SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Warfarin 5 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg warfarin sodium.

Excipient with known effect:

Each tablet contains 92.80 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Pink tablet (diameter 8 mm) with WFN above and 5 below a breakline on one side and twin triangle on reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Acute venous thrombosis and pulmonary embolism (initially together with heparin or low molecular weight heparin). Prophylaxis of venous thrombosis. Acquired heart disease with a particular risk of embolism, e.g. chronic atrial fibrillation, cardiomyopathy and large transmural myocardial infarction. Elective electrical cardioversion of atrial fibrillation/flutter of more than 2 days' duration. Prosthetic heart valves and vessels.

Reference should be made to the current guidelines for antivitamin K treatment.

4.2 Posology and method of administration

Posology

Adults

Initial dosage
Day 1: 5-10 mg warfarin, depending on the patient's genetic make-up, weight, age and general health, etc. (see below).
Day 2: 5-7.5 mg warfarin.
Day 3: Preliminary maintenance dose, based on the effect of the initial dose on INR (International Normalised Ratio) on day 3.

A high initial dosage can result in excessive anticoagulation or, alternatively, hypercoagulation during the adjustment phase because of an imbalance between pro- and anticoagulation factors. For patients with no need for a rapid treatment effect, e.g. where you have concomitant treatment with heparin or low molecular weight heparin, it is possible to opt to start with the estimated maintenance dose (5-7.5 mg warfarin per day) and to first check the INR value on days 3–4.

Maintenance dose
The maintenance dose is normally 2.5-10 mg warfarin daily, but can vary from less than 1.25 mg to 25 mg warfarin daily in some patients.

The entire daily dose should be taken at one time. Effective prevention of thrombosis is generally only achieved after 5 days of treatment at the earliest, provided the INR value has reached the recommended therapeutic level.

Managing anticoagulation treatment
A coagulation test should be done before the start of treatment. This is done by measuring prothrombin complex (PC) levels in blood samples and the value is expressed as the International Normalised Ratio (INR), with a normal value of 1.0. Warfarin has a narrow therapeutic window and sensitivity to warfarin varies from person to person and even within the same person. Therefore treatment intensity should be checked on a regular basis. Sensitivity to warfarin increases with age and lower body weight (see section 5.2). Some patients may have increased sensitivity because of genetic factors (see below and sections 4.4, 5.1 and 5.2), acquired causes such as pronounced heart failure or impaired hepatic function (see below and sections 4.3 and 4.4) and other concomitant medication (see section 4.5).

INR values are checked every day to every other day during the first week and subsequently once or twice a week until the patient is on the maintenance dose. Once a stable level is achieved, the interval between checks can often be extended to 4–6 weeks or sometimes longer periods.

<u>Therapeutic levels of INR</u>
For patients with venous thrombosis, pulmonary embolism, atrial fibrillation, confirmed cardiomyopathy, complicated valve disease, prosthetic biological heart valve and secondary prophylaxis after myocardial infarction, the recommended target value is INR 2.5 (± 0.5).

In the case of treatment failures at normal treatment intensity and after complicated acute myocardial infarction, a higher intensity, equivalent to a target value of INR 3.0 (± 0.5), is recommended. For patients with a prosthetic mechanical mitral valve, an INR of between 2 and 3 or 2.5 and 3.5 may be recommended, depending on the type of prosthesis.

For patients with a particularly high bleeding risk and for those who are unable to cope with a normal intensity due to age or other reason, a lower intensity may be considered, even if this can be associated with a weaker effect.

It should be pointed out that the above therapeutic areas are only general outlines and should be modified depending on the condition being treated, the degree of relative contraindications, local treatment guidelines, and the patient's ability to co-operate.

Due to local or regional treatment recommendations and different analytical methods, there may be variations in therapeutic INR. The recommended INR value can vary in other countries due to different analytical methods. Before any foreign travel, the patient should be informed that warfarin tablets of many different strengths can be found abroad.

Combination with heparin
In acute cases, it is recommended that warfarin be combined with heparin to ensure a rapid anticoagulant effect.

Special patient groups

Paediatric population
Data on the use of warfarin in children is limited. The initial dose is usually 0.2 mg/kg per day for children with normal hepatic function and 0.1 mg/kg for children with impaired hepatic function. The dose is then adjusted to a similar target INR to that for adults. The maintenance dose per kg body weight is dependent on age and reduces with increasing age from <1 year to about 15 years (see section 5.2).

Treatment with warfarin is not recommended for newborns on account of the risk of simultaneous vitamin K deficiency. The therapeutic INR for younger children is not fully known. In practice, therapeutic values for adults have been used, with a target value of INR of 2.5 (± 0.5). Treatment of children, and especially small children, requires specialist knowledge.

Elderly
Elderly patients require lower doses than younger adults. The initial dose should be 5-7.5 mg, which is then adjusted based on INR. It is not known what the reduced dose requirement is due to, but it is likely that there is a combination of pharmacokinetic and pharmacodynamic changes.

Impaired hepatic function
Impaired hepatic function can enhance the effect of warfarin through inhibited synthesis of clotting factors and reduced metabolism of warfarin. Close monitoring of INR is required (see sections 4.4 and 5.2). A reduction of the initial dose should be considered. Warfarin is contraindicated in patients with severely impaired hepatic function (see section 4.3).

Impaired renal function
Although renal clearance plays little role for warfarin (see section 5.2), clinical practice shows that patients with impaired renal function require lower warfarin doses, have poorer coagulation control and have a higher risk of severe bleeding. Warfarin may need to be given at a lower starting dose and monitored more closely in patients with moderate to severe chronic kidney disease compared with the normal population (see section 4.4).

Patients with genetically abnormal enzyme types
A markedly abnormal INR response may be due to genetic factors, particularly a genetically induced reduction of the activity of the enzyme CYP2C9 and increased sensitivity of vitamin K epoxide reductase (VKOR), the pharmacological target of warfarin.

Patients with the alleles CYP2C9*2 or CYP2C9*3 in the enzyme CYP2C9 have reduced metabolism of (S)-warfarin and may therefore require lower initial and maintenance doses (see sections 4.4, 4.8 and 5.2). It can also take longer to reach steady state for warfarin and its therapeutic effect.

Genetic differences in the gene VKORC1 that encodes the vitamin K epoxide reductase enzyme, the target of warfarin, have also been shown to influence the dose requirement by increasing the sensitivity to warfarin (see sections 4.4, 4.8 and 5.1).

Genotyping may be considered when treating particularly sensitive patients for whom it is particularly important to avoid an excessive anticoagulant effect.

Method of administration

Oral

The entire daily dose should be taken at one time.

4.3 Contraindications

- Hypersensitivity to the active ingredient 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)
- Use of products containing St John's wort (Hypericum perforatum) and other drugs where interactions may lead to a significantly increased risk of bleeding (see section 4.5)
- Use during the first trimester and the last four weeks of pregnancy (see section 4.6) and within 48 hours postpartum.
- Severely impaired hepatic function (see section 4.2).
- Patients at serious risk of haemorrhage, such as:
    - patients with haemorrhagic disorders
    - gastrointestinal, urogenital or respiratory bleeding tendency
    - oesophageal varices
    - arterial aneurysm
    - spinal puncture
    - peptic ulcer disease
    - severe wounds (including surgical wounds)
    - bacterial endocarditis
    - malignant hypertension.

4.4 Special warnings and precautions for use

It is important to assess the patient's ability to follow the treatment instructions given. Patients with drug abuse such as alcoholism, or patients suffering from depression or dementia, may have difficulty following the stated dosage regimen.

There is a high risk of drug interactions that result in alteration of the treatment effect of warfarin. Intensified monitoring of the therapeutic response is therefore recommended in association with the initiation or withdrawal or dose adjustment of other medicinal products (see section 4.5).

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

Commencement of therapy

Monitoring

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

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

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

Thrombophilia

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

Risk of haemorrhage

The most frequently reported adverse effect of all oral anticoagulants is haemorrhage. Warfarin should be given with caution to patients where there is a risk of serious haemorrhage (e.g. concomitant NSAID use including acetylsalicylic acid (see section 4.5), 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 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 including dental surgery

In the case of tooth extractions and other surgical procedures, caution should be observed and the INR should be adjusted to a level suitable for the procedure (in tooth extractions and minor surgery with no risk of severe bleeding often 2.2 ± 0.2).
In the case of major surgery and organ punctures, an individually adapted programme for warfarin treatment should be developed.

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.

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, and necessitate a reduction of dosage:

- loss of weight
- acute illness (including infection)
- cessation of smoking

The following may reduce the effect of warfarin, and require the dosage to be increased:

- weight gain
- diarrhoea
- vomiting

A number of factors can alter the therapeutic effect of warfarin, such as:

- heart failure with congestive hepatopathy
- very low or very high intake of vitamin K due to changes in dietary habits (e.g. switching to a vegetarian diet or extreme dieting) or malabsorption
- malabsorption of other causes.

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

Elimination of warfarin is slower in patients with certain mutations in the gene for the enzyme CYP2C9-metabolising (S)-warfarin. These patients require a lower maintenance dose and have a risk of excessive bleeding if a high initial dose is given. In addition, it will take longer to achieve the new efficacy level after adjusting the dose. Also, patients with genetic variations of the enzyme VKORC1 may require lower doses due to increased sensitivity to warfarin (see sections 4.2, 5.1 and 5.2).

If a family association with these polymorphisms is known extra care is warranted.

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 haematuria (including microscopic).

Excipient(s)

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

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of 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.

Warfarin is eliminated primarily via metabolism. The enzyme that is most relevant for the metabolism of (S)-warfarin is CYP2C9 and for (R)-warfarin CYP1A2 and CYP3A4. The risk of pharmacokinetic interactions therefore exists primarily for drugs metabolised by the same enzyme or that act by inducing or inhibiting this enzyme.

As warfarin is highly protein bound, there is also the risk of interactions due to displacement from the binding site on plasma proteins.

The net effect of an interaction can be difficult to predict and can also vary over time. Intensified monitoring of the treatment response is therefore recommended in association with the initiation and withdrawal or dose adjustment of other medicinal products until a stable level is reached again.

The following table gives some guidance about the expected effect of other medicinal products on warfarin.

Interacting drug	Effect of initiation	Effect of withdrawal
Inducers of CYP1A2, CYP2C9 or CYP3A4	Decreased warfarin plasma concentrations with risk for subtherapeutic treatment.	Increased warfarin plasma concentrations with risk for supratherapeutic treatment.
Inhibitors (substrates) of CYP1A2, CYP2C9 or CYP3A4	Increased warfarin plasma concentrations with risk for supratherapeutic treatment.	Decreased warfarin plasma concentrations with risk for subtherapeutic treatment.

Interactions via enzyme inhibition are concentration-dependent. Maximum interaction occurs when steady state of both the inhibitory drug and warfarin is reached. The interaction effect can be modified by dose adjustment of the inhibitory drug.

Interactions via induction of drug-metabolising enzymes are both concentration- and time-dependent. The interaction progresses until a new steady-state concentration of the enzyme has been reached. This can be estimated at about 3 weeks plus the time to steady state for the inducer. If treatment with the inducer is discontinued or modified, it takes the same length of time for the induction to cease or change, respectively.

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, reteplase, alteplase; tenecteplase and urokinase are contra-indicated in patients receiving warfarin.

St John's wort (*Hypericum perforatum*)

Drugs which should be avoided if possible

Examples of drugs that reduce the effect of warfarin (reduced INR)	
Pronounced effect/Combination should be avoided	
- phenazone	A study of five warfarin patients showed that phenazone reduced the plasma

	concentration of warfarin by about a half. The mechanism is probably induction of metabolising enzymes.
- St John's wort	Increased metabolism of warfarin via enzyme induction of CYP3A4, CYP1A2 and CYP2C9. The induction capacity varies between different St John's wort preparations and possibly also between different production batches of the same product. The combination should be avoided (see section 4.3).

Examples of drugs that increase the effect of warfarin (increase INR)	
Pronounced effect/Combination should be avoided	
- anticoagulants/platelet aggregation inhibitors, such as abciximab, tirofiban, eptifibatide, clopidogrel and heparin	Increase risk of bleeding via different mechanisms.
- celecoxib	Spontaneous reports indicate that elderly patients in particular are sensitive. The mechanism is probably competitive inhibition of CYP2C9.
- fluorouracil - capecitabine	Reduced metabolism of warfarin (via down-regulation of CYP2C9). Capecitabine: A study of four cancer patients undergoing three treatment cycles with 1250 mg/m^2 capecitabin showed a 57% increase in AUC for (S)-warfarin and a 51% increase in the half-life of the same enantiomer.
- antimycotics (e.g. fluconazole, metronidazole, voriconazole, see also below)	Reduced metabolism of warfarin (via inhibition of CYP3A4 and CYP2C9). Fluconazole: In a study, the half-life of (S)-warfarin and (R)-warfarin increased by 275% and 210%, respectively. AUC increased by 284% for (S)-warfarin and 207% for (R)-warfarin. Metronidazole: A study showed a 42% increase in AUC for racemic warfarin. Voriconazole: The combination of voriconazole (300 mg twice daily) with warfarin (30 mg as a single dose) approximately doubled the prothrombin time.
- selective serotonin re-uptake inhibitors, SSRIs (e.g. fluoxetine, fluvoxamine, sertraline, paroxetine)	Epidemiological studies showed an increased bleeding risk with the combination of SSRIs and warfarin. Fluoxetine: Fluoxetine is believed to

	inhibit CYP2C9, the enzyme that metabolises (S)-warfarin. In addition, both fluoxetine and warfarin are strongly bound to albumin and the combination of the drugs can result in them displacing one another from the binding site on the protein. Fluvoxamine: 2 weeks' co-administration of warfarin and fluvoxamine caused a 98% increase in the plasma concentration of warfarin.
- imatinib	Reduced metabolism of warfarin via inhibition of CYP2C9, CYP2D6 and CYP3A4.
- leflunomide	Reduced metabolism of warfarin via inhibition of CYP2C9. In a couple of case reports, marked increases in INR were noted.
- noscapine	An increased effect of warfarin has been reported during concomitant treatment with noscapine. Patients treated with warfarin should therefore be monitored carefully when initiating or discontinuing noscapine treatment. The mechanism may be reduced metabolism of warfarin via inhibition of CYP2C9 and CYP3A4.
- NSAIDs including acetylsalicylic acid and phenylbutazone	Competitive inhibition of metabolism of warfarin via CYP2C9. Inhibition of platelet aggregation. Gastric erosion. Displacement of warfarin from plasma proteins.
- simvastatin	In a study of 29 patients with a stable warfarin dose, mean INR increased by 27% and the mean warfarin dose decreased by 9% following initiation of simvastatin. The mechanism is probably competition for CYP3A4-mediated metabolism.
- sulfamethoxazole	Inhibition of the metabolism of warfarin. Displacement of warfarin from the binding site on plasma proteins.
- tamoxifen	Unknown mechanism.
- testosterone	Effect on coagulation factors, hepatic synthesis and competition for the binding site on plasma proteins.

The following examples should also be avoided, or administered with caution with increased clinical and laboratory monitoring:

- Sulfinpyrazone
- Thrombin inhibitors such as bivalirudin, dabigatran
- Dipyridamole
- Fondaparinux, rivaroxaban
- Prostacyclin
- Other drugs which inhibit haemostasis, clotting or platelet action

Low-dose acetylsalicylic acid 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.

Drugs with a moderate effect

Examples of drugs that reduce the effect of warfarin (reduced INR)	
Moderate effect	
- aprepitant - certain antiviral drugs (e.g. nevirapine, ritonavir)	Induces CYP2C9, which increases the metabolism of (S)-warfarin. Aprepitant: A three-day treatment (125 mg on day 1, 80 mg on days 2 and 3) with aprepitant in healthy volunteers adjusted to a stable dose of warfarin resulted in a 34% reduction in the lowest concentration of (S)-warfarin and a 14% reduction in INR. Use with caution or seek a therapeutic alternative.
- bosentan	Induces CYP3A4 and possibly also CYP2C9, which increases the metabolism of warfarin.
- cholestyramine	Reduces the absorption of warfarin and interferes with enterohepatic recirculation.
- certain antibiotics (e.g. dicloxacillin and rifampicin)	Increased metabolism of warfarin via enzyme induction. Rifampicin: High doses of warfarin (20 mg/day or over) may be required to maintain sufficient anticoagulation and consideration should be given to reducing the dose by 50% 1-2 weeks after discontinuing rifampicin. Close INR monitoring is recommended in the first weeks after initiation and withdrawal of rifampicin.
- antiepileptics (e.g. carbamazepine, phenytoin, fosphenytoin) - barbiturates such as phenobarbital - aminoglutethimide	Increased metabolism of warfarin (via enzyme induction). Phenytoin: Can increase the metabolism of warfarin, possibly via induction of

	CYP 2C9, for which reason co-administration for prolonged periods can result in a reduced effect of warfarin. Note, however, that the combination can initially lead to an increased effect of warfarin due to displacement of warfarin from the binding sites on plasma proteins, see below.
- daranuvir - disopyramide - flucloxacillin, cloxacillin - griseofulvin	Unknown mechanism. For most of these, the opposite effect has also been reported, see below.
- azathioprine - mercaptopurine	Decreased absorption and increased metabolism of warfarin.
- phytomenadione (vitamin K) - menadiol (vitamin K3)	Reduce the anticoagulant effect of warfarin.
- mianserin	May induce the metabolism of warfarin.

Examples of drugs that increase the effect of warfarin (increase INR)	
Moderate effect	
- atazanavir - fosamprenavir	Increased warfarin levels via competition for CYP3A4-mediated metabolism/inhibition of metabolism of warfarin via CYP3A4.
- amiodarone	Inhibits the metabolism of warfarin. The effect occurs gradually during the first month of treatment. The effect can persist for up to three months after the end of treatment with amiodarone. A 25% reduction of the warfarin dose is recommended at the start of concomitant amiodarone treatment. Further dose adjustments may be needed in the first four weeks and close INR monitoring is recommended. If amiodarone treatment is ended, the interaction gradually subsides. A gradual increase of the warfarin dose may be necessary.
- danazol	Inhibition of metabolism of warfarin and/or direct effect of danazol on coagulation and fibrinolytic system.
- fluvastatin	Inhibition of metabolism of warfarin via CYP2C9.
- miconazole	Reduction of intrinsic clearance and increase of the free fraction of warfarin

	in plasma. Inhibition of CYP450-mediated metabolism of warfarin.
- paracetamol	Inhibition of metabolism of warfarin. Effect on formation of coagulation factors.
- amitriptyline	Reduced metabolism of warfarin. Increased absorption of warfarin.
- cimetidine - disulfiram - macrolides (e.g. azithromycin, erythromycin, clarithromycin) - antimycotics (e.g. itraconazole, ketoconazole) - chloramphenicol	Reduced metabolism of warfarin.
- propafenone	Reduced clearance of warfarin.
- proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole)	Reduced metabolism of the less active R enantiomer of warfarin.
- ethacrynic acid	Displacement of warfarin from plasma proteins.
- phenytoin, fosphenytoin	Displacement of warfarin from the binding site on plasma proteins can result initially in an increased effect of warfarin. In the longer term, however, phenytoin/fosphenytoin can cause a reduced effect of warfarin, see above.
- gemfibrozil	Reduced metabolism of warfarin. Displacement of warfarin from the binding site on plasma proteins.
- thyroid hormones (levothyroxine, liothyronine)	Increased metabolism of vitamin K-dependent coagulation factors.
- penicillins (e.g. amoxicillin, cloxacillin) - quinolones (e.g. ciprofloxacin, norfloxacin) - dextropropoxyphene - disopyramide - flutamide - glucosamine - ifosfamide - mesna - prednisolone/prednisone - rofecoxib - rosuvastatin - tramadol	Unknown mechanism. Disopyramide/cloxacillin: The opposite effect has also been reported, see above. Glucosamine: Elevated INR has been reported in patients taking glucosamine and vitamin K antagonists. Patients treated with oral vitamin K antagonists should therefore be closely monitored at the time of initiation or withdrawal of glucosamine therapy.

Other interactions	
Alcohol	A moderate alcohol intake does not alter the effect of warfarin. Chronically high

	alcohol consumption can increase or reduce the effect of warfarin by interfering with its metabolism.
Herbal medications	
- St John's wort	The combination should be avoided (see above and section 4.3)
Foodstuffs	
- foodstuffs with a high vitamin K content such as cabbage, broccoli, avocado and spinach	Can reduce the anticoagulant effect of warfarin by direct antagonism or by altering the absorption of warfarin. A large day-to-day variation in the consumption of vitamin K-rich foodstuffs can contribute to problems with the correct adjustment of the dose. The normal variation in the ingestion of vitamin K-rich foodstuffs usually does not interfere with the effect of warfarin.
- cranberry	Increased effect of warfarin. Death from internal bleeding has been reported following co-administration of warfarin and an unknown amount of cranberry juice.
Vitamins and food supplements	
- coenzyme Q10	Reduced effect of warfarin due to similarity in chemical structure between coenzyme Q10 and vitamin K2
- food supplements; vitamin A, E	Increased effect of warfarin. Unknown mechanism.

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

Examples of drugs which potentiate the effect of warfarin
allopurinol, erlotinib, methylphenidate, zafirlukast, fibrates
Examples of drugs which antagonise the effect of warfarin
primidone, oral contraceptives
Example of drugs with variable effect
Corticosteroids

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.

Many other herbal products and food supplements 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.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Warfarin rapidly crosses the placenta. Use of warfarin during pregnancy is not recommended unless absolutely necessary and is contraindicated in the first trimester and during the last four weeks of pregnancy (see section 4.3). Warfarin can cause severe malformations, fetal bleeding and fetal death.

The use of warfarin during pregnancy can result in fetal warfarin syndrome, a chondrodysplasia punctata-like syndrome, characterised by nasal hypoplasia, stippled cartilage on X-ray (particularly in the spine and tubular bones), small fingers and hands, optic atrophy, cataract leading to total or partial blindness, growth and mental retardation and microcephaly.
In special circumstances, treatment may be considered by a specialist clinician.

Breast-feeding

Warfarin passes into the breast milk but at therapeutic doses of warfarin no effect on the child is expected. Warfarin can be used during breast-feeding.

Fertility
Fertile women should use effective contraception during treatment with warfarin.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Treatment with warfarin can cause bleeding, in some cases serious, from any organ, including epistaxis, haemoptysis, haematuria, gingival bleeding, haematomas, vaginal bleeding, subconjunctival haemorrhage, gastrointestinal haemorrhage, cerebral haemorrhage and prolonged and extensive bleeding following surgery or trauma. Bleeding that results in death, hospitalisation or a transfusion requirement has been reported among patients on long-term anticoagulant treatment.

Independent risk factors for major haemorrhage during anticoagulant treatment with warfarin are:
- advanced age
- treatment intensity

- previous cerebral haemorrhage
- previous gastrointestinal haemorrhage.

Subjects with genetic variants of the polymorphic enzymes CYP2C9 and VKOR (see sections 4.2, 4.4, 5.1 and 5.2), which cause increased sensitivity to warfarin, are at increased risk of an excessive anticoagulant effect during warfarin treatment, which can increase the risk of bleeding complications. Haemoglobin levels and INR should be closely monitored.

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

MedDRA system organ class	**Adverse Reactions**	**Frequency**
Infections and infestations	Fever	Not known
Blood and lymphatic system disorders	Bleeding from any organ	Very common
	Increased sensitivity to warfarin following long-term treatment	Common
	Anaemia	Uncommon
Immune system disorders	Hypersensitivity	Very rare
Metabolism and nutrition disorders	Calciphylaxis	Not known
Nervous system disorders	Cerebral haemorrhage; Cerebral subdural haematoma	Not known
Vascular disorders	Blue toe syndrome	Very rare
	Haemorrhage	Not known
Respiratory, thoracic and mediastinal disorders	Haemothorax, epistaxis	Not known

Gastrointestinal disorders	Diarrhoea; nausea; vomiting	Uncommon
	Melaena	Very rare
	Gastroinestinal haemorrhage, rectal haemorrhage, haematemesis; pancreatitis; abdominal pain (secondary to haemorrhage)	Not known
Hepatobiliary disorders	Jaundice; hepatic dysfunction	Rare
Skin and subcutaneous disorders	Rash; alopecia; infarction and skin necrosis; urticaria, itching	Rare
	Purpura; erythematous swollen skin patches leading to ecchymosis	Not known
Renal and Urinary disorders	Haematuria; anticoagulant-related nephropathy (see section 4.4)	Not known
Investigations	Unexplained drop in haematocrit; haemoglobin decreased	Not known

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

4.9 Overdose

Symptoms

The primary effect of warfarin overdose is an increased INR value and subsequent risk of haemorrhage. The increase in INR correlates with the half-life of factor VII, usually appears within 24 hours and peaks between 36 and 72 hours after intake.

Clinical manifestations begin a few days or weeks after ingestion and include epistaxis, gingival bleeding, pallor, haematomas around joints and buttocks and blood in urine and faeces. Other symptoms can include back pain, bleeding lips, mucous membrane haemorrhage, abdominal pain, vomiting and petechiae. Later symptoms are paralysis due to cerebral haemorrhage and finally haemorrhagic shock and death.

Treatment

It is recommended to contact the poison information centre.
Gastric lavage if justified. Treatment with activated charcoal (50 g for adults; 1g/kg for children) may be considered within one hour after ingestion of more than 0.25 mg/kg or more than the patient's therapeutic dose.

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. Due to the half-life of warfarin of 20-60 hours, the patient should be monitored for several days. Always discuss with the coagulation expert in case of doubt.

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 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 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 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: anticoagulants, vitamin K antagonists, ATC code: B01AA03

Warfarin is a synthetic anticoagulant of the coumarin type. Warfarin sodium is a readily soluble salt that can be given both orally and parenterally. The warfarin in Warfarin Tablets is also a racemate of (S)-warfarin and (R)-warfarin.

Warfarin induces an anticoagulant effect by blocking the vitamin K cycle. Vitamin K is necessary to complete the synthesis of coagulation factors II, VII, IX and X in the liver. In order for these coagulation factors to become coagulatively active, glutamic acid in the factors must be carboxylated. This occurs by vitamin K_1 (from food) first being reduced by means of vitamin K reductase to vitamin KH_2. Vitamin KH_2 is then oxidised to vitamin K 2,3-epoxide in a reaction in which the glutamic acid in factors II, VII, IX and X (together with the coagulation inhibitors protein C and its cofactor protein S) are carboxylated. Vitamin K 2,3-epoxide is then reduced back to K_1 with the aid of vitamin K epoxide reductase. Warfarin blocks vitamin K epoxide reductase (VKOR), and to a certain extent vitamin K reductase, thereby inhibiting the conversion of vitamin K 2,3 epoxide back to vitamin K_1 and vitamin KH_2, which in turn results in fewer active coagulation factors.

Genetic differences in the gene for vitamin K epoxide reductase (VKORC1) have been shown to be relevant for the necessary dose of warfarin. In studies, a factor of approximately two has been reported for the difference between the highest and lowest average dose for different haplotype groups. Caucasians are relatively evenly distributed between the groups, while Asians mostly have genes that require a reduced dose (see sections 4.2, 4.4, 4.8 and 5.2).

The half-life for the coagulation factors varies from 4-7 hours for factor VII to 50 hours for factor II. This means that the system first achieves a new equilibrium after several days. The anticoagulant effect becomes established within 36 to 72 hours and the maximum effect after 5-7 days. The duration of the effect after the end of treatment depends on how rapidly resynthesis of the vitamin K-dependent coagulation factors occurs, which usually takes 4-5 days.

5.2 Pharmacokinetic Properties

<u>Absorption</u>
Warfarin is absorbed rapidly from the gastrointestinal region with little interindividual variation.

<u>Distribution</u>

Warfarin's distribution volume is relatively small, with an apparent distribution volume of 0.14 l/kg. Warfarin has high protein binding, with a binding rate of 98–99%.

Biotransformation

The warfarin in Warfarin Tablets is a racemate of (S)-warfarin and (R)-warfarin. After administration of the racemate, (R)- and (S)-warfarin exhibit similar systemic exposure with an S:R exposure ratio of about 1:2. However, pharmacokinetic/pharmacodynamic studies show that the anticoagulant effect of racemic warfarin is due almost exclusively to (S)-warfarin, which is approximately 1000 times as potent as (R)-warfarin based on PK/PD modelling. The metabolites formed in the liver are either inactive or very weakly active. The R- and S-isomers are metabolised by different routes so that each isomer gives rise to two different alcohols. (S)-warfarin is metabolised predominantly via CYP2C9 and (R)-warfarin mainly by CYP1A2 and CYP3A4. Patients with abnormal forms of CYP2C9 such as the alleles CYP2C9*2 and CYP2C9*3 metabolise (S)-warfarin less effectively and therefore have an increased risk for excessive anticoagulation and bleeding complications. For further information, see the section Special patient groups below.

Elimination

Warfarin is excreted as inactive metabolites in the bile, after which they are reabsorbed and eliminated in the urine. The elimination half-life of warfarin is 20 to 60 hours. For (R)-warfarin, the half-life varies between 37 and 89 hours and for (S)-warfarin between 21 and 43 hours. Renal clearance of (S)- and (R)-warfarin is negligible (see section 4.2).

Special patient factors

Elderly

Oral clearance of (S)-warfarin decreases linearly with increasing age in adults (see section 4.2).

Body weight

The dose of warfarin needed increases by about 11% per 0.25 m^2 of body surface area.

Paediatric population

Body weight-normalised oral clearance of (S)-warfarin in children decreases from 18.1 ml/min/kg in prepubertal children to 12.6 ml/min/kg in pubertal children and reaches adult values after puberty. This trend is correlated with the development of the liver (see section 4.2).

CYP2C9-genotype

(S)-warfarin is primarily eliminated by metabolism catalysed by the enzyme CYP2C9. CYP2C9 presents genetic polymorphism. The alleles *1, *2 and *3 are most common in the Caucasian population. The allele *1 provides "normal" enzyme activity. The alleles *2 and *3 provide reduced enzyme activity and thus reduced clearance (and increased half-life) of warfarin. The most marked reduction of clearance is obtained in patients with two *3 alleles. Among Caucasians, this genotype is present in 0.5% of

the population. Allele frequency and the significance of the genotype for the warfarin dose needed are presented below.

	Relative allele frequency by ethnicity		
	*1	*2	*3
Caucasians	74.3%	14.3%	10.9%
African Americans	95.3%	0.0%	0.8%
Japanese	98.4%	0.0%	1.6%

Genotype	Observed reduction in the dose needed
*1/*1	0% (reference)
*1/*2	20%
*1/*3	34%
*2/*2	36%
*2/*3	57%
*3/*3	78%

Renal impairment
Renal function does not appear to affect systemic exposure of warfarin, but there are other reasons for special treatment recommendations, see section 4.2.

Hepatic impairment
Impaired hepatic function can enhance the effect of warfarin by inhibited synthesis of coagulation factors and reduced metabolism of warfarin (see sections 4.2, 4.3 and 4.4).

There is no information about the effect of impaired hepatic function on the pharmacokinetics of warfarin. Increased systemic exposure is expected in the case of moderate to severe functional impairment.

5.3 Preclinical Safety Data

There is no preclinical information about general toxicity, genotoxicity and carcinogenicity considered to be of relevance to clinical safety over and above the information given elsewhere in the summary of product characteristics. Increased bleeding frequency and fetal death have been seen in the offspring of rats treated with warfarin at doses 1-500 times the doses used in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate
Maize Starch
Pregelatinised Starch (Maize)
Erythrosine E127
Aluminium Oxide
Sodium Starch Glycolate Type A
Magnesium Stearate

Purified Water

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 the original container or package.

6.5 Nature and Contents of Container

Polypropylene containers fitted with tamper-evident polyethylene closures or polypropylene containers fitted with tamper-evident polypropylene closures or 250 µm/1.37 g/cm^3 PVC coated with 60 g/m^2 PVdC backed by 20 µm/65 gm^{-2} Aluminium Blister Packs in pack sizes of 7, 14, 21, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120 and 500 tablets.

Bulk pack size: 10,000 and 100,000

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited,
Ridings Point,
Whistler Drive,
Castleford,
WF10 5HX,
United Kingdom

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10 DATE OF REVISION OF THE TEXT

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