

## Marcoumar®

Phenprocoumon

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### Anticoagulant for oral administration

### Composition

*Active ingredient:* phenprocoumon  
Tablets (cross-scored) 3 mg

### Properties and Effects

Marcoumar inhibits coagulation specifically by displacing vitamin K from an enzyme system responsible for the formation in the liver of the coagulation factors II (prothrombin), VII, IX and X. It may thus be regarded as an antivitamin K. The coagulation factors already formed are not impaired by Marcoumar. For this reason, Marcoumar, unlike heparin for instance, produces no immediate inhibition of coagulation. It is thus ineffective *in vitro*. Onset of action is after one to two days, and the full effect is seen four to six days after administration.

Increasing the dosage of Marcoumar does not reduce the latency time. The degree of anticoagulation is monitored by determining the thromboplastin time or an appropriate modification of this method. Measured coagulation times can be converted into Quick values, prothrombin ratios or, preferably, into INR values.

Marcoumar is characterized by a prolonged and uniform action, which builds up gradually and is obtainable with a very low dosage. Since Marcoumar acts specifically on the vitamin K enzyme system, it has no deleterious effect on the liver. For this reason, it is particularly suitable for treatment over months or even years (long-term anticoagulation).

Phytomenadione (vitamin K<sub>1</sub>) counteracts the delay in coagulation produced by Marcoumar.

## **Pharmacokinetics**

### *Absorption*

Phenprocoumon, the active ingredient of Marcoumar, is absorbed rapidly from the gastrointestinal tract.

### *Distribution*

A small but fairly constant proportion of the total blood content of phenprocoumon is present in the free, pharmacologically active form; 99% is bound to plasma proteins, chiefly albumin, and in this way exerts a depot function. Owing to the long sojourn of protein-bound phenprocoumon in the plasma, the steady state is not reached until some days after the maintenance dose has been changed.

### *Metabolism*

Free phenprocoumon is hydroxylated in the liver to practically inert metabolites; these are then excreted through the kidneys.

### *Elimination*

The elimination half-life from plasma is approximately 160 hours.

### *Pharmacokinetics in special situations*

Renal insufficiency has no significant effect on the elimination half-life. The effect of Marcoumar may be weakened by metabolic induction, for instance by barbiturates, or may be intensified by displacement from the protein-binding site, for instance by antiinflammatory drugs.

## **Indications**

Prophylaxis of thrombosis, thrombosis, embolism, myocardial infarction.

## **Dosage and administration**

### *Standard dosage*

Treatment with Marcoumar must be monitored by determination of the thromboplastin time or another appropriate test such as the chromogenic substrate method (see section Supervision of

Marcoumar therapy). The first determination must be made before beginning treatment with Marcoumar.

Pretreatment Quick level	Dosage 1st day (single dose)	Dosage 2nd day	Total first two days
80-100%	5 tablets	3 tablets	8 tablets
70%	5 tablets	2 tablets	7 tablets
60%	4 tablets	2 tablets	6 tablets
<60%	Perform liver function tests		

On the third day a further assay must be made and the dosage adjusted accordingly. As a general rule, treatment should lower the Quick level to 15-25% (INR\* 2.5-5.0) or, in the event of increased risk of bleeding, to 20-30% (INR 1.5-2.5).

\*INR - International Normalized Ratio, as given in the ICSH/ICTH recommendations for reporting prothrombin time in oral anticoagulant control. *Acta Haematol (Basel)* 72, 405-407 (1984).

Treatment continues with lower doses of Marcoumar, ½-2 tablets daily as a maintenance dose. Response to treatment varies greatly from one patient to another, and for this reason continuous monitoring of coagulation parameters is the only accurate way of establishing individual dosage.

The tablets should be swallowed whole with liquid. Do not dissolve first.

### Special dosage instructions

#### *Prophylaxis*

For most patients in danger of thrombosis, three to four weeks' prophylaxis with Marcoumar is indicated; anticoagulants should be given at least until such time as the patient has regained an adequate degree of mobility. Premature cessation of therapy increases the danger of thrombosis. After operations or childbirth, Marcoumar should be given from the second or third day on.

### *Therapy*

In the presence of acute thrombosis or embolism, anticoagulant therapy must begin with i.v. administration of heparin. After the acute phase has passed (i.e. after not less than two days, and in severe cases up to ten days or more) treatment may be continued with Marcoumar. On the first day of transition, the full initial dose of Marcoumar should be given together with an undiminished dose of heparin; the latter has no delayed action, whereas the anticoagulant effect of Marcoumar is preceded by the above-mentioned latency. During this period of transition the coagulation parameters must be checked with particular care. The duration of heparin therapy depends on the time taken until the desired degree of anticoagulation is reached. Treatment with Marcoumar is determined according to clinical needs; it may continue for several months or even years.

### *Supervision of Marcoumar therapy*

It is essential to check the effect of Marcoumar by means of the prothrombin time (Quick value) or another suitable test (such as the chromogenic substrate method) carried out first before treatment begins and then daily or every other day. When the maintenance dose has been established and the effects is known from prolonged experience, it is possible - owing to the drug's constant action - to extend the intervals (e.g. to once a month), as long as there is no sudden change in the patient's condition or in concurrent medication. Checks must be made more frequently when other drugs affecting the action or clearance of anticoagulants (antimicrobials, salicylates, etc.) are being given (see Interactions).

The therapeutic range is determined by the relevant data applicable to the determination method or the thromboplastin reagent used. In terms of human brain thromboplastin, the range is limited to Quick values 15-25%, or to the corresponding INR values (2.5-5.0). In preoperative and perioperative prophylaxis an INR range of 1.5-2.5 is recommended.

### *Reversal of anticoagulation*

If, during treatment with Marcoumar, the degree of anticoagulation falls below the therapeutic minimum, it is advisable to adjust the dosage and determine the coagulation values anew two days later.

Mild hemorrhage is usually controlled by oral or slow i.v. administration of 5-10 mg vitamin K<sub>1</sub>. If, after eight to twelve hours, sufficient coagulation is not attained or bleeding does not stop, a second - and possibly larger - dose of vitamin K<sub>1</sub> should be given.

Single doses of 20 mg and total doses of 40 mg vitamin K<sub>1</sub> should be regarded as the maximum. Excessive doses (more than 40 mg) should be avoided as further therapy with Marcoumar is made more difficult.

In life-threatening conditions (such as suspected intracranial hemorrhage, massive gastrointestinal bleeding, emergency operations), transfusion of a concentrate of vitamin-K-dependent clotting factors or freshly frozen plasma must be given immediately.

### **Contraindications**

Marcoumar must not be given to patients with hemorrhagic diathesis, severe liver parenchyma damage, manifest renal failure, gastrointestinal ulcers, endocarditis lenta, after neurosurgery or to patients with increased capillary fragility (e.g. in advanced arteriosclerosis or severe hypertension).

Angiography should not be performed during treatment with anticoagulants.

Menstrual bleeding is not a contraindication for Marcoumar.

### **Precautions**

Patients should be kept under particularly close surveillance after pulmonary resection, surgery of the genitalia, stomach or bile ducts, as well as in congestive heart failure, arteriosclerosis and hypertension, and in mild hepatopathy.

Heavy drinkers may experience a diminished anticoagulant effect, although the anticoagulant effect may be increased in the presence of liver impairment.

Phenylbutazone and its derivative oxyphenbutazone should not be given to patients receiving Marcoumar.

### **Pregnancy, nursing mothers**

Since Marcoumar, like other coumarin derivatives, may be associated with congenital malformation, it must not be used during pregnancy. Women of childbearing potential who

are being treated with Marcoumar must take effective contraceptive measures which should continue for 3 months after the last dose.

In nursing mothers, the active ingredient passes into the breast milk, though in such small amounts that no adverse reactions are likely to occur in the infant. As a precaution, however, prophylaxis involving the administration of 1 mg vitamin K<sub>1</sub> weekly to the infants concerned is recommended.

### **Undesirable effects**

Intramuscular injections should be avoided as far as possible during anticoagulant therapy owing to the danger of hemorrhage or hematoma. This complication rarely occurs on subcutaneous and never on intravenous injection. Outpatients receiving Marcoumar therapy should be instructed to carry vitamin K<sub>1</sub> with them, together with indications for their use and a doctor's certificate stating that they are under anticoagulant therapy.

When salicylates or antimicrobials are administered concurrently, the clotting time should be checked frequently (see Interactions).

Skin necrosis (usually cutaneous infarction) may occur at the beginning of anticoagulant treatment. In such a case, Marcoumar therapy must be stopped and its effect counteracted by means of vitamin K<sub>1</sub> and the patient immediately switched to heparin therapy. Prednisone may be administered in addition.

Allergic skin reactions may also occur during Marcoumar therapy.

Gastrointestinal intolerance is seldom observed. The administration of Marcoumar, or of other coumarin derivatives, has in rare cases resulted in reversible hair loss. There is evidence to suggest that coumarin-induced hepatitis can occur, with or without jaundice, though the patient generally recovers after discontinuation of Marcoumar. Although the incidence of hepatitis is minimal the liver function of patients receiving long-term treatment with Marcoumar should be monitored.

Due to the nature of phenprocoumon, the possibility of bleeding involving different organs and especially life-threatening hemorrhages involving the Central Nervous System and

Marcoumar can intensify the effect of sulfonylureas when taken concurrently (hence risk of hypoglycemia).

### **Overdosage**

See section Reversal of anticoagulation.

### **Special remarks**

#### *Stability*

This medicine should not be used after the expiry date (EXP) shown on the pack.

### **Packs**

Tablets (cross-scored) 3 mg: 25 and 100

Medicine: keep out of reach of children
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Current at April 2000