SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Warfarin 5 Biotech, 5 mg, tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg warfarin sodium.

Warfarin 5 Biotech contains sugar (lactose: 139 mg/ tablet, sucrose: 8 mg/tablet).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Warfarin 5 Biotech is indicated for:

- the prevention and management of deep vein thrombosis.
- the prevention and management of pulmonary embolism.
- the prevention of thromboembolism in:
  - atrial fibrillation.
  - prosthetic heart valves.

- post myocardial infarction.
- the treatment of transient ischaemic attacks.

4.2 Posology and method of administration

Posology

The administration and dosage of Warfarin 5 Biotech must be individualised for each patient according to the patient's sensitivity as indicated by the international normalised ratio (INR).

INR 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 INR for maintenance, vary with the condition treated and the risk of thromboembolism.

<u>INR 2,0 – 2,5 (PT ratio 1,3 – 1,5)</u>

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

<u>INR 2,0 – 3,0 (PT ratio 1,3 – 1,5)</u>

Prophylaxis of DVT in hip surgery and fractured femur operations.

Prevention of thromboembolism in myocardial infarction, mitral stenosis with embolism, atrial fibrillation, tissue prosthetic heart valves.

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

<u>INR 3,0 – 4,5 (PT ratio 1,5 – 2,0)</u>

Recurrent DVT and pulmonary embolism. Arterial disease including myocardial infarction. Prosthetic heart valves. The correlation between the INR and the PT ratio is based on thromboplastin with an International sensitivity index of 2,3.

Treatment should be commenced with a 5 mg dose once daily. The dose should be titrated according to INR results, to the desired INR, according to the condition. Maintenance doses usually range from 2,5 to 10 mg

daily.

Doses should be given at the same time each day.

Method of administration

For oral administration.

4.3 Contraindications

- Known hypersensitivity to warfarin or to any of the excipients listed in section 6.1;
- Haemorrhagic states;
- Haemorrhagic stroke (see section 4.4);
- Clinically significant bleeding;
- Within 72 hours of major surgery with risk of severe bleeding (see section 4.4);
- Peptic ulceration or other gastrointestinal disorders involving bleeding;
- Conditions involving bleeding from respiratory or genito-urinary tract;
- Severe wounds (including surgical);
- Prosthetic heart valves;
- Infective endocarditis;
- Impaired liver function;
- Impaired kidney function;
- Hypertension;
- Cerebrovascular haemorrhage;
- Aneurysm (cerebral or aortic);
- Pericarditis, pericardial effusion;
- Neuro- or ophthalmic surgery - recent or contemplated;
- Surgery involving large exposed raw surfaces;
- Within 48 hours postpartum;
- Polyarthritis;

- Vitamin C deficiency;
- Major regional block anaesthesia;
- Inadequate laboratory facilities or lack of patient co-operation;
- Threatened abortion;
- Safety in children younger than 18 years has not been established;
- Medicines where interactions may lead to a significantly increased risk of bleeding (see section 4.5);
- Fibrinolytic medicines (see section 4.5);
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

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.

Patient monitoring

Dosage should be individualised for each patient and periodic determinations of prothrombin time should be done (see section 4.2).

Patients should be given a patient information leaflet and informed of symptoms for which they should seek medical attention.

Patients should be given detailed instructions concerning their medicine, the importance of compliance and advice concerning modification of their lifestyle if necessary. The possibility of interactions-should be explained.

Patients should carry an anticoagulant card or other proof that they are on anticoagulants.

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

Commencement of therapy

When therapy with Warfarin 5 Biotech 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 (see section 4.2).

Thrombophilia

Patients with protein C deficiency are at risk of developing skin necrosis when starting Warfarin 5 Biotech treatment. In patients with protein C deficiency, therapy should be introduced without a loading dose of Warfarin 5 Biotech even if heparin is given. Patients with protein S deficiency may also be at risk and it is advisable to introduce Warfarin 5 Biotech therapy slowly in these circumstances.

Cessation of therapy

Abrupt cessation of anticoagulant therapy is not recommended. The dose should be tapered over three to four weeks.

Haemorrhage

The most frequently reported adverse effect of all oral anticoagulants is haemorrhage. Warfarin 5 Biotech 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) (see section 4.3)

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 5 Biotech 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 medical practitioners' signs and symptoms of bleeding.

Checking the INR and reducing or omitting doses depending on INR level is essential. 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.

Unexpected bleeding at therapeutic levels should always be investigated and INR monitored (see section 4.3).

Special populations

Special care is required in the elderly, in patients with Vitamin K deficiency and in patients with hyperthyroidism. The rate of warfarin metabolism depends on thyroid status. Therefore, patients with hyper- or hypothyroidism should be closely monitored on starting treatment with Warfarin 5 Biotech.

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.

Warfarin 5 Biotech should be used with caution in patients with:

- Prolonged dietary deficiency;
- Infectious diseases or disturbances of intestinal flora, sprue, antibiotic therapy;
- Polycythaemia vera, vasculitis, severe diabetes, allergic or anaphylactic disorders.

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 5 Biotech is beneficial, but the risk of early recurrent embolism is low and therefore a break in treatment after ischaemic stroke is justified. Warfarin 5 Biotech treatment should be re-started 2 to 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.

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, 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 5 Biotech.

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 5 Biotech 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 5 Biotech cannot be stopped 3 days beforehand, anticoagulation should be reversed with low-dose vitamin K.

The timing for re-instating Warfarin 5 Biotech therapy depends on the risk of post-operative haemorrhage. In most instances Warfarin 5 Biotech treatment can be re-started as soon as the patient has an oral intake.

The need for modification of therapy before elective operative procedures or in women contemplating pregnancy should be discussed.

Dental Surgery

The management of patients who undergo dental or any surgical procedures requires close liaison between doctors, surgeons and dentists. An adjustment of dosage may be necessary or Warfarin 5 Biotech 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 not be treated with Warfarin 5 Biotech (see section 4.3).

Interactions

Non-steroidal anti-inflammatory medicine should not be used with Warfarin 5 Biotech.

Many medicines and foods interact with warfarin and affect the prothrombin time (see section 4.5). 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.

Additional circumstances where changes in dose may be required

The following also may exaggerate the effect of Warfarin 5 Biotech, and necessitate a reduction of dosage:

- Loss of weight
- Acute illness
- Cessation of smoking

The following may reduce the effect of Warfarin 5 Biotech, and require the dosage to be increased:

- Weight gain
- Diarrhoea
- Vomiting

Inherited warfarin resistance

Acquired or inherited warfarin resistance should be suspected if larger than usual daily doses of Warfarin 5 Biotech are required to achieve the desired anticoagulant effect.

Genetic variability

Genetic variability particularly in relation to CYP2C9 and VKORC1 can significantly affect dose requirements for Warfarin 5 Biotech. If a family association with these polymorphisms is known extra care is warranted.

Effects on the blood

In clinical studies the risk of intracranial bleeding is higher in the elderly. Although cumulative risk of bleeding was related to duration of anticoagulation therapy, risk may be highest early in treatment.
Withdrawal of Warfarin 5 Biotech therapy may lead to rebound hypercoagulability, Warfarin 5 Biotech should therefore be withdrawn gradually, although there is no clinical evidence to support this.

Effects on the musculoskeletal system

Vitamin K is involved in bone metabolism and vitamin K deficiency is associated with an increased risk of osteoporotic fractures. Patients on long-term treatment with oral anticoagulants such as Warfarin 5 Biotech that are vitamin K antagonists may be at increased risk of osteoporosis and fractures. Special care is required.

Effects on the reproductive system

There have been reports of priapism in patients taking Warfarin 5 Biotech. As with warfarin-induced skin necrosis, priapism appears to be associated with protein C-deficiency, and the two conditions frequently occur together.

Dermatological effects

Skin and soft-tissue necrosis is a less frequent but well-established side effect of Warfarin 5 Biotech. It is characterised by a localised, painful skin lesion, initially erythematous or haemorrhagic in appearance but which becomes bullous and eventually culminates in gangrenous necrosis. Fatalities have occurred. Areas of increased subcutaneous fat such as breast, thigh, and buttock have most often been involved. The aetiology is unknown. Patients with protein C-deficiency appear to be at highest risk.

Effect on eye

Intra-ocular haemorrhage leading to loss of vision can occur in patients with neovascular (wet) age-related macular degeneration receiving Warfarin 5 Biotech. Caution is advised in such patients.

Warfarin 5 Biotech contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take Warfarin 5 Biotech.

Warfarin 5 Biotech contains sucrose

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take Warfarin 5 Biotech.

4.5 Interaction with other medicines and other forms of interaction

A wide variety of interactions may occur, increasing or diminishing the anticoagulant response with different mechanisms involved. Not all interactions have been identified and some interacting medicines do so by more than one mechanism therefore the nett effect may be unpredictable.

Warfarin 5 Biotech 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.

Mechanisms of interaction include:

- Displacement from albumin binding sites;
- Altering metabolism of medicines by inhibition or induction of hepatic microsomal enzymes;
- Interference with absorption or metabolism of Warfarin 5 Biotech or vitamin K;

- Additional anticoagulant effects by medicines that inhibit platelet function.

Pharmacodynamic interactions

Medicines that 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 5 Biotech, increasing the risk of bleeding.

Fibrinolytic medicines such as streptokinase and alteplase are contraindicated in patients receiving Warfarin 5 Biotech (see section 4.3).

Medicines which should be avoided if possible

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

- Clopidogrel.
- Non-steroidal anti-inflammatory drugs (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.
- Selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) antidepressants.
- Other medicines which inhibit haemostasis, clotting or platelet action.

Dipyridamole and aspirin can cause bleeding when given to patients taking anticoagulants, but without any

alteration in INR.

Low-dose aspirin with Warfarin 5 Biotech may the risk of gastrointestinal bleeding. Warfarin 5 Biotech may initially be given in conjunction 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.

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, the Warfarin 5 Biotech dosage may need to be reduced and the level of monitoring increased.

Conversely, medicines which induce these metabolic pathways may decrease warfarin plasma concentrations and INR, potentially leading to reduced efficacy. When these medicines are co-administered, Warfarin 5 Biotech 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 in a clinically significant way.

Medicines which potentiate the effect of warfarin

allopurinol, capecitabine, erlotinib, disulfiram, azole antifungals (ketoconazole, fluconazole, miconazole) omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate zafirlukast, fibrates, statins (not pravastatin; predominantly associated with fluvastatin)

erythromycin, telithromycin, co-trimoxazole, metronidazole, chloramphenicol, cimetidine, clofibrate, danazol, glucagon, quinidine, dextropropoxyphene, vitamin E, thyroid hormones, diazoxide,

aminoglycosides**,** alcohol**,** triclofos, chloral hydrate, sulphonamides, sulphonylurea-type antidiabetic medicines, phenylbutazone and other pyrazolones, anabolic steroids, sulphinpyrazone, aspirin and other NSAIDS, and amiodarone.

Medicines which antagonise the effect of warfarin

Barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives, rifampicin, azathioprine, phenytoin, phytomenadione, glutethimide, vitamin K, glucocorticoids and cholestyramine.

Medicines with variable effect

Corticosteroids, nevirapine, ritonavir

The following factors may be responsible for an increase in prothrombin time

Carcinoma, collagen disease, congestive heart failure, diarrhoea, elevated temperature, hepatic disorders, infectious hepatitis, jaundice and a poor nutritional state.

The following factors may be responsible for a decrease in prothrombin time

Diabetes mellitus, oedema, hereditary resistance to Warfarin 5 Biotech therapy, hyperlipaemia and hypothyroidism.

Other interactions

Broad spectrum antibiotics may potentiate the effect of Warfarin 5 Biotech 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 5 Biotech.

Increased INR has been reported in patients taking glucosamine and Warfarin 5 Biotech. 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 5 Biotech, 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 5 Biotech; however, most of these interactions are not proven. Patients should generally avoid taking any herbal medicines or food supplements whilst taking Warfarin 5 Biotech and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

Alcohol

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

Interactions with food and food supplements

A possible interaction between Warfarin 5 Biotech and cranberry juice may occur and, 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 5 Biotech and regular cranberry juice.

Grapefruit juice may cause a modest rise in INR in some patients taking Warfarin 5 Biotech.

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 5 Biotech; however, most of these interactions are not proven. Patients should generally avoid taking any food supplements whilst taking Warfarin 5 Biotech and should be told to advise their doctor if they are taking any, as more frequent monitoring is advisable.

Laboratory tests

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing age who are taking Warfarin 5 Biotech should use effective contraception during treatment and for at least 1 month after the final dose of Warfarin 5 Biotech.

Pregnancy

Warfarin is a recognised teratogen.

Treatment with Warfarin 5 Biotech during pregnancy should be avoided (see section 4.3).

Breastfeeding

Treatment with Warfarin 5 Biotech during breastfeeding should be avoided (see section 4.3).

4.7 Effects on ability to drive and use machines

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that Warfarin 5 Biotech does not adversely affect their ability to do so safely (see section 4.8).

4.8 Undesirable effects

MedDRA System organ class	**Frequency**	**Undesirable effect**
Infections and infestations	frequency not known	Fever
Blood and lymphatic system disorders	less frequent	Leukopenia, granulocytosis
Immune system disorders	frequency not	Hypersensitivity

	known	
Metabolism and nutrition disorders	less frequent	Inhibits vitamin K synthesis, lipid emboli, including systemic athero-emboli and cholesterol emboli
Nervous system disorders	frequency not known	Cerebral haemorrhage; Cerebral subdural haematoma
Vascular disorders	frequency not known	Haemorrhage with consequent effects of haematomas and anaemia
Respiratory, thoracic and mediastinal disorders	frequency not known	Haemothorax, epistaxis
Gastrointestinal disorders	less frequent	Diarrhoea; nausea; vomiting; bloated stomach or gas; loss of appetite; stomach cramps or pain; melaena
	frequency not known	Gastrointestinal haemorrhage, rectal haemorrhage, haematemesis; pancreatitis
Hepato-biliary disorders	frequency not known	Jaundice; hepatic dysfunction; hepatotoxicity, usually asymptomatic and seen on laboratory results, dark urine
Skin and subcutaneous tissue disorders	frequency not known	Rash; alopecia; purpura; 'purple toes' syndrome; erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis, calciphylaxis, precipitating venous limb gangrene syndrome, sores, ulcers or white spots in the mouth or throat
Musculoskeletal and connective tissue disorders	less frequent	Increased risk of osteoporotic fracture due to vitamin K deficiency. Patients on long-term Warfarin 5 Biotech treatment may be at increased risk
Renal and urinary disorders	less frequent	Haematuria, renal damage with resultant oedema and proteinuria, with difficulty in urination

Investigations	frequency not known	Unexplained drop in haematocrit; haemoglobin decreased

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

Excessive bleeding may occur.

Treatment

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 treatment, give prothrombin complex concentrate (factors II, VII, IX, and X) 30 to 50 units/kg or (if no concentrate available) fresh frozen plasma 15 mL/kg.

Non-life-threatening haemorrhage

Where anticoagulation can be suspended, give slow intravenous injection of phytomenadione (vitamin K_1) 10 to 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 to 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 K_1) 0,5 to 1 mg for adults, 0,015–0,030 mg/kg (15 to 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 to 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 to 8,0, no bleeding or minor bleeding - stop warfarin, restart when INR reaches appropriate target levels.
- INR <6,0 but more than 0,5 units above target value - reduce dose or stop warfarin, restart when INR reaches appropriate target levels.

For patients NOT on long-term anticoagulants without major haemorrhage

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

- If the INR remains normal for 24 to 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 to 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

A 8.2 Anticoagulants.

Pharmacotherapeutic group: Antithrombotic agents, Vitamin K antagonists

ATC code: B01AA03

Mechanism of action

Warfarin is a coumarin-type anticoagulant and acts by depressing synthesis of Vitamin-K dependent coagulation factors in the liver. The resultant *in vivo* effect is a sequential depression of Factors VII, IX, X and II.

5.2 Pharmacokinetic properties

Absorption

Warfarin is readily absorbed from the gastro-intestinal tract. After oral administration, absorption is essentially complete and maximal plasma concentrations are reached in 2 to 8 hours. Approximately 99 % is bound to albumin in the plasma.

Distribution

The half-life ranges from 20 to 60 hours with a mean of 40 hours.

The duration of action is 2 to 5 days.

Food in the gastrointestinal tract can decrease the rate of absorption.

Biotransformation

Warfarin is transformed to inactive metabolites by the liver and kidneys.

Elimination

It is excreted in the urine and stool.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Sucrose

Maize starch

Purified water

Pregelatinised starch

Magnesium stearate

Erythrosin aluminium lake (E127)

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original packing.

6.5 Nature and contents of container

Warfarin 5 Biotech are packed in Opaque blisters. Each blister contains 14 tablets, which are placed in an outer carton containing 2 blisters.

6.6 Special precautions for disposal and other handling

No special requirements for disposal

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Ground Floor Block K West

Central Park, 400 16th Road

Randjespark, Halfway House

Midrand, 1685

South Africa

8. REGISTRATION NUMBER(S)

56/8.2/0658

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

September 2023

10. DATE OF REVISION OF THE TEXT

September 2023