Brand Name : **FARIN-5 TABLETS** **Generic Name** : Warfarin Tablets BP 5 mg		2020
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing Information (Summary of Products Characteristics)

1. NAME OF DRUG PRODUCT

1. Name of drug product

Warfarin Tablets BP 5 mg

1.1 (Trade) name of product

FARIN-5 TABLETS

1.2 Strength

Each uncoated tablet contains:
Warfarin Sodium BP 5 mg

1.3 Pharmaceutical Dosage Form

Uncoated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS

2.1 Qualitative Declaration

Each uncoated tablet contains:
Warfarin Sodium BP 5 mg

2.2 Quantitative Declaration

Ingredients	Specification	Label Claim	Overages	Qty. / Tab.	Use
ACTIVE					
Warfarin Sodium Clathrate BP Equivalent to Warfarin Sodium 5 mg	BP	5.00 mg	-	5.400 mg	Active
NON ACTIVE					
Lactose		-	-	100.00 mg	Diluent
Micro Crystalline Cellulose		-	-	30.00 mg	Diluent
Powder Pre Gelatinized Starch		-	-	17.72 mg	Diluent
Methyl Paraben Sodium		-	-	0.100 mg	Preservative
Propyl Paraben Sodium		-	-	0.050 mg	Preservative
Maize Starch		-	-	15.00 mg	Diluent
Talcum		-	-	3.00 mg	Lubricant
Magnesium Stearate		-	-	1.00 mg	Lubricant
Sodium Starch glycolate		-	-	3.00 mg	Disintegrating agent
Sodium Lauryl Sulphate		-	-	1.00 mg	Disintegrating agent
Colloidal Silicon Dioxide		-	-	2.00 mg	Glident
Cross Carmellose Sodium		-	-	3.00 mg	Lubricant
Polyplasdone XL-10 (Cross Povidone)		-	-	2.00 mg	Disintegrating agent

BP 2019 = British Pharmacopoeia 2019.
USNF 37 = United States National Formulary 37.
USP 42 = United States Pharmacopoeia 42.

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3. PHARMACEUTICAL DOSAGE FORM

Uncoated tablets

White, circular, flat, uncoated tablets having breakline on one side and other side is plain of each tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For prophylaxis against venous thrombosis and pulmonary embolism, and for use in the treatment of these conditions to prevent their extension. For the prophylaxis of systemic embolisation in patients with rheumatic heart disease and atrial fibrillation.

4.2 Posology and Method of Administration

Posology

An initial daily dose of 10mg on the first two days. Subsequent daily doses should be adjusted according to the results of the prothrombin time or other appropriate coagulation tests. The single daily maintenance requirement is usually between 5mg and 12mg, but can vary between 2mg and 30mg.

The maintenance dose is omitted if the prothrombin time is excessively prolonged.

Use in elderly patients: The elderly are generally more sensitive to the effects of warfarin and often require a smaller dose on a weight for weight basis than younger patients

Method of administration : Oral

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Haemorrhagic stroke (see section 4.4 for further details)
- Clinically significant bleeding
- Within 72 hours of major surgery with risk of severe bleeding

- Within 48 hours postpartum
- Pregnancy
- Drugs where interactions may lead to a significantly increased risk of bleeding.

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.

Patients should be given a patient-held information booklet ('warfarin card') and informed of symptoms for which they should seek medical attention.

Commencement of therapy

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 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 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 section 4.5). 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. 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 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.

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.

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 postoperative 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, eg, 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 recognise 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 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.

Thyroid disorders

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

Additional circumstances where changes in dose may be required

The following also may exaggerate the effect of warfarin tablets, and necessitate a reduction of dosage:

- Loss of weight
- Acute illness
- Cessation of smoking

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

- Weight gain
- Diarrhoea
- Vomiting

Other warnings

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

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.

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

This product also contains tartrazine lake (E102) and amaranth lake (E123) Contains tartrazine lake (E102) and amaranth lake (E123). May cause allergic reactions.

4.5 Interaction with Other Drugs, Other Forms of 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.

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4.6 Use in Pregnancy and Lactation

Pregnancy:

Based on human experience warfarin causes congenital malformations and foetal death when administered during pregnancy.

Warfarin is contraindicated in pregnancy in the first and third trimester.

Women of child-bearing age who are taking Warfarin Tablets should use effective contraception during treatment.

Breast-feeding:

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

4.7 Effects on ability to drive and operate machine

Warfarin has no influence on the ability to drive and use machines.

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention: very common (>1/10); common (>1/100 to <1/10); uncommon (>1/1,000 to <1/100); rare (>1/10,000 to <1/1,000); very rare (<1/10,000) and not known -cannot be estimated from the available data.

4.9 Overdoses

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) 30-50 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 (eg, 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 therapy without major haemorrhage

- INR > 8 0, no bleeding or minor bleeding—stop warfarin, and give

phytomenadione (vitamin K_1) 05-1 mg for adults, 0015-0 030 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 eg, 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 reestablishment 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:

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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.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmaco-Kinetic Properties

Absorption

Warfarin Sodium is readily absorbed from the gastro-intestinal tract; it can also be absorbed through the skin.

Distribution

It is extensively bound to plasma proteins and its plasma half-life is about 37 hours. It crosses the placenta but does not occur in significant quantities in breast milk. Warfarin is administered as a racemic mixture.

Biotransformation

The s-isomer is reported to be more potent; the R and S isomers are both metabolised in the liver, though at different rates; the stereo-isomers may also be affected differently by other drugs.

Elimination

The inactive metabolites are excreted in the urine following reabsorption from the bile.

5.2 Pharmaco-dynamic properties

Pharmacotherapeutic group: Antithrombotic agents, Vitamin K antagonists ATC code: B01AA03 Mechanism of action

Warfarin is a coumarin anticoagulant which depresses the hepatic vitamin K-dependent synthesis of coagulation factors II (Prothrombin), VII, IX and X. It acts indirectly, with no effect on existing clots.

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6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose	BP	100.00 mg
Micro Crystalline Cellulose Powder	BP	30.00 mg
Pre Gelatinized Starch	BP	17.72 mg
Methyl Paraben Sodium	BP	0.100 mg
Propyl Paraben Sodium	BP	0.050 mg
Maize Starch	BP	15.00 mg
Talcum	BP	3.00 mg
Magnesium Stearate	BP	1.00 mg
Sodium Starch glycolate	BP	3.00 mg
Sodium Lauryl Sulphate	BP	1.00 mg
Colloidal Silicon Dioxide	BP	2.00 mg
Cross Carmellose Sodium	BP	3.00 mg
Polyplasdone XL-10 (Cross Povidone)	BP	2.00 mg

6.2 Incompatibilities

None reported

6.3 Shelf-Life

36 months from the date of manufacture.

6.4 Special Precautions for Storage

Store under normal storage conditions (15°C to 30˚C).
Protect from light.

6.5 Nature and Contents of Container

Jar pack of 28 tablets

ANIL K. PANDEY
DIRECTOR

Date :
Director of the manufacturer
(Signature, Full name, Stamp)

AGOG PHARMA LTD. VASAI

ANIL K. PANDEY
DIRECTOR

Date :
Director of applicant company
(Signature, Full name, Stamp)

AGOG PHARMA LTD. VASAI