Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Warfarin Teva 1 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains warfarin sodium clathrate equivalent to 1 mg warfarin sodium.

Excipients with known effect: 197.6mg of lactose anhydrous and 0.20 mg of E129 (allura red AC).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Tablet
Brown, flat, capsule shaped, scored tablet with 'WARFARIN' on top of 'TARO' engraved on one side and '1' on the other side. 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

Warfarin is indicated in adults.

Warfarin is indicated for the prophylaxis of venous thrombosis and pulmonary embolism, and for use in the treatment of these conditions to prevent their extension.

Warfarin is indicated for the prophylaxis of systemic embolisation in patients with rheumatic heart disease and atrial fibrillation.

4.2 Posology and method of administration

Posology

Adults
The usual induction dose of warfarin is 10mg daily for 2 days, but this should be tailored to individual requirements. A baseline coagulation screen and liver function tests should be performed before initiating warfarin therapy. Subsequent daily doses should be adjusted according to the results of the prothrombin time, usually reported as the INR (international normalised ratio).

The daily maintenance dose of warfarin is usually in the range 3 to 9mg, taken at the same time each day. The maintenance dose is omitted if the INR is excessively high.

Paediatric population
The safety and efficacy of warfarin in children have not been established.

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.

In emergencies, anticoagulant therapy should be initiated with heparin and warfarin together. Where there is less urgency, as in patients disposed to or at special risk of thromboembolism, anticoagulant therapy may be initiated with warfarin alone.

Method of administration

Warfarin Tablets are for oral use.

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
- Drugs where interactions may lead to a significantly increased risk of bleeding (see section 4.5)
- Any physical condition in which the risk of haemorrhage might be greater than the potential clinical benefits of anticoagulation (see also section 4.4).

4.4 Special warnings and precautions for use

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

This product contains allura red AC (E129), which may cause allergic reactions.

If this preparation replaces or is replaced by another warfarin product, the patient should be monitored closely in the period immediately following the change.

When warfarin therapy is introduced, patients should be informed about the symptoms and told what to do if bleeding occurs in an appropriate way (such as information booklet or warfarin card).

INR values should be obtained daily or on alternate days during the early stages of treatment. When the dose has been established and the patient well stabilised, the INR can be monitored at longer but regular intervals, as appropriate.

There is some evidence that abrupt conclusion or interruption of anticoagulant therapy may lead to complications in the form of relapses or exacerbations of the underlying disease. Therefore, it is recommended that where therapy has to be concluded, the oral anticoagulant should be tapered off.

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.

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) (see section 4.3).

Several factors are associated with an increased risk of bleeding complications during warfarin therapy.

Patients with any of the following risk-enhancing factors require careful clinical and laboratory monitoring to ensure that the INR is maintained in the therapeutic range and for early detection of possible bleeding complications:

Age: the elderly are generally more sensitive to the effects of warfarin (see section 4.2 Posology).

Genetic factors: genetic polymorphisms in the cytochrome P450 CYP2C9 gene result in impaired metabolism of Swarfarin. Affected individuals have an increased sensitivity to warfarin, manifesting as low-dose requirements and an increased risk of bleeding. The variant alleles occur at a higher frequency in white populations than in other ethnic groups studied.

Co-morbid conditions: there is an increased risk of bleeding when warfarin is used in patients with haemorrhagic blood dyscrasias, congestive cardiac failure, severe hypertension, cerebrovascular disease, bacterial endocarditis, surgical and other wounds, a history of gastrointestinal bleeding, impaired hepatic or renal function, hypermetabolic states e.g. hyperthyroidism or fever, vitamin K deficiency states, diarrhoea, acute illness, or malignancy.

Active peptic ulceration: due to a high risk of bleeding, patients with history of 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.

Dietary factors: weight loss or inadequate intake of vitamin K can increase sensitivity to warfarin.

Drug interactions: various drugs can potentiate the effects of warfarin (see section 4.5).

The anticoagulant effect of warfarin can be decreased by any of the following factors:

Genetic factors: there have been rare reports of hereditary resistance to warfarin. Resistance should be suspected if larger than usual doses of warfarin are required to achieve the desired anticoagulant effect.

Co-morbid conditions: the anticoagulant response to warfarin can be reduced in patients with hypothyroidism or with vomiting.

Dietary factors: weight gain or increased intake of vitamin K can decrease the anticoagulant effect of warfarin.

Drug interactions: various drugs can impair the anticoagulant effect of warfarin (see section 4.5).

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.

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.

Surgery

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

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.

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).

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.

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.

4.5 Interaction with other medicinal products and other forms of interactions

Warfarin can interact with many other drugs. Unless a drug is known not to interact with warfarin, its introduction or deletion requires monitoring for possible changes in anticoagulant effect.

Paediatric population
Interaction studies have only been performed in adults.

Known interactions include those listed below, but prescribers of other or newly available medicines should refer to the relevant prescribing information or appropriate monograph.

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.

Many factors either potentiate or antagonise the effect of warfarin:

Effect of drugs:

Examples of drugs which potentiate the effect of warfarin
allopurinol, capecitabine, erlotinib, disulfiram, aspirin, azole antifungals (ketoconazole, fluconazole etc), chloral hydrate, chloramphenicol, cimetidine, ciprofloxacin, clarithromycin, danazole, dextropropoxiphene, gemfibrozil, glibenclamide, phenylbutazone, quinidine, stanozolol, sulfinpyrazone, thyroxine and triclofos, 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, aminoglutethimide, cholestyramine, phenazone and sucralfate.
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.

Herbal preparations
The enzyme-inducing effects of the herbal preparation St John's wort (Hypericum perforatum) can increase the metabolism and decrease the anticoagulant effect of warfarin. These effects may persist for at least 2 weeks after withdrawal of St John's wort. Herbal preparations containing St John's wort should not be used during treatment with warfarin. If a patient is already taking St John's wort, the herbal preparation should be withdrawn and the INR should be monitored closely, as a rise in the INR may necessitate a reduction in the dosage of warfarin.

Other factors
Age, genetic and dietary factors, and certain co-morbid diseases can increase or decrease the effect of warfarin. The sensitivity to warfarin can increase the risk of bleeding complications (see section 4.4).

Alcohol
Alcohol may inhibit liver enzymes, leading to a reduced dosage requirement of warfarin. Chronic ingestion of large amounts can decrease the anticoagulant effect caused by enzyme induction. In patients with liver damage, heavy drinking may result in large fluctuations in prothrombin time.

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.

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 is 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).

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
Warfarin is a recognised teratogen. Maternal ingestion of warfarin during pregnancy can cause warfarin embryopathy, foetal haemorrhage, intrauterine death, neonatal haemorrhage and maternal bleeding in the perinatal period. For these reasons, warfarin is contraindicated in pregnancy.

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

Fertility
No fertility data are available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Blood and lymphatic system disorders:
Bleeding. The most significant types of bleeding associated with warfarin use are gastrointestinal haemorrhage and cerebral haemorrhage.

Bleeding is the most common adverse effect of warfarin. The principal determinants of bleeding are the intensity of anti-coagulation, patient characteristics, drug interactions and the duration of therapy. Bleeding may occur at therapeutic INR values, in which case the possibility of an underlying condition that predisposes to haemorrhage should be investigated. Management of bleeding is discussed in section 4.9.

Immune system disorders:
Hypersensitivity reactions

Skin and subcutaneous tissue disorders:
Purpura and ecchymoses are common in over-anticoagulated patients.
Skin necrosis, vasculitis, pruritic skin rashes have been reported, including macular, papular, vesicular and urticarial lesions, purple toes syndrome, alopecia.

Skin necrosis is a rare but serious side effect of warfarin. It occurs mainly in obese, female patients, usually within 3 to 10 days of starting therapy, and is associated with the use of high induction doses. Patients with protein C or protein S deficiency are at particular risk. Initially, the lesions consist of painful, indurated, reddened areas, which progress through a stage of blood-filled blisters into well-demarcated blackened necrotic patches. Areas of skin with underlying fatty tissue, such as breasts, flanks and buttocks are most often affected. Pain in a particular area of skin is a premonitory symptom, and withdrawal of the oral anticoagulant at this stage, reversal of its effect with vitamin K or fresh frozen plasma, and the use of heparin may limit the extent of tissue damage.

The purple toes syndrome is a rare complication of warfarin therapy. Typically, the syndrome presents 3 to 8 weeks after initiation of warfarin therapy as a sometimes painful blue-tinged discoloration of the plantar aspects and sides of the toes. Cholesterol emboli released from atheromatous plaques have been implicated as the cause. If the syndrome occurs, it is recommended that warfarin therapy be withdrawn, if possible, as the affected tissue may undergo ischaemic necrosis.

Frequency 'not known': Calciphylaxis

Gastrointestinal disorders:
Diarrhoea, nausea and vomiting, pancreatitis

Hepatobiliary disorders:
Jaundice and hepatic dysfunction

Renal and urinary disorders:
Anticoagulant-related nephropathy

Infections and infestations:
Fever

Investigations:
Unexplained drop in haematocrit

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 16762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Overdosage may cause bleeding from any tissue or organ and possible manifestations include epistaxis, haematuria, melaena or spontaneous bruising.

Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing warfarin and, if necessary, administering vitamin K1. In cases of major bleeding, vitamin K therapy should be accompanied by tranfusions of fresh frozen plasma or concentrates of vitamin K-dependent coagulation factors.

The degree of reversal of anticoagulation must be decided on an individual basis. Full reversal with vitamin K may result in prolonged resistance to warfarin, giving rise to the possibility of valve thrombosis and thrombo-embolism in patients with prosthetic heart valves.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agent (Vitamin K Antagonist) ATC Code: BO1 AA03

Warfarin is a coumarin anticoagulant. It inhibits the synthesis of vitamin K-dependent coagulation factors II (prothrombin), VII, IX and X, and the anticoagulant proteins C and S. Although an anticoagulant effect is generally apparent within 24 hours of commencing warfarin therapy, several days are required for the drug to exert its full antithrombotic effect. Warfarin can prevent thrombosis and embolism, but has no direct effect on an established thrombus. However, once a thrombus has formed, warfarin can prevent its extension and embolisation.

5.2 Pharmacokinetic properties

Absorption
Warfarin is a racemic mixture of the two enantiomers R- and S- warfarin, the latter having the greater anticoagulant potency. Following oral administration, the absorption of warfarin is essentially complete and peak plasma concentrations are generally achieved within 4 hours.

Distribution
Approximately 99% of warfarin is bound to plasma proteins, mainly to albumin. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 L/kg. It crosses the placenta but does not occur in significant quantities in breast milk.

Elimination
Warfarin is eliminated almost entirely by hepatic metabolism, and only traces of the unchanged drug appear in urine.

The two enantiomers of warfarin are differentially metabolised by human cytochromes P450 in the liver. Genetic polymorphisms affecting the P450 CYP2C9 enzyme can occur, resulting in impaired metabolism of S-warfarin (see section 4.4). The half-life of racemic warfarin is generally in the range 35 to 45 hours.

5.3 Preclinical safety data

Warfarin has been shown to be teratogenic in animal studies; experience in human pregnancy has shown that warfarin is a teratogen, and its use is contraindicated in pregnancy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose anhydrous
Starch, pregelatinised
Magnesium Stearate
Quinoline Yellow Lake E104
FD&C Red No.40 (Allura Red AC) E129
FD&C Blue No.2 (Indigotine) Lake E132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in original container in order to protect from light.

6.5 Nature and contents of container

PVC/ACLAR aluminium foil blisters containing 10, 20, 28, 30, 50, 56 or 100 tablets.
PVC/PE/PVDC aluminium foil blisters containing 10, 20, 28, 30, 50, 56 or 100 tablets.
White, round HDPE plastic bottles and polypropylene caps containing 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132JH Hoofddorp
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2050/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 26th October 2007

Date of last last renewal: 26th October 2012

10 DATE OF REVISION OF THE TEXT

January 2022