

Product Summary

1. Trade Name of the Medicinal Product

Warfarin Tablets 5mg

2. **Qualitative and Quantitative Composition**

Each tablet contains 5 mg warfarin sodium (as clathrate).

3. **Pharmaceutical Form**

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

4. **CLINICAL PARTICULARS**

- 4.1. **Therapeutic indications**

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

- 4.2. **Posology and method of administration**

Warfarin tablets are for oral administration.

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.

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

Target INR

By referring to the target INR (see below), the dosage of warfarin can be adjusted depending on the deviation of the patient's INR from the target value. An INR within 0.5 INR units of the target is considered to be generally satisfactory.

The following target INR values are based on guidelines from The British Society for Haematology:

<i>Indication</i>	<i>Target INR</i>
Pulmonary embolus	2.5
Proximal deep vein thrombosis	2.5
Calf vein thrombosis in non-surgical patients with no persistent risk factors	2.5
Post-operative calf vein thrombosis without persistent risk factors	2.5
Recurrence of venous thromboembolism when no longer on warfarin therapy	2.5
Recurrence of venous thromboembolism whilst on warfarin therapy	3.5
Symptomatic inherited thrombophilia	2.5
Antiphospholipid syndrome	3.5
Non-rheumatic atrial fibrillation	2.5
Atrial fibrillation due to rheumatic heart disease, congenital heart disease, thyrotoxicosis	2.5
Cardioversion	2.5
Mural thrombus	2.5
Cardiomyopathy	2.5
Mechanical prosthetic heart valve	3.5

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)

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 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.

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 ≥ 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.

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, 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

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.

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 CYP450 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 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. 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.

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.

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 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

Nil.

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	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
Renal and Urinary disorders	Haematuria
Investigations	Unexplained drop in haematocrit; haemoglobin decreased

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.

Pharmacological Properties

5.1. Pharmacodynamic Properties

Warfarin is a coumarin anticoagulant which depresses the hepatic vitamin K-dependent synthesis of coagulation factors II (Prothrombin), VII, IX and X. It acts indirectly, with no effect on existing clots.

5.2. Pharmacokinetic Properties

Warfarin Sodium is readily absorbed from the gastro-intestinal tract; it can also be absorbed through the skin. It is extensively bound to plasma proteins and its plasma half-life is about 37 hours. It crosses the placenta but does not occur in significant quantities in breast milk. Warfarin is administered as a racemic mixture. The s-isomer is reported to be more potent; the R and S isomers are both metabolised in the liver, though at different rates; the stereoisomers may also be affected differently by other drugs. The inactive metabolites are excreted in the urine following reabsorption from the bile.

5.3. Preclinical Safety Data

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

Pharmaceutical Particulars

6.1. List of Excipients

Lactose, Maize Starch, Sodium Starch Glycollate, Magnesium Stearate, Erythrosine Lake (E127), Alumina.

6.2. Incompatibilities

None Known

6.3. Shelf Life

Securitainers: 5 years
HDPE containers: 5 years
Blister packs: 3 years

6.4. Special Precautions for Storage

Store below 25°C.
Protect from light and moisture.

6.5. Nature and Contents of Container

Antigen International Ltd.: Polypropylene securitainers with tamper evident lid.
APS Ltd.: HDPE containers with LDPE lids or child resistant caps.
Pack size : 100 tablets, 500 tablets.
Blister strips of 14 tablets.
Pack size: 28 tablets, 56 tablets.

6.6. Instruction for Use/Handling

Use as directed by the physician.

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd.,
Roscrea,
Co. Tipperary,
Ireland.

8. MARKETING AUTHORISATION NUMBER

PL 02848/0187

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

22 November 1995

10 DATE OF REVISION OF THE TEXT

16/04/2010