

DATA SHEET

MAREVAN TABLETS

Warfarin Tablets BP 1mg, 3mg and 5mg

Qualitative and quantitative composition

MAREVAN Tablets 1mg: uncoated flat circular tablets, 8mm in diameter and 2mm deep, engraved DF/M1 on one side. Each tablet contains 1mg warfarin sodium.

MAREVAN Tablets 3mg: blue uncoated flat circular tablets, 8mm in diameter and 2mm deep, engraved DF/M3 on one side. Each tablet contains 3mg warfarin sodium.

MAREVAN Tablets 5mg: pink uncoated flat circular tablets, 8mm in diameter and 2mm deep, engraved DF/M5 on one side. Each tablet contains 5mg warfarin sodium.

MAREVAN Tablets comply with the specification for Warfarin Tablets BP.

Pharmaceutical form

Tablets

Uses

Therapeutic Indications

Coronary occlusion; deep vein thrombosis; pulmonary embolism; peripheral vascular thromboembolic states; mesenteric and retinal thromboembolism.

In emergencies, such as the conditions listed above, anticoagulant therapy should be initiated with heparin and MAREVAN together. Where there is less urgency, as in patients disposed to or at special risk of thromboembolism, anticoagulant therapy may be initiated with MAREVAN alone. Appropriate indications include predisposition to thromboembolism following surgery and chronic embolic pulmonary hypertensive disease.

Dosage and Administration

10 to 15mg daily, according to age and body weight, and adjusted with relation to the results of daily control tests until the desired level of anticoagulant activity is achieved - usually three to six days after the initiation of treatment.

Control tests should be made at regular intervals and the MAREVAN maintenance dosage must be adjusted in accordance to the results obtained.

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

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

Contraindications

This medicinal product 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 ulceration, 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, pancreatitis, exsufflation and haemothorax indicate that warfarin should be discontinued immediately (see section Adverse Effects).

Tissue necrosis

Haemorrhagic necrosis has been reported rarely during anticoagulant therapy. When it occurs, fatty tissues are most 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 Effects*).

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.

Changes in the patients clinical status, especially associated with intercurrent illness, or liver disease will require more frequent INR monitoring.

More frequent monitoring is necessary if any new medication, including non-prescription medication is added to or withdrawn from the regimen of a patient stabilised on warfarin, or if the dose of a concurrently used medication is changed.

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.

If therapy is well controlled, bleeding is rare. The occurrence of gastrointestinal haemorrhage during anticoagulant therapy, particularly if prothrombin time is within therapeutic range, may indicate the presence of an underlying haemorrhagic occult lesion which requires further investigation.

Haemorrhage can indicate an overdose of warfarin has been taken. For advice on treatment of haemorrhage (see Overdose section)

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.

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

Weight loss and decreased intake of vitamin K will enhance warfarin effects while weight gain, increased intake of vitamin K and gastrointestinal upset will necessitate a higher maintenance dose.

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 or glucosegalactose malabsorption should not take this medicine. Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Pregnancy and lactation

Fertility

There are no relevant data available

Pregnancy

Warfarin is contraindicated in pregnancy in the first and third trimester.

Oral anticoagulants cross the placenta. Congenital malformations have been reported in infants born to mothers taking these agents during pregnancy. The critical period of exposure is the 6th to 9th week of gestation. Also, during the second and third trimesters foetal or neonatal haemorrhage, foetal death in utero and increased risk of maternal haemorrhage have been reported. If the mother's condition necessitates anticoagulation, heparin should be used from the start of the 6th gestational week through the end of the 12th week, and again at term, in order to lessen risk of adverse outcome to the mother and foetus.

Women of child-bearing age who are taking warfarin tablets should use effective contraception during treatment.

Lactation

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

Ability to perform tasks that require judgement, motor or cognitive skills

There are no relevant data available.

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. Increased monitoring should be considered when commencing any new therapy if there is any doubt as to the extent of interaction.

Warfarin interacts with many other medications. Not all interactions have been identified. Some drugs may interact by more than one mechanism and in several cases, both increased and decreased anticoagulation have been reported for the same interacting substance. Care is required when any medication is added to or withdrawn from patients on anticoagulant therapy. Patient monitoring should be more frequent in such cases.

Pharmacodynamic interactions

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).

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

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 is a small subset of drugs for which interactions are known; however their clinical effect on the INR is variable. In these cases increased monitoring on starting and stopping therapy is advised.

Care should also be taken when stopping or reducing the dose of a metabolic inhibitor or inducer, once patients are stable on this combination (offset effect).

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

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

- Sulfinpyrazone, sulphonamides, phenylbutazone, cimetidine primarily by hepatic microsomal enzyme inhibitions,
- Non-steroidal anti-inflammatory agents including diflunisal, mefenamic acid, flurbiprofen, piroxicam, sulindac, phenylbutazone, azapropazone, dextropropoxyphene, indometacin and possibly others (azapropazone markedly enhances anticoagulant effect),
- Antiarrhythmics - amiodarone, propafenone, quinidine,
- Anabolic steroids - stanozolol, oxymetholone and others,
- Antidepressants - amitriptyline, nortriptyline, paroxetine, fluvoxamine,
- Antidiabetics – tolbutamide, metformin, glucagons,
- Antibacterials - some cephalosporins, chloramphenicol, ciprofloxacin, cotrimoxazole, erythromycin, metronidazole, sulfamethoxazole and possibly nalidixic acid, neomycin, norfloxacin, tetracyclines, other broad spectrum antibiotics such as ampicillin and trimethoprim,
- Antifungals - 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 inhibit the effect of warfarin include the following:

- Aminoglutethimide, barbiturates, rifampicin, glutethimide,
- 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,

Drugs which have been reported to both potentiate and inhibit warfarin effects include:

- 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

Cholestyramine and sucralfate potentially decrease absorption of warfarin.

Glucosamine

Glucosamine may potentiate the effect 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.

It is not known whether other cranberry products, such as capsules or concentrates, might also interact with warfarin. Therefore similar caution should be observed with these products.

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.

Drugs which increase risk of bleeding

Drugs which increase risk of bleeding due to their antiplatelet effects include diflunisal, salicylates, dipyridamole, phenylbutazone and erlotinib.

Salicylates, diflunisal and phenylbutazone also have additional detrimental effects on the gastrointestinal mucosa (e.g. erosion).

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.

Adverse Effects

Post Marketing Data

Adverse reactions are ranked under headings of frequency using the following convention:

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1000$ to $< 1/100$

Rare $\geq 1/10000$ 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, subdural haematoma

Vascular disorders

Not known: haemorrhage, blue toe syndrome, infarction

Respiratory, thoracic and mediastinal disorders

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 function abnormal

Skin and subcutaneous tissue disorders

Not known: rash, alopecia, purpura, erythema, ecchymosis, skin necrosis, skin haemorrhage

Renal and urinary disorders

Not known: haematuria, renal injury, proteinuria

General disorders and administration site conditions

Not known: pyrexia, oedema

Overdosage

Symptoms and signs

Abnormal bleeding is the main sign of warfarin overdose and may be manifested by blood in the stools, haematuria, melaena, 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 available) fresh frozen plasma 15 mL/kg.

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.

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

Mechanism of Action and Pharmacodynamic effects

MAREVAN is a synthetic 4-hydroxycoumarin derivative which acts by preventing the formation of active procoagulation factors II, VII, IX and X in the liver by inhibiting the vitamin K-mediated gamma-carboxylation of precursor proteins. Full therapeutic activity is not achieved until circulating coagulation factors have been removed by normal catabolism. This occurs at different rates for each factor, with factor VII having the shortest half-life. Warfarin has no direct thrombolytic effect, though it may limit the extension of existing thrombi.

Pharmacokinetics

Warfarin sodium is readily absorbed from the gastro-intestinal tract. It is extensively bound to plasma proteins and its plasma half-life is about 40 hours. The time to reach peak plasma concentration is 24 to 48 hours. Warfarin sodium is metabolised in the liver and is excreted in the urine, mainly as metabolites. The metabolites of warfarin sodium include 7-hydroxywarfarin, 6-hydroxywarfarin and two warfarin alcohols. These are all inactive. Warfarin crosses the placenta.

Special patient populations

Renal impairment

In the presence of hepatic dysfunction, there may be impaired metabolism of warfarin and/or impaired synthesis of clotting factors. Renal damage may reduce the rate of excretion of warfarin and thus decrease the dose requirement (see section Dosage and Administration).

Patients with nephrotic syndrome may require a higher dose of warfarin; this may be due to a shortened half-life of the anticoagulant caused by proteinuria and excretion of medicine bound to albumin (see Dosage and Administration).

Hepatic impairment

In the presence of hepatic dysfunction, there may be impaired metabolism of warfarin and/or impaired synthesis of clotting factors.

Pharmaceutical Precautions

Shelf Life

36 months when stored below 25° C

Special Precautions for Storage

Replace cap securely and protect from light.

Store at room temperature (below 25°C).

Medicines Classification

Prescription Only Medicine

Package Quantities

Containers of 100 tablets.

Name and Address

GlaxoSmithKline NZ Limited

Private Bag 106600

Downtown

Auckland 1143

NEW ZEALAND

Telephone: (09) 367 2900

Fax: (09) 367 2506

Date of Preparation

16 November 2011

Version 2.0

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