1. NAME OF THE MEDICINAL PRODUCT

ORFARIN TABLET 3MG
ORFARIN 5MG TABLET

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Warfarin sodium 3 mg/tablet
Warfarin sodium 5 mg/tablet
Excipients: Orfarin (3 mg) tablet contains lactose monohydrate equivalent to 85.1 mg lactose.
Orfarin (5 mg) tablet contains lactose monohydrate equivalent to 84.6 mg lactose.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ORFARIN TABLET 3MG: Light blue or light blue may be spotted, flat bevelled edged and scored uncoated tablets with a diameter of 7 mm and code ORN 17.
ORFARIN 5MG TABLET: Pink or pink may be spotted, , flat bevelled edged and scored uncoated tablets with a diameter of 7 mm and code ORN 18.

4. CLINICAL PARTICULARS

4.1. Indications

Treatment and prevention of deep venous thrombosis and pulmonary embolism.
Prevention of thromboembolic complications (stroke or systemic embolism) after myocardial infarct.
Prevention of thromboembolic complications(stroke or systemic embolism) in patients with atrial fibrillation, cardiac valvular disease or prosthetic heart valves.

4.2. Posology and method of administration

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 Special warnings and special precautions for use) or medication (see Interaction with other medicinal products and other forms of interaction) affecting the efficacy of anticoagulant therapy, the recommended initial dose is 5 mg of warfarin (*) 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 2.0 to 2.4 2.5 to 2.9 3.0 to 3.4 3.5 to 4.0 >4.0	10 (5*) 5 3 2.5 1.5 miss one day
4.-6.	<1.4 1.4 to 1.9 2.0 to 2.4 2.5 to 2.9 3.0 to 3.9 4.0 to 4.5 >4.5	10 7.5 5 4.5 3 miss one day, then 1.5 miss two days, then 1.5
7.-	 1.1 to 1.4 1.5 to 1.9 2.0 to 3.0 3.1 to 4.5 >4.5	Weekly warfarin dose increase weekly dose by 20% increase weekly dose by 10% maintain the dose decrease weekly dose by 10% 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.a. 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 pediatricians. 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 1.1 to 1.3 1.4 to 1.9 2.0 to 3.0 3.1 to 3.5 >3.5	Maintenance dose : Repeat initial dose 50% of the initial dose 50% of the initial dose 25% of the initial dose Hold until INR <3.5, then restart at 50% less than the previous dose
Maintenance, if the INR is 1.1 to 1.4 1.5 to 1.9 2.0 to 3.0 3.1 to 3.5 >3.5	Action : Increase weekly dose by 20% Increase weekly dose by 10% No change to the weekly dose Decrease weekly dose by 10% Hold until INR <3.5, then restart at 20% less then 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 Overdose).
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 K_1 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 (see 4.4 and 5.2).
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 (see 4.3 and 4.4).

4.3. Contraindications

- First trimester and last four weeks of pregnancy (see also section 4.6)
- Bleeding tendency (von Willebrand disease, hemophilia, thrombocytopenia, and platelet function disorders).
- Severe hepatic insufficiency and hepatic cirrhosis.
- Untreated or uncontrolled hypertension.
- Recent intracranial hemorrhage. Other conditions predisposing to intracranial haemorrhage, e.g. aneurysms of cerebral arteries
- Tendency to fall.
- Surgery of the central nervous system or the eye.
- Conditions predisposing to the gastrointestinal or urinary tract haemorrhage, e.g. previous gastrointestinal bleeding complications, diverticulosis, or malignancies.
- Infectious endocarditis (see also Special warnings and special precautions for use), pericarditis or pericardial effusion.
- Dementia, psychoses, alcoholism, and other situations where compliance may be not satisfactory and the anticoagulant treatment can not be administered safely.
- Hypersensitivity to warfarin or to any of the excipients.
- Co-administration with miconazole oral gel (see Interactions).

4.4. Special warnings and special precautions for use

If a rapid antithrombotic effect is needed, heparin therapy must be initiated. After this, heparin therapy is continued along with the initiated warfarin therapy for at least 5 to 7 days until the INR has been at the target level (See Posology and method of administration) for at least two days.
Interactions
There is a large risk for interactions when warfarin is used concomitantly with other drugs, herbal medications or food supplements. An intensified monitoring of the therapeutic response to warfarin is therefore recommended when treatment with other drugs is initiated or withdrawn during warfarin treatment.
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.
Co-administration with topical miconazole (see Interactions).
Genetic variations
Genetic variations depending upon CYP2C9 and VKORC1 alleles, are known to exist for the response and dosing requirements of warfarin, and may vary widely across individuals and ethnic groups. Dose adjustment may be required based on the genotype of the patient. Patients which are classified as poor CYP2C9 metabolisers generally needs lower initial and maintenance doses.
Resistance to warfarin is a very rare phenomenon. Only a case reports have been published on that. These patients need 5 to 20 fold warfarin doses to achieve therapeutic response. If the response of the patient to warfarin treatment is poor, other more plausible causes should be ruled out: patient incompliance, , interaction with food or other medicinal products and potential laboratory errors.
Coumarin necrosis
To avoid coumarin necrosis (See Undesirable effects), patients with a hereditary deficiency of antithrombotic protein C or S must first be treated with heparin. Concomitantly initiating warfarin loading doses must not exceed 5 mg. Heparin treatment must be continued for 5 to 7 days.
Elderly patients
Special caution must be exercised when treating elderly patients. The patient compliance and the abilities to follow strict rules on dosage must be ascertained. Hepatic metabolism of warfarin as well as the synthesis of clotting factors are slowed down in the elderly. This may easily result in an excessive warfarin effect. Treatment must be initiated cautiously (See Posology and method of administration).
Surgery
In surgical procedures, caution should be observed and the INR should be adjusted to a level suitable for the procedure
Nutrition
Drastic changes in dietary habits should be avoided as the amount of vitamin K in food may affect therapy with warfarin. Conditions which may affect therapy are transition to a vegetarian diet, extreme dieting, depression, vomiting, diarrhea, steatorrhea or malabsorption of other causes.
Bleeding
If bleeding occurs during warfarin treatment, regardless of the current INR level, local causes should be suspected. Bleeding from the gastrointestinal tract could be due to ulcer or tumor and bleeding from the urogenital tract could be caused by tumor or infection
Special conditions
Hyperthyroidism, fever and uncompensated cardiac insufficiency may enhance the warfarin effect. In hypothyroidism the warfarin effect may be reduced. In moderate hepatic insufficiency the effect of warfarin is enhanced. In renal insufficiency and nephrotic syndrome, the free fraction of warfarin in plasma may be elevated, which depending on the comorbidity of the patient may lead to either, enhance or reduce the warfarin effect). The clinical status of the patient and the INR values must be carefully monitored under these circumstances.
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
Excipients
The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicine contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5. Interactions with other medicinal products and other forms of interaction

Warfarin has a narrow therapeutic range and care is required with all concomitant therapy. The individual product information for any new concomitant therapy should be 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 coadministered, 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 coadministered, 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 the platelets and primary hemostasis (e.g. acetylsalicylic acid, clopidogrel, ticlopidine, dipyridamole, tirofiban, direct-acting oral anticoagulants like dabigatran and apixaban and most of the non-steroidal anti-inflammatory drugs) may result in a pharmacodynamic interaction and predispose the patient for severe bleeding complications.
Penicillins in large doses have the same effect on primary hemostasis.
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 K_2 produced by the intestinal bacteria. In these patients, many antibiotics may reduce the synthesis of vitamin K_2, leading to an enhanced 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. Heavy use of alcohol with concomitant hepatic failure potentiates the warfarin effect.
Quinine contained in Tonic-water may also potentiate the warfarin effect.
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.
The following drugs have been reported to potentiate or reduce the warfarin effect (the list is not exhaustive):
Increased effect:
All non-steroidal anti-inflammatory agents (NSAIDs) and anticoagulants
Analgesics: Dexstropropoxyphene, 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, doxicycline, 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))

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Antigout drugs: Allopurinol, sulfinpyrazone
Antineoplastic and immunomodulating agents: Cabecitabine, cyclophosphamide, etoposide, fluorouracil, flutamide, ifosfamide, leflunomide, mesna, methotrexate, sulofenur, tamoxifen, tegafur, EGFR inhibitors (e.g. gefitinib), monoclonal antibodies (e.g. trastuzumab)
Cardiovascular drugs: Digoxin, metolazone, propranolol
Gastrointestinal drugs: Cimetidine, proton-pump inhibitors (e.g. omeprazole)
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.
There are reports suggesting that noscapine as well as 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
Others: Aminoglutethimide, colestyramine, disopyramide, griseofulvin, mesalazine, nevirapine, trazodone, aprepitant, bosentan, vitamin C.
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.
Food supplements should be used with caution during the warfarin treatment.
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.

4.6. Pregnancy and lactation
Pregnancy
Warfarin crosses the placenta. Warfarin is contraindicated during the first trimester as teratogenic effects (fetal warfarin-syndrome and CNS-malformations) have been reported with use during early pregnancy. Fetal warfarin syndrome is characterized by nasal hypoplasia, stippling in the epiphyseal regions, limb hypoplasia, optic atrophy, microcephaly, mental and growth retardation, as well as cataract that could lead to total or partial blindness.
Use of warfarin is also contraindicated during the last four weeks of pregnancy as coumarin-derivatives have been associated with an increased risk of maternal and fetal bleeding, and fetal lethality especially during delivery. If possible, warfarin should be avoided during the whole period of pregnancy.
In special circumstances treatment may be considered by specialist clinician.
Breastfeeding
Warfarin is not excreted in the breast milk. Breast feeding can be continued during warfarin treatment.

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

4.8 Undesirable effects
Commonly reported (1-10%) undesirable effects of warfarin treatment are the bleeding complications. The over-all rate for bleeding is about 8% per year for total bleeding, consisting of minor bleedings (6% per year), severe bleedings (1 % per year) and fatal (0.25% per year). The most common risk factor for intracranial bleeding is untreated or uncontrolled hypertension. Likelihood of bleeding increases as the INR elevates significantly above the target range. If bleeding occurs when the INR is within the target range, there usually exists another comorbid condition which should be investigated. Other common undesirable effects are nausea, vomiting and diarrhoea.
Coumarin necrosis is a rare (<0.1%) complication of warfarin therapy. It manifests initially as swelling and darkening skin lesions usually in the lower extremities or buttocks, but may appear elsewhere as well. Later the lesions become necrotic. 90% of the patients are women. Lesions appear on the 3rd to 10th day of warfarin treatment and the aetiology involves a relative deficiency of antithrombotic proteins C and S. Hereditary deficiency of proteins C or S may predispose the patient to the complication. For this reason, the warfarin treatment in these patients must be initiated concomitantly with heparin and using small doses of warfarin. If the complication occurs, warfarin treatment must be discontinued and heparin treatment continued until the lesions have healed or become scarred.
Purple toe -syndrome is an even more rare complication of warfarin therapy. Patients, usually male and typically have arteriosclerotic disease. Warfarin is thought to cause hemorrhages to the atheromatous plaques leading to microembolization. Symmetrical purple skin lesions in toes and soles occur and the lesions are associated with burning pain. Warfarin treatment must be discontinued and the skin lesions usually slowly disappear.
Other rare adverse events reported during warfarin treatment are vasculitis, tracheal calcification, reversible hepatic enzyme elevation, cholestatic hepatitis, reversible alopecia, rash, priapism and allergic reactions (manifested usually as skin rash).
Skin and subcutaneous tissue disorders: Frequency 'not known': Calciphylaxis.

4.9 Overdose
Toxicity data are contradictory. A potentially toxic dose for children is 0.5 mg/kg. The lowest reported lethal dose for adults is 6-15 mg/kg.
Symptoms: All symptoms are due to disturbance of coagulation. Symptoms of bleeding from almost any organ are possible. Sometimes the only finding is pathological laboratory data. In some cases symptoms are minor bleedings such as mucous membrane bleeding, haematuria. Pronounced poisoning may lead to e.g., haemoptysis, haematemesis, melaena, petechiae, ecchymoses, intracranial haemorrhage, haemorrhagic shock.
Treatment: If justified gastric lavage and charcoal may be used. INR is monitored repeatedly for several days. Based on coagulation tests and clinical symptoms, 10 mg vitamin K is given intravenously 1-4 times/day (half the dose for children under 12 years). In the event of severe poisoning, higher doses of vitamin K are given, and, in the event of severe bleeding, supplementation with clotting factors in the form of plasma (preferably freshly frozen) or clotting factor concentrate (prothrombin complex concentrate), and possibly tranexamic acid. Always discuss cases with local haematologist or poison center if in doubt. Only clotting factors (and not vitamin K) are given to patients receiving anticoagulant therapy and where a complete reversal is not desirable.
The half-life for warfarin is 20-55 hours. Overdoses thus require prolonged observation and treatment with vitamin K.

5. PHARMACOLOCIGAL PROPERTIES

5.1. Pharmacodynamics
Pharmacotherapeutic group: Vitamin K antagonist. ATC-code B01AA03.
Orfarin contains warfarin sodium, which is a synthetic coumarin anticoagulant. Orfarin is a readily soluble salt and differs from other preparations in this group because it can be given orally and parenterally.
Warfarin induces an anticoagulative effect by competitively blocking (vitamin K epoxide reductase and vitamin K reductase) the reduction of vitamin K and its 2,3 epoxide to vitamin KH_2. Vitamin KH_2 is required in order for some vitamin K-dependent coagulation proteins (prothrombin factor VII, IX and X) to be able to be carboxylated with gamma glutamic acid and thus become coagulatively active.
The naturally occurring vitamin K-dependent coagulation inhibitors protein C and its cofactor protein S are also affected to a corresponding degree. By inhibiting the conversion of vitamin K, treatment with Orfarin results in the liver producing and excreting partially carboxylated and decarboxylated coagulation protein. The half-life for the clotting factors varies from 4-7 hours for factor VII to 50 hours for factor II. This means that the system first achieves a new equilibrium after several days. Effective prevention of thrombosis is generally achieved after five days of treatment and the therapeutic effect subsides over 4-5 days after the end of treatment. The anticoagulative effect of Orfarin can be counterbalanced with a lower dose of vitamin K, while higher doses can lead to warfarin resistance that can last more than one week. The effect of Orfarin can be affected by pharmacodynamic factors as well as pharmacokinetic factors such as absorption and metabolic clearance, i.e. the same dose can have different effects on different people, with a few appearing resistant and possibly requiring 5-10 times the normal dose, and a not insignificant proportion of patients needing only very low doses.

5.2. Pharmacokinetics
Orfarin is a racemic mixture of (S)-warfarin and (R)-warfarin. S-warfarin is 2-5 times more potent than the R form in terms of anticoagulative effect. Warfarin's kinetics is not dose-dependent.
Absorption
Warfarin is absorbed quickly and completely.
Distribution
Warfarin's distribution volume is relatively small, with an apparent distribution volume of 0.14 l/kg. Warfarin has high protein binding, with a binding rate of 98-99%.
Elimination
Warfarin is almost completely eliminated via metabolism to inactive metabolites. (R)-warfarin is metabolised by, among other things, CYP1A2, CYP3A4 and carbonyl reductase, while (S)-warfarin is metabolised almost completely via the polymorphic enzyme CYP2C9. The polymorphism of CYP2C9, which causes considerable interindividual differences in the ability to metabolise S-warfarin, means that the same dose can result in large variations in achieved concentrations of S-warfarin. The half-life for R-warfarin varies between 37 and 89 hours, while for S-warfarin it varies between 21 and 43 hours. Studies of radioactively-labelled warfarin have shown that up to 90% of an oral dose is found in urine, mainly in the form of metabolites. After the conclusion of warfarin therapy, the prothrombin level normalises after approx. 4-5 days.
Special patient groups
The elderly: Limited data indicates that warfarin's pharmacokinetics are not age-dependent (see 4.2)
Impaired renal function: Renal clearance does not appear to affect the anticoagulative effect of warfarin. The initial dose does not therefore need to be adjusted in patients with impaired renal function (see 4.4).
Impaired hepatic function: Impaired hepatic function can enhance the effect of warfarin through inhibited synthesis of clotting factors and reduced metabolism of warfarin (see 4.2 and 4.3)

5.3 Preclinical safety data
Not applicable.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients
Orfarin 3 mg and Orfarin 5 mg tablets:
Lactose monohydrate
Maize starch
Gelatin
Magnesium stearate
Indigocarmine (E 132) (3 mg tablets)
Erythrosine (E 127) (5 mg tablets).

6.2 Incompatibilities
Not applicable.

6.3. Shelf life
24 months

6.4. Special precautions for storage
Orfarin 3 mg Tablet: Store below 30 ºC.
Orfarin 5 mg Tablet: Store below 25 ºC.
Store in the original package with a desiccant capsule. Keep the jar tightly closed and in the outer carton in order to protect from light and moisture.
Keep out of reach of children.

6.5. Nature and contents of container
100 Tablets, polyethylene plastic jar.

7. Manufactured by
Orion Corporation
Espoo, Finland

Date of revision: 19 July 2022

ORION PHARMA