 24-36 hours.

Warfarin is highly protein bound (97%) to albumin. Its mean half-life is about 44 hours, but there is a 12 fold variation in half-life between individuals.

Warfarin undergoes oxidative biotransformation in the liver producing Warfarin alcohols which have some minor anticoagulant activity. Enterohepatic re-cycling occurs. Less than 1% of the drug is excreted unchanged in the urine.

5.3 Preclinical safety data

There are no other pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Sucrose

Maize starch

Purified water

Magnesium stearate

Pregelatinised maize starch

Dispersed Indigo Carmine Lake 15009 (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Opaque plastic containers: 3 years

Blister packs: 2 years

6.4 Special precautions for storage

Opaque plastic containers: Do not store above 25°C. Keep the tablet container tightly closed.

Blister packs: Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Warfarin tablets are packed in the following containers and closures.

1. Opaque plastic containers composed of polypropylene tubes and polyethylene- made tamper-evident closures in pack sizes of 50, 100, 250, 500 and 1000.

2. Opaque plastic containers with child-resistant /tamper-evident caps, composed of polypropylene and/or polyethylene with a packaging inclusion of standard polyether foam or polyethylene made filler in pack sizes of 28 and 100.

3. Blister packs composed of 20 MU hard temper aluminium foil and 250 MU white opaque PVC. It is subsequently packed in boxboard cartons in pack sizes of 28 (14 tablets per strip) and 100 (10 tablets per strip).

6.6 Special precautions for disposal and other handling

No special instructions for use/handling.

Administrative Data

7. MARKETING AUTHORISATION HOLDER

Sandoz Ltd

200 Frimley Business Park

Frimley

Camberley

Surrey

GU16 7SR

8. MARKETING AUTHORISATION NUMBER(S)

PL 04416/0527

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 September 2004

10. DATE OF REVISION OF THE TEXT

07/08/2010