AUSTRALIAN PRODUCT INFORMATION

MAREVAN®

warfarin sodium

1 NAME OF THE MEDICINE

Warfarin sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each MAREVAN tablet contains 1 mg, 3 mg or 5 mg of warfarin sodium as the active ingredient.

Excipients of known effect: sugars as lactose and sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

MAREVAN 1 mg tablets are a flat fawn coloured tablet with bevelled edge, scored and embossed with "M" above and "1" below.

MAREVAN 3 mg tablets are flat blue coloured tablet with bevelled edge, scored and embossed with "M" above and "3" below.

MAREVAN 5 mg tablets are flat pink coloured tablet with bevelled edge, scored and embossed with "M" above and "5" below.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

MAREVAN is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension and pulmonary embolism.

MAREVAN is indicated for the prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation.

MAREVAN is not indicated in patients with lone atrial fibrillation who are less than 60 years of age with no risk factors (e.g. previous thromboembolism (TIA, ischaemic stroke), diabetes mellitus, hypertension) and an otherwise normal heart.

MAREVAN is indicated for use as an adjunct in the treatment of coronary occlusion.

4.2 DOSE AND METHOD OF ADMINISTRATION

It cannot be emphasised too strongly that treatment of each patient is a highly individualised matter. MAREVAN, a narrow therapeutic range (index) drug, may be affected by factors such as other drugs, dietary Vitamin K and genetic variations in CYP2CP and VKORC1 enzymes. Dosage should be controlled by periodic determinations of International Normalised Ratio (INR) or other suitable coagulation tests and the condition being treated (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Administration).

The following ranges of INR may be considered for the following listed conditions or procedures; however prescribers should consult local clinical guidelines for current recommended target INR ranges:

2.0 to 2.5 Prophylaxis of deep-vein thrombosis including high risk surgery.

2.0 to 3.0 Treatment of deep-vein thrombosis, pulmonary embolism, atrial fibrillation.

2.5-3.5 Recurrent deep-vein thrombosis and pulmonary embolism; arterial disease including myocardial infarction, arterial grafts; cardiac prosthetic valves and grafts.

An INR of greater than 4.0 is associated with a higher risk of bleeding.

Patients on smaller doses of warfarin are more likely to experience large clinical changes in their INR with small changes to their dose. Caution is advised as these patients are at increased risk of bleeding should the INR increase.

Administration

The dosage and administration of MAREVAN must be individualised for each patient according to the particular patient's sensitivity to the drug. The dosage should be adjusted based upon the results of the one-stage prothrombin time (PT). Different thromboplastin reagents vary substantially in their responsiveness to sodium warfarin-induced effects on prothrombin time. To define the appropriate therapeutic regimen, it is important to be familiar with the sensitivity of the thromboplastin reagent used in the laboratory and its relationship to the International Reference Preparation (IRP)*, a sensitive thromboplastin reagent prepared from human brain.

** A system of standardising the prothrombin time in oral anticoagulant control was introduced by the World Health Organisation in 1983. It is based upon the determination of an International Normalised Ratio (INR) which provides a common basis for communication of PT results and interpretations of therapeutic ranges. The INR is derived from calibrations of commercial thromboplastin reagents against a sensitive human brain thromboplastin, the IRP. The INR can be calculated as:*

$$INR = (\text{observed PT ratio})^{ISI}$$

where the ISI (International Sensitivity Index) is an exponential calibration factor used to relate the observed ratio to the INR and is available from the manufacturers of the thromboplastin reagent.

Initial Dose

MAREVAN therapy is commonly started above anticipated maintenance dosage levels. A commonly used regimen for MAREVAN is 10 mg/day for 2 to 4 days; with daily dosage adjustments based on the results of PT determinations. Use of a large loading dose (i.e. 30 mg) may increase the incidence of haemorrhage and other complications, does not offer more rapid protection against thrombi formation and is not recommended. Lower doses are recommended for elderly and/or debilitated patients and patients with increased sensitivity (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). People's genetic makeup may influence how they respond to the drug. Specifically, people with variations in two genes may need lower warfarin doses than people without these genetic variations. The two genes are called CYP2C9 and VKORC1. The CYP2C9 gene is involved in the breakdown (metabolism) of warfarin and the VKORC1 gene helps regulate the ability of warfarin to prevent blood from clotting.

Maintenance

Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tables in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of Therapy

The duration of therapy in each patient should be individualised. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Patients with Atrial Fibrillation

The preferred time to start treatment is 48 to 72 hours after diagnosis of NVAF. Treatment is continued for at least one month after the establishment of normal sinus rhythm unless serious bleeding or any other contraindication arises.

Laboratory Control

The prothrombin time (PT) reflects the depression of vitamin K dependent Factors VII, IX, X and II. There are several modifications of the one-stage PT and the physician should become familiar with the specific

method used in his laboratory. The degree of anticoagulation indicated by any range of prothrombin times may be altered by the type of thromboplastin used; the appropriate therapeutic range must be based on the experience of each laboratory. The PT should be determined daily after the administration of the initial dose until PT results stabilise in the therapeutic range. Intervals between subsequent PT determinations should be based upon the physician's judgement of the patient's reliability and response to MAREVAN in order to maintain the individual within the therapeutic range. Acceptable intervals for PT determinations are normally within the range of one to four weeks. To ensure adequate control, it is recommended that additional prothrombin time tests are done when other warfarin products are interchanged with MAREVAN.

Treatment During Dentistry and Surgery

The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. In patients who must be anticoagulated prior to, during or immediately following dental or surgical procedures, adjusting the dosage of MAREVAN to maintain the PT at the low end of the therapeutic range, may safely allow for continued anticoagulation. The operative site should be sufficiently limited and accessible to permit the effective use of local procedures for haemostasis. Under these conditions, dental and surgical procedures may be performed without undue risk of haemorrhage.

Conversion from Heparin Therapy

Since the onset of the MAREVAN effect is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to MAREVAN may begin concomitantly with heparin therapy or may be delayed 3 to 6 days. As heparin may affect the PT, patients receiving both heparin and MAREVAN should have blood for PT determination, drawn at least:

– 5 hours after the last IV bolus dose of heparin, or

– 4 hours after cessation of a continuous IV infusion of heparin, or

– 24 hours after the last subcutaneous heparin injection.

When MAREVAN has produced the desired therapeutic range or prothrombin activity, heparin may be discontinued.

Conversion to and from New Oral Anticoagulants (NOACs/DOACs) (such as apixaban, dabigatran and rivaroxaban)

Transitioning between warfarin and a NOAC is considered a high-risk situation. Patients may be at an increased risk of inadequate or over-anticoagulation. Specific advice on switching patients between warfarin and NOACs is available in the relevant NOAC Product Information.

4.3 CONTRAINDICATIONS

- Anticoagulation is contraindicated in any localised or general physical condition or personal circumstances in which the hazard of haemorrhage might be greater than the potential clinical benefits of anticoagulation

- Haemorrhagic tendencies or blood dyscrasias

- Recent or contemplated surgery of:

  (1) central nervous system;

  (2) eye;

  (3) traumatic surgery resulting in large open surfaces

- Bleeding tendencies associated with active ulceration or overt bleeding of:

  (1) gastrointestinal, genitourinary or respiratory tracts;

(2) cerebrovascular haemorrhage;

(3) aneurysms-cerebral, dissecting aorta;

(4) pericarditis and pericardial effusions;

(5) bacterial endocarditis

- Threatened abortion, eclampsia and preeclampsia
- Inadequate laboratory facilities or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation
- Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding
- Major regional, lumbar block anaesthesia and malignant hypertension
- Pregnancy

MAREVAN is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal haemorrhage to the fetus in utero (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Dose Individualisation

It cannot be emphasised too strongly that treatment of each patient is a highly individualised matter. MAREVAN, a narrow therapeutic range (index) drug, may be affected by factors such as other drugs, dietary Vitamin K and genetic variations in CYP2CP and VKORC1 enzymes. Dosage should be controlled by periodic determinations of prothrombin time (PT)/International Normalised Ratio (INR) or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. For recommendations of when heparin and MAREVAN are administered concomitantly see Section 4.2 DOSE AND METHOD OF ADMINISTRATION – Conversion from Heparin Therapy.

Do not interchange MAREVAN and COUMADIN. Bioequivalence between these two brands of warfarin has not been established.

Haemorrhagic and Necrosis Risks

The most serious risks associated with anticoagulant therapy with warfarin sodium are haemorrhage in any tissue or organ and less frequently (< 0.1%), necrosis and/or gangrene of skin and other tissues. The risk of haemorrhage is related to the level of intensity and the duration of anticoagulant therapy.

Haemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. See below for information on predisposing conditions. These and other risks associated with anticoagulant therapy must be weighed against the risk of thrombosis or embolisation in untreated cases.

Caution should be observed when MAREVAN is administered in any situation or in the presence of any predisposing condition where added risk of haemorrhage or necrosis is present.

A severe elevation (> 50 seconds) in activated partial thromboplastin time (aPPT) with a PT/INR in the desired range has been identified as an as an indication of increased risk of postoperative haemorrhage.

Anticoagulant-related nephropathy

There have been post-marketing reports of anticoagulant-related nephropathy (ARN) following anticoagulant use, presenting as acute kidney injury.

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).

Systemic Atheroemboli and Cholesterol Microemboli

Anticoagulation therapy with warfarin may enhance the release of atheromatous plague emboli, thereby increasing the risk of complications from systemic cholesterol microembolisation, including the "purple toes syndrome". Discontinuation of warfarin therapy is recommended when such phenomena are observed.

Systemic atheroemboli and cholesterol microemboli can present with a variety of signs and symptoms including purple toes syndrome, livedo reticularis, rash, gangrene, abrupt and intense pain in the leg, foot or toes, foot ulcers, myalgia, penile gangrene, abdominal pain, flank or back pain, haematuria, renal insufficiency, hypertension, cerebral ischemia, spinal cord infarction, pancreatitis, symptoms simulating polyarteritis or any other sequelae of vascular compromise due to embolic occlusion. The most commonly involved visceral organs are the kidneys followed by the pancreas, spleen, and liver. Some cases have progressed to necrosis or death.

Purple toes syndrome is a complication of oral anticoagulation characterised by a dark, purplish or mottled colour of the toes, usually occurring between 3 to 10 weeks, or later, after the initiation of therapy with warfarin or related compounds. Major features of this syndrome include purple colour of plantar surfaces and sides of the toes that blanches on moderate pressure and fades with elevation of the legs; pain and tenderness of the toes, waxing and waning of the colour over time. While the "purple toes syndrome" is reported to be reversible, some case progress to gangrene or necrosis which may require debridement of the affected area or may lead to amputation.

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 but also in patients with known risk factors such as hyperphosphataemia, hypercalcaemia or low serum albumin levels. Rare cases of calciphylaxis have been reported in patients receiving warfarin, also in the absence of renal disease. When calciphylaxis is diagnosed in these patients, start appropriate supportive treatment and consider stopping treatment with warfarin.

Considerations for Increased Bleeding Risk

MAREVAN is a narrow therapeutic range (index) drug and caution should be observed when warfarin is administered to certain patients such as the elderly or debilitated or when administered in any situation or physical condition where added risk of haemorrhage is present. Reported risk factors for bleeding include high intensity of anticoagulation (INR > 4.0), age ≥ 65, highly variable INRs, history of gastrointestinal bleeding, hypertension, cerebrovascular disease, serious heart disease, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs and long duration of warfarin therapy. Identification of risk factors for bleeding and certain genetic variations in CYP2CP and VRORC1 in a patient may increase the need for more frequent INR monitoring and the use of lower warfarin doses.

Intramuscular (I.M.) injection of concomitant medication should be confined to the upper extremities which permits easy access for manual compression, inspections for bleeding and use of pressure bandages.

Caution should be observed when MAREVAN (or warfarin) is administered concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, to be certain that no change in anticoagulation dosage is required. In addition to specific drug interactions that might affect PT/INR, NSAIDs, including aspirin, can inhibit platelet aggregation and can cause gastrointestinal bleeding, peptic ulceration and/or perforation (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Acquired or inherited warfarin resistance should be suspected if large daily doses of MAREVAN are required to maintain a patient's PT/INR within a normal therapeutic range (see Section 5.2 PHARMACOKINETIC PROPERTIES – Pharmacogenomics).

Other Clinical Settings with Increased Risks

The decision to administer anticoagulants in the following conditions must be based upon clinical judgement in which the risks of anticoagulant therapy are weighed against the benefits.

- Severe to moderate hepatic or renal insufficiency
- Infectious diseases or disturbances of intestinal flora: Sprue (Coeliac disease), antibiotic therapy
- Trauma which may result in internal bleeding
- Surgery or trauma resulting in large exposed raw surfaces
- Indwelling catheters
- Severe to moderate hypertension
- Known or suspected deficiency in protein C mediated anticoagulant response: Hereditary or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis following warfarin administration. Not all patients with these conditions develop necrosis and tissue necrosis occurs in patients without these deficiencies. Inherited resistance to activated protein C has been described in many patients with venous thromboembolic disorders but has not yet been evaluated as a risk factor for tissue necrosis. The risk associated with these conditions, both for recurrent thrombosis and for adverse reactions, is difficult to evaluate since it does not appear to be the same for everyone. Decisions about testing and therapy must be made on an individual basis. It has been reported that concurrent anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with MAREVAN may minimise the incidence of this tissue necrosis. MAREVAN therapy may be initiated concomitantly with heparin. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation
- Polycythaemia vera
- Vasculitis
- Severe diabetes
- In patients with acquired or inherited warfarin resistance, decreased therapeutic responses to MAREVAN have been reported. Exaggerated therapeutic responses have been reported in other patients (see Section 5.2 PHARMACOKINETIC PROPERTIES – Pharmacogenomics).

Miscellaneous

- Minor and severe allergic/hypersensitivity reactions and anaphylactic reactions have been reported
- Patients with congestive heart failure may exhibit a greater than expected PT/INR response to MAREVAN, thereby requiring more frequent laboratory monitoring and reduced doses of MAREVAN

- Concomitant use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous (please note recommendations accompanying these preparations)

Periodic determination of PT/INR or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence the response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional PT/INR determinations in the period immediately after discharge from the hospital and whenever other medications are initiated, discontinued or taken irregularly.

The following factors are listed for reference; however, other factors including exogenous factors (such as diet and other drug treatments) may also affect the anticoagulant response.

Endogenous Factors

The following factors, alone or in combination, may be responsible for **increased** PT/INR response:

Blood dyscrasias – see Section 4.3 CONTRAINDICATIONS	hyperthyroidism
elevated temperature	congestive heart failure
infectious hepatitis	poor nutritional state
cancer	diarrhoea
jaundice	steatorrhoea
collagen vascular disease	hepatic disorders
	vitamin K deficiency

The following endogenous factors, alone or in combination, may be responsible for **decreased** PT/INR response:

- oedema
- hereditary coumarin resistance
- hyperlipaemia
- hypothyroidism
- nephrotic syndrome

Exogenous Factors

The following exogenous factors, alone or in combination, may be responsible for **decreased** PT/INR response (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS):

- diet high in vitamin K
- unreliable PT/INR determinations

The following exogenous factors, alone or in combination, may be responsible for **increased** PT/INR response (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS):

- other medications affecting blood elements which may modify haemostasis
- dietary deficiencies
- prolonged hot weather

- unreliable PT/INR determinations

Because a patient may be exposed to a combination of the above factors, the net effect of MAREVAN on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with coumarins are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

Information for Patients

The objective of anticoagulant therapy is to decrease the clotting ability of the blood so that thrombosis is prevented, while avoiding spontaneous bleeding. Effective therapeutic levels with minimal complications are in part dependent upon cooperative and well-instructed patients who communicate effectively with their physician.

Patients should be advised: strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, including salicylates (e.g. aspirin and topical analgesics) and other over-the-counter medications except on the advice of a physician. Avoid alcohol consumption. Do not take MAREVAN during pregnancy and do not become pregnant while taking it (see Section 4.3 CONTRAINDICATIONS). Avoid any activity or sport that may result in traumatic injury. Prothrombin time tests and regular visits to the physician or clinic are needed to monitor therapy. Carry identification stating that MAREVAN is being taken. If the prescribed dose of MAREVAN is forgotten, notify the physician immediately. Take the dose as soon as possible on the same day but do not take a double dose of MAREVAN the next day to make up for missed doses.

The amount of vitamin K in food may affect therapy with MAREVAN. Eat a normal, balanced diet maintaining a consistent amount of vitamin K. Avoid drastic changes in dietary habits, such as eating large amounts of green leafy vegetables. Contact the physician to report any illness, such as diarrhoea, infection or fever.

Notify the physician immediately if any unusual bleeding or symptoms occur. Signs and symptoms of bleeding include: pain, swelling or discomfort, prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, nosebleeds, bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools, headache, dizziness or weakness. If therapy with MAREVAN is discontinued, patients should be cautioned that the anticoagulant effects of MAREVAN may persist for about 2 to 5 days.

A Warfarin Patient Information Booklet is available from Mylan upon request.

Use in Hepatic Impairment

Hepatic dysfunction can potentiate the response to warfarin through impaired synthesis of clotting factors and decreased metabolism of warfarin.

Use in Renal Impairment

Renal clearance is considered to be a minor determinant of anticoagulant response to warfarin. No dosage adjustment is necessary for patients with renal failure.

Use in the Elderly

There are no significant age-related differences in the pharmacokinetics of racemic warfarin. Limited information suggests that there is no difference in the clearance of S-warfarin in elderly versus young subjects. However, there may be a slight decrease in the clearance of R-warfarin in the elderly compared to the young. Older patients (60 years or older) appear to exhibit greater than expected PT/INR response to the anticoagulant effects of warfarin. As patient age increases, less warfarin is required to produce a therapeutic level of anticoagulation. The cause of this response to warfarin is not known.

Paediatric Use

Safety and effectiveness in children below the age of 18 have not been established in randomised, controlled clinical trials. However, the use of MAREVAN in paediatric patients is well-documented for the prevention

and treatment of thromboembolic events. Difficulty achieving and maintaining therapeutic PT/INR ranges in the paediatric patient has been reported. More frequent PT/INR determinations are recommended because of possible warfarin requirements.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

The safety of warfarin is maintained by frequent International Normalised Ratio (INR) monitoring. This is particularly important in situations that can lead to a change in a patient's INR result. The INR can be affected if a patient changes their medicines, including starting a new medicine, stopping a medicine or changing the dose of a medicine, or if there is a change in their health status or diet.

Drugs may interact with warfarin through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic mechanisms for drug interactions with warfarin are synergism (impaired haemostasis, reduced clotting factor synthesis), competitive antagonism (vitamin K), and alteration of the physiologic control loop for vitamin K metabolism (hereditary resistance).

Pharmacokinetic mechanisms for drug interactions with warfarin are mainly enzyme induction, enzyme inhibition, and reduced plasma protein binding. It is important to note that some drugs may interact by more than one mechanism.

More frequent INR monitoring should be performed when starting or stopping other drugs, including botanicals, or when changing dosages of other drugs, including drugs intended for short-term use (e.g. antibiotics, antifungals, corticosteroids).

Consult the product information of all concurrently used drugs to obtain further information about interactions with warfarin or adverse reactions pertaining to bleeding.

CYP450 Interactions

CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. The more potent warfarin S-enantiomer is metabolised by CYP2C9 while the R-enantiomer is metabolised by CYP1A2 and 3A4.

- **Inhibitors** of CYP2C9, 1A2, and/or 3A4 have the potential to increase the effect (increase INR) of warfarin by increasing the exposure of warfarin and increase the risk of bleeding

- **Inducers** of CYP2C9, 1A2, and/or 3A4 have the potential to decrease the effect (decrease INR) of warfarin by decreasing the exposure of warfarin and increase the risk of thromboembolic events

Examples of inhibitors and inducers of CYP2C9, 1A2, and 3A4 are described below in Tables 1 and 2; however, this list should not be considered all-inclusive. Consult the labelling of all concurrently used drugs to obtain further information about CYP450 interaction potential. The CYP450 inhibition and induction potential should be considered when starting, stopping, or changing dose of concomitant medications. Closely monitor INR if a concomitant drug is a CYP2C9, 1A2, and/or 3A4 inhibitor or inducer.

Table 1: Examples of CYP450 Inhibitors (co-administration with inhibitors of CYP450 may increase the effect of warfarin and increase the risk of bleeding)

Enzyme	Inhibitors
CYP2C9	Amiodarone, capecitabine, trimethoprim/sulfamethoxazole, etravirine, fluconazole, fluvastatin, fluvoxamine, metronidazole, miconazole, oxandrolone, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
CYP1A2	Aciclovir, allopurinol, caffeine, cimetidine, ciprofloxacin, disulfiram, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, norfloxacin, oral contraceptives,

	phenylpropanolamine, propafenone, propranolol, terbinafine, thiabendazole, ticlopidine, verapamil, zileuton
CYP3A4	Alprazolam, amiodarone, amlodipine, amprenavir, aprepitant, atorvastatin, atazanavir, bicalutamide, cilostazol, cimetidine, ciprofloxacin, clarithromycin, conivaptan, ciclosporin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, nilotinib, oral contraceptives, posaconazole, ranitidine, ranolazine, ritonavir, saquinavir, telithromycin, tipranavir, voriconazole, zileuton

Table 2: Examples of CYP450 Inducers (co-administration with inducers of CYP450 may decrease the effect of warfarin and increase the risk of thromboembolic events)

Enzyme	Inducer
CYP2C9	Aprepitant, bosentan, carbamazepine, phenobarbital (phenobarbitone), rifampicin
CYP1A2	Montelukast, moricizine, omeprazole, phenobarbital (phenobarbitone), phenytoin, cigarette smoking
CYP3A4	Armodafinil, amprenavir, aprepitant, bosentan, carbamazepine, efavirenz, etravirine, modafinil, nafcillin, phenytoin, pioglitazone, prednisone, rifampicin, rufinamide

Drugs that Increase Bleeding Risk

Examples of drugs known to increase the risk of bleeding are presented in Table 3.

Because bleeding risk is increased when these drugs are used concomitantly with warfarin, closely monitor patients receiving any such drug with warfarin.

Table 3: Drugs that Can Increase the Risk of Bleeding

Drug Class	Specific Drugs
Anticoagulants	Argatroban, dabigatran, bivalirudin, desirudin, heparin, lepirudin
Antiplatelet agents	Aspirin, cilostazol, clopidogrel, dipyridamole, prasugrel, ticlopidine
Non-steroidal anti-inflammatory agents	Celecoxib, diclofenac, diflunisal, fenoprofen, ibuprofen, indometacin, ketoprofen, ketorolac, mefenamic acid, naproxen, oxaprozin, piroxicam, sulindac
Serotonin reuptake inhibitors	Citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline, venlafaxine, vilazodone

It has been reported that concomitant administration of warfarin and ticlopidine may be associated with cholestatic hepatitis.

Antibiotics and Antifungals

There have been reports of changes in INR in patients taking warfarin and antibiotics or antifungals, but clinical pharmacokinetic studies have not shown consistent effects of these agents on plasma concentrations of warfarin.

Closely monitor INR when starting or stopping any antibiotic or antifungal in patients taking warfarin.

Botanical (herbal) Products and Foods

More frequent INR monitoring should be performed when starting or stopping botanicals. Few adequate, well-controlled studies evaluating the potential for metabolic and/or pharmacologic interactions between botanicals and warfarin exist. Due to a lack of manufacturing standardisation with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation.

Some botanicals may cause bleeding events when taken alone (e.g. garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the

anticoagulant effects of warfarin. Conversely, some botanicals may decrease the effects of warfarin (e.g. co-enzyme Q10, St. John's wort, ginseng). Some botanicals and foods can interact with warfarin through CYP450 interactions (e.g. echinacea, grapefruit juice, ginkgo, goldenseal, St. John's wort).

The amount of vitamin K in food may affect therapy with warfarin. Advise patients taking warfarin to eat a normal, balanced diet maintaining a consistent amount of vitamin K. Patients taking warfarin should avoid drastic changes in dietary habits, such as binge eating large amounts of green leafy vegetables.

Miscellaneous Interactions

Direct Acting Antivirals for the Treatment of Hepatitis C Viral Infection

Close monitoring of INR is recommended during treatment of Hepatitis C virus infection with direct acting antivirals, as liver function may improve.

The following drugs and drug classes, alone or in combination, may be responsible for **increased** PT/INR response [* describes where increased *and* decreased PT/INR responses have been reported]:

Potential drug interactions with MAREVAN are listed below by drug class and by specific drugs.

Classes of Drugs

Adrenergic stimulants, central
Alcohol abuse reduction preparations
Analgesics
Anaesthetics, inhalation
Antiarrhythmics*

Aminoglycosides (oral)
Cephalosporins, parenteral
Macrolides
Miscellaneous
Penicillins, intravenous, high dose
Quinolones (fluoroquinolones)
Sulphonamides, long acting
Tetracyclines

Anticonvulsants*
Antidepressants*
Antimalarial agents
Antineoplastics*
Antiparasitic/Antimicrobials

Antithyroid drugs*
Beta-adrenergic blockers
Cholelitholytic agents
Diabetes agents, oral
Diuretics*
Fungal medications, systemic*
Gastric acidity and peptic ulcer agents*
Gastrointestinal, ulcerative colitis agents
Gout treatment agents
Haemorrheologic agents
Hepatotoxic drugs
Hyperglycaemic agents
Hypertensive emergency events
Hypnotics*
Hypolipidaemics*
Monoamine oxidase inhibitors
Narcotics, prolonged

Psychostimulants
Salicylates

Steroids, adrenocortical*
Steroids, anabolic (17-alkyl testosterone derivatives)
Thrombolytics
Thyroid drugs
Tuberculosis agents*
Uricosuric agents
Vaccines
Vitamins*

Specific Drugs Reported

Alcohol*
Aminosalicylic acid**

Azithromycin
Cefamandole
Cefazolin
Cefotetan**
Cefoxitin
Ceftriaxone
Chloral hydrate*
Chloramphenicol
MAREVAN overdosage
Methyldopa
Methylphenidate
Methylsalicylate ointment (topical)
Metronidazole

Nalidixic acid**

Neomycin

Ofloxacin
Olsalazine

Chlorpropamide**
Colestyramine*

Clofibrate
MAREVAN overdosage
Cyclophosphamide*
Danazol
Dextran
Dextrothyroxine**
Diazoxide
Dicoumarol**
Disulfiram
Doxycycline

Etacrynic acid

Fluorouracil

Glucagon
Halothane
Heparin
Ibuprofen

Influenza virus vaccine

Levamisole**
Levothyroxine
Liothyronine
Lovastatin

Oxandralone**
Oxymetholone**
Paracetamol

Penicillin G, intravenous
Pentoxifylline
Phenylbutazone

Piperacillin

Propoxyphene
Propylthiouracil*
Quinidine**
Quinine

Sertraline
Simvastatin
Stanozolol**
Streptokinase
Sulphamethizole
Sulphamethoxazole
Sulphinpyrazone**
Ifosfamide
Tamoxifen
Tetracycline
Thyroid
Ticarcillin
Tissue plasminogen activator (t-PA)
Tolbutamide
Trimethoprim/sulphamethoxazole
Urokinase
Valproate
Vitamin E

** Not listed on ARTG

The following drugs and drug classes, alone or in combination, may be responsible for **decreased** PT/INR response [* describes where increased *and* decreased PT/INR responses have been reported]:

Classes of Drugs

Adrenal cortical steroid inhibitors
Antacids
Antianxiety agents
Antiarrhythmics*

Anticonvulsants*
Antidepressants*
Antihistamines
Antineoplastics*
Antipsychotic medications*
Antithyroid drugs
Barbiturates

Diuretics*
Enteral nutritional supplements

Gastric acidity and peptic ulcer agents*
Hypnotics*
Hypolipidaemics*
Immunosuppressives
Oral contraceptives, estrogen containing
Steroids, adrenocortical*
Tuberculosis agents*
Vitamins*

Specific Drugs Reported

Alcohol*
Aminoglutethimide**
Amobarbital
Azathioprine

Chloral hydrate*

MAREVAN underdosage
Meprobamate**
6-mercaptopurine
Nafcillin**
Paraldehyde
Pentobarbital**

Chlordiazepoxide**
Chlorthalidone**
Colestyramine*
Corticotropin
Cortisone
Cyclophosphamide*
Dicloxacillin
Glutethimide**
Griseofulvin
Haloperidol
Phenytoin*
Prednisone*
Primidone
Propylthiouracil*
Ranitidine*
Rifampicin
Spironolactone
Sucralfate
Vitamin C (high dose)
Vitamin K

** Not listed on ARTG

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

The reproductive effects of MAREVAN have not been evaluated.

Use in Pregnancy

Pregnancy category: D

MAREVAN is contraindicated in women who are or may become pregnant because the drug passes through the placental barrier and may cause fatal haemorrhage to the fetus in utero (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy.

Embryopathy characterised by nasal hypoplasia with or without stippled epiphyses (chondrodysplasia punctata) has been reported in the children of pregnant women exposed to warfarin during the first trimester. Central nervous system abnormalities also have been reported, including dorsal midline dysplasia characterised by agenesis of the corpus callosum, Dandy-Walker malformation, and midline cerebellar atrophy. Ventral midline dysplasia characterised by optic atrophy and eye abnormalities have been observed. Mental retardation, blindness and other central nervous system abnormalities have been reported in association with second and third trimester exposure. Although rare, teratogenic reports following in utero exposure to warfarin include urinary tract anomalies such as single kidney, asplenia, anencephaly, spina bifida, cranial nerve palsy, hydrocephalus, cardiac defects and congenital heart disease, polydactyly, deformities of toes, diaphragmatic hernia and corneal leucoma.

Spontaneous abortion, perinatal bleeding and still birth are known to occur and a higher risk of fetal mortality is associated with the use of warfarin. It should not be used in the last few weeks of pregnancy. All anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and fetal loss.

Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus and the possibility of termination of the pregnancy should be discussed in light of those risks.

Use in Lactation

MAREVAN appears in the milk of nursing mothers in an inactive form. Infants nursed by MAREVAN treated mothers had no change in prothrombin times (PTs). Effects in premature infants have not been evaluated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person’s ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Potential adverse reactions to MAREVAN may include:

Haemorrhage: see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- Fatal or nonfatal haemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs, symptoms and severity will vary according to the location and degree or extent of the bleeding. Haemorrhagic complications may present as paralysis; paraesthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock. Therefore, the possibility of haemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints that do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with PT/INR (see Section 4.9 OVERDOSE – Treatment and Warfarin Reversal).

- Bleeding which occurs when the PT/INR is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion e.g. tumour, ulcer etc.

Renal and urinary disorders, Frequency: Not known, Anticoagulant-related nephropathy (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE), haematuria.

Necrosis of skin and other tissues: see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Post-marketing Experience

The following adverse reactions have been reported infrequently:

Immune system disorders: hypersensitivity

Vascular disorders: purple toes syndrome, vasculitis

Hepatobiliary disorders: hepatitis, cholestatic liver injury, jaundice

Investigations: elevated liver enzymes

General disorders and administration site conditions: oedema, fever, fatigue, lethargy, malaise, asthenia, pain, cold intolerance, chills

Skin and subcutaneous tissue disorders: rash, dermatitis, bullous eruption, urticaria, pruritus, alopecia

Gastrointestinal disorders: abdominal pain, flatulence, bloating, nausea, vomiting, diarrhoea

Nervous system disorders: headache, dizziness, taste perversion, paraesthesia

Rare events of tracheal or tracheobronchial calcification have been reported in association with long-term warfarin therapy. The clinical significance of this event is unknown.

Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Signs and Symptoms

Suspected or overt abnormal bleeding (e.g. appearance of blood in stools or urine, haematuria, excessive menstrual bleeding, melaena, petechiae, excessive bruising or persistent oozing from superficial injuries) are early manifestations of excessive anticoagulation beyond a safe and satisfactory level.

Treatment and Warfarin Reversal

The treatment of excessive anticoagulation is based on the INR level, the presence or absence of bleeding and clinical circumstances.

Consult local clinical guidelines on warfarin reversal.

For patients with elevated INR, no bleeding and no high risk of bleeding, reversal of excessive anticoagulation may be achieved by discontinuing warfarin and if necessary, by administration of oral or parenteral vitamin K1.

For immediate reversal of excessive anticoagulation, prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) may be considered to replace the low levels of factors II, VII, IX and X induced by warfarin. Administration of Vitamin K1 is necessary for sustaining the reversal achieved by PCC or FFP.

Use of vitamin K1 reduces response to subsequent warfarin therapy. Patients may return to a pre-treatment thrombotic status following the rapid reversal of a prolonged INR. Resumption of warfarin administration reverses the effect of vitamin K and a therapeutic INR can again be obtained by careful dosage adjustment. If rapid anticoagulation is indicated, heparin may be preferable for initial therapy.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Warfarin and other coumarin anticoagulants act by inhibiting the synthesis of vitamin K dependent coagulation factors. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischaemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications, which may result in serious and possible fatal sequelae.

Mechanism of Action

Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex, thereby reducing the regeneration of vitamin K1 epoxide. The degree of depression is dependent upon the dosage administered and, in part by the patient's VKORC1 genotype. Therapeutic doses of warfarin decrease the total amount of the active form of each vitamin K dependent clotting factor made by the liver by approximately 30% to 50%.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Warfarin is a racemic mixture of the R- and S-enantiomers. The S-enantiomer exhibits 2 to 5 times more anticoagulant activity than the R-enantiomer in humans, but generally has a more rapid clearance.

Absorption

Warfarin is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours.

Distribution

There are no differences in the apparent volumes of distribution after intravenous and oral administration of single doses of warfarin solution. Warfarin distributes into a relatively small apparent volume of distribution of about 0.14 L/kg. A distribution phase lasting 6 to 12 hours is distinguishable after rapid intravenous or oral administration of an aqueous solution. Using a one compartment model and assuming complete bioavailability, estimates of the volumes of distribution of R- and S-warfarin are similar to each other and to that of the racemate. Concentrations in fetal plasma approach the maternal values, but warfarin has not been found in human milk (see Section 4.6 FERTILITY, PREGNANCY AND LACTATION – Use in Lactation). Approximately 99% of the drug is bound to plasma proteins.

Metabolism

The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolised by hepatic microsomal enzymes (cytochrome P450) to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols). The warfarin alcohols have minimal anticoagulant activity. The metabolites are principally excreted into the urine and, to a lesser extent, into the bile. The metabolites of warfarin that have been identified include dehydro-warfarin, two diastereoisomer alcohols, 4'-, 6-, 7-, 8- and 10-hydroxywarfarin. The cytochrome P450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2 and 3A4. 2C9 likely to be the principal form of human liver CY P450 which modulates the in vivo anticoagulant activity of warfarin.

The S-enantiomer of warfarin is mainly metabolised to 7-hydroxywarfarin by CYP2C9, a polymorphic enzyme. The variant alleles CYP2C9*2 and CYP2C9*3 result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of S- warfarin. The frequencies of these alleles in Caucasians are approximately 11% and 7% for CYP2C9*2 and CYP2C9*3, respectively[1]. Patients with one or more of these variant CYP2C9 alleles have decreased S-warfarin clearance[2] (Table 4).

Table 4: Relationship Between S-Warfarin Clearance and CYP2C9 Genotype in Caucasian Patients

CYP2C9 Genotype	N	S-Warfarin Clearance/Lean Body Weight (mL/min/kg) Mean (SD)[a]
*1/*1	118	0.065 (0.025)[b]
*1/*2 or *1/*3	59	0.041 (0.021)[b]
*2/*2, *2/*3 or *3/*3	11	0.020 (0.011)[b]
Total	188	

[a] SD = standard deviation.
[b] $p < 0.001$. Pairwise comparisons indicated significant differences among all 3 genotypes.

Other CYP2C9 alleles associated with reduced enzymatic activity occur at lower frequencies, including *5, *6, and *11 alleles in populations of African ancestry and *5, *9 and *11 alleles in Caucasians.

Excretion

The terminal half-life of warfarin after a single dose is approximately one week; however, the effective half-life ranges from 20 to 60 hours with a mean of about 40 hours. The clearance of R-warfarin is generally half that of S-warfarin, thus as the volumes of distribution are similar, the half-life of R-warfarin is longer than that of S-warfarin. The half-life of R-warfarin ranges from 37 to 89 hours, while that of S-warfarin ranges from 21 to 43 hours. Studies with radiolabelled drug have demonstrated that up to 92% of the orally

1 Yasar U, Eliasson E, Dahl M, Johansson I, Ingelman-Sundberg,M, Sjoqvist F. Validation of methods for CYP2C9 genotyping: Frequencies of mutant alleles in Swedish population. *Biochem Biophys Res Comm.* 1999; 254:628-631.

2 Herman D, Locatelli I, Grabnar I, et al. Influence of CYP2C9 polymorphisms, demographic factors and concomitant drug therapy on warfarin metabolism and maintenance dose. *Pharmacogenomics J*. 2005;5:193-202.

administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Pharmacogenomics

A meta-analysis of 9 qualified studies including 2775 patients (99% Caucasian) was performed to examine the clinical outcomes associated with CYP2C9 gene variants in the warfarin-treated patients[3]. In this meta-analysis, 3 studies assessed bleeding risks and 8 studies assessed daily dose requirements. The analysis suggested an increased bleeding risk for patients carrying either the CYP2C9*2 or CYP2C9*3 alleles. Patients carrying at least one copy of the CYP2C9*2 allele required a mean daily warfarin dose that was 17% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele. For patients carrying at least one copy of the CYP2C9*3 allele, the mean daily warfarin dose was 37% less than the mean daily dose for patients homozygous for the CYP2C9*1 allele.

In an observational study, the risk of achieving INR > 3 during the first 3 weeks of warfarin therapy was determined in 219 Swedish patients retrospectively grouped by CYP2C9 genotype. The relative risk of over anticoagulation as measured by INR > 3 during the first 2 weeks of therapy was approximately doubled for those patients classified as *2 or *3 compared to patients who were homozygous for the *1 allele[4].

Warfarin reduces the regeneration of vitamin K epoxide in the vitamin K cycle, through inhibition of vitamin K epoxide reductase (VKOR), a multiprotein enzyme complex. Certain single nucleotide polymorphisms in the VKORC1 gene (especially the -1639G>A allele) have been associated with lower dose requirements for warfarin. In 201 Caucasian patients treated with stable warfarin doses, genetic variations in the VKORC1 gene were associated with lower warfarin doses. In the study, about 30% of the variance in warfarin dose could be attributed to variations in VKORC1 gene alone; about 40% of the variance in warfarin dose could be attributed to variations in the VKORC1 and CYP2C9 genes combined[5]. About 55% of the variability in warfarin dose could be explained by the combination of VKORC1 and CYP2C9 genotypes, age, height, body weight, interacting drugs, and indication for warfarin therapy in Caucasian patients[5]. Similar observations have been reported in Asian patients[6],[7].

5.3 PRECLINICAL SAFETY DATA

Carcinogenesis and Mutagenesis

Carcinogenicity and mutagenicity studies have not been performed with MAREVAN.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive ingredients: lactose monohydrate, magnesium stearate, maize starch, pregelatinised maize starch, sodium starch glycollate, indigo carmine (1 mg and 3 mg only), iron oxide red (1 mg only), iron oxide yellow (1 mg only) and erythrosine (5 mg only).

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3 Sanderson S, Emery J, Higgins J. CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: A HuGEnet™ systemic review and meta-analysis. *Genet Med*. 2005;7:97-104.

4 Lindh JD, Lundgren S, Holm L, Alfredsson L, Rane A. Several-fold increase in risk of overanticoagulation by CYP2C9 mutations. *Clin Pharmacol Ther*. 2005;78:540-550.

5 Wadelius M, Chen LY, Downes K, et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J. 2005;5:262-270.

6 Veenstra DL, You JHS, Rieder MJ, et al. Association of Vitamin K epoxide reductase complex 1 (VKORC1) variants with warfarin dose in a Hong Kong Chinese patient population. *Pharmacogenet Genomics*. 2005;15-687-691.

7 Takahashi H, Wilkinson GR, Nutescu EA, et al. Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population differences in maintenance doses of warfarin in Japanese, Caucasians and African Americans. *Pharmacogenet Genomics*. 2006;16:101-110.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: HDPE bottle with a PP child resistant closure.

Pack size: 50

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 12511 – MAREVAN warfarin sodium 1mg tablet bottle

AUST R 12513 – MAREVAN warfarin sodium 3mg tablet bottle

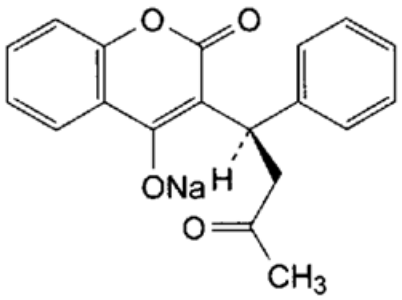
AUST R 12514 – MAREVAN warfarin sodium 5mg tablet bottle

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure



and enantiomer

MAREVAN (warfarin sodium) is a vitamin K dependent factor anticoagulant. Warfarin is 4-hydroxy-3-(3-oxo-1-phenylbutyl) coumarin which is present as a racemic mixture.

Warfarin sodium is a white hygroscopic powder, very soluble in water and in alcohol.

Molecular formula: $C_{19}H_{15}NaO_4$

Molecular weight: 330.3

CAS Number

129-06-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

13/08/1991

10 DATE OF REVISION

16/12/2022

Summary Table of Changes

Section Changed	Summary of New Information
4.4, 4.8	Addition of warning and adverse effect of anticoagulant-related nephropathy

MAREVAN_pi\Dec22/02