Approved Professional Information for Medicines for Human Use:
WARFARIN 1/3/5 mg AUSTELL

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

WARFARIN 1 mg AUSTELL 1 mg tablets.

WARFARIN 3 mg AUSTELL 3 mg tablets.

WARFARIN 5 mg AUSTELL 5 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each WARFARIN 1 mg AUSTELL 1 mg tablet contains 1 mg warfarin sodium.

Each WARFARIN 3 mg AUSTELL 3 mg tablet contains 3 mg warfarin sodium.

Each WARFARIN 5 mg AUSTELL 5 mg tablet contains 5 mg warfarin sodium.

Contains sugar.

WARFARIN 1 mg AUSTELL 1 mg contains lactose monohydrate 142,700 mg/tablet and sucrose 8,00 mg/tablet.

WARFARIN 3 mg AUSTELL 3 mg contains lactose monohydrate 141,00 mg/tablet and sucrose 8,00 mg/tablet.

WARFARIN 5 mg AUSTELL 5 mg contains lactose monohydrate 139,00 mg/tablet and sucrose 8,00 mg/tablet.

Contains less than 1 mmol sodium per dose.

Each WARFARIN 1 mg AUSTELL 1 mg tablet contains 0,07 mg (0,003 mmol) sodium.

Each WARFARIN 3 mg AUSTELL 3 mg tablet contains 0,21 mg (0,009 mmol) sodium.

Each WARFARIN 5 mg AUSTELL 5 mg tablet contains 0,35 mg (0,015 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

WARFARIN 1 mg AUSTELL 1 mg:

Brown coloured, circular, flat faced bevelled edged uncoated tablets with ‘1’ embossing on one side and plain the other.

WARFARIN 3 mg AUSTELL 3 mg:

Blue coloured, circular, flat faced bevelled edged uncoated tablets with ‘3’ embossing on one side and plain on the other.

WARFARIN 5 mg AUSTELL 5 mg:

Pink coloured, round, flat faced bevelled edged uncoated tablets with breakline on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention and management of deep vein thrombosis and pulmonary embolism.

Prevention of thromboembolism in:

- Atrial fibrillation
- Prosthetic heart valves
- Post myocardial infarction

Treatment of transient ischaemic attacks.

4.2 Posology and method of administration

Posology

The administration and dosage of WARFARIN 1/3/5 mg AUSTELL must be individualised for each patient according to the patient's sensitivity as indicated by the prothrombin time (PT) or international normalised ratio (INR).

PT measurements should be carried out before treatment, on the 2nd and 3rd days of treatment and then on alternate days until the maintenance dose is established. Thereafter the patient should be monitored monthly.

Satisfactory levels of PT or INR for maintenance, vary with condition treated and the risk of thromboembolism.

INR 2,0 – 2,5 (PT ratio 1,3 - 1,5)

Prophylaxis of deep vein thrombosis (DVT), including surgery in high-risk patients.

INR 2,0 – 3,0 (PT ratio 1,3 - 1,6)

Prophylaxis of deep vein thrombosis (DVT) in:

- hip surgery
- fractured femur operations.

Prevention of thromboembolism in:

- atrial fibrillation
- mitral stenosis with embolism
- myocardial infarction
- tissue prosthetic heart valves.

Treatment of DVT, pulmonary and systemic embolism, and transient ischaemic attacks.

INR 3,0 – 4,5 (PT ratio 1,6 – 2,0)

Pulmonary embolism.

Recurrent DVT.

Arterial disease including myocardial infarction.

Mechanical prosthetic heart valves.

The correlation between the INR and the PT ratio is based on thromboplastin with an International Sensitivity Index of 2,3.

Initial doses are usually within the range of 10 - 15 mg daily for 3 days. Maintenance doses range from 2,5 – 10 mg daily.

Paediatric population

WARFARIN 1/3/5 mg AUSTELL is contraindicated in children under 18 years as safety has not been established (see section 4.3). No data are available.

Method of administration

Oral.

Doses should be given at the same time each day.

WARFARIN 1/3/5 mg AUSTELL can be taken before or after a meal.

Patients must be advised that certain foods and food supplements may affect therapy with WARFARIN 1/3/5 mg AUSTELL (see section 4.5).

4.3 Contraindications

- Hypersensitivity to warfarin, other coumarins or to any of the excipients listed in section 6.1
- Bleeding disorders, including haemophilia or leukaemia
- Peptic ulceration or other bleeding gastrointestinal disease
- Bleeding from respiratory or genitourinary tract
- Large open wounds, including surgical wounds, or surgery involving large exposed raw surfaces
- Infective endocarditis, pericarditis or pericardial effusion
- Impaired liver- or renal function
- Hypertension
- Cerebrovascular bleeding, cerebral or aortic aneurysm
- Recent or contemplated neuro- or ophthalmic surgery
- Polyarthritis
- Vitamin C deficiency
- Major regional block anaesthesia
- Inadequate laboratory facilities or lack of patient cooperation
- Breastfeeding mothers
- Pregnancy (see section 4.6)
- Threatened abortion
- Within 48 hours postpartum
- Medicines where interactions may lead to a significantly increased risk of bleeding (see section 4.5)
- Children under 18 years, as safety has not been established.

4.4 Special warnings and precautions for use

Over anticoagulation

Most adverse events reported with WARFARIN 1/3/5 mg AUSTELL 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.

Individualised dosage, cessation and patient instructions

The dosage of WARFARIN 1/3/5 mg AUSTELL should be individualised for each patient and periodic INR monitoring should be done (see section 4.2). The abrupt cessation of WARFARIN 1/3/5 mg AUSTELL is not recommended. The dose should be tapered over three to four weeks.

Patients should carry an anticoagulant card or other proof that they are on anticoagulants and be given a patient-held information booklet and informed of symptoms for which they should seek medical attention.

Patients should be given detailed instructions regarding the use of WARFARIN 1/3/5 mg AUSTELL, the importance of compliance and advised on the modification of their lifestyle if necessary. The possibility of interactions occurring should be explained.

Commencement of therapy

Monitoring

When WARFARIN 1/3/5 mg AUSTELL is started using a standard dosing regimen the INR should be determined daily or on alternate days in the early days of treatment. Once the INR has stabilised in the target range the INR can be determined at longer intervals.

INR should be monitored more frequently in patients at an increased risk of over coagulation e.g., patients with severe hypertension, liver or renal disease.

Patients for whom adherence may be difficult should be monitored more frequently.

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 1/3/5 mg AUSTELL should be given with caution to patients where there is a risk of serious haemorrhage (e.g., those with haemorrhagic blood disorders, peptic ulcer disease, severe wounds (including surgical wounds), cerebrovascular disorders, 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 medicines (see section 4.5). All patients treated with WARFARIN 1/3/5 mg AUSTELL 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 doctors any 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 medicines should be used with caution due to an increased risk of bleeding.

Haemorrhage

Haemorrhage can indicate an overdose of WARFARIN 1/3/5 mg AUSTELL has been taken. For advice on treatment of haemorrhage see section 4.9.

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 1/3/5 mg AUSTELL 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 1/3/5 mg AUSTELL treatment should be stopped for 14 days.

Calciphylaxis

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin as in WARFARIN 1/3/5 mg AUSTELL 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 1/3/5 mg AUSTELL.

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 1/3/5 mg AUSTELL 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 1/3/5 mg AUSTELL 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 1/3/5 mg AUSTELL need not be stopped before routine dental surgery, e.g., tooth extraction. The management of patients who undergo dental and surgical procedures requires close liaison between doctors, surgeons and dentists. The dose of WARFARIN 1/3/5 mg AUSTELL tablets may need to be adjusted.

Active peptic ulceration

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

Interactions

Many medicines and foods interact with WARFARIN 1/3/5 mg AUSTELL and affect the prothrombin time (see section 4.5). Any change to medication, including self-medication with OTC products and complementary medicines, 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 1/3/5 mg AUSTELL metabolism depends on thyroid status. Therefore, patients with hyper- or hypothyroidism should be closely monitored on starting warfarin therapy.

Additional circumstances where changes in dose may be required

The following also may exaggerate the effect of WARFARIN 1/3/5 mg AUSTELL, and necessitate a reduction of dosage:

- Loss of weight
- Acute illness
- Cessation of smoking.

Other warnings

The following may increase INR:

- diarrhoea
- elevated temperature
- hepatic disorders
- carcinoma
- collagen disease
- congestive heart failure
- infectious hepatitis
- jaundice
- poor nutritional state.

The following may decrease INR:

- hypothyroidism

- diabetes mellitus
- hyperlipidaemia
- oedema
- hereditary resistance to warfarin therapy. Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of WARFARIN 1/3/5 mg AUSTELL are required to achieve the desired anticoagulant effect.

WARFARIN 1/3/5 mg AUSTELL tablets should be used with caution in patients with:

- elderly age
- vitamin K deficiency
- hyperthyroidism
- prolonged dietary deficiencies
- infectious diseases or disturbances of intestinal flora
- candidiasis
- antibiotic therapy
- polycythaemia vera
- vasculitis
- severe diabetes
- allergic or anaphylactic disorders.

Laboratory tests

Heparins and danaparoid may prolong the prothrombin time, therefore a sufficient time interval should be allowed after administration before performing the test.

Genetic information

Genetic variability particularly in relation to CYP2C9 and VKORC1 can significantly affect dose requirements for WARFARIN 1/3/5 mg AUSTELL. If a family association with these polymorphisms is known extra care is warranted.

Excipient: lactose

This medicine contains lactose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Excipient: sucrose

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

Sodium

Contains less than 1 mmol sodium per dose.

Each WARFARIN 1/3/5 mg AUSTELL 1 mg tablet contains 0,07 mg (0,003 mmol) sodium.

Each WARFARIN 1/3/5 mg AUSTELL 3 mg tablet contains 0,21 mg (0,009 mmol) sodium.

Each WARFARIN 1/3/5 mg AUSTELL 5 mg tablet contains 0,35 mg (0,015 mmol) sodium.

Paediatric population

Safety in children younger than 18 years has not been established (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

Warfarin as in WARFARIN 1/3/5 mg AUSTELL 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 1/3/5 mg AUSTELL 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.

Various medicines interact with WARFARIN 1/3/5 mg AUSTELL, increasing or diminishing the anticoagulant response with different mechanisms involved. Some interacting medicines do so by more than one mechanism, resulting in unpredictable effects.

Mechanisms of interaction include:

- Displacement of warfarin from plasma protein (albumin) binding sites.
- Increased or decreased metabolism of WARFARIN 1/3/5 mg AUSTELL by inhibition or induction of hepatic microsomal enzymes.
- Interference with absorption or metabolism of either WARFARIN 1/3/5 mg AUSTELL or vitamin K.
- Additional anticoagulant effects by medicines that inhibit platelet function.

Pharmacodynamic interactions

Medicines which are contraindicated

Concomitant use of medicines used in the treatment or prophylaxis of thrombosis, or other medicines with adverse effects on haemostasis may increase the pharmacological effect of WARFARIN 1/3/5 mg AUSTELL, increasing the risk of bleeding.

Fibrinolytic medicines such as streptokinase and alteplase are contraindicated in patients receiving WARFARIN 1/3/5 mg AUSTELL.

Medicines which should be avoided if possible

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

- Clopidogrel
- NSAIDs (including aspirin and COX-2 specific NSAIDS)
- Sulfinpyrazone
- Thrombin inhibitors such as bivalirudin, dabigatran
- Dipyridamole
- Unfractionated heparins and heparin derivatives, low molecular weight heparins
- Fondaparinux, rivaroxaban
- Glycoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab
- Prostacyclin
- SSRI and SNRI antidepressants
- Other medicines 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 is increased. WARFARIN 1/3/5 mg AUSTELL may initially be given with a heparin in the initial treatment of thrombosis, until the INR is in the correct range.

Metabolic interactions

WARFARIN 1/3/5 mg AUSTELL 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.

Medicines 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 medicines are co-administered, WARFARIN 1/3/5 mg AUSTELL dosage may need to be reduced and the level of monitoring increased.

Conversely, medicines which induce these metabolic pathways may decrease WARFARIN 1/3/5 mg AUSTELL plasma concentrations and INR, potentially leading to reduced efficacy. When these medicines are co-administered, WARFARIN 1/3/5 mg AUSTELL dosage may need to be increased and the level of monitoring increased.

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

Care should 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 medicines which are known to interact with WARFARIN 1/3/5 mg AUSTELL in a clinically significant way

Examples of medicines which potentiate the effect of WARFARIN 1/3/5 mg AUSTELL:

allopurinol, capecitabine, erlotinib, disulfiram, azole antifungals (ketoconazole, fluconazole, miconazole etc), omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone,

tamoxifen, methylphenidate, zafirlukast, fibrates, statins (not pravastatin; predominantly associated with fluvastatin), erythromycin, sulfamethoxazole, metronidazole, triclofos, chloral hydrate, danazol, diazoxide, aminoglycosides, chloramphenicol, quinidine, dextropropoxyphene, vitamin E, glucagon, anabolic steroids, sulfonamides, sulfonylurea-type antidiabetic medicines, cimetidine, clofibrate, phenylbutazone and other pyrazolones, thyroid hormones.

Examples of medicines which antagonise the effect of WARFARIN 1/3/5 mg AUSTELL:
Barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives, rifampicin, azathioprine, phenytoin, glutethimide and vitamin K which is a specific antagonist.

Examples of medicines with variable effect:
Corticosteroids, nevirapine, ritonavir

Other medicine interactions
Broad spectrum antibiotics may potentiate the effect of WARFARIN 1/3/5 mg AUSTELL by reducing the gut flora which produce vitamin K. Similarly, orlistat may reduce absorption of vitamin K. Cholestyramine 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 medicines

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 as in WARFARIN 1/3/5 mg AUSTELL.

Many other herbal medicines have a theoretical effect on WARFARIN 1/3/5 mg AUSTELL; however, most of these interactions are not proven. Patients should generally avoid taking any herbal medicines or food supplements whilst taking WARFARIN 1/3/5 mg AUSTELL and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

Alcohol

Acute ingestion of a large amount of alcohol may inhibit the metabolism of WARFARIN 1/3/5 mg AUSTELL and increase INR. Conversely, chronic heavy alcohol intake may induce the metabolism of WARFARIN 1/3/5 mg AUSTELL. Moderate alcohol intake can be permitted.

Interactions with food and food supplements

Individual case reports suggest a possible interaction between WARFARIN 1/3/5 mg AUSTELL 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 1/3/5 mg AUSTELL and regular cranberry juice.

Limited evidence suggests that grapefruit juice may cause a modest rise in INR in some patients taking WARFARIN 1/3/5 mg AUSTELL.

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.

There are limited data on possible medicine interactions with glucosamine but increments in the INR parameter have been reported with 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.

Many other food supplements have a theoretical effect on WARFARIN 1/3/5 mg AUSTELL; however, most of these interactions are not proven. Patients should generally avoid taking any food supplements whilst taking WARFARIN 1/3/5 mg AUSTELL and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age who are taking WARFARIN 1/3/5 mg AUSTELL tablets should use effective contraception during treatment. The need for modification of therapy in women contemplating pregnancy should be discussed.

Pregnancy

WARFARIN 1/3/5 mg AUSTELL is contraindicated in pregnancy and 48 hours postpartum as it is a recognised teratogen (see section 4.3).

When warfarin as in WARFARIN 1/3/5 mg AUSTELL is given in the first trimester of pregnancy it can cause the foetal warfarin syndrome. CNS or warfarin embryopathy abnormalities may develop following use in any trimester but appear most likely after use in the second trimester. Spontaneous abortion and stillbirth have been reported.

Lactation

WARFARIN 1/3/5 mg AUSTELL is contraindicated during breastfeeding in lactation as it is a recognised teratogen (see section 4.3).

Warfarin as in WARFARIN 1/3/5 mg AUSTELL is distributed into milk only in its active form; studies in infants who are breast-fed while their mothers were taking warfarin did not find any effect on prothrombin time, however, breast-fed infants (especially neonates) are very sensitive to oral anticoagulants because of the low concentrations of vitamin K in breast milk.

4.7 Effects on ability to drive and use machines

WARFARIN 1/3/5 mg AUSTELL has no influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The major risk of WARFARIN 1/3/5 mg AUSTELL therapy is of haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia.

b. Tabulated summary of adverse reactions

The frequencies of adverse reactions reported with warfarin as in WARFARIN 1/3/5 mg AUSTELL are summarised in Table below by system organ class (in MedDRA) and by frequency.

System Organ Class	**Adverse reaction**	**Frequency**
Infections and infestations	Fever	Not known
Immune system disorders	Hypersensitivity	Not known
Metabolism and nutrition disorders	Inhibits vitamin K synthesis, lipid emboli, including systemic atheroemboli and cholesterol emboli	Less frequent
Nervous system disorders	Cerebral haemorrhage, Cerebral subdural haematoma	Not known
Vascular disorders	Haemorrhage	Not known
Respiratory, thoracic and mediastinal disorders	Haemothorax, epistaxis	Not known

Gastrointestinal disorders	Bloated stomach or gas, loss of appetite, stomach cramps or pain	Less frequent
	Gastrointestinal haemorrhage, rectal haemorrhage, haematemesis, pancreatitis, diarrhoea, nausea, vomiting, melaena	Not known
Hepatobiliary disorders	Hepatotoxicity, usually asymptomatic and seen on laboratory results, dark urine and jaundice. Hepatic injury resolved on withdrawal of warfarin	Less frequent
	Jaundice, hepatic dysfunction	Not known

Skin and subcutaneous tissues disorders	Rash, alopecia, purpura, 'purple toes' syndrome, erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis, calciphylaxis	Not known
Musculoskeletal and connective tissue disorders	Increased risk of osteoporotic fracture due to vitamin K deficiency. Patients on long-term warfarin treatment may be at increased risk	Less frequent
Renal and urinary disorders	Renal damage with resultant oedema and proteinuria, with difficulty in urination	Less frequent
	Haematuria	Not known
Investigations	Unexplained drop in haematocrit, decreased haemoglobin	Not known

Description of selected adverse reactions

Skin and subcutaneous tissues disorders

Purple toe syndrome - a reversible, sometimes painful, bluish discolouration (due to cholesterol embolization) of the toes may occur. Warfarin appears to precipitate the syndrome of venous

limb gangrene, spreading rapidly and requiring disfiguring debridement or occasionally amputation. Sores, ulcers or white spots in the mouth or throat.

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 to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

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; 1 g/kg for children).

In cases of life-threatening haemorrhage

Stop WARFARIN 1/3/5 mg AUSTELL 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 K_1) 10 – 20 mg for adults (250 micrograms/kg for a child).

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

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

For patients on long-term WARFARIN 1/3/5 mg AUSTELL therapy without major haemorrhage

- Excessive haemorrhage may occur in the event of an excessively long PT or INR or if there is minor bleeding, omission of one or more doses of warfarin may be sufficient to return levels to the therapeutic range.
- INR >8,0; no bleeding or minor bleeding—stop warfarin and give phytomenadione (vitamin K_1) 0,5 – 1 mg for adults, 0,015 – 0,030 mg/kg (15 – 30 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 haemorrhage.

Measure the INR (prothrombin time) at presentation and sequentially every 24 – 48 hours after ingestion depending on the initial dose and initial INR.

- If the INR remains normal for 24 – 48 hours and there is no evidence of bleeding, there should be no further monitoring necessary.
- Give vitamin K_1 (phytomenadione) if:
  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 K_1 is 10 – 20 mg orally (250 micrograms/kg body weight for a child). Delay oral vitamin K_1 at least 4 hours after any activated charcoal has been given. Repeat INR at 24 hours and consider further vitamin K_1.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.8.2 Anticoagulants.

Pharmacotherapeutic group: Antithrombotic agents, Vitamin K antagonists.

ATC code: B01AA03

Mechanism of action

Warfarin is a member of the coumarin-type anticoagulants. It acts in the liver, where it inhibits the synthesis of vitamin K dependent coagulation factors. The resultant *in vivo* effects include the sequential depression of Factors Vll, IX, X and II and the anticoagulant factors protein C and S.

5.2 Pharmacokinetic properties

Absorption

Warfarin is well absorbed orally. Maximum plasma concentrations are reached within 2 – 8 hours. Nearly complete bioavailability is obtained with oral administration. The half-life ranges between 20 and 60 hours with a mean of 40 hours. The rate of absorption may be reduced by food in the gastrointestinal tract. The duration of action of warfarin sodium is 2 to 5 days.

Distribution

Plasma protein binding is high (approximately 99 % binds to albumin). The volume of distribution of warfarin is approximately 0,14 L/kg. Active warfarin is not found in breastmilk.

Biotransformation

Warfarin is metabolised in the liver and kidneys. Warfarin sodium is administered as a racemic mixture of S- and R-warfarin. In the liver, both isomers are metabolised where the S-isomer is metabolised more rapidly than the R-isomer, mainly by the cytochrome P450 isoenzyme CYP2C9.

Elimination

Inactive metabolites are excreted in the urine and stool following reabsorption from the bile.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Magnesium stearate

Maize starch

Pregelatinised starch

Purified water

Sucrose.

Colourants

WARFARIN 1 mg AUSTELL 1 mg: Colour pigment blend brown

WARFARIN 3 mg AUSTELL 3 mg: Indigo carmine aluminium lake (E132)

WARFARIN 5 mg AUSTELL 5 mg: Erythrosine aluminium lake (E127).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

PVDC coated PVC/Aluminium blister packs: 36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light. Keep in original packaging until required for use.

6.5 Nature and contents of container

WARFARIN 1/3/5 mg AUSTELL tablets are packed in white opaque PVDC coated PVC/Aluminium blister strips of 2 x 10, 3 x 10 or 10 x 10 which are further packed in printed cartons in pack sizes of 20, 30 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

WARFARIN 1 mg AUSTELL: 49/8.2/1054

WARFARIN 3 mg AUSTELL: 49/8.2/1055

WARFARIN 5 mg AUSTELL: 49/8.2/1056

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 October 2022

10. DATE OF REVISION OF THE TEXT