# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Warfarin 5 mg Tablets

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Warfarin Sodium 5 mg.

Excipients with known effect: Each tablet contains 139.00 mg of lactose monohydrate and 8.00 mg of sucrose.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Tablet.

Pink coloured, circular, flat faced bevelled edged uncoated tablet with '5' embossing on one side and 'BL' embossing on the other.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation.

Prophylaxis after insertion of prosthetic heart valves.

Prophylaxis and treatment of venous thrombosis and pulmonary embolism.

Transient attacks of cerebral ischaemia.

### 4.2 Posology and method of administration

Posology

Adults:

The typical induction dose is 10 mg daily for 2 days but this should be tailored to individual requirements. The daily maintenance dose is usually 3 to 9 mg taken at the same time each day. The exact maintenance dose depends on the prothrombin time or other appropriate coagulation tests.

Control tests should be made at regular intervals and the maintenance dose should be adjusted according to the results obtained. Once the maintenance dose is established, it is rarely necessary to alter it.

In emergencies, anticoagulant therapy should be initiated with heparin and Warfarin together.

Concomitant therapy with heparin affects the results of control tests, and should be discontinued at least six hours before the first test is carried out.

Elderly:

As for adults, but dosage may need to be lowered. The elderly are generally more sensitive to the effects of warfarin and often require a smaller dose.

Paediatric population:

Warfarin Tablets are not recommended for use in children due to insufficient data on safety and efficacy.

Method of administration

Oral.

## 4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Haemorrhagic stroke (see section 4.4 for further details)
- Clinically significant bleeding
- Use within 72 hours of major surgery with risk of severe bleeding (for information on other surgery, see section 4.4)
- Use within 48 hours postpartum
- Pregnancy (especially in the first and third trimesters, 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 than 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.

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

*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 stabilised 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.

For patients with any impairment that may influence their ability to take the correct dosage safely, the assistance of a carer to administer the dose may be required.

*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. If the benefit of anticoagulation outweighs the risk, 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 also 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, impaired hepatic function, haemorrhagic blood dyscrasias, hypermetabolic states e.g. hyperthyroidism, or fever, acute illness, vitamin K deficiency state, diarrhoea, concomitant drugs (see section 4.5).

Genetic factors: Genetic polymorphisms in the cytochrome P450 CYP2C9 gene result in impaired metabolism of S-warfarin. 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 studies. Genetic variability particularly in relation to VKORC1 can significantly affect dose requirements for warfarin. If a family association with these polymorphisms is known extra care is warranted.

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.

If haemorrhage occurs overdose should be suspected (see section 4.9).

Bleeding may occur at therapeutic INR values, in which case the possibility of an underlying condition that predisposes the haemorrhage should be investigated.

*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.

*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 minor surgical procedures where there is no risk of severe bleeding, surgery can be performed with an INR of <2.5. However the local recommendation should be considered.

For surgery, other surgical procedures, where there is a risk of severe bleeding, warfarin should be stopped 3-5 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*

In most cases warfarin need not be stopped before routine dental surgery, e.g, tooth extraction.

*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.

*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.

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 Section 4.5).

*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.

Important information regarding the ingredients of this medicine
This medicine contains lactose monohydrate.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This medicine contains sucrose.
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 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 is a small subset 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 etc) omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate, chloral hydrate, chloramphenicol, cimetidine, danazol, dextropropoxyphene, glibenclamide, phenylbutazone, quinidine, stanozolol, thyroxine, triclofos ,zafirlukast, fibrates, statins (not pravastatin; predominantly associated with fluvastatin) , erythromycin, sulfamethoxazole, metronidazole, clarithromycin, levofloxacin, propranolol, levothyroxine. |
| **Examples of drugs which antagonise the effect of warfarin** |
| Barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives, rifampicin, azathioprine, phenytoin, aminogluthethimide, phenazone, spironolactone, flucloxacillin. |
| **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 andoral 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**.**

**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. 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 two 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.

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. Care is required with all concomitant therapy. Known interactions include the following, but, prescribers of other or newly available medicines should refer to the manufacturer's information or the appropriate monograph.

## 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 trimesters.

Fertility

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 breast-feeding child are anticipated. Warfarin can be used during breast-feeding.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

Frequency categories are unknown for the following reported adverse reactions and therefore have not been included.

| 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 | Gastrointestinal 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 Calciphylaxis (unknown frequency) |
| Renal and urinary disorders | Haematuria |
| Investigations | Unexplained drop in haematocrit; haemoglobin decreased |

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 effects with vitamin k or fresh frozen plasma, and the use of heparin may limit the extent of tissue damage.

'Purple toes' which 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.

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 the Yellow Card Scheme www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

## 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; 1 g/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 K1) 10–20 mg for adults (250 micrograms/kg for a child).

Where rapid re-anticoagulation is desirable (eg, 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 K1) 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 eg, 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 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).

The adult dose of vitamin K1 is 10–20 mg orally (250 micrograms/kg body weight for a child). 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.

*For the dosages to be used for phytomenadione or prothrombin complex concentrate* (factors II, VII, IX, and X, please refer to the relevant product SPC.

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 thromboembolism in patients with prosthetic heart valves.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacetherapeutic Category: Antithrombotic agent (Vitamin K Antagonist)

ATC Code: BO1 AA03

Warfarin is a synthetic anticoagulant of the coumarin series. It acts by inhibiting the formation of active clotting factors II, VII, IX and X.

## 5.2 Pharmacokinetic properties

Warfarin is readily absorbed from the gastro-intestinal tract. Its plasma half-life is about 40 hours. It is metabolised in the liver, and is excreted in the urine mainly as metabolites.

## 5.3 Preclinical safety data

Warfarin has been shown to be teratogenic in animal studies and may cause abnormalities and foetal death when administered during pregnancy in humans.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Lactose monohydrate

Erythrosine Aluminium lake (E127)

Sucrose

Maize starch

Pregelatinised starch

Magnesium stearate

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

Blisters: 3 years

HDPE containers: 2 years

**6.4 Special precautions for storage**

For Blisters:

- Do not store above 25° C.
- Store in the original package.

For Bulk containers:

- Do not store above 25° C.
- Keep the container tightly closed.

**6.5 Nature and contents of container**

**Blister strips comprising of 250 micron PVC foil coated with 90gsm PVDC and 20 micron aluminium foil**

1) 14 tablets. Blister strips packaged into outer carton to give total of 28, 56 or 112 tablets.
2) 10 tablets. Blister strips packaged into outer carton to give total of 20 tablets.

Bulk HDPE containers of 100 or 500 tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements.

## 7 MARKETING AUTHORISATION HOLDER

Bristol Laboratories Limited
Unit 3, Canalside
Northbridge Road
Berkhamsted
Hertfordshire
HP4 1EG
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 17907/0105

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/10/2006

## 10 DATE OF REVISION OF THE TEXT

04/05/2018