Public Assessment Report

Decentralised Procedure

Warfarin Sodium 1mg/1ml Oral Suspension

PL 00427/0156

UK/H/2151/01/DC

Rosemont Pharmaceuticals Limited
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Rosemont Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal product Warfarin Sodium 1mg/1ml Oral Suspension (product licence number: PL 00427/0156) on 11 November 2010. This medicine is available on prescription only.

Warfarin belongs to a group of medicines called anti-coagulants. It is used to thin your blood and prevent your blood from clotting.

The data submitted in support of this application for Warfarin Sodium 1mg/1ml Oral Suspension raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

### Information about Decentralised Procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Warfarin Sodium 1mg/1ml Oral Suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of application</td>
<td>Generic (Article 10.1)</td>
</tr>
<tr>
<td>Name of the active substance (INN)</td>
<td>Warfarin sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Vitamin K antagonists (B01AA03)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength</td>
<td>Oral solution, 1mg/ml</td>
</tr>
<tr>
<td>Reference number for the Decentralised Procedure</td>
<td>UK/H/2151/01/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Ireland</td>
</tr>
<tr>
<td>Start of Decentralised Procedure</td>
<td>29 July 2009</td>
</tr>
<tr>
<td>End date of Decentralised Procedure</td>
<td>14 October 2010</td>
</tr>
<tr>
<td>Marketing Authorisation number</td>
<td>PL 00427/0156</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Rosemont Pharmaceuticals Limited</td>
</tr>
<tr>
<td></td>
<td>Rosemont House</td>
</tr>
<tr>
<td></td>
<td>Yorkdale Industrial Park</td>
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<tr>
<td></td>
<td>Braithwaite Street</td>
</tr>
<tr>
<td></td>
<td>Leeds LS11 9XE</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Warfarin Sodium 1mg/1ml Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 1ml of suspension contains Warfarin Sodium 1mg.
Excipients:
Liquid Maltitol
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Oral Suspension
A white to off white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
• Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation.
• Prophylaxis after insertion of prosthetic heart valves.
• Prophylaxis of venous thrombosis and pulmonary embolism and for use in the treatment of these conditions to prevent their extension.

4.2 Posology and method of administration
For oral administration only.
A baseline coagulation screen and liver function tests should be performed before initiating warfarin therapy.
Adults: The typical induction dose is 10 mg daily for 2 days but this should be tailored to individual requirements.
The daily maintenance dose is usually 3 to 9 mg taken at the same time each day. The exact maintenance dose depends on the prothrombin time, usually reported as the INR (international normalised ratio), or other appropriate coagulation tests.
Control tests should be made at regular intervals and the maintenance dose should be adjusted according to the results obtained. Once the maintenance dose is established, it is rarely necessary to alter it (see Section 4.4 Commencement of Therapy).
In emergencies, anticoagulant therapy should be initiated with heparin and warfarin together.
Elderly: As for adults, but dosage may need to be lowered. The elderly are generally more sensitive to the effects of warfarin and often require a smaller dose.
Children:
Dosage for children has not been established. Warfarin 1mg/ml Oral Suspension is not recommended for use in children.

4.3 Contraindications
Known hypersensitivity to warfarin or to any of the ingredients contained in warfarin suspension.

Haemorrhagic stroke (see section 4.4 for further details)

Clinically significant bleeding

Use within 72 hours of surgery with risk of severe bleeding (for further information see section 4.4)

Use within 48 hours postpartum.

Warfarin is contraindicated in pregnancy.

Drugs where interactions lead to a significantly increased risk of bleeding (see section 4.5).

Anticoagulation is contraindicated in any physical condition in which the risk of haemorrhage might be greater than the potential clinical benefits of anticoagulation (see also section 4.4).

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
If this preparation replaces or is replaced by another warfarin product, the patient should be monitored closely in the period immediately following the change.

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.

For patients with any impairments that may influence their ability to take the correct dosage safely, the assistance of a carer to administer the dose may be required.

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. If the benefit of anticoagulation outweighs the risk, warfarin should be given with extreme caution to patients where there is a risk of haemorrhage (e.g. concomitant NSAID use, recent ischaemic stroke, bacterial endocarditis, previous gastrointestinal bleeding). See also 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 including congestive cardiac failure, risk of falling, anaemia, malignancy, trauma, renal insufficiency, impaired hepatic function, haemorrhagic blood dyscrasias, hypermetabolic states e.g. hyperthyroidism, or fever, acute illness, vitamin K deficiency state, diarrhoea concomitant drugs (see section 4.5).

Genetic factors: genetic polymorphisms in the cytochrome P450 CYP2C9 gene result in impaired metabolism of S-warfarin. Affected individuals have an increased sensitivity to warfarin, manifesting as low dose requirements and an increased risk of bleeding. The variant alleles occur at a higher frequency in white populations than in other ethnic groups studies.

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.

If haemorrhage occurs overdose should be suspected (see section 4.9).

Bleeding may occur at therapeutic INR values, in which case the possibility of an underlying condition that predisposes the haemorrhage should be investigated.

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.

**Surgery**
Minor surgical procedures with low risk of bleeding can be performed in general with an INR of <2.5. However the local recommendation should be considered.
For surgery, other surgical procedures, where there is a risk of severe bleeding, warfarin should be stopped 3-5 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 post-operative haemorrhage. In most instances warfarin treatment can be re-started as soon as the patient has an oral intake.

**Dental Surgery**
In most cases warfarin need not be stopped before routine dental surgery, e.g. tooth extraction.

**Active peptic ulceration**
Due to a high risk of bleeding, patients with history of 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.
The anticoagulant effect of warfarin may be increased or decreased by concomitant use of herbal medicines. One such example is the interaction between warfarin and St. John’s wort (see Section 4.5).

**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 suspension, and necessitate a reduction of dosage:
- Loss of weight
- Acute illness
• Cessation of smoking

The following may reduce the effect of warfarin suspension, 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.

Ingredients in the formulation
The product contains liquid maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

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.

Pharmacodynamic interactions
Drugs which are contraindicated
Concomitant use of drugs used in the treatment or prophylaxis of thrombosis, or other drugs with adverse effects on haemostasis may increase the pharmacological effect of warfarin, increasing the risk of bleeding.

Fibrinolytic drugs such as streptokinase and alteplase are contraindicated in patients receiving warfarin.

Drugs which should be avoided if possible
The following examples should be avoided, or administered with caution with increased clinical and laboratory monitoring:
• Clopidogrel
• NSAIDs (including aspirin and cox-2 specific NSAIDS)
• Sulfinpyrazone
• Thrombin inhibitors such as bivalirudin, dabigatran
• Dipyridamole
• Unfractionated heparins and heparin derivatives, low molecular weight heparins
• Fondaparinux, rivaroxaban
• Glycoprotein IIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abeiximab
• Prostacyclin
• SSRI and SNRI antidepressants
Other drugs which inhibit haemostasis, clotting or platelet. Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. Warfarin may initially be given 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.

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.

There is a small subset of drugs for which interactions are known; however their 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 drugs which are known to interact with warfarin in a clinically significant way.

<table>
<thead>
<tr>
<th>Examples of drugs which potentiate the effect of warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>allopurinol, capecitabine, erlotinib, disulfiram,azole antifungals (ketoconazole, fluconazole etc)</td>
</tr>
<tr>
<td>omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate, chloral hydrate, chloramphenicol, cimetidine, danazol, dextropropoxyphene, glibenclamide, phenylbutazone, quinidine, stanozolol, thyroxine, triclofos</td>
</tr>
<tr>
<td>zafirlukast, fibrates, statins (not pravastatin; predominantly associated with fluvastatin)</td>
</tr>
<tr>
<td>erythromycin, sulfamethoxazole, metronidazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examples of drugs which antagonise the effect of warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives, rifampicin, azathioprine, phenytoin, aminoglutethimide, phenazone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examples of drugs with variable effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids, nevirapine, ritonavir</td>
</tr>
</tbody>
</table>
Other drug interactions
Broad spectrum antibiotics may potentiate the effect of warfarin by reducing the gut flora which produce vitamin K. Similarly, orlistat may reduce absorption of vitamin K. Colestyramine and sucralfate potentially decrease absorption of warfarin.
Increased INR has been reported in patients taking glucosamine and warfarin. This combination is not recommended.

Interactions with herbal products
Herbal preparations containing St John's Wort (Hypericum perforatum) must not be used whilst taking warfarin due to a proven risk of decreased plasma concentrations and reduced clinical effects of warfarin. The enzyme-inducing effects of the herbal preparation St John’s wort (Hypericum perforatum) can increase the metabolism and decrease the anticoagulant effect of warfarin. These effects may persist for at least two weeks after withdrawal of St. John’s wort. Herbal preparations containing St John’s wort should not be used during treatment with warfarin. If a patient is already taking St. John’s wort, the herbal preparation should be withdrawn and the INR should be monitored closely, as a rise in the INR may necessitate a reduction in the dosage of warfarin.

Many other herbal products have a theoretical effect on warfarin; however most of these interactions are not proven. Patients should generally avoid taking any herbal medicines or food supplements whilst taking warfarin, 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
Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. Patients should be advised to avoid cranberry products. Increased supervision and INR monitoring should be considered for any patient taking warfarin and regular cranberry juice.

Limited evidence suggests that grapefruit juice may cause a modest rise in INR in some patients taking warfarin.

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; however most of these interactions are not proven. Patients should generally avoid...
taking any food supplements whilst taking warfarin, 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. Care is required with all concomitant therapy. Known interactions include the following, but, prescribers of other or newly available medicines should refer to the manufacturer’s information or the appropriate monograph.

4.6 **Pregnancy and lactation**

*Pregnancy*
Based on human experience warfarin causes congenital malformations and foetal death when administered during pregnancy.
Warfarin is contraindicated in pregnancy.
Women of child-bearing age who are taking warfarin suspension should use effective contraception during treatment.

*Lactation*
Warfarin is excreted in breast milk in small amounts. However, at therapeutic does 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 use machines**
Warfarin has no influence on the ability to drive and use machines.

4.8 **Undesirable effects**
Frequency categories are unknown for the following reported adverse reactions and therefore have not been included.

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Fever</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Cerebral haemorrhage; cerebral subdural haematoma</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Haemothorax, epistaxis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastrointestinal haemorrhage; rectal haemorrhage; haematemesis; pancreatitis; diarrhoea; nausea; vomiting; melaena</td>
</tr>
</tbody>
</table>
Table: Common Adverse Reactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>Rash; alopecia; purpura; erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Jaundice; hepatic dysfunction</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Haematuria</td>
</tr>
<tr>
<td>Investigations</td>
<td>Unexplained drop in haematocrit; haemoglobin decreased</td>
</tr>
</tbody>
</table>

MedDRA is a dictionary of medical terminology used by the MHRA to enter data into the Yellow Card database. The dictionary is organized by system organ class.

Skin necrosis is a rare but serious side effect of warfarin. It occurs mainly in obese, female patients, usually within 3 to 10 days of starting therapy, and is associated with the use of high induction doses. Patients with protein C or protein S deficiency are at particular risk. Initially, the lesions consist of painful, indurated, reddened areas, which progress through a stage of blood-filled blisters into well-demarcated blackened necrotic patches. Areas of skin with underlying fatty tissue, such as breasts, flanks and buttocks are most often affected. Pain in a particular area of skin is a premonitory symptom, and withdrawal of the oral anticoagulant at this stage, reversal of its effects with vitamin K or fresh frozen plasma, and the use of heparin may limit the extent of tissue damage.

‘Purple toes’ which is a rare complication of warfarin therapy. Typically, the syndrome presents 3 to 8 weeks after initiation of warfarin therapy as a sometimes painful blue-tinged discoloration of the plantar aspects and sides of the toes. Cholesterol emboli released from atheromatous plaques have been implicated as the cause. If the syndrome occurs, it is recommended that warfarin therapy be withdrawn, if possible, as the affected tissue may undergo ischaemic necrosis.

4.9 Overdose

The benefit of gastric decontamination is uncertain. If the patient presents within 1 hour of ingestion of more than 0.25 mg/kg or more than the patient’s therapeutic dose, consider activated charcoal.

In cases of life-threatening haemorrhage

Stop warfarin treatment, give prothrombin complex concentrate* (factors II, VII, IX, and X) or (if no concentrate available) fresh frozen plasma. 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 K1).
Where rapid re-anticoagulation is desirable (e.g., valve replacements) give prothrombin complex concentrate* (factors II, VII, IX, and X) or (if no concentrate available) fresh frozen plasma.

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 K1) by slow intravenous injection or by mouth (for partial reversal of anticoagulation give smaller oral doses of phytomenadione using the intravenous preparation orally); repeat dose of phytomenadione if INR still too high after 24 hours. Large doses of phytomenadione may completely reverse the effects of warfarin and make re-establishment of anticoagulation difficult.

- INR 6·0–8·0, no bleeding or minor bleeding—stop warfarin, restart when INR <5·0

- INR <6·0 but more than 0·5 units above target value—reduce dose or stop warfarin, restart when INR <5·0

For patients NOT on long-term anticoagulants without major haemorrhage

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

- If the INR remains normal for 24–48 hours and there is no evidence of bleeding, there should be no further monitoring necessary.

- Give vitamin K1 (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).

*For the dosages to be used for phytomenadione or prothrombin complex concentrate* (factors II, VII, IX, and X, please refer to the relevant product SPC.

The degree of reversal of anticoagulation must be decided on an individual basis. Full reversal with vitamin K may result in prolonged resistance to warfarin, giving rise to the possibility of valve thrombosis and thromboembolism in patients with prosthetic heart valves.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

Pharmacotherapeutic Category: Antithrombotic agent (Vitamin K Antagonist)
ATC Code: BO1 AA03

Warfarin is a synthetic anticoagulant of the coumarin series. It acts by inhibiting the formation of active clotting factors II, VII, IX and X.

5.2 Pharmacokinetic properties

Warfarin is readily absorbed from the gastro-intestinal tract. Its plasma half-life is about 40 hours. It is metabolised in the liver, and is excreted in the urine mainly as metabolites.

5.3 Preclinical safety data

Warfarin has been shown to be teratogenic in animal studies and may cause abnormalities and foetal death when administered during pregnancy in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene Glycol (E1520)
Benzoic Acid (E210)
Xanthan Gum (E415)
Polysorbate 80 (E433)
Citric Acid (E330)
Disodium Phosphate (E339)
Aluminium Magnesium Silicate
Liquid Maltitol (E965)
Masking Flavour
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Closed: 18 months
After first opening: 28 days

6.4 Special precautions for storage

Do not store above 25 C

6.5 Nature and contents of container

Bottle: Amber (Type III glass)
Closure: HDPE, EPE wadded, child resistant closure
Dosing Device: LDPE body, polystyrene plunger with a capacity of 12.5ml

Pack: 1 bottle containing 150ml of suspension.
6.6 Special precautions for disposal
Any unused product or waste material should be disposed of in accordance
with local requirements.

7 MARKETING AUTHORITY OF THE PRODUCT
Rosemont Pharmaceuticals Limited
Rosemont House
Yorkdale Industrial Park
Braithwaite Street
Leeds
LS11 9XE
United Kingdom

8 MARKETING AUTHORIZATION NUMBER(S)
PL 00427/0156

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
11/11/2010

10 DATE OF REVISION OF THE TEXT
11/11/2010
Module 3

Product Information Leaflet
If you stop taking warfarin

Do not stop taking warfarin unless your doctor tells you to. It may be dangerous to do so.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, warfarin can cause side effects although not everybody gets them.

Stop taking warfarin and see a doctor or go to a hospital straight away if you notice the following serious side effect:

- you may need urgent medical treatment

- **Allergic reaction** - the signs may include swelling of your face, lips, tongue or throat, difficult breathing or swallowing, severe itching of your skin with raised bumps.

Tell your doctor or go to a hospital straight away if you get any of the following side effects. Your doctor may decide to stop your warfarin treatment:

- Any bleeding at all as this is a sign that your clotting levels are low. Examples of bleeding that have been noted with the use of warfarin are:
  - nose bleeds without any obvious reason
  - loss of consciousness, fits, numbness, headache, dizziness, feeling or being sick, blurred vision. These could be signs that there is a bleed in your brain
  - change in colour of your urina - a dark red or brown urine might be due to bleeding in your kidneys or bladder
  - black or red stools can mean you have internal bleeding
  - red or purple weals/patches on your skin that look like bruises
  - purplish red patches on inner surfaces of the mouth and/or throat (manner)
  - purple nail beds.

If you get any of the above, please tell your doctor or go to hospital straight away.

Tell your doctor if you get any of these side effects:

- feel sick or vomit
- diarrhoea
- skin rash

If you get any of the above, please tell your doctor.

If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store warfarin

- Keep out of the reach and sight of children.
- Do not store above 25°C.

- Do not use after the expiry date of the leaflet.

- Do not use the medicine if the bottle is cracked or has leaked.

- Do not store warfarin suspension if you notice anything wrong with the medicine. Talk to your pharmacist.

- Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicine no longer required. These measures will help to protect the environment.

6. Further information

What warfarin suspension contains

- The active ingredient is warfarin sodium. This medicine contains long of warfarin sodium in each 1ml of suspension
- The other ingredients are propylene glycol (E1520), benzyl alcohol (E200), xanthan gum (E415), polysorbate 80 (E433), citric acid (E330), sodium metabisulphite (E223), sodium hydroxide, distilled water, distilled water.

- Warfarin suspension looks like and contains of the pack

- It comes in a brown glass bottle holding 30ml of suspension, packed in a cardboard box with a 12.5ml syringe.

- Marketing Authorisation Holder and Manufacturer:
  - Rosemont Pharmaceuticals Ltd, Yorks Industrial Park, Brathay street, Leeds, LS11 8BE, UK.

- This leaflet was last approved in November 2010

- MHRA PAR; WARFARIN SODIUM 1MG/1ML ORAL SUSPENSION, PL 00427/0156

- PMS256

Package Leaflet: Information for the User

Warfarin Sodium 1mg/1ml Oral Suspension

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed only for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects listed above affect you, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. What warfarin is and what it is used for

The name of your medicine is Warfarin sodium 1mg/1ml Oral Suspension (sodium warfarin in this leaflet). Warfarin belongs to a group of medicines called anticoagulants. It is used to thin your blood and prevent your blood from clotting.

- If you are seeing another doctor or are going to the hospital, tell them that you are taking warfarin. They may want to contact your doctor.

2. Before you take warfarin

Do not take warfarin:

- you are allergic (hypersensitive) to warfarin or any of the other ingredients of this medicine (listed in Section 6). An allergic reaction can include swelling of your face, lips, tongue or throat, difficulty breathing or swallowing, severe itching of your skin with raised bumps.

- you have severe uncontrollable bleeding

- you have had a stroke as a result of bleeding from a brain vessel in the brain

- you are pregnant, planning to become pregnant or have just had a baby. In the last 6 weeks (please see Section 2 "Pregnancy and breast-feeding")

- you have had surgery or had the last 2 weeks or are about to have surgery in the next 2 weeks

- you are taking medications that may increase your risk of bleeding or other medicines that stop the blood from clotting (please see Section 2 "Take special care with warfarin" and "Taking other medicines")

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor before taking warfarin.

Take special care with warfarin.

Check with your doctor or pharmacist before taking this medicine if any of the following apply to you. You may need to be more closely monitored by your doctor:

- you are an older person (over 65)
- you drink large amounts of alcohol
- you have diabetes and are sick
- you have any problem (have or have recently been ill such as having the flu or feeling run down)
- you have raised blood pressure that is not controlled by medicine
- you have liver or kidney problems
- you have ever had a stomach ulcer or bleeding
- you have had a stroke
- you have an infection of the lining of your heart (bacterial endocarditis)
- you have eaten, drunk foods that cause bleeding
- you have had surgery including operative heart failure
- you have problems with circulation of blood to the brain (cerebrovascular disease)
- you have had heart surgery
- you have had your heart problems
- you have very low levels of alcohol
- you have low levels of a substance called "protamine C" or "Protamine S". These stop blood clots
- you take part in sports activities, particularly those with a high risk of injury or falling
- you are taking any medicines that may increase your risk of bleeding such as non-steroidal anti-inflammatory drugs (NSAIDs) e.g.

- aspirin or other medicines that stop the blood from clotting.

- Continued overleaf
you are going to have surgery. The doctor may have to change your dose or stop your warfarin treatment.

you are changing your diet or have recently lost or gained a lot of weight. Keep your diet and level of activity as close to normal as possible (please see section 2 "Taking warfarin with food and drink" for more information).

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking warfarin. You may need to be more closely monitored by your doctor.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

This includes medicines obtained without a prescription, including herbal medicines. This is because warfarin can affect the way some other medicines work. Also some other medicines can affect the way warfarin works. Other medicines can make you more likely to bleed or you may need to take more warfarin because of what you are already taking.

Do not take warfarin and tell your doctor if you are taking any of the following medicines:

- other medicines used to thin your blood (anticoagulants) or stop clotting such as clopidogrel, dipyrindamole, dipyridamole, bromidrinate, heparin, low molecular weight heparin, roxification, tidroline, aliskiren and prostacyclins. If you are changing to warfarin from another anticoagulant you should tell your doctor
- medicines to treat depression such as SSRIs (selective serotonin reuptake inhibitors), for example, fluoxetine and citalopram or SNRIs (selective noradrenergic reuptake inhibitors) such as venlafaxine
- omeprazole – used for gut
- St. John’s Wort – a herbal remedy used for depression.

Do not take warfarin and tell your doctor if you are taking any of the above medicines. If you are not sure, talk to your doctor or pharmacist.

The following medicines may increase the effect of your warfarin. Tell your doctor or pharmacist if you are taking:

- medicines for gout, pain and inflammation called non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, salicylates
- medicines for heart problems such as amiodarone, propafenone or quinidine
- medicines that reduce high levels of fats in your blood such as bezafibrate or gemfibrozil or lower your cholesterol levels such as fluvastatin
- corticosteroids – used for flushing and dermatitis in some illnesses
- vitamin K which can be found in vitamin supplements and some foods
- medicines to help you sleep such as chloral hydrate or trichloroethane which may relax your muscles
- nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen
- medicines for pain and inflammation in illnesses like rheumatism and arthritis such as paracetamol, ibuprofen or phenylbutazone
- medicines for infections such as cefadroxil, dicloxacillin, ciprofloxacin, co-amoxiclav, erythromycin, metronidazole, norfloxacin, sulphonamides or tetracyclines
- medicines for fungal infections such as fluconazole or ketoconazole
- medicines for diabetes such as glibenclamide
- medicines for thyroid problems
- clonidine, clonazepam or oxcarbazepine – used for stomach ulcers or too much stomach acid
- loratadine, sertraline, alprazolam – used to treat cancer
- domperidone – used for mental problems or endometriosis
- methacrylamides – used for hyperthyroid disorder
- clofibrate – used for alcohol addiction
- cetirizine/levocetirizine – used for pain.

If any of the above apply to you (or you are not sure) talk to your doctor or pharmacist before taking warfarin.

The following medicines may decrease the effect of your warfarin. Tell your doctor or pharmacist if you are taking:

- medicines for epilepsy such as phenytoin, phenobarbital, primidone or carbamazepine
- medicines for arthritis such as salazosulphapyridine or glucosamine
- ranitidine – used for infections like TB (tuberculosis)
- glibenclamide – used for fungal infections
- alprazolam – used to help weight loss
- phenylbutazone – used for pain
- cortisone/steroids (the "P" class)
- amitriptyline/trimipramine – used for cancer.

If any of the above apply to you (or you are not sure), talk to your doctor or pharmacist before taking warfarin.

Taking Warfarin with food and drink

Do not drink large amounts of alcohol while you are taking warfarin.

It is best not to have cranberry juice or any other cranberry products. This is because cranberry may increase the effects of warfarin and cause bleeding.

If you have been advised to have cranberry products for medical reasons (such as bladder infections), talk to your anticoagulant doctor or health advisor before taking this medicine. They may ask you to stop drinking or reduce the amount of cranberry or monitor you more often while you are taking warfarin.

It is important to keep your diet as close to normal as possible while taking warfarin. This is because making changes in your diet may affect how your body responds to warfarin. This is particularly likely to happen with foods which contain vitamin K such as leafy green vegetables.

Driving and using machines

This medicine should not affect your ability to drive or operate machinery.

Important information about what is in warfarin suspension

Warfarin Suspension contains liquid milk fat as type of sugar. If your doctor has told you that you cannot tolerate some sugars, talk to your doctor before taking this medicine.

3. How to take warfarin

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Taking this medicine

- Shake the bottle well before use to make sure you get the correct dose.
- If you find it difficult to measure the dose or take the medicine accurately, you may need the help of a carer.
- It is important that the dose is measured correctly.

This medicine contains 1 milligram (mg) of Warfarin in each 1 millilitre (ml) of suspension. Always use this syringe to measure out your dose. The numbers on the side show how many millilitres (ml) of liquid you have inside the syringe.

1. Put the syringe into the bottle and lift the liquid until the liquid end of the syringe is resting at the top of the bottle.
2. Pull the plunger slowly upwards until the mark for your dose is showing on the plunger just above the tipped end of the syringe.
3. Take the syringe out of the bottle.
4. Make sure there are no air bubbles in the medicine in the syringe.
5. Put the end of the syringe into your mouth and push the plunger slowly down to take the medicine.
6. Wash the syringe with water and let it dry before you use it again.

How much to take

The usual doses are given below. The correct dose will be decided by your doctor based on your response (DR) to this medicine. Follow your doctor’s instructions carefully.

Adults

- On days one to two, the usual starting dose is 1mg (1ml), taken at the same time each day
- On days 3 and onwards, the usual dose is 1mg (1ml) to 2mg (2ml) to limit, taken at the same time each day
- If you are an older person (over 65) your doctor may give you a lower dose.

Children

Warfarin is not recommended for use in children.

Blood tests

Your doctor will do blood tests during your treatment and may change your dose depending on the results.

If you take more warfarin than you should

If you take more of this medicine than you should, talk to a doctor or go to your nearest hospital straight away. Take the medicine pack with you.

If you forget to take warfarin

- If you forget a dose and remember within two or three hours, you can still take that dose.
- If you forget your dose for longer than three hours, do not take that dose. Instead, wait until the next dose is due.
- Do not take a double dose to make up for a forgotten dose.
- Tell your doctor that you have forgotten a dose when you next see them or when you have your blood test.

Continued overleaf
Module 4

Labelling

Label:
Module 5

Scientific Discussion

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Warfarin Sodium 1mg/1ml Oral Suspension in the prevention and treatment of thromboembolism could be approved.

EXECUTIVE SUMMARY

Problem statement
This Decentralised application was submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that that the proposed product is a generic version of the product Marevan 1 mg Tablets (PL 10972/0034), which was first licensed to Goldshield Pharmaceuticals in the UK on 22 September 1993.

With the UK as the Reference Member State in this Decentralised Procedure, Rosemont Pharmaceuticals Limited is applying for a Marketing Authorisation for Warfarin Sodium 1mg/1ml Oral Suspension in Ireland.

About the product
Warfarin is a vitamin K inhibitor. It inhibits the vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX and X. It is an anticoagulant indicated for:

• Prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation.
• Prophylaxis after insertion of prosthetic heart valves.
• Prophylaxis of venous thrombosis and pulmonary embolism and for use in the treatment of these conditions to prevent their extension.

Warfarin is currently available mainly in a tablet form. This is an oral suspension containing 1 mg of warfarin per 1 ml of the suspension.

General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossier regarding the quality, non-clinical and clinical parts have been submitted.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of
current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

**GLP**

No new non-clinical studies were submitted in support of this application, an none are needed for an application of this type.

**GCP**

Statements have been provided confirming that the submitted bioequivalence study was conducted in compliance with Good Clinical Practices (GCP), as referenced in the ICH guidelines (ICH E6), local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Drug substance**

rINN: Warfarin sodium  
Compendial name: Warfarin sodium  
Chemical name: Sodium 2-oxo-3-[(1RS)-3-oxo-1-phenylbutyl]-2H-1-benzopyran-4-olate  
CAS registry number: 129-06-6  
Structure:

Molecular formula: C_{19}H_{15}NaO_{4}  
Molecular weight: 330.3  
Appearance: almost white, hygroscopic amorphous powder. Very soluble in water, ethanol (96%), soluble in acetone, very slightly soluble in methylene chloride

The drug substance holds a valid certificate of suitability. The quality of the substance is suitably controlled by the current edition of the Ph. Eur. monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate
specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the drug substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Certificate of analysis for all working standards have been provided.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and certificates of analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.

Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**Medicinal product**

Warfarin Sodium 1mg/1ml Oral Suspension contains the pharmaceutical excipients propylene glycol (E1520), benzoic acid (E210), xanthan gum (E415), polysorbate 80 (E433), citric acid (E330), disodium phosphate (E339), aluminium magnesium silicate, liquid maltitol (E965), masking flavour and purified water.

All excipients comply with their respective European Pharmacopoeia monograph, with the exception of citric acid (E330), disodium phosphate (E339) and masking flavour. Citric acid (E330) and disodium phosphate (E339) are pharmacopoeial and are controlled by appropriate specifications. Masking flavour is controlled by an appropriate specification and full testing to confirm compliance is routinely carried out. Satisfactory certificates of analysis have been provided for all excipients. Suitable declarations issued by suppliers of the excipients to confirm compliance with the requirements of the relevant guideline and Directives with regard to TSE are provided.

**Pharmaceutical development**

The objective of the development programme was to formulate an oral liquid containing 1mg of warfarin sodium per 1ml of product.

A satisfactory account of the pharmaceutical development has been provided.

**Manufacturing process**

A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished product specification**

The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.
**Container-closure system**
The finished product is stored in an amber (Type III) glass bottle with an HDPE, EPE wadded, child resistant closure. An LDPE (body) and polystyrene (plunger) dosing device with a capacity of 12.5ml is also included.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for product stored in an unopened container, with a shelf-life of 28 days after first container opening. The storage instructions are “Do not store above 25°C”.

**Product literature**
The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) forms**
The MAA form is pharmaceutically satisfactory.

**Expert report**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Quality conclusion**
There are no objections to the approval of Warfarin Sodium 1mg/1ml Oral Suspension from a quality point of view.

**Non-clinical aspects**

**Non-clinical overview**
The pharmacological, pharmacokinetic and toxicological properties of warfarin are well known. As warfarin is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

**Expert report**
The non-clinical overview has been written by a medical doctor. His experience and qualifications are acceptable. The overview cites 30 references from the published
literature which are dated up to 2009. The overview is dated 21 March 2009 and is satisfactory in view of the fact that the toxicological properties of warfarin are well known.

**Environmental risk assessment**

A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all warfarin-containing products, which in turn is unlikely to increase exposure of the environment to warfarin.

**Product literature**

The product literature is acceptable from a non-clinical point of view.

**Non-clinical conclusion**

There are no objections to the approval of Warfarin Sodium 1mg/1ml Oral Suspension from a non-clinical point of view.

**Clinical aspects**

**Pharmacokinetics**

To support the application, the applicant has submitted the clinical study report of an open label, randomised, two-treatment, two-period, two-sequence, single dose crossover truncated relative bioavailability study comparing Warfarin 1mg/1ml Oral Suspension of Rosemont Pharmaceuticals Limited, with Marevan® (Warfarin) 5mg tablet of Goldshield Pharmaceuticals Limited in healthy adult human male subjects under fasting conditions. The pharmacokinetic parameters evaluated are $C_{\text{max}}$, $\text{AUC}_{0-1}$, $\text{AUC}_{0-\infty}$ and $T_{\text{max}}$. As the reported half-life for warfarin is between 20 and 60 hours, the sampling period for the study was extended to 192 hours.

A total of 24 healthy male subjects between the ages of 20-35 years were enrolled and randomised. Three subjects were withdrawn, all before period II. Two subjects were withdrawn due to the adverse event epistaxis and one subject withdrew due to work commitments. A total of 21 subjects completed the clinical and analytical phase of the study.

**Results**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Test</th>
<th>Reference</th>
<th>*Ratio (90% CI)</th>
<th>CV (%) (Intra-subject)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>$\text{AUC}_{0-1}$ (ng/ml/h)</td>
<td>$\text{AUC}_{0-\infty}$ (ng/ml/h)</td>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>$t_{\text{max}}$ (h)</td>
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<tr>
<td>Test</td>
<td>20676.74</td>
<td>23691.60</td>
<td>575.27</td>
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<tr>
<td>Reference</td>
<td>20447.94</td>
<td>23856.59</td>
<td>540.80</td>
<td>1.65</td>
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<tr>
<td>*Ratio (90% CI)</td>
<td>101.41% (93.54 – 109.94%)</td>
<td>99.69% (91.43 – 108.71%)</td>
<td>106.40% (96.96 – 116.75%)</td>
<td>63.92% (39.42 – 79.81%)</td>
</tr>
<tr>
<td>CV (%) (Intra-subject)</td>
<td>15.20%</td>
<td>16.31%</td>
<td>17.52%</td>
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<tr>
<td>Symbol</td>
<td>Definition</td>
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<td>--------</td>
<td>---------------------------------------------</td>
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<tr>
<td>AUC_{0-\infty}</td>
<td>area under the plasma concentration-time curve from time zero to infinity</td>
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<tr>
<td>AUC_{0-t}</td>
<td>area under the plasma concentration-time curve from time zero to t hours</td>
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<tr>
<td>C_{max}</td>
<td>maximum plasma concentration</td>
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<tr>
<td>T_{max}</td>
<td>time for maximum concentration</td>
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</tr>
<tr>
<td>T_{1/2}</td>
<td>half-life</td>
<td></td>
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</tbody>
</table>

*ln-transformed values

The 90% geometric confidence intervals for AUC_{0-t} and AUC_{0-\infty} are within the acceptance range of 90–111.11%. The 90% geometric confidence intervals for C_{max} is within 80 – 125%. Therefore, bioequivalence has been demonstrated between the test and reference products.

**Pharmacodynamics**

The pharmacodynamic characteristics of warfarin sodium have been well-studied in the past. There would be no particular concerns for a generic medicinal product. No new data have been submitted and none are required.

**Clinical efficacy and safety**

No new efficacy data are presented and none is required. A comprehensive review of the published literature has been provided by the applicant, citing the well established clinical pharmacology, efficacy and safety of warfarin sodium.

**Pharmacovigilance system**

The RMS considers that the pharmacovigilance system fulfils the requirements. The Applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

**Risk management plan**

No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this application.

**Expert report**

A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory, non-critical summary of the clinical part of the dossier.

**Product literature**

All product literature (SPC, PIL and labelling) is medically satisfactory.

**Clinical conclusion**

There are no objections to the approval of Warfarin Sodium 1mg/1ml Oral Suspension from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Warfarin Sodium 1mg/1ml Oral Suspension are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of these type.

EFFICACY
The use of warfarin in the prevention and treatment of thromboembolism is well established. It has been in clinical use for over 20 years. The applicant has submitted a clinical study report of a bioequivalence study in which bioequivalence has been demonstrated between the applicant’s Warfarin Sodium 1mg/1ml Oral Suspension and its respective reference product. New efficacy data is, therefore, not needed.

SAFETY
No new or unexpected safety concerns arise from these applications.

The SPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory labelling has also been submitted.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with warfarin sodium is considered to have demonstrated the therapeutic value of the compound. The risk-benefit ratio is, therefore, considered to be positive. A Marketing Authorisation should be granted.