SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Warfarin Orion 2.5 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 2.5 mg warfarin sodium.

Excipient with known effect: 1 tablet contains 51.4 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

White to off-white, round biconvex uncoated tablet, 7 mm in diameter and with a cross-line on both sides.

The tablet can be divided into two equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment and prevention of deep venous thrombosis and pulmonary embolism
- Prevention of thromboembolic complications after a large transmural myocardial infarction
- Prevention of thromboembolic complications in some patients with atrial fibrillation or prosthetic heart valves

4.2 Posology and method of administration

Posology
Warfarin Orion is absorbed rapidly and completely. The same dose can therefore be administered orally, parenterally or intravenously.

Initial dose: Day 1 and 2: 3(2–4) Warfarin Orion 2.5 mg tablets (7.5 mg (5–10 mg)), depending on patient's weight, age and overall health, etc. Day 3: Preliminary maintenance dose, based on the effect of the initial dose on the coagulative activity (International Normalized Ratio, INR value) on day 3.

For patients with no need for a rapid treatment effect, e.g. when there is concomitant treatment with heparin or low-molecular-weight heparin, it is possible to initiate with the estimated maintenance dose and to first check the INR value on days 3–4. This helps to avoid possible hypercoagulation, which can appear during the adjustment phase because of an imbalance between pro- and anticoagulation factors.

Maintenance dose: The maintenance dose is normally 1–4 tablets (2.5–10 mg) daily, but individual differences are large (dose can vary from less than ½ a tablet to 10 tablets in some patients).

The entire daily dose should be taken at one time and at the same time every day. Dosage boxes (pill organizers) may be useful. Effective prevention of thrombosis is generally only achieved after 5 days of treatment, provided the INR value has reached the recommended therapeutic level.

Managing anticoagulation treatment
Sensitivity to Warfarin Orion varies from person to person and even within the same patient. Therefore the treatment intensity should be checked on a regular basis. This is done by measuring prothrombin complex (PC) levels in blood samples, and the value is expressed as the International Normalized Ratio (INR), with a normal value of 1.0. Sensitivity to Warfarin Orion increases with age and lower body weight. Some patients may have increased sensitivity because of acquired causes such as pronounced heart failure or impaired hepatic function (see sections 4.3 and 5.2) or concomitant drug treatments (see section 4.5).

INR values are checked every day to every other day during the first week, and subsequently once or twice a week until the patient is on the maintenance dose. Once a stable level is achieved, the interval between checks can often be extended to 4–6 weeks or sometimes longer periods.

Therapeutic levels of INR
For patients with venous thrombosis, pulmonary embolism, atrial fibrillation, secondary prophylaxis after myocardial infarction in combination with acetylsalicylic acid, and for patients with a later model of a prosthetic mechanical aortic valve, the recommended target value is INR 2.5 (± 0.5).

For patients with a prosthetic mechanical mitral valve or a double prosthetic valve, patients with failures at normal treatment intensity, and after myocardial infarction, a higher intensity, equivalent to a target value of INR 3.0 (± 0.5), may be recommended.
It should be pointed out that the above therapeutic areas are only general outlines and should be modified depending on the condition being treated, the degree of relative contraindications, local treatment guidelines, and the patient's ability to cooperate.

Combination with heparin
In acute cases, it is recommended that Warfarin Orion be combined with heparin or low-molecular-weight heparin to ensure a rapid anticoagulation effect. INR should be therapeutic for at least 2 days before discontinuation of heparin, unfractionated or low-molecular-weight heparin.

A Warfarin Orion tag to wear can be requested from Orion Pharma.

Paediatric population
Data from controlled clinical trials are very limited. The initial dose is 0.1–0.2 mg/kg per day for children with normal hepatic function, which is then adjusted based on INR values. The maintenance dose is dependent on age and reduces with increasing age from < 1 year to 11–18 years.

Treatment with Warfarin Orion is not recommended for newborns on account of the risk of simultaneous vitamin K deficiency. There is no definitive therapeutic INR range for younger children. In practice, therapeutic values for adults have been used, with a target value of INR 2.5 (± 0.5). Treatment of children, and especially small children, requires specialist knowledge.

Elderly
Elderly patients require lower doses than younger adults. The initial dose should be 2 (1–3) Warfarin Orion 2.5 mg tablets (5 mg (2.5–7.5 mg)), which is then adjusted based on INR values. 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 Orion (see sections 4.4 and 5.2).

Impaired hepatic function: Patients with impaired hepatic function may need lower dose of Warfarin Orion. Impaired hepatic function can enhance the effect of warfarin through inhibited synthesis of clotting factors and reduced metabolism of warfarin (see sections 4.3 and 4.4).

Patients with genetically abnormal enzyme types
Substantially deviating INR response may be due to genetic factors, particularly genetic reduction of the activity of the enzyme CYP2C9 and increased susceptibility of VKOR (the pharmacological target of warfarin) to the inhibition of warfarin.

Patients with the alleles CYP2C9*2 or CYP2C9*3 in the enzyme CYP2C9 have reduced metabolism of (S)-warfarin and may therefore require lower initial and maintenance doses (see sections 4.4, 4.8, 5.1 and 5.2). A meta-analysis showed that the average daily dose of warfarin was 20% lower in patients with a CYP2C9*2 allele and 34% lower in those with a CYP2C9*3 allele. Patients with two of these genes (homozygotes) needed a dose reduction of 36% and 78%, respectively. It can also take longer to reach steady state for warfarin and its therapeutic effect.
Also genetic differences in the gene *VKORC1* that encodes the vitamin K epoxide reductase enzyme, the target of warfarin, have been shown to influence the dose requirement by increasing the sensibility to warfarin. In studies, a factor of approximately two has been reported for the difference between the highest and lowest average dose for different haplotype groups. Caucasians are relatively evenly distributed between the groups, while Asians mostly have genes that require a reduced dose. Genotyping may be considered when treating particularly sensitive patients for whom it is particularly important to avoid an excessive anticoagulative effect.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- First trimester and last four weeks of pregnancy (see also section 4.6)

Warfarin is contraindicated in patients with an increased risk of bleeding:
- Bleeding tendency (von Willebrand disease, hemophilias, thrombocytopenia, and platelet function disorders)
- Severe hepatic insufficiency and hepatic cirrhosis
- Untreated or uncontrolled hypertension
- Recent intracranial bleeding. Conditions predisposing to intracranial bleeding, e.g. aneurysms of cerebral arteries
- Tendency to frequent falls due to neurological or other health-related conditions
- Surgery of the central nervous system or the eye
- Conditions predisposing to the gastrointestinal or urinary tract bleeding, e.g. previous gastrointestinal bleeding complications, diverticulitis, or malignancies
- Infectious endocarditis (see also section 4.4) or pericardial effusion
- Dementia, psychoses, alcoholism, and other situations where the compliance may not be satisfactory and the anticoagulant treatment cannot be administered safely
- Concomitant administration with St. John's wort (*Hypericum perforatum*)
- Other oral anticoagulant therapy, except during changes of anticoagulant therapy, such as switching to or from non-vitamin K oral anticoagulant therapy (see section 4.5).

4.4 Special warnings and precautions for use

If a rapid antithrombotic effect is needed, heparin treatment must be initiated first. After this, heparin treatment is continued along with the initiated warfarin treatment for at least 5 to 7 days until the INR has been at target level (see section 4.2) for at least two days.

<u>Interactions</u>
There is a large risk for interactions when warfarin is used concomitantly with other drugs. An intensified monitoring of the therapeutic response to warfarin is therefore recommended when treatment with other drugs is initiated or withdrawn during warfarin treatment (see section 4.5).

Genetic variations
Elimination of warfarin is slower in patients with certain mutations in the gene for the enzyme CYP2C9 metabolising (S)-warfarin. These patients only require a low maintenance dose and have a risk of excessive bleeding if a high initial dose is given. In addition, it will take longer to achieve the new efficacy level after adjusting the dose. Also patients with genetic variations of the enzyme VKOR may require lower doses due to increased sensitivity to warfarin (see sections 4.2, 5.1 and 5.2).

Resistance
Resistance to warfarin is a very rare phenomenon. Only 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 other medicaments or food, and also laboratory errors.

Coumarin necrosis
To avoid coumarin necrosis (see section 4.8) 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 as described above.

Elderly patients
Special caution must be exercised when treating elderly patients. The patient compliance and the capabilities of following strict rules on dosage must be ascertained. Hepatic metabolism of warfarin, as well as the synthesis of clotting factors, is slowed down in the elderly. This may easily result in an excessive warfarin effect. Treatment must be initiated cautiously (see section 4.2).

Surgery
Tooth extractions can usually be carried out at INR 2–2.2. In other 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
Hyperthyreosis, fever and uncompensated cardiac insufficiency may enhance the warfarin effect. In hypothyreosis 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 is elevated, which depending on the comorbidity of the patient may lead to either enhanced or reduced warfarin effect. The clinical situation of the patient and the INR values must be carefully monitored under all these circumstances.

Due to local or regional treatment recommendations and different bioanalytical methods, there may be variations in therapeutic INR.

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

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 (see section 2). Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol (23 mg) sodium per tablet, that is to say essentially ”sodium-free”.

4.5 Interaction 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 co-administered, warfarin dosage may need to be reduced and the level of monitoring increased.

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

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

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

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

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

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

Medications affecting platelet aggregation (e.g. acetylsalicylic acid, clopidogrel, ticlopidine, dipyridamole, tirofiban, and most of the non-steroidal anti-inflammatory drugs) may result in a pharmacodynamic interaction and predispose the patient for severe bleeding complications. Penicillins in large doses could have the same effect on primary hemostasis. Other oral anticoagulant medications such as direct acting oral anticoagulants should not be used concomitantly with warfarin except under specific circumstances such as switching of anticoagulant therapy (see section 4.3).

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. Heavy use of alcohol with concomitant hepatic failure potentiates the warfarin effect. Quinine contained in Tonic-water may also potentiate the warfarin effect.

Protease inhibitors (e.g. ritonavir, lopinavir) may alter warfarin plasma concentrations. Frequent INR monitoring is recommended when concomitant treatment is initiated.

SNRIs (e.g. venlafaxine, duloxetine) and SSRIs (e.g. fluoxetine, sertraline) antidepressants may increase the risk of bleeding in concomitant use with warfarin.

Cranberry juice and other cranberry products may potentiate the effect of warfarin and therefore concomitant use should be avoided.

If the patient needs temporary relief of pain while on warfarin, the recommended medications are paracetamol or opioids.

Warfarin may potentiate the effect of oral sulphonylurea antidiabetics.

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

Increased effect:

All non-steroidal anti-inflammatory agents (NSAIDs) and anticoagulants

Analgesics: 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))

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), trastuzumab

Cardiovascular drugs: Digoxin, metolazone, propranolol

Gastrointestinal drugs: Cimetidine, proton-pump inhibitors (e.g. omeprazole). The clinical relevance of the interaction with proton-pump inhibitors is not clear.

Lipid regulating drugs: Bezafibrate, clofibrate, fenofibrate, fluvastatin, gemfibrozil, lovastatin, simvastatin

Vitamins: Vitamin A, vitamin E

Others: Carboxyuridine, chloral hydrate, codeine, disulfiram, ethacrynic acid, fluvoxamine, influenza vaccine, interferon alpha and beta, phenytoin, proguanil, quinine, (anabolic and androgenic) steroid hormones, thyroid hormones, troglitazone, valproic acid, zafirlukast

There are reports suggesting that noscapine as well as glucosamine with or without chondroitin sulphate may increase the INR in patients on warfarin

Increased INR has been reported in patients taking glucosamine and oral vitamin K antagonists. Patients treated with oral vitamin K antagonists should therefore be closely monitored at the time of initiation or termination of glucosamine therapy.

Decreased effect:

Antibacterials: Cloxacillin, dicloxacillin, flucloxacilline, nafcillin, rifampicin

Antiepileptics: Carbamazepine, phenobarbital, primidone

Antineoplastic and immunomodulating agents: Azathioprine, ciclosporin, mercaptopurine, mitotane

Anxiolytic sedatives, hypnotics, and antipsychotics: Barbiturates, chlordiazepoxide

Diuretics: Chlortalidone, spironolactone

Vitamins: Vitamin C

Others: Aminoglutethimide, colestyramine, disopyramide, griseofulvin, mesalazine, nevirapine, trazodone, aprepitant, fosaprepitant, bosentan

Herbal medications can either potentiate the warfarin effect, e.g. ginkgo (*Ginkgo biloba*), garlic (*Allium sativum*), dong quai (*Angelica sinensis*, contains coumarins), papaya (*Carica papaya*) or danshen (*Salvia miltiorrhiza*, decreases the warfarin elimination), or reduce it, e.g. ginseng (*Panax spp*.). The effect of warfarin can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum*). This is due to induction of drug metabolizing enzymes by St. John's wort. Herbal preparations containing St. John's wort should therefore not be combined with warfarin. The inducing effect may persist for as long as 2 weeks after cessation of treatment with St. John's wort. If a patient is already taking St. John's wort, check the INR and stop St. John's wort. Monitor INR closely as this may rise on stopping St. John's wort. The dose of warfarin may need adjusting.

Ingestion of vitamin K containing foodstuffs during warfarin treatment should be as steady as possible. The most abundant vitamin K sources are green vegetables and leaves, such as: amaranth leaf, avocado, broccoli, brussels sprout, cabbage, canola oil, chayote leaf, chives, coriander, cucumber skin (but not cucumber without skin), endives, kale leaf, kiwifruit, lettuce leaf, mint leaf, mustard greens, olive oil, parsley, peas, pistachio nuts, purple seaweed laver, spinach leaf, spring onion, soybeans, soybean oil, tea leaves (but not tea), turnip greens, or watercress.

Smoking may increase warfarin clearance, and smokers may require slightly higher doses than nonsmokers. 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 Fertility, 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.

Breast-feeding
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 Orion has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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)
Not known (cannot be estimated from the available data)

	Common	Rare	Very rare	Not known
Vascular disorders	Bleeding	Coumarin necrosis, purple toe -syndrome	Vasculitis	
Respiratory, thoracic and mediastinal disorders			Tracheal calcification	
Gastrointestinal disorders	Nausea, vomiting, diarrhoea			
Hepatobiliary disorders			Reversible hepatic enzyme elevation, cholestatic hepatitis	
Skin and subcutaneous tissue disorders			Reversible alopecia, rash	Calciphylaxis
Renal and urinary disorders				Anticoagulant-related nephropathy (see section 4.4)

	Common	Rare	Very rare	Not known
Reproductive system and breast disorders			Priapism	
General disorders and administration site conditions			Allergic reactions (manifested usually as skin rash)	
Investigations			Cholesterol embolism	

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.

Coumarin necrosis 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 these proteins may predispose to the complication. For this reason, the warfarin treatment in these patients must be initiated concomitantly with heparin and using small initial doses of warfarin. If the complication occurs, warfarin treatment must be discontinued and heparin treatment must be continued until the lesions heal or become scarred.

Purple toe syndrome is an even more rare complication of warfarin treatment. Patients are usually male and typically have an arteriosclerotic disease. Symmetric purple lesions of skin 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.

Persons with genetic variations of the polymorphic enzymes CYP2C9 and VKOR (see section 4.2, 4.4, 5.1 and 5.2) resulting in increased susceptibility for warfarin have an increased risk for excessive anticoagulative effect of warfarin treatment, which can increase the risk of bleeding complications. Haemoglobin levels and INR must be monitored carefully.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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. The table below suggests measures for treatment of overdose:

Clinical situation	**Dose adjustment/other treatment**
No bleeding, INR > 4	Wait 1 day. Adjust the dose.
No bleeding, INR > 6	Wait 1–2 days. Adjust the dose. New check quickly.
No bleeding, INR > 8	Consider vitamin K. 1–2 mg s.c., i.v. or orally. Wait 2 days. Check next day. Adjust the dose.
Minor bleeding	Wait with warfarin 1–2 days. Possibly vitamin K as per above.
Severe bleeding	Reduce INR quickly to 1.5–1.6. 10 ml/kg fresh frozen plasma is estimated to reduce INR from 7 to 4 or 4 to 2.2. One unit of coagulation factor concentrate is equivalent to 1 ml plasma. The effect is instantaneous, but diminishes after 6 hours. If the effect of warfarin can be suspended, 5–10 mg vitamin K (i.v.) is administered concomitantly with plasma/coagulation factor concentrate. A lower dose of vitamin K (2–5 mg) is given, if it is expected that treatment with warfarin will continue. It takes 6–12 hours until the vitamin K is effective, with peak effect after 24 hours.
Intoxication/ poisoning	If bleeding, see above. 10 mg vitamin K 3–4 times daily until the effect of warfarin is estimated to be eliminated. Treatment may be required for several days.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, Vitamin K antagonists
ATC-code: B01AA03.

Warfarin Orion contains warfarin sodium, which is a synthetic coumarin anticoagulant. Warfarin sodium 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 warfarin results in the liver producing and excreting partially carboxylated and decarboxylated coagulation protein.

Genetic differences in the gene for vitamin K epoxide reductase (*VKORC1*) have been shown to be relevant for the necessary dose of warfarin, see sections 4.2, 4.4, 4.8 and 5.2.

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 warfarin 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 warfarin 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 Pharmacokinetic properties

Warfarin Orion 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%.

Biotransformation
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. Patients with abnormal forms of CYP2C9 such as the alleles CYP2C9*2 and CYP2C9*3 metabolise (S)-warfarin less effectively and therefore have an increased risk for excessive anticoagulation and bleeding complications. For further information, see the section Special patient groups below.

Elimination
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 is not age-dependent (see section 4.2).

CYP2C9 genotype: (S)-warfarin is primarily eliminated by metabolism catalysed by the enzyme CYP2C9. CYP2C9 presents genetic polymorphism. The alleles *1, *2 and *3 are most common in the Caucasian population. The allele *1 provides ”normal” enzyme activity. The alleles *2 and *3 provide reduced enzyme activity and thus reduced clearance (and increased half-life) of warfarin. The most marked reduction of clearance is obtained in patients with two *3 alleles. Among Caucasians, this genotype is present in 0.5% of the population. Allele frequency and the significance of the genotype for the warfarin dose needed are presented below.

	Relative allele frequency per ethnicity		
	*1	*2	*3
Caucasians	74.3%	14.3%	10.9%
African Americans	95.3%	0.0%	0.8%
Japanese	98.4%	0.0%	1.6%

Genotype	Observed reduction in the dose level needed
*1/*1	0% (reference)
*1/*2	20%
*1/*3	34%
*2/*2	36%
*2/*3	57%
*3/*3	78%

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 section 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 sections 4.2 and 4.3).

5.3 Preclinical safety data

Animal studies have shown warfarin to be teratogenic. In other respects, available preclinical safety data do not reveal further relevant information for humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose
Maize starch
Calcium phosphate
Povidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE bottle, HDPE screw cap.
Pack size: 100 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBERS

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

2026-09-25