MAFORAN 1 MG / 2 MG / 3 MG / 5 MG TABLET

COMPOSITION
Each **MAFORAN 1 mg, 2 mg, 3 mg** and **5 mg Tablet** contains Warfarin Sodium 1 mg, 2 mg, 3 mg and 5 mg (as Warfarin Sodium Clathrate) respectively.

DESCRIPTION
MAFORAN 1 mg Tablet: White flat round tablet with a bisect and debossed with "MAFORAN", "1" on one side, plain on the other.
MAFORAN 2 mg Tablet: Orange flat round tablet with a bisect and debossed with "MAFORAN", "2" on one side, plain on the other.
MAFORAN 3 mg Tablet: Dark blue flat round tablet with a bisect and debossed with "MAFORAN", "3" on one side, plain on the other.
MAFORAN 5 mg Tablet: Pink flat round tablet with a bisect and debossed with "MAFORAN", "5" on one side, plain on the other.

PHARMACODYNAMICS
Warfarin is an anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX and X, and the anticoagulant proteins C and S. Half-lives of these clotting factors are as follows: Factor II-60 hours, VII-4-6 hours, IX-24 hours, and X- 48-72 hours. The half-lives of proteins C and S are approximately 8 hours and 30 hours, respectively.
The resultant in vivo effect is a sequential depression of Factors VII, IX, X and II activities. Vitamin K is an essential cofactor for the post ribosomal synthesis of the vitamin K-dependent clotting factors. Vitamin K promotes the biosynthesis of γ-carboxyglutamic acid residues in the proteins that are essential for biological activity. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the C1 subunit of 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. 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%.
An anticoagulation effect generally occurs within 24 hours after drug administration. However, peak anti-coagulant effect may be delayed 72 to 96 hours. The duration of action of a single dose of racemic warfarin is 2 to 5 days. The effects of warfarin may become more pronounced as effects of daily maintenance doses overlap.
Anticoagulants have no direct effect on an established thrombus, nor they reverse ischemic tissue damage. However, once a thrombus has occurred, the goal of anticoagulant treatment is to prevent further extension of the formed clot and prevent secondary thromboembolic complications, which may result in serious and possibly fatal sequalae.

PHARMACOKINETICS
Warfarin is a racemic mixture of the R- and S-enantiomers with the S-enantiomer exhibiting 2-5 times greater 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 reached within the first 4 hours. Solid dosage forms of warfarin are also essentially completely bioavailable (> 90%).

Distribution
Warfarin shows a volume of distribution of about 0.14 L/kg. Approximately 99% of the drug is bound to plasma proteins.

Metabolism
The elimination of warfarin is almost entirely by metabolism. Warfarin is stereoselectively metabolized by hepatic cytochrome P-450 (CYP450) microsomal enzymes to inactive hydroxylated metabolites (predominant route) and by reductases to reduced metabolites (warfarin alcohols) with minimal anticoagulant activity. Identified metabolites of warfarin include dehydrowarfarin, two diastereoisomer alcohols, and 4'-, 6-, 7-, 8-, and 10- hydroxywarfarin. The CYP450 isozymes involved in the metabolism of warfarin include CYP2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. CYP2C9, a polymorphic enzyme, is likely to be the principal form of human liver CYP450 that modulates the in vivo anticoagulant activity of warfarin. Patients with one or more variant CYP2C9 alleles have decreased S-warfarin clearance.

Elimination
The terminal half-life of warfarin after a single dose is approximately 1 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 administered dose is recovered in urine. Very little warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

INDICATIONS
MAFORAN is indicated for:
- Prophylaxis and/or treatment of venous thrombosis and its extension, and pulmonary embolism.
- Prophylaxis and/or treatment of the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement.
- Reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction in patients with poor LV function.

RECOMMENDED DOSAGE
The target INR range of oral anticoagulant therapy:
Prophylaxis of thromboembolic complications in patients with prosthetic heart valves: INR 2.5 – 3.5
Other indications: INR 2.0 – 3.0

Adults:
Patients in normal weight and the spontaneous INR under 1.2 are administered 10 mg of warfarin on three consecutive days. The dosing is continued according to the table below, based on the INR-measured on the fourth day.
In open care and for patients with inherited protein C or protein S deficiency the recommended initial dose is 5 mg of warfarin (*) in three days. The dosing is continued according to the table below, based on the INR-measured on the fourth day.
For elderly patients, for those small in size, for those with the spontaneous INR over 1.2, or for those who have a disease (see Warnings and Precautions) or medication (see Drug Interactions) affecting the efficacy of anticoagulant therapy, the recommended initial dose is 5 mg of warfarin (see*) for two days. The dosing is continued according to the table below, based on the INR-measurement performed on the third day:

Therapy Day	INR	Warfarin dose, mg/day
1.	-	10 (5*)
2.	-	10 (5*)
3.	< 2.0	10 (5*)
	2.0 to 2.4	5
	2.5 to 2.9	3
	3.0 to 3.4	2.5
	3.5 to 4.0	1.5
	> 4.0	Miss one day
4.-6.	< 1.4	10
	1.4 to 1.9	7.5
	2.0 to 2.4	5
	2.5 to 2.9	4.5
	3.0 to 3.9	3
	4.0 to 4.5	Miss one day, then 1.5
	> 4.5	Miss two days, then 1.5
7.-		Weekly warfarin dose
	1.1 to 1.4	Increase weekly dose by 20%
	1.5 to 1.9	Increase weekly dose by 10%
	2.0 to 3.0	Maintain the dose
	3.1 to 4.5	Decrease weekly dose by 10%
	> 4.5	Miss until INR < 4.5, then continue with 20% smaller dose

INR measurements are carried out daily until the therapeutic level has been achieved (usually this takes 5 to 6 days). Intervals of INR measurements are then extended weekly. In long-term follow-up the measurement intervals are dependent i.e. on the patient's compliance and clinical status, targeting, however, on 4-weekly measurement intervals. If large fluctuations exist in the INR values or if the patient has a disease affecting liver function or the absorption of vitamin K, the measuring interval must be shorter than this. Many medicines may potentiate or weaken the effect of warfarin, which must be considered in the follow-up when initiating or discontinuing other medications. In long-term follow-up the adjustments required based on the INR measurements are made to the weekly dose. Thereafter the effect of the adjustment is checked by measuring the INR after 1 or 2 weeks of the adjustment. After this, the intervals are targeted on the same 4-weekly measurement intervals.

Children:
The initiation and follow up of anticoagulant therapy in children is carried out by paediatricians. Dosage can be adjusted according to the following table.

Therapy day 1, if spontaneous INR 1.0 to 1.3	Initial dose = 0.2 mg/kg p.o.
Therapy days 2 to 4, if the INR is	Maintenance dose :
1.1 to 1.3	Repeat initial dose
1.4 to 1.9	50% of the initial dose
2.0 to 3.0	50% of the initial dose
3.1 to 3.5	25% of the initial dose
> 3.5	Miss until INR < 3.5, then restart at 50% less than the previous dose
Maintenance, if the INR is	Action :
1.1 to 1.4	Increase weekly dose by 20%
1.5 to 1.9	Increase weekly dose by 10%
2.0 to 3.0	No change to the weekly dose
3.1 to 3.5	Decrease weekly dose by 10%
> 3.5	Miss until INR < 3.5, then restart at 20% less than the previous dose

Elective surgery
Pre-, peri- and postoperative anticoagulant therapy the following dosage can be applied (if an urgent reversal of oral anticoagulant effect is needed, see Symptoms and Treatment of Overdosage).

Determine the INR one week prior to the scheduled surgery.
Discontinue warfarin 1 to 5 days prior to surgery.
If the patient is in high risk of thromboembolism, subcutaneous low molecular weight heparin should be given at therapeutic doses. The effect of heparin can be monitored by measuring the prophylactic effect of FXa when the effective therapeutic level is 0.3 to 0.7 anti-FXa activity units/ml.

The extent of warfarin pause depends on the INR value. Discontinue warfarin
- 5 days prior to surgery if the INR > 4.0
- 3 days prior to surgery if the INR = 3.0 to 4.0
- 2 days prior to surgery if the INR = 2.0 to 3.0

Determine the INR in the evening before surgery. If INR > 1.8, administer 0.5 to 1 mg vitamin K1 intravenously or orally.
Consider the need for unfractionated heparin infusion or prophylactic low molecular weight heparin during the day of surgery.
Continue subcutaneous low molecular weight heparin for 5 to 7 days concomitantly with reintroduced warfarin therapy.
Continue warfarin with normal maintenance doses on the evening of day of minor surgery, and on the day the patient begins enteral nutrition after major surgery.
The elderly: Elderly patients require lower doses than younger adults. Warfarin pharmacokinetics is unaffected by age.
The reduced dose requirement is due to pharmacodynamic changes.
Impaired renal function: Patient with impaired renal function, depending on the comorbidity, may require lower or higher dose of warfarin.
Impaired hepatic function: Patients with impaired hepatic function may need lower dose of warfarin. Impaired hepatic function can enhance the effect of warfarin through inhibited synthesis of clotting factors and reduced metabolism of warfarin.

METHOD OF ADMINISTRATION
The administration and dosage of **MAFORAN** must be individualized according to the patient's responsiveness to the drug. The dosage should be adjusted according to results of the patient's PT ratio/INR. Measurement of warfarin induced effects on PT can vary substantially due to the sensitivity of different thromboplastin reagents.
Maintenance: Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets 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 individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.
Missed Dose: The anticoagulant effect of warfarin persists beyond 24 hours. If the patient forgets to take the prescribed dose of **MAFORAN** at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not take the missed dose by doubling the daily dose to make up for missed doses, but should refer back to his or her physician.

ROUTE OF ADMINISTRATION
For oral administration. May be taken with or without food.

CONTRAINDICATIONS
- Hypersensitivity to warfarin or any component of the formulation.
- Pregnancy, or women of child-bearing potential (see Pregnancy and Lactation).
- Haemorrhagic tendencies or blood dyscrasias.
- Co-administration with miconazole oral gel (see Drug Interactions).
- Recent or contemplated surgery of the central nervous system (CNS) or eye, or traumatic surgery resulting in large open surfaces.
- Major regional or lumbar block anaesthesia.
- Untreated or uncontrolled hypertension.
- Severe hepatic insufficiency and hepatic cirrhosis.
- Bleeding tendencies associated with:
  - Active ulceration or overt bleeding of the gastrointestinal, genitourinary, or respiratory tract;
  - Central nervous system haemorrhage;
  - Cerebral aneurysms, dissecting aorta;
  - Pericarditis and pericardial effusions;
  - Bacterial endocarditis.
- Threatened abortion, eclampsia and preeclampsia.
- Patients who has a history of falls or is a significant fall risk.
- Dementia, psychoses, alcoholism and other situations where the compliance may be poor and the treatment cannot be carried out safely in practice.
- Drugs where interactions may lead to a significantly increased risk of bleeding (see Drug Interactions).
- Anticoagulation is contraindicated in any physical condition in which the risk of haemorrhage might be greater that the potential clinical benefits of anticoagulation (see Warnings and Precautions).

WARNINGS AND PRECAUTIONS
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 stabilized in the target range the INR can be determined at longer intervals. INR should be monitored more frequently in patients at an increased risk of over coagulation e.g. patients with severe hypertension, liver or renal disease. Patients for whom adherence may be difficult should be monitored more frequently.

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

Risk of haemorrhage
The most frequently reported adverse effect of all oral anticoagulants is haemorrhage. Warfarin should be given with caution to patients where there is a risk of serious haemorrhage (e.g. concomitant NSAID use, recent ischaemic stroke, bacterial endocarditis, previous gastrointestinal bleeding). Risk factors for bleeding include high intensity of anticoagulation (INR >4.0), age ≥65, highly variable INRs, history of gastrointestinal bleeding, uncontrolled hypertension, cerebrovascular disease, serious heart disease, risk of falling, anaemia, malignancy, trauma, renal insufficiency, concomitant drugs (see Drug Interactions). All patients treated with warfarin should have INR monitored regularly. Those at high risk of bleeding may benefit from more frequent INR monitoring, careful dose adjustment to desired INR, and a shorter duration of therapy. Patients should be instructed on measures to minimise risk of bleeding and to report immediately to physicians signs and symptoms of bleeding.
Checking the INR and reducing or omitting doses depending on INR level is essential, following consultation with anticoagulation services if necessary. If the INR is found to be too high, reduce dose or stop warfarin treatment; sometimes it will be necessary to reverse anticoagulation. INR should be checked within 2–3 days to ensure that it is falling. Any concomitant anti-platelet drugs should be used with caution due to an increased risk of bleeding.

Haemorrhage
Haemorrhage can indicate an overdose of warfarin has been taken. Unexpected bleeding at therapeutic levels should always be investigated and INR monitored.

Ischaemic stroke
Anticoagulation following an ischaemic stroke increases the risk of secondary haemorrhage into the infarcted brain. In patients with atrial fibrillation long-term treatment with warfarin is beneficial, but the risk of early recurrent embolism is low and therefore a break in treatment after ischaemic stroke is justified. Warfarin treatment should be re-started 2–14 days following ischaemic stroke, depending on the size of the infarct and blood pressure. In patients with large embolic strokes, or uncontrolled hypertension, warfarin treatment should be stopped for 14 days.

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240mm

170mm

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.

Active peptic ulceration

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

Interactions

Many drugs and foods interact with warfarin and affect the prothrombin time (see Drug Interactions). Any change to medication, including self-medication with OTC products, warrants increased monitoring of the INR. Patients should be instructed to inform their doctor before they start to take any additional medications including over the counter medicines, herbal remedies or vitamin preparations.

Thyroid disorders

The rate of warfarin metabolism depends on thyroid status. Therefore, patients with hyper- or hypothyroidism should be closely monitored on starting warfarin therapy.

Tissue necrosis

Necrosis and/or gangrene of skin and other tissues is an uncommon but serious risk. It may 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. Necrosis has in some cases been reported to result in death or permanent disability. 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.

Systemic atheroemboli and cholesterol microemboli

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

Anticoagulant-related nephropathy

In patient with altered glomerular integrity or with a history of kidney disease, acute kidney injury may occur, possibly in relation to episodes of excessive anticoagulation and haematuria. A few cases have been reported in patients with no pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with a supratherapeutic INR and haematuria (including microscopic).

Warfarin resistance

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

Genetic information

Genetic variability particularly in relation to CYP2C9 and VKORC1 can significantly affect dose requirements for warfarin. If a family association with these polymorphisms is known extra care is warranted.

CAUTION

Topical preparations containing methyl salicylate should be used with care in patients on **Warfarin** and excessive usage is to be avoided as potentially dangerous drug interaction can occur.

Special Warnings and Precautions for Use

• Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.
• Co-administration with topical miconazole (see Drug Interactions).

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

MAFORAN has no known effect on the ability to drive or operate machines.

DRUG INTERACTIONS

Warfarin has a narrow therapeutic range and care is required with all concomitant therapy. The individual product information for any new concomitant therapy should be consulted for specific guidance on warfarin dose adjustment and therapeutic monitoring. If no information is provided the possibility of an interaction should be considered. Increased monitoring should be considered when commencing any new therapy if there is any doubt as to the extent of interaction.

Warfarin is a mixture of enantiomers. R-warfarin is metabolised primarily by CYP1A2 and CYP3A4. S-warfarin is metabolised primarily by CYP2C9.

Drugs that compete as substrates for these cytochromes or inhibit their activity may increase warfarin plasma concentrations and INR, potentially increasing the risk of bleeding.

When these drugs are co-administered, warfarin dosage may need to be reduced and the level of monitoring increased.

Conversely, drugs which induce these metabolic pathways may decrease warfarin plasma concentrations and INR, potentially leading to reduced efficacy. When these drugs are co-administered, warfarin dosage may need to be increased and the level of monitoring increased.

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

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

* For substances that act as inducers, the effect can persist for several weeks after withdrawal.

Absorption or enterohepatic recirculation of warfarin may be affected by some medications, e.g. colestyramine. Induction (e.g. antiepileptics or antituberculotics) or inhibition (e.g. amiodarone or metronidazole) of the hepatic metabolism of warfarin can take place. Cessation of induction or inhibition has to be taken into account as well.

Warfarin can be displaced from the plasma protein bonds, which increases the free fraction and, unless the patient has hepatic failure, the metabolism and elimination of warfarin are enhanced leading to a reduced effect.

Medications affecting platelet aggregation (e.g. acetylsalicylic acid, clopidogrel, ticlopidine, dipyridamole, tirofiban, and most of the nonsteroidal anti-inflammatory drugs) may result in a pharmacodynamic interaction and predispose the patient for severe bleeding complications. Penicillins in large doses could have the same effect on primary haemostasis.

Anabolic steroids, azapropazone, erythromycin, and some cephalosporins reduce directly the vitamin K dependent synthesis of the clotting factors and potentiate the warfarin effect. An ample supply of dietary vitamin K reduces the warfarin effect. Reduced absorption of vitamin K due to e.g. diarrhoea may potentiate the warfarin effect. Patients with inadequate supply of foodstuffs containing vitamin K are dependent on vitamin K2 produced by the intestinal bacteria. In these patients, many antibiotics may reduce the synthesis of vitamin K2, leading to an enhanced warfarin effect. Heavy use of alcohol with concomitant hepatic failure potentiates the warfarin effect. Quinine contained in Tonic-water may also potentiate the warfarin effect.

Protease inhibitors (e.g. ritonavir, lopinavir) may alter warfarin plasma concentrations. Frequent INR monitoring is recommended when concomitant treatment is initiated.
SNRIs (e.g. venlafaxine, duloxetine) and SSRIs (e.g. fluoxetine, sertraline) antidepressants may increase the risk of bleeding in concomitant use with warfarin.
Cranberry juice and other cranberry products may potentiate the effect of warfarin and therefore concomitant use should be avoided.
If the patient needs temporary relief of pain while on warfarin, the recommended medications are paracetamol or opioids.
Warfarin may potentiate the effect of oral sulphonylurea antidiabetics.
Fibrinolytic drugs such as streptokinase and alteplase are contraindicated in patients receiving warfarin.

Following medications have been reported to change the warfarin effect (the list is not exhaustive):

Increased effect:

- All non-steroidal anti-inflammatory agents (NSAIDs) and anticoagulants
- Analgesics: Dextropropoxyphene, paracetamol (the effect evident after 1 to 2 weeks of continuous use), tramadol
- Antiarrhythmics: Amiodarone, propafenone, quinidine
- Antibacterials: Amoxicillin, azithromycin, cefalexin, cefamandole, cefmenoxime, cefmetazole, cefoperazone, cefuroxime, chloramphenicol, ciprofloxacin, clarithromycin, clindamycin, doxycycline, erythromycin, gatifloxacin, grepafloxacin, isoniazid, latamoxef, levofloxacin, metronidazole, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, roxithromycin, sulfafurazole, sulfamethizole, sulfamethoxazole-trimethoprim, sulfaphenazole, tetracycline
- Antifungals: Azole antifungals (e.g. fluconazole, itraconazole, ketoconazole and miconazole (also oral gel))
- Antigout drugs: Allopurinol, sulfinpyrazone
- Antineoplastic and immunomodulating agents: Capecitabine, cyclophosphamide, etoposide, fluorouracil, flutamide, ifosfamide, lefluномide, mesna, methotrexate, sulofenur, tamoxifen, tegafur, EGFR inhibitors (e.g. gefitinib), trastuzumab
- Cardiovascular drugs: Digoxin, metolazone, propranolol
- Gastrointestinal drugs: Cimetidine, proton-pump inhibitors (e.g. omeprazole). The clinical relevance of the interaction with proton-pump inhibitors is not clear.
- Lipid regulating drugs: Bezafibrate, clofibrate, fenofibrate, fluvastatin, gemfibrozil, lovastatin, simvastatin
- Vitamins: Vitamin A, vitamin E
- Others: Carboxyuridine, chloral hydrate, codeine, disulfiram, ethacrynic acid, fluvoxamine, influenza vaccine, interferon alpha and beta, phenytoin, proguanil, quinine, (anabolic and androgenic) steroid hormones, thyroid hormones, troglitazone, valproic acid, zafirlukast

The following drugs have been reported to potentiate the warfarin effect (increase INR):

- Miconazole

There are reports suggesting that noscapine as well as glucosamine with or without chondroitin sulphate may increase the INR in patients on warfarin. Increased INR has been reported in patients taking glucosamine and oral vitamin K antagonists. Patients treated with oral vitamin K antagonists should therefore be closely monitored at the time of initiation or termination of glucosamine therapy.

Decreased effect:

- Antibacterials: Cloxacillin, dicloxacillin, flucloxacilline, nafcillin, rifampicin
- Antiepileptics: Carbamazepine, phenobarbital, primidone
- Antineoplastic and immunomodulating agents: Azathioprine, ciclosporin, mercaptopurine, mitotane
- Anxiolytic sedatives, hypnotics, and antipsychotics: Barbiturates, chlordiazepoxide
- Diuretics: Chlortalidone, spironolactone
- Vitamins: Vitamin C
- Others: Aminoglutethimide, colestyramine, disopyramide, griseofulvin, mesalazine, nevirapine, trazodone, aprepitant, fosaprepitant, bosentan
- Herbal medications can either potentiate the warfarin effect, e.g. ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong quai (*Angelica sinensis*, contains coumarins), papaya (*Carica papaya*) or danshen (*Salvia miltiorrhiza*, decreases the warfarin elimination), or reduce it, e.g. ginseng (*Panax spp.*). The effect of warfarin can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum*). This is due to induction of drug metabolizing enzymes by St. John's wort. Herbal preparations containing St. John's wort should therefore not be combined with warfarin. The inducing effect may persist for as long as 2 weeks after cessation of treatment with St. John's wort. If a patient is already taking St. John's wort, check the INR and stop St. John's wort. Monitor INR closely as this may rise on stopping St. John's wort. The dose of warfarin may need adjusting.

Ingestion of vitamin K containing foodstuffs during warfarin treatment should be as steady as possible. The most abundant vitamin K sources are green vegetables and leaves, such as: amaranth leaf, avocado, broccoli, Brussels sprout, cabbage, canola oil, chayote leaf, chives, coriander, cucumber skin (but not cucumber without skin), endives, kale leaf, kiwifruit, lettuce leaf, mint leaf, mustard greens, olive oil, parsley, peas, pistachio nuts, purple seaweed laver, spinach leaf, spring onion, soybeans, soybean oil, tea leaves (but not tea), turnip greens, or watercress.
Smoking may increase warfarin clearance, and smokers may require slightly higher doses than non-smokers. On the other hand, smoking cessation may enhance warfarin effects. Therefore, it is necessary to monitor INR closely when a chronic smoker undergoes smoking cessation.

PREGNANCY AND LACTATION

Pregnancy

Based on human experience warfarin causes congenital malformations and foetal death when administered during pregnancy. Warfarin is contraindicated in pregnancy especially in the first and third trimester because of the risk of the warfarin embryopathy or 'foetal warfarin syndrome' during first trimester and fatal bleeding and stillbirth during third trimester of pregnancy. Warfarin is rarely prescribed in the pregnancy and patients should be switched on to other anticoagulants during pregnancy or after conception. Women of child-bearing age who are taking warfarin tablets should use effective contraception during treatment.

Lactation

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

SIDE EFFECTS

System organ class	Frequency	Adverse Reaction
Infections and infestations	Not known	Fever
Immune system disorders	Not known	Hypersensitivity
Nervous system disorders	Not known	Cerebral haemorrhage; cerebral subdural haematoma
Vascular disorders	Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	Not known	Haemothorax, epistaxis
Gastrointestinal disorders	Not known	Gastrointestinal haemorrhage, rectal haemorrhage, haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena
Hepatobiliary disorders	Not known	Jaundice; hepatic dysfunction
Skin and subcutaneous tissue disorders	Not known	Rash; alopecia; purpura;'purple toes' syndrome; erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis; calciphylaxis
Renal and urinary disorders	Not known	Haematuria, Anticoagulant-related nephropathy (see Warnings and Precautions)
Investigations	Not known	Unexplained drop in haematocrit; haemoglobin decreased

SYMPTOMS AND TREATMENT OF OVERDOSAGE

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 anticoagulation beyond a safe and satisfactory level.

Treatment: Excessive anticoagulation, with or without bleeding, may be controlled by discontinuing warfarin therapy and if necessary, by administration of oral or parenteral vitamin K1 (please see recommendations accompanying vitamin K1 preparations prior to use). Such use of vitamin K1 reduces responses to subsequent warfarin therapy. Patients may return to a pre-treatment thrombotic status following the rapid reversal of a prolonged PT. Resumption of warfarin administration reverses the effect of vitamin K1, and a therapeutic PT can again be obtained by careful dosage adjustment. If rapid anticoagulation is indicated, heparin may be preferable for initial therapy.
If minor bleeding progresses to major bleeding, give 5 to 25 mg (rarely up to 50 mg) parenteral vitamin K1. In emergency situations of severe haemorrhage, clotting factors can be returned to normal by administering 200 to 500 mL of whole blood or fresh frozen plasma, or by giving commercial Factor IX complex.
A risk of hepatitis and other viral diseases is associated with the use of these blood products; Factor IX complex is also associated with an increased risk of thrombosis. Therefore, these preparations should be used only in exceptional or life-threatening bleeding episodes secondary to warfarin overdosage. Purified Factor IX preparations should not be used because they cannot increase the levels of prothrombin, Factor VII and Factor X, which are also depressed along with the levels of Factor IX as a result of warfarin treatment, packed red blood cells may also be given if significant blood loss has occurred. Infusions of blood or plasma should be monitored carefully to avoid precipitating pulmonary oedema in elderly patients or patients with heart disease.

DOSAGE FORM AND PACKAGING AVAILABLE

Blister pack of 100 tablets.

STORAGE CONDITION

Do not store above 30°C.
Protect from light.
Keep out of reach of children.
Jauhi daripada kanak-kanak.

SHELF-LIFE: Please refer to the outer box label.

PRODUCT REGISTRATION HOLDER:

GOODSCIENCE SDN BHD
No. 7, Jalan KPK 4/3, Kawasan Perindustrian Kundang,
Kundang Jaya, 48020 Rawang,
Selangor, Malaysia.

NAME & ADDRESS OF MANUFACTURERS

Packed and released by:
GOODSCIENCE SDN BHD
No. 7, Jalan KPK 4/3, Kawasan Perindustrian Kundang,
Kundang Jaya, 48020 Rawang,
Selangor, Malaysia.

Manufactured by:

SPS SRIPRASIT

SRIPRASIT PHARMA CO., LTD.
216 Moo 6, Suanluang, Krathum Baen,
Samut Sakhon 74110, Thailand.

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