

## **Public Assessment Report**

**Warfarin 1mg Tablets  
PL 17907/0103**

**Warfarin 3mg Tablets  
PL 17907/0104**

**Warfarin 5mg Tablets  
PL 17907/0105**

**WARFARIN 1MG TABLETS  
PL 17907/0103**

**WARFARIN 3MG TABLETS  
PL 17907/0104**

**WARFARIN 5MG TABLETS  
PL 17907/0105**

**UKPAR**

**TABLE OF CONTENTS**

|   | <b>Page</b> |
|---|-------------|
| Lay Summary                               | 3           |
| Scientific discussion                     | 4           |
| Steps taken for assessment                | 16          |
| Steps taken after authorisation – summary | 17          |
| Summary of Product Characteristics        | 18          |
| Patient Information Leaflet               | 39          |
| Labelling                                 | 42          |

**WARFARIN 1MG TABLETS  
PL 17907/0103**

**WARFARIN 3MG TABLETS  
PL 17907/0104**

**WARFARIN 5MG TABLETS  
PL 17907/0105**

**LAY SUMMARY**

The Medicines and Healthcare products Regulatory Agency (MHRA) has granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Warfarin 1mg, 3mg and 5mg Tablets (PLs 17907/0103-5). These are prescription only medicines [POMs] used to prevent blood clotting in various conditions.

The active ingredient, warfarin, belongs to a group of drugs known as anticoagulants. It interferes in the formation of certain chemicals that aid clotting.

The clinical data presented to the MHRA, before licensing, demonstrated that Warfarin 1mg, 3mg and 5mg Tablets are essentially similar or equivalent to the approved products, Marevan Tablets 1mg, 3mg and 5mg, and as such can be used interchangeably.

No new or unexpected safety concerns arose from these applications and it was decided that the benefits of using Warfarin 1mg, 3mg and 5mg Tablets outweigh the risks, hence Marketing Authorisations have been granted.

**WARFARIN 1MG TABLETS  
PL 17907/0103**

**WARFARIN 3MG TABLETS  
PL 17907/0104**

**WARFARIN 5MG TABLETS  
PL 17907/0105**

**SCIENTIFIC DISCUSSION**

**TABLE OF CONTENTS**

|   | <b>Page</b> |
|---|-------------|
| Introduction                                    | 5           |
| Pharmaceutical assessment                       | 6           |
| Preclinical assessment                          | 11          |
| Clinical assessment                             | 12          |
| Overall conclusions and risk benefit assessment | 15          |

## **INTRODUCTION**

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the medicinal products Warfarin 1mg, 3mg and 5mg Tablets (PLs 17907/0103-5) to Bristol Laboratories Limited on 26 October 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to Article 10.1(a)(iii) of Directive 2001/83/EC, claiming essential similarity to Marevan Tablets, initially authorised in 1972.

These products contain the active ingredient warfarin and are indicated for: prophylaxis of systemic embolism in patients with rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valves; prophylaxis and treatment of venous thrombosis and pulmonary embolism; and transient attacks of cerebral ischaemia.

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

## **PHARMACEUTICAL ASSESSMENT**

**PL NUMBER:** PLs 17907/0103-0105  
**PRODUCT:** Warfarin 1mg, 3mg & 5mg Tablets  
**ACTIVE:** Warfarin Sodium Ph.Eur.  
**COMPANY:** Bristol Laboratories Ltd  
**E.C. ARTICLE:** Article 10.1(a)(iii), first paragraph  
**LEGAL STATUS:** POM

### **INTRODUCTION**

These national abridged applications are for conventional tablets containing warfarin sodium. The originator product is Marevan Tablets, which was first authorised to Duncan-Flockhart and Co Ltd in 1972. The tablets are currently licensed to Goldshield Pharmaceuticals UK as PLs 10972/0034-6. The UK reference product, Marevan Tablets 5mg, has been used in the biostudy.

### **DRUG SUBSTANCE**

A Certificate of Suitability for warfarin sodium from a named source is provided.

#### **Control of Drug Substance**

##### ***Specification***

Warfarin sodium is the subject of a Ph.Eur. monograph. The tests included in the Certificate of Suitability and the specification are as per the Ph.Eur. with some additional in-house tests.

Certificates of Analysis are provided by the drug substance manufacturer.

##### ***Analytical procedures and validation***

The methods in the specification are pharmacopoeial.

Validation is provided for additional non-pharmacopoeial methods.

##### ***Batch Analyses***

The results of batch analyses demonstrate compliance with the specification.

##### **Stability**

The results of the stability studies indicate that warfarin sodium is stable through the retest period.

A commitment to carry out yearly stability studies has been provided by the drug substance manufacturer.

## DRUG PRODUCT

### Description and composition of the drug product

Warfarin 1mg Tablets are peach, circular, flat faced bevelled edged uncoated tablets with “1” embossing on one side and “BL” on the other.

Warfarin 3mg Tablets are blue, circular, flat faced bevelled edged uncoated tablets with “3” embossing on one side and “BL” on the other.

Warfarin 5mg Tablets are pink, circular, flat faced bevelled edged uncoated tablets with “5” embossing on one side and “BL” on the other.

The applicant has justified the choice of the peach colour rather than the long-established brown colour for the 1mg tablet strength.

### Composition

| Name                  | Function               | Reference to Standards |
|-----------------------|------------------------|------------------------|
| Warfarin sodium       | Drug substance         | Ph.Eur.                |
| Lactose monohydrate   | Diluent                | Ph.Eur.                |
| Sucrose               | Diluent                | Ph.Eur.                |
| Maize starch          | Binder                 | Ph.Eur.                |
| Pregelatinised starch | Disintegrant/Lubricant | Ph.Eur.                |
| Magnesium stearate    | Glidant                | Ph.Eur.                |

In addition to the above, the 1mg tablets contain Quinoline Yellow and Ponceau 4R; the 3mg tablets contain Indigo Carmine Aluminium Lake; the 5mg tablets contain Erythrosine Aluminium Lake.

The tablets are packaged in opaque PVdC/PVC/aluminium blisters or in HDPE bulk containers.

### Pharmaceutical development

Satisfactory details are provided by the applicant.

### Manufacture

#### *Manufacturer*

Batch release takes place at Bristol Laboratories Ltd, Berkhamsted, Herts, UK. Evidence of inspection and of GMP compliance has been provided.

#### *Batch Formula*

The batch formulae for production scale batches for all three strengths are provided.

***Description of manufacturing process and process controls and Control of critical steps and intermediates***

A flow diagram of the manufacturing procedure together with in-process controls has been provided.

***Process validation and/or Evaluation***

Pivotal batches of the tablets have demonstrated that the process produces suitable drug products. Batch analyses and stability data indicate consistent quality.

The first full scale commercial production batches manufactured will be validated according to a validation protocol provided by the applicant. Any significant deviations will be reported to the regulatory authorities immediately.

**Control of excipients**

***Specifications  
Analytical procedures***

Most excipients are controlled by their respective Ph.Eur. monographs. Analytical procedures for the excipients are performed as per the monographs specified. Certificates of Analysis are provided as evidence of compliance with the proposed specifications.

The colourants are controlled to in-house specifications. Analytical procedures have been provided.

***Validation of analytical procedures  
Justification of specification***

Not required as the proposed tests and methods are pharmacopoeial.

***Excipients of human or animal origin***

It is stated that lactose is produced from milk fit for human consumption. All other suppliers of the other excipients (and drug substance) have provided certificates stating that the materials are not from animal sources.

**Control of Drug Product**

***Specification***

The specification is acceptable. The assay limits are satisfactory for a drug substance with a narrow therapeutic index.

***Analytical procedures  
Validation of analytical procedures***

Satisfactory details are provided.



### ***Batch analyses***

The batch analysis data provided demonstrated compliance with the specification.

### **Justification of specification(s)**

The applicant has included acceptable justifications for the proposed specification and limits.

### **Container closure system**

The tablets are packed in opaque PVdC/PVC/aluminium blister packs or HDPE containers. The blisters are constructed of PVdC, coated PVC, and aluminium foil.

Specifications have been provided.

The packaging is standard and it is stated that the packaging complies with relevant EC requirements including food contact requirements. It is further stated that none of the raw materials used in the manufacturing of the packaging is of animal origin.

### **Stability**

Stability studies were carried out on batches of the drug products. The samples were packed in the proposed marketing packs at 25°C/60%RH and 40°C/75%RH.

The results indicate stable products.

A shelf life of 2 years was proposed for Warfarin Tablets when stored below 25°C and in the original packaging. All results are within specification and there are no untoward trends so the proposals on storage and shelf life may be considered satisfactory.

## **SUMMARY OF PRODUCT CHARACTERISTICS PATIENT INFORMATION LEAFLET LABELLING**

Satisfactory.

## **BIOAVAILABILITY, BIOEQUIVALENCE**

A single dose two-way crossover study in healthy male volunteers under fasting conditions using the 5mg strength and Marevan 5mg as comparator was carried out. Biowaiver criteria in line with CPMP/1401/98 to exempt the lower strengths have been satisfactorily discussed.

Pharmacokinetic parameters calculated are as follows:

Comparison of the pharmacokinetic parameters of Warfarin 5mg Tablets and Marevan 5mg Tablets (untransformed data)

| Parameters                     | Test (warfarin) |        | Reference (Marevan) |        |
|--------------------------------|-----------------|--------|---------------------|--------|
|                                | Mean            | ± SD   | Mean                | ± SD   |
| T <sub>max</sub> (h)           | 1.44            | 0.87   | 1.93                | 1.5    |
| C <sub>max</sub> (ng/mL)       | 810.5           | 179.4  | 748.3               | 175.9  |
| AUC <sub>0-t</sub> (ng.h/mL)   | 33521           | 8034   | 31212               | 7366   |
| AUC <sub>0-inf</sub> (ng.h/mL) | 36339           | 8772   | 34324               | 7721   |
| λ <sub>Z</sub> (1/h)           | 0.0101          | 0.0017 | 0.0094              | 0.0023 |
| T <sub>1/2</sub> (h)           | 70.14           | 11.7   | 77.8                | 18.89  |
| AUC %Extrap_obs (%)            | 7.68            | 2.18   | 9.15                | 2.6    |

Comparison of ANOVA performed on the ln-transformed data

| End points (Units)             | Mean Values      |                       | Ratio least mean squares (B/A)% | 90% CI  |         | Intra subject CV (%) |
|--------------------------------|------------------|-----------------------|---------------------------------|---------|---------|----------------------|
|                                | Test product (B) | Reference Product (A) |                                 | Lower   | Upper   |                      |
| C <sub>max</sub> (ng/mL)       | 791.9            | 728.7                 | 108.7                           | 100.10% | 118.0%  | 16.7                 |
| AUC <sub>0-t</sub> (ng.h/mL)   | 32702            | 30481                 | 107.3                           | 103.92% | 110.76% | 6.4                  |
| AUC <sub>0-inf</sub> (ng.h/mL) | 35430            | 33563                 | 105.6                           | 101.94% | 109.32% | 7.1                  |

On the basis that the 90% CI fell within the acceptance range of 80% to 125% for untransformed and ln-transformed C<sub>max</sub>, AUC<sub>(0-t)</sub> and AUC<sub>(0-inf)</sub>, it was concluded that the two products are bioequivalent.

**ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE**

Marketing Authorisations can be granted.

## **PRECLINICAL ASSESSMENT**

No new preclinical data have been supplied with this application and none are required.

## **CLINICAL ASSESSMENT**

**PL NUMBER:** PLs 17907/0103-0105  
**PRODUCT:** Warfarin 1mg, 3mg & 5mg Tablets  
**ACTIVE:** Warfarin Sodium Ph.Eur.  
**COMPANY:** Bristol Laboratories Ltd  
**E.C. ARTICLE:** Article 10.1(a)(iii), first paragraph  
**LEGAL STATUS:** POM

### **INTRODUCTION**

These are applications based on essential similarity. The reference product is Marevan Tablets (PLs 10972/0034-6, MA holder: Goldshield Pharmaceuticals, UK).

### **BACKGROUND**

Warfarin is a known oral anticoagulant and has been used clinically for many years. It is used widely to prevent thrombus formation in patients with heart valve disease, those with prosthetic valves, transient attacks of cerebral ischaemia and prevention and treatment of pulmonary embolism.

### **INDICATIONS**

See SPCs Section 4.1.

### **DOSE & DOSE SCHEDULE**

See SPCs Section 4.2.

### **TOXICOLOGY**

The expert concludes that all excipients in the formulation proposed for marketing are well established and do not give rise to safety concerns. Warfarin is a known teratogen and the interactions with other drugs are numerous. However, the proposed Summaries of Product Characteristics for Warfarin Tablets contain the appropriate warning.

### **CLINICAL PHARMACOLOGY**

A single bioequivalence study has been submitted. This is acceptable for “essential similarity” applications.

#### **Bioequivalence**

Bioequivalence was investigated in a two-way crossover study in healthy volunteers. The study was conducted according to GLP and GCP criteria and was randomised, two-treatment, two-period, two sequence, single dose and comparative. The test product was Warfarin 5mg Tablets and the reference product was Marevan Tablets 5mg. Tablets were administered after overnight fasting.

A total of 28 subjects (including 4 standby subjects), healthy males between 18 and 55 years of age were enrolled. Three subjects discontinued from the trial. In all, 25 subjects completed both periods of the trials. The plasma samples of 24 completed subjects were analysed.

The applicant has attempted to justify the analysis of data from only 24 subjects by stating that the target, as defined in the protocol, was for 24 subjects to complete the study. It would have been preferable if analysis had been carried out on all 25 subjects that eventually did complete the study. Nevertheless, the confidence intervals for  $C_{max}$  and AUC are well within the recommended limits and it is unlikely that addition of data from one more subject will significantly alter the  $C_{max}$  or AUC.

Ln-transformed least square mean of the ratios and 90% Confidence Interval (n=24)

| End Point<br>(Units)            | Mean Values      |                       | Ratio<br>(B/A) % | 90% Confidence Interval |         |
|---------------------------------|------------------|-----------------------|------------------|-------------------------|---------|
|                                 | Test Product (B) | Reference Product (A) |                  | Lower                   | Upper   |
| $C_{max}$ (ng/mL)               | 791.923          | 728.656               | 108.7            | 100.10%                 | 118.00% |
| AUC <sub>0-4</sub><br>(ng.h/mL) | 32701.815        | 30480.957             | 107.3            | 103.92%                 | 110.76% |
| AUC <sub>0-∞</sub><br>(ng.h/mL) | 35430.447        | 33562.926             | 105.6            | 101.94                  | 109.32  |

The  $T_{max}$  for the test product and the reference product were  $1.438 \pm 0.8731$  (h) and  $1.927 \pm 1.5009$  (h) respectively. The  $t_{1/2}$  values were  $70.143 \pm 11.6959$  (h) and  $77.797 \pm 18.8938$  (h) respectively.

## EFFICACY

No new data is submitted and none is required. The efficacy of warfarin is well established through its extensive use in clinical practice.

## SAFETY

No new data has been submitted and none is required. The safety profile of warfarin is known. Bleeding, the main adverse effect, is actually an extension of warfarin's therapeutic effect.

## EXPERT REPORT

The expert is appropriately qualified. Limited published references have been provided to support efficacy and safety.

## SUMMARY OF PRODUCT CHARACTERISTICS PATIENT INFORMATION LEAFLET LABELLING

Satisfactory.

## **DISCUSSION**

Warfarin is a well established drug. It has been used in clinical practice for many years. The efficacy in the proposed indications and the safety profile is known. Bioequivalence has been demonstrated between the applicant's products and Marevan Tablets.

## **CONCLUSIONS**

Marketing authorisations can be granted.

## **OVERALL CONCLUSION AND RISK-BENEFIT ASSESSMENT**

### **QUALITY**

The important quality characteristics of Warfarin 1mg, 3mg and 5mg Tablets 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 this type.

### **EFFICACY**

Bioequivalence has been demonstrated between the applicant's Warfarin Tablets and Marevan Tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with those of Marevan Tablets.

### **RISK-BENEFIT ASSESSMENT**

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. Extensive clinical experience with the active ingredient warfarin is considered to have demonstrated the therapeutic value of the compound. The risk-benefit assessment is therefore considered to be favourable.

**WARFARIN 1MG TABLETS  
PL 17907/0103**

**WARFARIN 3MG TABLETS  
PL 17907/0104**

**WARFARIN 5MG TABLETS  
PL 17907/0105**

**STEPS TAKEN FOR ASSESSMENT**

|    |  |
|----|--|
| 1  | The MHRA received the marketing authorisation applications for Warfarin 1mg, 3mg and 5mg Tablets on 4 May 2005.            |
| 2  | The MHRA's assessment of the submitted quality data was completed in December 2005.  |
| 3  | Further information (quality) was requested from the company on 13 December 2005.  |
| 4  | The MHRA's assessment of the submitted clinical data was completed in January 2006.  |
| 5  | Further information (clinical) was requested from the company on 25 January 2006.  |
| 6  | The applicant's responses to further information (quality and clinical) requests were sent in letters dated 23 March 2006. |
| 7  | Further information (clinical) was requested from the company on 24 May 2006.  |
| 8  | The applicant's response to further information (clinical) request was sent on 22 June 2006.                               |
| 9  | Further information (quality) was requested from the company on 15 August 2006.  |
| 10 | The applicant's response to further information (quality) request was sent in a letter dated 4 September 2006.             |
| 11 | The applications were determined on 26 October 2006.   |



**WARFARIN 1MG TABLETS  
PL 17907/0103**

**WARFARIN 3MG TABLETS  
PL 17907/0104**

**WARFARIN 5MG TABLETS  
PL 17907/0105**

**STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

| <b>Date submitted</b> | <b>Application type</b> | <b>Scope</b> | <b>Outcome</b> |
|-----------------------|-------------------------|--------------|----------------|
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |
|                       |                         |              |                |

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Warfarin 1 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Warfarin Sodium 1 mg.

For a full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Tablet.

Peach coloured, circular, flat faced bevelled edged uncoated tablet with '1' embossing on one side and 'BL' embossing on the other.

### 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 and treatment of venous thrombosis and pulmonary embolism.

Transient attacks of cerebral ischaemia.

#### 4.2 Posology and method of administration

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 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.

In emergencies, anticoagulant therapy should be initiated with heparin and Warfarin together.

Concomitant therapy with heparin affects the results of control tests, and should be discontinued at least six hours before the first test is carried out.

Elderly: As for adults.

Children: Warfarin Tablets are not recommended for use in children due to insufficient data on safety and efficacy.

Method of administration : Oral.

### 4.3 Contraindications

- Known hypersensitivity to warfarin or to any of the inactive ingredients contained in warfarin tablets.
- Severe hepatic or renal disease.
- Bacterial endocarditis.
- Actual or potential haemorrhagic conditions, such as peptic ulcer or uncontrolled hypertension.
- Use within 24 hours of surgery or labour should be undertaken with caution, if at all.
- Warfarin is contraindicated in pregnancy.
- This medicinal product contains lactose. It is therefore unsuitable for people with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.
- This medicinal product contains sucrose. It is therefore unsuitable in hereditary fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase-isomaltase deficiency.

### 4.4 Special warnings and precautions for use

The following may exaggerate the effect of Warfarin Tablets, and necessitate a reduction of dosage:

Loss of weight. Elderly patients, acute illness, deficient renal function, decreased dietary intake of Vitamin K, Administration of some drugs(see interactions).

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

Weight gain. Diarrhoea, vomiting, increased dietary intake of Vitamin K, fats and oils, administration of some drugs (see interactions).

Careful additional control tests are necessary if a patient is changed from one anticoagulant formulation to another.

Reversal of warfarin anticoagulants by Vitamin K takes several days. In emergency situation, fresh-frozen plasma should be given.

Sensitivity to other drugs taken concomitantly with Warfarin Tablets should be considered. Patients who are sensitive to Warfarin Tablets usually tolerate other anticoagulant therapy.

#### 4.5 Interaction with other medicinal products and other forms of interaction

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.

##### Potential effect:

- Alcohol (large or chronic amounts, especially in patients with impaired liver function), Amiodarone, Amitriptylline/ Nortriptylline, anabolic steroids, anti-inflammatory analgesics, Allopurinol, Azapropazone, Aztreonam, Bezafibrate, broad spectrum antibiotics.
- Cephmandole, Chloral hydrate, Chloramphenicol, Cimetidine, Ciprofloxacin, Clofibrate, Co-Trimoxazole.
- Cholestyramine may decrease absorption of VitaminK and thus increase coumarin anticoagulant activity.
- Danazol, Dextropropoxyphene, Dextrothyroxine, Diflunisal, Dipyridamole, Disulfiram.
- Erythromycin.
- Feprazone, Fluconazole, Flurbiprofen, Fluoroxamine.
- Glucagon, Gemfibrocil.
- Hepatotoxic drugs(potentially).
- Indomethacin.
- Ketaconazole.
- Latamoxef.
- Metronidazole, Mefenamic Acid, Methylpenidate, Miconazole.
- Nalidixic acid, Neomycin, Norfloxacin.
- Omeprazole, Oxyphenbutazone.
- Paracetamol, Phenformin, Phenylbutazone, Phenylramidol, Piroxicam, Propafenone.
- Quinidine.
- Salicylates, Sulindac, Sulphonamides.
- Tamoxifen, tetracyclines, Tolbutamide, Thyroid drugs, Triclofos.

##### Decrease in effect :

- Aminoglutethimide.
- Barbiturates.
- Carbamazepine.
- Dichloralphenazone.
- Ethchlorvynol.
- Gluthethimide, Griseofulvin.
- Oral contraceptives.
- Primidone.
- Rifampicin.
- Sucralfate.
- Vitamin K(enteral feeds, for example).

#### Potential/inhibition of effect:

- ACTH.
- Corticosteroids.
- Phenytoin.
  
- The effect of warfarin can be reduced by concomitant use of the herbal remedy *St John's wort*(*Hypericum perforatum*).
  
- Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. It is not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin should be advised to avoid this drink unless the health benefits are considered to outweigh any risks. Increased medical supervision and INR monitoring should be considered for any patient taking warfarin and a regular intake of cranberry juice.
- It is not known whether other cranberry products, such as capsules or concentrates, might also interact with warfarin. Therefore, similar caution should be observed with these products.

#### **4.6 Pregnancy and lactation**

##### Pregnancy

Oral anticoagulants should not be used in pregnancy, particularly because of possible teratogenicity and foetal haemorrhage near term. It is suggested that heparin, which does not cross the placenta, is used during the first trimester and after 37 weeks gestation. However, heparin during pregnancy is not absolutely safe and specialist guidance should be obtained before anticoagulant therapy is given to pregnant women. Women of child-bearing age who are taking Warfarin Tablets should be cautioned about the possible complications of pregnancy.

##### Lactation

Breast- fed infants are at no risk.

#### **4.7 Effects on ability to drive and use machines**

Warfarin Tablets have 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.

| <b>MedDRA system organ class</b>                | <b>Adverse Reaction</b>  |
|---|--|
| Infections and infestations                     | Fever  |
| Blood and lymphatic system disorders            | Haemorrhage; epistaxis   |
| Immune system disorders                         | Hypersensitivity   |
| Skin and subcutaneous disorders                 | Rash; alopecia; purpura; ‘purple toes’ syndrome; erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis |
| Respiratory, thoracic and mediastinal disorders | Haemothorax  |
| Gastrointestinal disorders                      | Diarrhea; nausea; vomiting; pancreatitis   |
| Hepatobiliary disorders                         | Jaundice; hepatic dysfunction  |
| Investigations                                  | Unexplained drop in haematocrit  |

#### 4.9 Overdose

If therapy is controlled as recommended, bleeding due to overdosage is rare. An episode of bleeding during Warfarin therapy must be investigated fully and must not be regarded as an indication of overdosage.

If haemorrhage occurs, or a potential bleeding state arises, excessive depression of coagulation activity can be corrected by temporary withdrawal of Warfarin Tablets and, if necessary, by infusion of fresh-frozen plasma or whole blood. Vitamin K1, 5 to 10 mg orally or intravenously, may be required to supplement specific treatment with factor concentrates.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**PHARMACOLOGICAL CATEGORY: Antithrombotic agent (Vitamin K Antagonist) ATC CODE: B01 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**

Lactose monohydrate  
Quinoline yellow (E104)  
Ponceau 4R (E124)  
Sucrose  
Maize starch  
Pregelatinised starch  
Magnesium stearate

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

2 years

## **6.4 Special precautions for storage**

For Blisters:

- Do not store above 25° C.
- Store in the original package.

For Bulk containers:

- Do not store above 25° C.
- Keep the container tightly closed.

## **6.5 Nature and contents of container**

Aluminium/PVDC coated PVC blister strips containing:

1)14 tablets. Blister strips packaged into outer carton to give total of 28,56 or 112 tablets.

2)10 tablets. Blister strips packaged into outer carton to give total of 20tablets.

Bulk HDPE containers of 100 or 500 tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Bristol Laboratories Limited  
Unit 3, Canalside, Northbridge Road,  
Berkhamsted, Hertfordshire,  
HP4 1EG, UK

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 17907/0103

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26/10/2006

## **10 DATE OF REVISION OF THE TEXT**

26/10/2006



## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Warfarin 3 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Warfarin Sodium 3 mg.

For a full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Tablet.

Blue coloured, circular, flat faced bevelled edged uncoated tablet with '3' embossing on one side and 'BL' embossing on the other.

### 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 and treatment of venous thrombosis and pulmonary embolism.

Transient attacks of cerebral ischaemia.

#### 4.2 Posology and method of administration

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 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.

In emergencies, anticoagulant therapy should be initiated with heparin and Warfarin together.

Concomitant therapy with heparin affects the results of control tests, and should be discontinued at least six hours before the first test is carried out.

Elderly: As for adults.

Children: Warfarin Tablets are not recommended for use in children due to insufficient data on safety and efficacy.

Method of administration: Oral.

### 4.3 Contraindications

- Known hypersensitivity to warfarin or to any of the inactive ingredients contained in warfarin tablets.
- Severe hepatic or renal disease.
- Bacterial endocarditis.
- Actual or potential haemorrhagic conditions, such as peptic ulcer or uncontrolled hypertension.
- Use within 24 hours of surgery or labour should be undertaken with caution, if at all.
- Warfarin is contraindicated in pregnancy.
- This medicinal product contains lactose. It is therefore unsuitable for people with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.
- This medicinal product contains sucrose. It is therefore unsuitable in hereditary fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase-isomaltase deficiency.

### 4.4 Special warnings and precautions for use

The following may exaggerate the effect of Warfarin Tablets, and necessitate a reduction of dosage:

Loss of weight. Elderly patients, acute illness, deficient renal function, decreased dietary intake of Vitamin K, Administration of some drugs(see interactions).

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

Weight gain. Diarrhoea, vomiting, increased dietary intake of Vitamin K, fats and oils, administration of some drugs (see interactions).

Careful additional control tests are necessary if a patient is changed from one anticoagulant formulation to another.

Reversal of warfarin anticoagulants by Vitamin K takes several days. In emergency situation, fresh-frozen plasma should be given.

Sensitivity to other drugs taken concomitantly with Warfarin Tablets should be considered. Patients who are sensitive to Warfarin Tablets usually tolerate other anticoagulant therapy.

If therapy is controlled as recommended, bleeding due to overdosage is rare. An episode of bleeding during Warfarin therapy must be investigated fully and must not be regarded as an indication of overdosage.

#### 4.5 Interaction with other medicinal products and other forms of interaction

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.

##### Potential effect:

- Alcohol (large or chronic amounts, especially in patients with impaired liver function), Amiodarone, Amitriptylline/ Nortriptylline, anabolic steroids, anti-inflammatory analgesics, Allopurinol, Azapropazone, Aztreonam, Bezafibrate, broad spectrum antibiotics.
- Cephmandole, Chloral hydrate, Chloramphenicol, Cimetidine, Ciprofloxacin, Clofibrate, Co-Trimoxazole.
- Cholestyramine may decrease absorption of VitaminK and thus increase coumarin anticoagulant activity.
- Danazol, Dextropropoxyphene, Dextrothyroxine, Diflunisal, Dipyridamole, Disulfiram.
- Erythromycin.
- Feprazone, Fluconazole, Flurbiprofen, Fluoroxamine.
- Glucagon, Gemfibrocil.
- Hepatotoxic drugs(potentially).
- Indomethacin.
- Ketaconazole.
- Latamoxef.
- Metronidazole, Mefenamic Acid, Methylpenidate, Miconazole.
- Nalidixic acid, Neomycin, Norfloxacin.
- Omeprazole, Oxyphenbutazone.
- Paracetamol, Phenformin, Phenylbutazone, Phenyramidol, Piroxicam, Propafenone.
- Quinidine.
- Salicylates, Sulindac, Sulphonamides.
- Tamoxifen, tetracyclines, Tolbutamide, Thyroid drugs, Triclofos.

##### Decrease in effect :

- Aminoglutethimide.
- Barbiturates.
- Carbamazepine.
- Dichloralphenazone.
- Ethchlorvynol.
- Gluthethimide, Griseofulvin.
- Oral contraceptives.
- Primidone.

- Rifampicin.
- Sucralfate.
- Vitamin K(enteral feeds, for example).

Potential/inhibition of effect:

- ACTH.
- Corticosteroids.
- Phenytoin.
- The effect of warfarin can be reduced by concomitant use of the herbal remedy *St John's wort(Hypericum perforatum)*.
- Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. It is not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin should be advised to avoid this drink unless the health benefits are considered to outweigh any risks. Increased medical supervision and INR monitoring should be considered for any patient taking warfarin and a regular intake of cranberry juice.
- It is not known whether other cranberry products, such as capsules or concentrates, might also interact with warfarin. Therefore, similar caution should be observed with these products.

#### **4.6 Pregnancy and lactation**

Pregnancy

Oral anticoagulants should not be used in pregnancy, particularly because of possible teratogenicity and foetal haemorrhage near term. It is suggested that heparin, which does not cross the placenta, is used during the first trimester and after 37 weeks gestation. However, heparin during pregnancy is not absolutely safe and specialist guidance should be obtained before anticoagulant therapy is given to pregnant women. Women of child-bearing age who are taking Warfarin Tablets should be cautioned about the possible complications of pregnancy.

Lactation

Breast- fed infants are at no risk.

#### **4.7 Effects on ability to drive and use machines**

Warfarin Tablets have 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.

| <b>MedDRA system organ class</b>                | <b>Adverse Reaction</b>  |
|---|--|
| Infections and infestations                     | Fever  |
| Blood and lymphatic disorders                   | Haemorrhage; epistaxis   |
| Immune system disorders                         | Hypersensitivity   |
| Skin and subcutaneous disorders                 | Rash; alopecia; purpura; ‘purple toes’ syndrome; erythematous swollen skin patches leading to ecchymosis, infarction and skin necrosis |
| Respiratory, thoracic and mediastinal disorders | Haemothorax  |
| Gastrointestinal disorders                      | Diarrhea; nausea; vomiting; pancreatitis   |
| Hepatobiliary disorders                         | Jaundice; hepatic dysfunction  |
| Investigations                                  | Unexplained drop in haematocrit  |

## 4.9 Overdose

If therapy is controlled as recommended, bleeding due to overdosage is rare. An episode of bleeding during Warfarin therapy must be investigated fully and must not be regarded as an indication of overdosage.

If haemorrhage occurs, or a potential bleeding state arises, excessive depression of coagulation activity can be corrected by temporary withdrawal of Warfarin Tablets and, if necessary, by infusion of fresh-frozen plasma or whole blood. Vitamin K1, 5 to 10 mg orally or intravenously, may be required to supplement specific treatment with factor concentrates.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**PHARMACOLOGICAL CATEGORY: Antithrombotic agent (Vitamin K Antagonist) ATC CODE: B01 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**

Lactose monohydrate  
Indigo carmine Aluminium lake (E132)  
Sucrose  
Maize starch  
Pregelatinised starch  
Magnesium stearate

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

2 years

## **6.4 Special precautions for storage**

For Blisters:

- Do not store above 25° C.
- Store in the original package.

For Bulk containers:

- Do not store above 25° C.
- Keep the container tightly closed.

## **6.5 Nature and contents of container**

Aluminium/PVDC coated PVC blister strips containing:

- 1)14 tablets. Blister strips packaged into outer carton to give total of 28, 56 or 112 tablets.
- 2)10 tablets. Blister strips packaged into outer carton to give total of 20tablets.

Bulk HDPE containers of 100 or 500 tablets.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Bristol Laboratories Limited  
Unit 3, Canalside, Northbridge Road,  
Berkhamsted, Hertfordshire,  
HP4 1EG, UK

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 17907/0104

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26/10/2006

## **10 DATE OF REVISION OF THE TEXT**

26/10/2006

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Warfarin 5 mg Tablets

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Warfarin Sodium 5 mg.

For a full list of excipients, see section 6.1

### 3 PHARMACEUTICAL FORM

Tablet.

Pink coloured, circular, flat faced bevelled edged uncoated tablet with '5' embossing on one side and 'BL' embossing on the other.

### 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.

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#### 4.2 Posology and method of administration

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 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.

In emergencies, anticoagulant therapy should be initiated with heparin and Warfarin together.

Concomitant therapy with heparin affects the results of control tests, and should be discontinued at least six hours before the first test is carried out.



Elderly: As for adults.

Children: Warfarin Tablets are not recommended for use in children due to insufficient data on safety and efficacy.

Method of administration: Oral.

### 4.3 Contraindications

- Known hypersensitivity to warfarin or to any of the inactive ingredients contained in warfarin tablets.
- Severe hepatic or renal disease.
- Bacterial endocarditis.
- Actual or potential haemorrhagic conditions, such as peptic ulcer or uncontrolled hypertension.
- Use within 24 hours of surgery or labour should be undertaken with caution, if at all.
- Warfarin is contraindicated in pregnancy.
- This medicinal product contains lactose. It is therefore unsuitable for people with lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.
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The following may reduce the effect of Warfarin Tablets, and require the dosage to be increased:

Weight gain. Diarrhoea, vomiting, increased dietary intake of Vitamin K, fats and oils, administration of some drugs (see interactions).

Careful additional control tests are necessary if a patient is changed from one anticoagulant formulation to another.

Reversal of warfarin anticoagulants by Vitamin K takes several days. In emergency situation, fresh-frozen plasma should be given.

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- Hepatotoxic drugs(potentially).
- Indomethacin.
- Ketaconazole.
- Latamoxef.
- Metronidazole, Mefenamic Acid, Methylpenidate, Miconazole.
- Nalidixic acid, Neomycin, Norfloxacin.
- Omeprazole, Oxyphenbutazone.
- Paracetamol, Phenformin, Phenylbutazone, Phenyramidol, Piroxicam, Propafenone.
- Quinidine.
- Salicylates, Sulindac, Sulphonamides.
- Tamoxifen, tetracyclines, Tolbutamide, Thyroid drugs, Triclofos.

##### Decrease in effect :

- Aminoglutethimide.
- Barbiturates.
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- The effect of warfarin can be reduced by concomitant use of the herbal remedy *St John's wort*(*Hypericum perforatum*).
  
- Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. It is not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin should be advised to avoid this drink unless the health benefits are considered to outweigh any risks. Increased medical supervision and INR monitoring should be considered for any patient taking warfarin and a regular intake of cranberry juice.
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#### **4.6 Pregnancy and lactation**

##### Pregnancy

Oral anticoagulants should not be used in pregnancy, particularly because of possible teratogenicity and foetal haemorrhage near term. It is suggested that heparin, which does not cross the placenta, is used during the first trimester and after 37 weeks gestation. However, heparin during pregnancy is not absolutely safe and specialist guidance should be obtained before anticoagulant therapy is given to pregnant women. Women of child-bearing age who are taking Warfarin Tablets should be cautioned about the possible complications of pregnancy.

##### Lactation

Breast-fed infants are at no risk.

#### **4.7 Effects on ability to drive and use machines**

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

#### **4.8 Undesirable effects**

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| Immune system disorders                         | Hypersensitivity   |
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| Gastrointestinal disorders                      | Diarrhea; nausea; vomiting; pancreatitis   |
| Hepatobiliary disorders                         | Jaundice; hepatic dysfunction  |
| Investigations                                  | Unexplained drop in haematocrit  |

#### 4.9 Overdose

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## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

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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**

Lactose monohydrate  
Erythrosine Aluminium lake (E127)  
Sucrose  
Maize starch  
Pregelatinised starch  
Magnesium stearate

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

2 years

## **6.4 Special precautions for storage**

### For Blisters:

- Do not store above 25° C.
- Store in the original package.

### For Bulk containers:

- Do not store above 25° C.
- Keep the container tightly closed.

## **6.5 Nature and contents of container**

Aluminium/PVDC coated PVC blister strips containing:

- 1) 14 tablets. Blister strips packaged into outer carton to give total of 28, 56 or 112 tablets.
- 2) 10 tablets. Blister strips packaged into outer carton to give total of 20 tablets.

Bulk HDPE containers of 100 or 500 tablets

Not all pack sizes are marketed

## **6.6 Special precautions for disposal**

No special requirements.

## **7 MARKETING AUTHORISATION HOLDER**

Bristol Laboratories Limited  
Unit 3, Canalside, Northbridge Road,  
Berkhamsted, Hertfordshire,  
HP4 1EG, UK

## **8 MARKETING AUTHORISATION NUMBER(S)**

PL 17907/0105

## **9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

26/10/2006

## **10 DATE OF REVISION OF THE TEXT**

26/10/2006

Patient Information Leaflet

**WARFARIN 1MG TABLETS  
PL 17907/0103**

**WARFARIN 3MG TABLETS  
PL 17907/0104**

**WARFARIN 5MG TABLETS  
PL 17907/0105**

PACKAGE LEAFLET: INFORMATION FOR USER

**WARFARIN 1MG, 3MG OR 5MG TABLETS**  
**Warfarin Sodium**

**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 pharmacist.
- This medicine has been prescribed 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 get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

- 1 What Warfarin Tablets are and what they are used for
- 2 Before you take Warfarin Tablets
- 3 How to take Warfarin Tablets
- 4 Possible side effects
- 5 How to store Warfarin Tablets
- 6 Further information

**WHAT WARFARIN TABLETS ARE AND WHAT THEY ARE USED FOR**

Warfarin belongs to a group of medicines called anticoagulants. Warfarin Tablets are given to help prevent blood clotting.

**BEFORE YOU TAKE WARFARIN TABLETS**

**Do not take Warfarin Tablets**

- If you are allergic (hypersensitive) to warfarin sodium or any of the other ingredients of Warfarin Tablets.
  - If you are pregnant.
  - If you have kidney or liver problems
  - If you have bacterial endocarditis (bacterial infection of the heart) or raised blood pressure
  - If you have any conditions which cause bleeding, or if you bruise easily
  - If you are about to undergo surgery or dental treatment or within 24 hours after surgery or dental treatment.
  - If you have, or have ever had, a stomach ulcer
  - If you have been told by your doctor that you have intolerance to some sugars, as this product contains sugars called lactose and sucrose.
- The Poncau 4R contained in the 1mg tablets may cause allergic reactions.

**Take special care with Warfarin Tablets**

- If you drink large amounts of alcohol
- If you are a female and trying to become pregnant
- If you have kidney problems
- If your weight changes rapidly. Keep your diet and level of activity as close to normal as possible, even when on any extended trips such as holidays
- If you are elderly
- If you are suffering from diarrhoea or vomiting
- If you take part in sports activities which have a high risk of injury
- If you change to another type of anticoagulant medication
- If you have to go to another doctor, to hospital, or to the dentist tell them that you are being treated with an anticoagulant and ask them to contact your own doctor.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those obtained without a prescription.

Some medicines used for the following conditions can potentiate the way Warfarin tablets work, if taken together with warfarin:

- Heart problems e.g. amiodarone, propafenone, quinidine
- Problems with platelet aggregation (blood cells sticking together) e.g. dipyridamole
- Depression e.g. amitriptyline or nortriptyline
- Pain and inflammation e.g. azapropazone, salicylates and diflunisal
- Pain e.g. paracetamol, dextropropoxyphene,
- High levels of lipids (fats) in the blood e.g. bezafibrate, gemfibrozil and clofibrate
- Infection e.g. cephalexin, chloramphenicol, ciprofloxacin, co-trimoxazole, erythromycin, fluconazole, ketoconazole, metronidazole, miconazole, nalidixic acid, norfloxacin, sulphoamides and neomycin
- Stomach ulcers or excessive production of stomach acid e.g. cimetidine, omeprazole
- Endometriosis, menstrual problems e.g. Danazol
- Diabetes e.g. tolbutamide and glucagon
- Gout and rheumatic diseases e.g. allopurinol, flurbiprofen, indomethacin, mefenamic, piroxicam, sulindac
- Cancer e.g. tamoxifen
- Insomnia e.g. chloral hydrate
- Hyperactivity e.g. methylphenidate
- Chronic alcoholism e.g. disulfiram
- Thyroid problems
- Epilepsy
- Anabolic steroids.
- Alcohol (in large amounts, especially if you suffer from liver problems.)
- Broad spectrum antibiotics e.g. Aztreonam
- Gastro-intestinal system (Cholestyramine may decrease absorption of Vitamin K and thus increase coumarin anticoagulant activity)
- Treatment of chronic alcohol dependence (under specialist supervision) e.g. disulfiram
- Treatment programme for attention-deficit hyperactivity disorder e.g. methylphenidate

Some medicines used for the following conditions can decrease the way Warfarin tablets work, if taken together with warfarin:

- Insomnia e.g. barbiturates
- Partial and secondary generalised tonic-clonic seizures e.g. carbamazepine
- Infection e.g. griseofulvin, rifampicin
- Oral contraceptives
- Epilepsy e.g. primidone
- Stomach ulcers e.g. sucralfate
- Vitamin K (enteral feeds, for example)

Some of the following medicines can potentiate inhibit the way Warfarin tablets work, if taken together with warfarin:

- Oral ulceration and inflammation e.g. corticosteroids

XXXX



- Epilepsy e.g. phenytoin
- The herbal remedy St. John's Wort (*Hypericum perforatum*) should not be taken at the same time as this medicine as it may inhibit the effect of Warfarin. If you already take St. John's Wort, consult your doctor before stopping St. John's Wort preparations.
- Individual case reports suggest a possible interaction between warfarin and cranberry juice, in most cases leading to an increase in INR or bleeding event. It is not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin should be advised to avoid this drink unless the health benefits are considered to outweigh any risks.

#### **Taking Warfarin Tablets with food and drink**

Drinking cranberry juice or taking other cranberry products (for example capsules or concentrates), might increase the effect of warfarin in 'thinning' the blood. You should, therefore, avoid drinking/taking these products whilst taking warfarin. If you have been advised to take cranberry juice or other products for medical reasons (e.g. bladder infections), or are regularly drinking or taking cranberry products, you should contact your anticoagulant clinic or health advisor before making any changes to the amount you drink/take. Your doctor or clinic may wish to monitor you more frequently while you are taking any cranberry product.

#### **Pregnancy and breast-feeding**

If you are female and think you may have become pregnant, contact your doctor as soon as possible. Warfarin Tablets can have an adverse effect on the unborn child, and alternative medicines are available if considered necessary by your doctor.

There is no risk to your baby if you breast-feed while taking Warfarin Tablets.

#### **Effects on Ability to Drive and Use Machines**

If you feel tired or dizzy while taking your tablets you should not drive or operate machinery.

#### **HOW TO TAKE WARFARIN TABLETS**

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

The usual starting dose of Warfarin Tablets is 10 mg daily for 2 days. After 2 days the dose is usually 3 mg to 9 mg taken at the same time each day. Your doctor may advise that you take more or fewer tablets, depending on the results of a blood test, which will be performed at intervals during your treatment. If you are not sure how many tablets to take, or when to take them, ask your doctor or pharmacist.

- Swallow the tablets whole with a drink of water.
- Try to take the tablets at the same time each day.
- Do not take more tablets than your doctor tells you to.
- Do not stop taking your tablets except on your doctor's advice.

#### **If you take more Warfarin Tablets than you should**

If you accidentally take too many Warfarin Tablets, tell your doctor immediately or contact your nearest Hospital Casualty / Accident and Emergency Department. Remember to take your tablets in the packaging with you, so that your doctor can easily see what you have taken.

#### **If you forget to take Warfarin Tablets**

If you miss a dose and remember within two or three hours, you can still take that dose. If you forget your dose for a longer time, do not take that dose to catch up, but take your next dose when it is due. Remember to tell your doctor when you see him/her next and have your blood test.

Do not take a double dose to make up for a forgotten dose.

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

#### **POSSIBLE SIDE EFFECTS**

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

If you get any of the following, tell your doctor, immediately:

- Skin rash or loss of hair
- Fever
- Nausea, vomiting or diarrhoea
- Jaundice (yellowing of the skin or whites of the eyes)
- Purple discoloration to any other part of your skin e.g. toes
- Changes in the amount or colour of the urine which you pass
- Bleeding from the nose without any apparent cause. Back or red faeces can indicate internal bleeding. Dark red or brown urine can indicate problems with the kidney or bladder
- Suddenly develop a fever, or unusual symptoms such as pain, swelling, discomfort or you have difficulty in breathing

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **HOW TO STORE WARFARIN TABLETS**

Keep out of reach and sight of children.

Do not use Warfarin Tablets after the "Expiry Date" which is stated on the container. The expiry date refers to the last day of that month.

For Blisters:

- Do not store above 25° C.
- Store in the original package in order to protect from light.

For Bulk containers:

- Do not store above 25° C.
- Keep the container tightly closed in order to protect from light.

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

#### **FURTHER INFORMATION**

##### **What Warfarin Tablets contain**

Each tablet contains respectively 1mg, 3mg, or 5mg of the active ingredient, Warfarin Sodium.

As well as Warfarin Sodium, the tablets also contain lactose monohydrate, maize starch, sucrose, pregelatinised starch, magnesium stearate and additional, for 1 mg tablets quinoline yellow (E104), and ponceau 4R (E124), for 3mg tablets indigo carmine aluminium lake (E132), and for 5mg tablets erythrosine aluminium lake (E127).

##### **What Warfarin Tablets look like and contents of the pack**

The 1mg tablet is peach coloured, circular, flat faced bevelled edged uncoated tablet with '1' embossing on one side and 'BL' embossing on the other. The 3mg tablet is blue coloured, circular, flat faced bevelled edged uncoated tablet with '3' embossing on one side and 'BL' embossing on the other. The 5mg tablet is pink coloured, circular, flat faced bevelled edged uncoated tablet with '5' embossing on one side and 'BL' embossing on the other. The tablets are packaged in aluminium blister packs of 28, 56, or 112 tablets or in bulk containers of 100 or 500 tablets. Not all pack sizes may be marketed.

##### **Marketing Authorisation Holder and Manufacturer**

Bristol Laboratories Ltd, Unit 3, Canalside, Northbridge Road, Berkhamsted, Hertfordshire, HP4 1EG, UK

This leaflet was last approved: MM/YYYY

IXXXX

## Labels/Packaging

# WARFARIN 1MG TABLETS

## PL 17907/0103



7423 C 7462 C 186 C 2728 C 424 C BLACK

Kaypee Design  
180806  
version 02

# WARFARIN 1MG TABLETS

## PL 17907/0103



Each tablet contains Warfarin Sodium 1 mg (as the active ingredient). Also contains lactose monohydrate, sucrose and colours E104, E124 (See leaflet for further information).

For oral administration only. Take as directed by a physician.

For further information please read the patient information leaflet provided.

**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.**

Do not store above 25°C, Keep the container tightly closed.

**Warfarin**  
Tablets

**1 mg**

**500**  
Tablets

**BRISTOL**

Bar code

BN :  
EXP:

Code: BL 501  
**PL 17907/0103** [POM]

PL Holder :  
**Bristol Laboratories Ltd.,**  
Berkhamsted, Herts, HP4 1EG, UK.

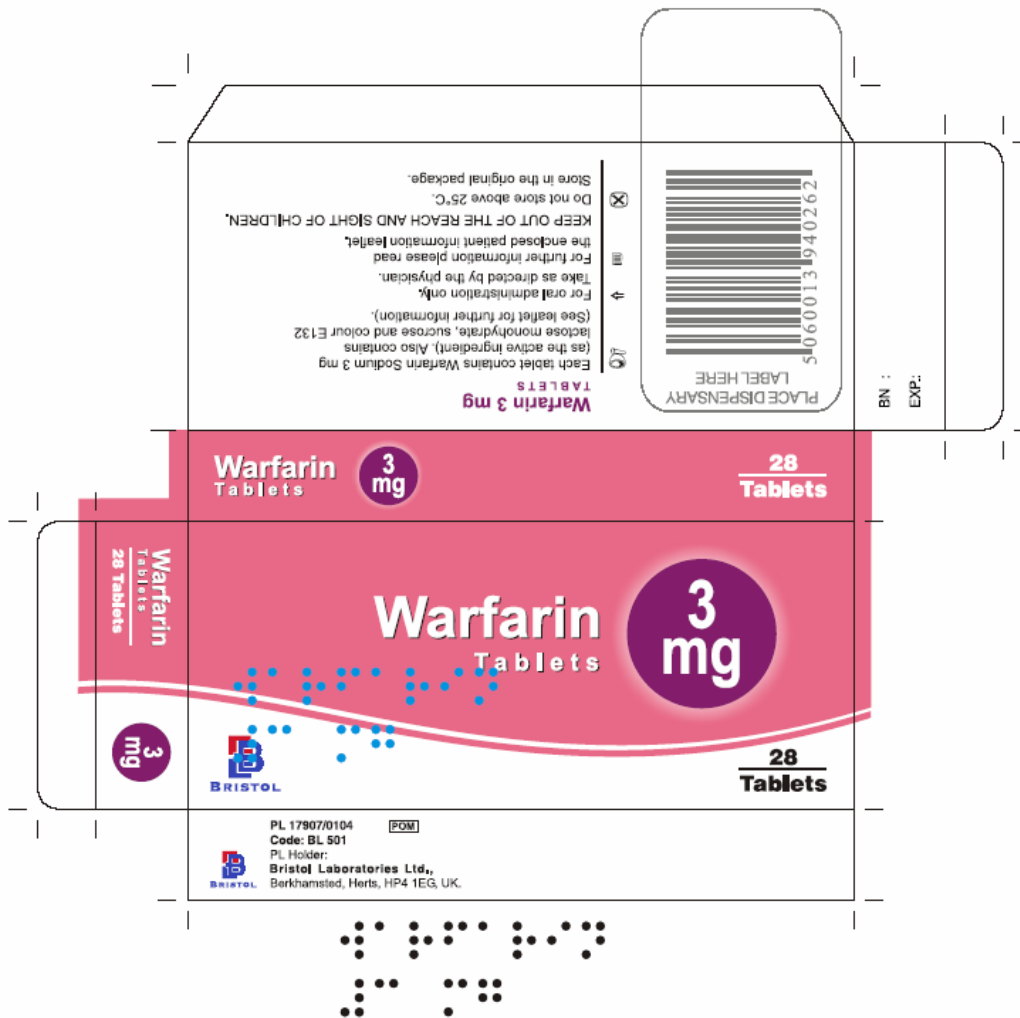
Size : 150 X 70 mm

■ 7423 C ● 7462 C ■ 186 C ■ 2728 C ■ 424 C ■ BLACK

Kaypee Design  
180806  
version 02

# WARFARIN 3MG TABLETS

## PL 17907/0104



7423 C ● 512 C ■ 186 C ■ 2728 C ■ 424 C ■ BLACK

Kaypee Design  
 180806  
 version 02

# WARFARIN 3MG TABLETS

## PL 17907/0104



Each tablet contains Warfarin Sodium 3 mg (as the active ingredient). Also contains lactose monohydrate, sucrose and colour E132 (See leaflet for further information).

For oral administration only. Take as directed by a physician.

For further information please read the patient information leaflet provided.

**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.**

Do not store above 25°C. Keep the container tightly closed.



BN :  
EXP:

Code: BL 501  
**PL 17907/0104** [POM]  
 PL Holder :  
**Bristol Laboratories Ltd.,**  
 Berkhamsted, Herts, HP4 1EG, UK.

Kaypee Design  
 180806  
 version 02

■ 7423 C ● 512 C ■ 186 C ■ 2728 C ■ 424 C ■ BLACK

**WARFARIN 5MG TABLETS**  
**PL 17907/0105**



■ 7423 C ● 281 C ■ 186 C ■ 2728 C ■ 424 C ■ BLACK

Kaypee Design  
180806  
version 02

# WARFARIN 5MG TABLETS

## PL 17907/0105


Each tablet contains Warfarin Sodium 5 mg (as the active ingredient). Also contains lactose monohydrate, sucrose and colour E127 (See leaflet for further information).

For oral administration only. Take as directed by a physician.

For further information please read the patient information leaflet provided.

**KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.**

Do not store above 25°C. Keep the container tightly closed.



**Warfarin**  
Tablets

**5 mg**

**500**  
Tablets

**BRISTOL**

Bar code

BN :  
EXP:

Code: BL 501

PL 17907/0105 POM

PL Holder :  
**Bristol Laboratories Ltd.,**  
Berkhamsted, Herts, HP4 1EG, UK.

Kaypee Design  
180806  
version 02



■ 7423 C ● 281 C ■ 186 C ■ 2728 C ■ 424 C ■ BLACK