New Zealand Data Sheet

1.PRODUCT NAME

COUMADIN 1 mg, 2 mg and 5 mg Tablets
COUMADIN is not to be marketed as substitutable for any other warfarin product as if the two products were bioequivalent.

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains 1mg, 2mg or 5mg warfarin sodium**.** For full lists of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets, 1mg - A beige/tan coloured, shallow, biconvex tablet. One face is bisected and embossed with a numerical "1" and the word "Coumadin". The other face is plain.

Tablets, 2mg - A lavender coloured, shallow, biconvex tablet. One face is bisected and embossed with a numerical "2" and the word "Coumadin". The other face is plain.

Tablets, 5mg - A green coloured, shallow, biconvex tablet. One face is bisected and embossed with a numerical "5" and the word "Coumadin". The other face is plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications COUMADIN is indicated for the prophylaxis and/or treatment of venous thrombosis and its extension, pulmonary embolism, thromboembolism associated with atrial fibrillation, and as an adjunct in the prophylaxis of systemic embolism after myocardial infarction.

4.2 Dose and method of administration

Administration: The administration and dosage of COUMADIN 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 standardizing 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 International Reference Preparation (IRP). For the three commercial rabbit brain thromboplastins currently used in North America, a PT ratio of 1.3 to 2.0 is equivalent to an INR of 2.0 to 4.0. For other preparations the INR can be calculated as:

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

Where the ISI (International Sensitivity Index) is the calibration factor and is available from the manufacturers of the thromboplastin reagent.

Initial Dosage: The dosing of COUMADIN must be individualised according
to patient's sensitivity to the drug as indicated by the INR and/or PT ratio. Use of a large loading dose may increase the incidence of haemorrhage and other complications, does not offer more rapid protection against thrombi formation, and is not recommended. Low initiation doses are recommended for elderly and/or debilitated patients and patients with increased sensitivity to COUMADIN (see Precautions section of this Data Sheet). It is recommended that COUMADIN therapy be initiated with a dose of 2 to 5mg per day with dosage adjustments based on the results of INR and/or PT ratio determinations.

Maintenance: Most patients are satisfactorily maintained at a dose of 2 to
10mg 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.

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 judgment of the patient's reliability and response to COUMADIN 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 after a stable dosage has been determined. To ensure adequate control, it is recommended that additional prothrombin time tests are done when other warfarin products are interchanged with COUMADIN and also if other medications are co-administered with COUMADIN (see Precautions).

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 COUMADIN 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 COUMADIN effect is delayed, heparin is preferred initially for rapid anticoagulation. Conversion to COUMADIN 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 COUMADIN 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 COUMADIN has produced the desired therapeutic range or prothrombin activity, heparin may be discontinued.

4.3 Contraindications

Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of haemorrhage might be greater than the potential clinical benefits of anticoagulation, such as:

- Known hypersensitivity to warfarin or to any of the excipients
- Haemorrhagic stroke and/or bleeding tendencies associated with active ulceration or overt bleeding of; (1) gastrointestinal, genirourinary or respiratory tracks; (2) cerebrovascular haemorrhage; (3) aneurysms- cerebral, dissecting aorta; (4) pericarditis and pericardial effusions; (5) bacterial endocarditis
- Clinically significant bleeding

- Within 72 hours of major surgery with risk of severe bleeding (for information on other surgery, see Warnings and Precautions)

- Within 48 hours postpartum

- Pregnancy (first and third trimesters, see Warnings and Precautions)

- Drugs where interactions may lead to a significantly increased risk of bleeding (see Interactions)

- 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

- Miscellaneous: major regional, lumbar block anawsthesia and malignant hypertension

4.4 Special warnings and precautions for use

It cannot be emphasised too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy.

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.

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 established in the target range the INR can be determined at longer intervals.

INR should be monitored more frequently in patients at an increased risk of over coagulation e.g. patients with severe

hypertension, liver or renal disease. Patients for whom adherence may be difficult should be monitored more frequently.

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

Risk of haemorrhage
The most frequently reported adverse effect of all ral 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, severe or moderate hepatic or renal insufficiency)

Risk factors for bleeding include high intensity of anticoagulation (INR > 4.0) age ≥ 65, high variable INRs, history of gastrointestinal bleeding, uncontrolled hypertension, cerebrovascular disease, serious heart disease, risk of failing, anaemia, malignancy, trauma, renal insufficiency, indwelling catheters, concomitant drugs (see interaction section). 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 failing.

Any concomitant anti-platelet drugs should be used with caution due to an increased risk of bleeding.

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 infracted 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 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, e.g. tooth extraction

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

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 protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients receiving 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.

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.

Necrosis
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, breast or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underline disease. Warfarin therapy should be discontinued when warfarin 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 embolization in untreated cases.

Purple Toes Syndrome
Anticoagulation therapy with COUMADIN may enhance the release of atheromatous plaque emboli, therapy increasing th erisk of complications from systemic cholesterol microembolization, including the “purple toes syndrome”. Discontinuation of COUMADIN therapy is recommended when such phenomena are observed.

Systemic artheroemboli and cholesterol microembolican 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, mvalgia, 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 characterized by a dark, purplish or mottled colour of the toes, usually occurring between 3-
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 cases progress to gangrene or necrosis which may require debridement of the affected area, or may lead to amputation.

Additional circumstances where changes in dose may be required
The following also may exaggerate the effect of warfarin tablets and necessitate a reduction of dosage:

- Loss of weight
- Acute illness
- Cessation of smoking

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

- Weight gain
- Diarrhoea
- Vomiting

Other warnings
Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of warfarin are required to achieve the desired anticoagulant effect.

Generic information
Generic 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.

Heparin prolongs the one-stage prothrombin time. When heparin and COUMADIN are administered concomitantly, refer below to CONVERSION FROM HEPARIN THERAPY for recommendations.

Known or suspected deficiency in protein C:
This hereditary or acquired condition, which should be suspected if there is a history of recurrent episodes of thromboembolic disorders in the patient or in the family, has been associated with an increased risk of developing necrosis following warfarin administration. Tissue necrosis may occur in the absence of protein C deficiency. It has been reported that concurrent anticoagulation therapy with heparin for 5 to 7 days during initiation of therapy with COUMADIN may minimise the incidence of this reaction. Warfarin therapy should be discontinued when warfarin is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.

Periodic determination of prothrombin time 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 response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference, however, other factors may also affect the anticoagulant response.

The following factors, alone or in combination, may be responsible for INCREASED PT response.

Endogenous factors

Cancer	elevated temperature
collagen disease	Hyperthyroidism
congestive heart failure	poor nutritional state
Diarrhoea	Steatorrhoea
Hepatic disorders	vitamin K deficiency

- infectious hepatitis
- jaundice

Exogenous factors:

Acetohexamide
alcohol*
Allopurinol
Aminosalicylic acid
amiodarone HCl
anabolic steroids
anaesthetics, inhalation
Antibiotics
anti-thyroid drugs
Aztreonam
Bromelains
Chenodiol
chloral hydrate*
chlorpropamide
Chymotrypsin
Cimetidine
Clofibrate
Cotrimoxazole
COUMADIN overdosage
Dextran
dextroproxyphene
dextrothyroxine
Diazoxide
Diflunisal
diuretics*
Disulfiram
ethacrynic acid
Fenoprofen
Fluconazole
fluoroquinolone Antibiotics
Fluvoxamine
Gemfibrozil
Glucagon
Hepatotoxic drugs
Ibuprofen
indomethacin
influenza virus vaccine
Lovastatin
mefenamic acid
Methyldopa
Methylphenidate
Metronidazole
Miconazole
monoamine oxidase inhibitors
moricizine hydrochloride*
nalidixic acid
Naproxen
narcotics, prolonged
Omeprazole
Paracetamol
Pentoxifylline
Phenformin
Phenylbutazone
Phenytoin
Propafenone
Pyrazolones
Quinidine
Quinine
ranitidine*
Salicylates
Sulfinpyrazone
sulfonamides, long acting
Sulindac
Tamoxifen
thyroid compounds
thryoid drugs
Ticrynafen
tolazamide
tolbutamide
trimethoprim/ sulfamethoxazole

also: other medications affecting blood elements which may modify haemostasis

dietary deficiencies

prolonged hot weather
unreliable prothrombin time determinations

* Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for DECREASED PT response:

Endogenous factors:
oedema
hereditary coumarin resistance
hyperlipaemia
hypothyroidism

Exogenous factors:
adrenocortical steroids
alcohol*
aminoglutethimide
antacids
antihistamines
barbiturates
carbamazepine
chloral hydrate*
chlordiazepoxide
cholestyramine
COUMADIN underdosage
diuretics*
ethchlorvynol
glutethimide
griseofulvin
haloperidol
meprobamate
moricizine hydrochloride*
nafcillin
oral contraceptives
paraldehyde
primidone
ranitidine*
rifampicin
sucralfate
trazodone
vitamin C

also:

diets high in vitamin K (e.g. large amounts of green leafy vegetables, dairy products fortified with vitamin K)
unreliable PT determinations

* Increased and decreased prothrombin time responses have been reported.

Because a patient may be exposed to a combination of the above factors, the net effect of COUMADIN on PT response may be

unpredictable. More frequent PT monitoring is therefore advisable. Medications of unknown interaction with warfarin are best regarded with caution. When these medications are started or stopped, more frequent PT monitoring is advisable.

Warfarin may also affect the action of other drugs. Hypoglycaemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

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

Special Risk Patients: Caution should be observed when warfarin sodium 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.

Intramuscular (IM) injections of concomitant medications 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 COUMADIN (or warfarin) is administered concomitantly with nonsteroidal anti-inflammatory agents, including aspirin, to be certain that no change in anticoagulation dosage is required. In addition to specific drug interactions that might affect PT, NSAIA's, including aspirin, can inhibit platelet aggregation, and can cause gastrointestinal bleeding, peptic ulceration and/or perforation.

4.5 Interaction with other medicines and other forms of interaction

Warfarin has a narrow therapeutic range and care is required with all concomitant therapy. The individual product information for any new concomitant therapy should be considered 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.

Paediatric Use: Safety and effectiveness in children below the age of 18 have not been established.

Pharmacodynamic interactions

Drugs which are contraindicated

Concomitant use of drugs used in the treatment or propylaxsis of thrombosis or other drugs with adverse effects on haemostasis may increase the pharmacological effect of warfarin, increasing the risk of bleeding.

Fibrinolytic drugs such as streptokinase and alteplase are contraindicated in patients receiving warfarin.

Drugs which should be avoided if possible

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

- Clopidogrel
- NSAIDs (including aspirin and cox-2 specific NSAIDs)
- Sulfinpyrazone
- Thrombin inhibitors such as bivalirudin, dabigatran
- Dipyridamole
- Unfractionated heparins and heparin derivatives, low molecular weight heparins
- Fondaparinux rivaroxaban
- Glucoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab
- Prostacyclin
- SSRI and SNRI antidepressants
- Other drugs which inhibit haemostasis, clotting or platelet action

Low-dose aspirin with warfarin may have a role in some patients but the risk
of gastrointestinal bleeding in 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 CYPP450 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 complete as substrates for these cytochromes or inhibit their activity may increase warfarin plasma concentration 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 reduced 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 or starting and stopping therapy is advised.

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

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

Examples of drugs which potentiate the effect of warfarin
Allopurinol, capecitabine, eriotinib, disulfiram, azole antifungals (ketoconazole, fluconazole etc.) omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate zafirlukast, fibrates, statins (not pravastatin: predominantly associated with fluvastatin) erythromycin, sulfamethoxazole, metronidazole
Examples of drugs which antagonise the effect of warfarin
Barbiturates, primidone, carbamazepine, griseofu;vin, oral contraceptive, rifampicin, azathioprine, phenytoin

Examples of drugs with variable effect
Cortocosteroids, nevirapine, ritonavir

Other drug interactions

Broad spectrum antibiotics may potentiate the effect of warfarin by reducing the gut flora which produces vitamin K. Similarly, orlistat may reduce absorption of vitamin K, Colestyramine and sucralfate potentially decrease absorption of warfarin.
Increased INR has been reported in patients taking glucosamine and warfarin. This combination is not recommended.

Interactions with herbal products

Herbal preparations containing St John's Wort (*Hypericum perforatum*) must not be used whilst taking warfarin due to a proven risk of decreased plasma concentrations and reduced clinical effects of warfarin.

Many other herbal products have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should generally avoid taking any herbal medicines or food supplements whilst taking warfarin, and should be told to advise their doctor if they are taking any, as more frequent monitoring advisable.

Alcohol

Acute ingestion of a large amount of alcohol may inhibit the metabolism of warfarin and increase INR. Conversely, chronic heavy alcohol intake may induce the metabolism of warfarin. Moderate alcohol intake can be permitted.

Interactions with food and food supplements

Individual case reports suggest a possible interaction between warfarin and cranberry juice in most cases leading to an increase in INR or bleeding event. Patients should be advised to avoid cranberry products. Increased supervision and INR monitoring should be considered for any patient taking warfarin and regular cranberry juice.

Limited evidence suggests that grapefruit juice may cause a modest rise in
INR in some patients taking warfarin.

Certain foods such as liver, broccoli, brussels sprouts and green

leafy vegetables contain large amounts of vitamin K. Sudden changes in diet can potentially affect control of anticoagulation. Patients should be informed of the need to seek medical advice before undertaking any major changes in diet.

Many other food supplements have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should 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.

Information for Patients: The objective of anticoagulant therapy is to control the coagulation mechanism 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. Various COUMADIN patient educational guides are available to physicians on request. Patients should be advised: Strict adherence to prescribed dosage schedule is necessary. Do not take or discontinue any other medication, except on advice of physician.
Avoid alcohol, salicylates (eg aspirin & topical analgesics), large amounts of green leafy vegetables, dairy products fortified with vitamin K and/or drastic changes in dietary habits, because they may affect COUMADIN therapy. COUMADIN may cause a red-orange discolouration of alkaline urine. The patient should notify the physician if any illness, such as diarrhoea, infection or fever develops or if any unusual symptoms, such as pain, swelling or discomfort appear or if prolonged bleeding from cuts, increased menstrual flow or vaginal bleeding, nosebleeds or bleeding of gums from brushing, unusual bleeding or bruising, red or dark brown urine, red or tar black stools or diarrhoea occurs.

4.6 Fertility, pregnancy and lactation

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenicity and mutagenicity studies have not been performed with COUMADIN. The reproductive effects of COUMADIN have not been evaluated.

Pregnancy

COUMADIN 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 foetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Embryopathy characterized by nasal hypoplasia with or without stippled epiphyses (chondrodyspiasia punctata) has been reported in pregnant women exposed to warfarin during the first trimester. Central nervous system abnormalities also have been reported, including dorsal midline dysplasia characterized by agenesis of the corpus callosum, Dandy-Walker malformation and midline cerebellar atrophy.

Warfarin is contraindicated in pregnancy in the first and third trimester. Women of child-bearing age who are taking warfarin tablets should use effective contraception during treatment.

Ventral midline dysplasia, characterized by optic atrophy and eye abnormalities has 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 leukoma.

Spontaneous abortion and still birth are known to occur and a higher risk of foetal mortality is associated with the use of warfarin.

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 foetus and the possibility of termination of the pregnancy should be discussed in light of those risks.

Lactation

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

4.8 Undesirable effects

Potential adverse reactions to COUMADIN may include:

MedDRA system organ class	**Adverse Reaction**
Infections and Infestation	Fever
Immune system disorders	Hypersensitivity
Nervous system disorders	Cerebral Haemorrhage: cerebral subdural haematoma
Vascular disorders	Haemorrhage
Respirotory, thoracic and mediastinal disorders	Haemothorax, epistaxis
Gastrointestinal disorders	Gastrointestinal haemorrhage; rectal haemorrhage; haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena
Hepatobiliary disorders	Jaundice; hepatic dysfunction
Skin and subcutaneous disorders	Rash; alopecia; purple; purple toes syndrome; erythematous swollen skin patches leading to ecchymosis infarction and skin Necrosis Frequency ‘not known’:Calciphylaxis
Renal and urinary disorders	Haematuria
Investigation	Unexplained drop in haematocrit; haemoglobin decreased

- Haemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Haemorrhagic complications may present as paralysis; headache, chest, abdomen, joint or other pain; shortness of breath, difficult breathing or swallowing; unexplained swelling; or unexplained shock.
- Therefore, the possibility of haemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See Overdoasge - Treatment.)
- Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion e.g. tumor, ulcer, etc.
- Necrosis of skin and other tissues. (See Warnings.)
- Other adverse reactions are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhoea, abdominal cramping, systemic cholesterol microembolisation, purple toes syndrome, cholestatic hepatic injury, and hypersensitivity reactions.
- causal Priapism has been associated with anticoagulant administration, however, a relationship has not been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

level.

The benefit of gastric decontamination is uncertain. If the patient presents within 1 hour of ingestion of more than 0.25 mg/kg or more than the patient's therapeutic dose, consider activated charcoal (50 g for adults; 1g/kg for children)

In cases of life-threatening haemorrhage
Stop warfarin treatment, give prothrombin complex concentrate (factors II, VII, IX and X) 30-50 units/kg or (if no concentrate available) fresh frozen plasma
15 mL/kg. Discuss with local haematologist or National Poisons Information
Service or both.

Non-life threatening haemorrhage
Where anticoagulation can be suspended give slow intravenous injection of phytomenadione (vitamin K1) 10-20 mg for adults (250 micrograms/kg for a child)

Where rapid re-anticoagulation is desirable (e.g. value replacements) give prothrombin complex concentrate (factors II, VII, IX and X) 30-50 units/kg or (if no concentrate available) fresh frozen plasma 15 mL/kg.

Monitor INR to determine when to restart normal therapy. Monitor INR for at least 48 hours post overdose.

For patients on long-term warfarin therapy without major haemorrhage

- INR > 8.0, no bleeding or minor bleeding – stop warfarin, and give phytomenadione (vitamin K1) 0.5 -1 mg for adult, 0.015 – 0.030 mg/kg (15-30 micrograms/kg) for children by slow intravenous injection or 5 mg by mouth (for partial reversal of anticoagulation give smaller oral doses of phytomenadione e.g. 0.5 -2.5 mg using the intravenous preparation orally); repeat dose of phytomenadione if INR still too high after 24 hours. Large doses of phytomenadione may completely reverse the effects of warfarin and make re- establishment of anticoagulation difficult.

- INR 6.0 – 8.0, no bleeding or minor bleeding – stop warfarin, restart when INR < 5.0.

- INR < 6.0 but more than 0.5 units above target value

reduce dose or stop warfarin, restart when INR< 5.0

For patients**,** NOT on long-term anticoagulants without major haemorrage

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 after and consider further vitamin K1.

For advice on the management of overdose please contact the National
Poisons Centre on 0800 POISON (0800 764766).

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

COUMADIN (warfarin sodium) is a vitamin K dependent factor anticoagulant. Warfarin is the coined generic name for 3-(α-Acetonyl-benzyl)-4- hydroxycoumarin.

COUMADIN 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 activities. 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.

5.2 Pharmcokinetic properties

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the long lasting response curve. COUMADIN is metabolized by hepatic, microsomal enzymes to inactive metabolites that are excreted into the bile, reabsorbed and excreted into the urine.

Coumadin is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap.
An anticoagulant effect generally occurs within 24 hours; however, peak anticoagulant effect may be delayed 72 to 96 hours.

6. PHARMACEUTICAL PRECAUTIONS

6.1 List of excipients

Maize starch, lactose, stearic acid, magnesium stearate, brilliant blue FCF (5mg only), quinoline yellow (1 & 5mg only), amaranth (1 & 2mg only), indigo carmine (2mg only).

6.3. Shelf life

1 mg: 36 months
2 mg: 36 months
5mg: 36 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Bottle, plastic, HDPE with Clic loc II 28 mm child resistant cap – 50 tablets

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pharmacy Retailing (NZ) Limited
Trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks

Auckland, New Zealand
Telephone (09) 9185 100
Email: aspen@aspenpharma.co.nz

9. DATE OF FIRST APPROVAL

14th September 2006

10. DATE OF REVISION OF TEXT

15th September 2017

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections revised	Update to the SPC-style format
Section 4.4	Inclusion of Calciphylaxis
Section 4.8	Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/ Inclusion of Calciphylaxis
Section 4.9	For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766)
A contact telephone number for the sponsor.	Phone number and email address included.