312643

MAREVAN

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Warfarin

QUALITATIVE AND QUANTITATIVE COMPOSITION

Warfarin sodium as 1 mg, 3 mg and 5 mg tablets.

Warfarin sodium, 1 mg, tablet

Each tablet contains 1 mg of warfarin sodium.

Warfarin sodium, 3 mg, tablet

Each tablet contains 3 mg of warfarin sodium.

Warfarin sodium, 5 mg, tablet

Each tablet contains 5 mg of warfarin sodium.

PHARMACEUTICAL FORM

Warfarin sodium, 1 mg, tablet

Brown round flat bevelled edge tablets engraved DF/M1

Warfarin sodium, 3 mg, tablet

Pale blue round flat bevelled edge tablets engraved DF/M3

Warfarin sodium, 5 mg, tablet

Pink round flat bevelled edge tablets engraved DF/M5

CLINICAL PARTICULARS

Indications

For:

- Prophylaxis of systemic embolisation in patients with rheumatic heart disease and atrial fibrillation.
- Prophylaxis of thromboembolism after insertion of prosthetic heart valves.
- Prophylaxis and treatment of venous thrombosis and pulmonary embolism.
- Transient attacks of cerebral ischaemia.

Dosage and Administration

For oral use.

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 warfarin dosage should be adjusted in accordance with 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 heparin therapy affects the results of control tests and should be discontinued at least 6 h before the first test is carried out.

Children:

Dosage for children has not been established.

Elderly:

As for adults, but dosage may need to be lowered.

Renal impairment:

Caution is advised in patients with renal impairment (see section *Warnings and Precautions*).

Hepatic impairment:

Caution is advised in patients with hepatic impairment (see section *Warnings and Precautions*).

Contraindications

Warfarin is contraindicated in:

- Known hypersensitivity to warfarin or to any of the excipients,
- Haemorrhagic stroke,
- Clinically significant bleeding,
- Within 72 hours of major surgery with risk of severe bleeding,
- Within 48 hours postpartum,
- Pregnancy (first and third trimesters, see section *Pregnancy and Lactation*),
- Concomitant use of fibrinolytic drugs such as streptokinase and alteplase and drugs where interactions may lead to a significantly increased risk of bleeding (see section *Interactions*),
- Bacterial endocarditis,
- Severe hepatic or renal disease,
- Actual or potential haemorrhagic conditions, e.g. haemophilia, hypertension, gastrointestinal ulcerations, threatened abortion.

Warnings and Precautions

Adverse events

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.

Purpura, fever, nausea and vomiting, pancreatic, epistaxis and haemothorax indicate that warfarin should be discontinued immediately (see section *Adverse Reactions*).

Tissue necrosis

Haemorrhagic necrosis has been reported rarely during anticoagulant therapy. When it occurs, fatty tissues are more often affected.

Concurrent use of heparin during the first five to seven days of anticoagulant therapy may decrease the risk of tissue necrosis. At the first sign of necrosis (an erythematous swollen patch), administration of vitamin K may prevent the development of ecchymosis and infarction (see section *Adverse Reactions*).

Monitoring

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

INR should be monitored more frequently in patients at increased risk of overcoagulation e.g. patients with severe hypertension, liver or renal disease. Patients for whom adherence may be difficult should be monitored more frequently. Changes in the patient's clinical status, especially associated with intercurrent illness, or liver disease will require more frequent INR monitoring.

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 *Interactions*). 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 (see section *Overdose*). 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 oral intake.

Dental surgery

Warfarin need not be stopped before routine dental surgery e.g. tooth extraction.

Active peptic ulceration

Due to a high risk of bleeding, patients with active peptic ulcers should be treated with caution. Such patients should be reviewed regularly and informed of how to recognise bleeding and what to do in the event of bleeding occurring.

Interactions

Many drugs and foods interact with warfarin and affect the prothrombin time (see section *Interactions*). 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.

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.

Additional circumstances where changes in dose may be required

The following factors may exaggerate the effects of warfarin and necessitate a reduction in dosage: weight loss, acute illness, cessation of smoking.

Factors which may reduce effects of warfarin and call for an increase in dosage include weight gain, diarrhoea and vomiting.

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 haematuria. 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).

Warfarin resistance

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.

Lactose

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

Interactions

Narrow therapeutic range

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. Increase 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 (see section *Contraindications*).

Drugs which should be avoided if possible

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

- Clopidogrel,
- NSAIDs (including aspirin and cox-2 specific NSAIDs),

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- 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
Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. Warfarin may initially be given with a heparin in the initial treatment of thrombosis, until the INR is in the correct range.

Metabolic interactions
Warfarin is a mixture of enantiomers which are metabolized by different CYP P450 cytochromes. R-warfarin is metabolized primarily by CYP1A2 and CYP3A4. S-warfarin is metabolized primarily by CYP2C9. The efficacy of warfarin is affected primarily when the metabolism of S-warfarin is altered.
Drugs that compete as substrates for these cytochromes or inhibit their activity may increase warfarin plasma concentrations and INR, potentially increasing the risk of bleeding. When these drugs are co-administered, warfarin dosage may need to be reduced and the level of monitoring increased.
Conversely, drugs which induce these metabolic pathways may decrease warfarin plasma concentrations and INR, potentially leading to reduced efficacy. When these drugs are co-administered, warfarin dosage may need to be increased and the level of monitoring increased.
There is a small subset of drugs for which interactions are known, however the clinical effect on the INR is variable; in these cases, increased monitoring on starting and stopping therapy is advised.
Care should 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.
Drugs which potentiate the effect of warfarin include the following:

- Sulfinpyrazone, sulphonamides, phenylbutazone, cimetidine primarily by hepatic microsomal enzyme inhibitors,
- Non-steroidal anti-inflammatory agents, including diflunisal, mefenamic acid, flurbiprofen, piroxicam, sulindac, phenylbutazone, azapropazone, dextropropoxyphene, indomethacin, and possibly others (azapropazone markedly enhances anticoagulant effect),
- Antiarrhythmics – amiodarone, propafenone, quinidine,
- Anabolic steroid – stanozolol, oxymetholone and others,
- Antidepressants – amitriptyline, nortriptyline, paroxetine, fluvoxamine,
- Antidiabetics – tolbutamide, metformin, glucagons,
- Antibacterial – some cephalosporins, chloramphenicol, ciprofloxacin, co-trimoxazole, erythromycin, metronidazole, sulfamethoxazole and possibly nalidixic acid, neomycin, norfloxacin, tetracyclines, other broad-spectrum antibiotics such as ampicillin and trimethoprim,
- Anti-fungals – miconazole, fluconazole, itraconazole, ketoconazole,
- Cytotoxics – etoposide, ifosfamide, sorafenib, fluorouracil, capecitabine, erlotinib,
- Others – paracetamol (prolonged regular use), omeprazole, thyroxine,
- Statins (not pravastatin, predominantly associated with fluvastatin), danazol, flutamide, tamoxifen, disulfiram, fibrates, allopurinol, clopidogrel, entacapone, levamisole, sitaxentan, testosterone, methylphenidate, zafirlukast,
- Other drugs which are potentially hepatotoxic.

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

- Aminoglutethimide, barbiturates, rifampicin, gluthetimide,
- Antiepileptics – carbamazepine, phenytoin, primidone primarily by hepatic microsomal enzyme induction,
- Others – oral contraceptives, griseofulvin, vitamin K (enteral feeds), acitretin,
- Cytotoxics – azathioprine, mercaptopurine, mitotane,
- Sucralfate – impairs warfarin absorption.

Examples of drugs with variable effect:

- Corticosteroid, nevirapine, ritonavir.

Other interactions
Antibiotics and orlistat
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
Cholestyramine and sucralfate potentially decrease absorption of warfarin.
Direct-acting antivirals (DAAV)
As liver function may change during treatment with direct-acting antivirals such as boceprevir, daclatasvir, dasabuvir, elbasvir, grazoprevir, ledipasvir, sofosbuvir, ombitasvir, paritaprevir, simeprevir, velpatasvir, a close monitoring of INR values is recommended.
Glucosamine
Increased INR has been reported in patients taking glucosamine and oral 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.
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 patients 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.
Imatinib
Because warfarin is metabolised by CYP2C9, patients who are receiving treatment with imatinib and require anticoagulation should receive low molecular weight or standard heparin instead of warfarin.

Pregnancy and Lactation
Fertility
There are no relevant data available.
Pregnancy
Warfarin is contraindicated in pregnancy in the first and third trimester (see section *Contraindications*).
Based on human experience, warfarin causes congenital malformations and foetal death when administered during pregnancy.
Women of child-bearing age receiving treatment with warfarin should use effective contraception during treatment.
Lactation
Warfarin can be used during breastfeeding.
Warfarin is excreted in breast milk in small amounts. However, at therapeutic doses of warfarin, no effects on the breastfed child are anticipated.
Ability to perform tasks that require judgement, motor or cognitive skills
Warfarin has no influence on the ability to drive and use machines.
Adverse Reactions
Clinical Trial Data
There are no relevant data available.
Post Marketing Data
Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency. Frequencies are defined as:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥1/10000 to <1/1000
Very rare <1/10000
Not known (cannot be estimated from the available data).
Blood and lymphatic system disorders:
Not known: haematocrit decreased, haemoglobin decreased, agranulocytosis, leukopenia
Immune system disorders:
Not known: hypersensitivity
Endocrine disorders:
Not known: adrenal insufficiency
Nervous system disorders:
Not known: cerebral haemorrhage, cerebral subdural haematoma
Vascular disorder:
Not known: haemorrhage, purple toe syndrome, infarction
Respiratory, thoracic and mediastinal disorders:
Very rare: tracheal or tracheobronchial calcification
Not known: haemothorax, epistaxis
Gastrointestinal disorders:
Not known: gastrointestinal haemorrhage, rectal haemorrhage, haematemesis, pancreatitis, diarrhoea, nausea, vomiting, melaena, gastrointestinal tract irritation, mouth ulceration
Hepatobiliary disorders:
Not known: jaundice, hepatic dysfunction
Skin and subcutaneous tissue disorder:
Not known: erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis, calciphylaxis, leukocytoclastic vasculitis, alopecia, purpura, rash
Renal and urinary disorders:
Not known: Anticoagulant-related nephropathy (see section *Warnings and Precautions*), haematuria, renal injury, proteinuria
General disorders and administration site condition:
Not known: pyrexia, oedema
Overdose
Signs and Symptoms
Abnormal bleeding is the main sign of warfarin overdose and may be manifested by blood in the stools, haematuria, malaena, petechiae, excessive menstrual bleeding, excessive bruising, or persistent oozing from superficial injuries.
Treatment
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 is available) fresh frozen plasma 15 mL/kg.
Non-life-threatening haemorrhage
When anticoagulation can be suspended, give slow intravenous injection of phytomenadione (vitamin K_1) 10-20 mg for adults (250 µg/kg for a child).
Where rapid re-anticoagulation is desirable (e.g. valve replacements), give prothrombin complex concentrate (factors II, VII, IX, and X) 30-50 units/kg or (if no concentrate available) fresh frozen plasma 15 mL/kg.
Monitor INR to determine when to restart normal therapy. Monitor INR for at least 48 hours post overdose.
Patients on long-term warfarin therapy without major haemorrhage

- INR >8.0, no bleeding or minor bleeding – stop warfarin, and give phytomenadione (vitamin K_1) 0.5-1 mg for adults, 0.015-0.030 mg/kg (15-30 µg/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 is 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, not 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.

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:
  - There is no active bleeding and the patient has ingested more than 0.25 mg/kg
    OR
  - The prothrombin time is already significantly prolonged (INR >4.0)

The adult dose of vitamin K_1 is 10-20 mg orally (250 µg/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.
Further management should be as clinically indicated or as recommended by the national poisons centre, where available.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Warfarin is a synthetic anticoagulant of the coumarin series and acts by inhibiting the formation of active clotting factors II, VII, IX and X.
An effect on prothrombin time is produced in 24 to 36 h after the initial dose. This reaches a maximum in 36 to 48 h and is maintained for 48 h or more after administration is stopped.
PHARMACEUTICAL PARTICULARS
Shelf Life
The expiry date is indicated on the packaging.
Special Precautions for Storage
Replace cap securely and protect from light.
Not all presentations are available in every country.
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