

# Sinthrome Tablets 1 mg

Summary of Product Characteristics Updated 05-Apr-2016 | Merus Labs Luxco S.a.R.L.

## 1. Name of the medicinal product

Sinthrome<sup>®</sup> Tablets 1mg.

## 2. Qualitative and quantitative composition

Acenocoumarol BP 1mg.

Excipient(s) with known effect:

Lactose (20 mg).

For the full list of excipients, see Section 6.1.

## 3. Pharmaceutical form

Tablets for oral administration.

White, round, flat tablets with slightly bevelled edges, with one side bearing the imprint "CG", and the other the imprint "AA".

## 4. Clinical particulars

### 4.1 Therapeutic indications

Treatment and prevention of thromboembolic diseases.

### 4.2 Posology and method of administration

#### Dosage

#### General target population

Sensitivity to anticoagulants varies from patient to patient and may also fluctuate during the course of treatment. Therefore, it is essential to perform regular testing of prothrombin time (PT)/International Normalised Ratio (INR) and to adjust the patient's dosage accordingly. If this is not possible, Sinthrome should not be used.

Sinthrome should be given in a single oral dose.

#### Initial dosage:

The dosing of Sinthrome must be individualised. If the PT/INR value is within the normal range before starting treatment, the following dosage schedule is recommended:

The usual starting dose is between 2 mg/day to 4 mg/day without administration of a loading dose. Treatment may also be initiated with a loading dose regimen, usually 6 mg on the first day followed by 4 mg on the second day.

If the initial thromboplastin time is abnormal, treatment should be instituted with caution.

Elderly patients ( $\geq 65$ ), patients with liver disease or severe heart failure with hepatic congestion or malnourished patients may require lower doses during treatment initiation and maintenance (see section 4.4 Special warnings and precautions for use).

Measurement of the thromboplastin time should be carried out daily in hospital starting from second or third dose of Sinthrome and up to the time when the coagulation status is stabilized within the target range. The interval between tests can later be extended, depending on the stability of PT/INR results. Blood samples for laboratory tests should always be taken at the same time of day.

#### Maintenance therapy and coagulation tests

The maintenance dose of Sinthrome varies from patient to patient and must be checked individually on the basis of PT/INR values. PT/INR should be assessed at regular intervals, i.e. at least once a month.

The maintenance dose generally lies between 1 to 8mg daily depending on the individual patient, the underlying disease, clinical indication and desired intensity of anticoagulation.

Depending on the clinical indication, the optimal intensity of anticoagulation or therapeutic range to be aimed at generally lies between INR values of 2.0 and 3.5 (see Table 1). Higher INR values up to 4.5 may be required in individual cases.

**Table 1 Recommended INR\* for Oral Anti-coagulant Therapy**

Indication	Recommended INR

Prophylaxis and treatment of venous thromboembolism (including pulmonary embolism)	2.0 – 3.0
Atrial fibrillation	2.0 – 3.0
Post-myocardial infarction (with increased risk for thromboembolic complications)	2.0 – 3.0
Bioprosthetic heart valves	2.0 – 3.0
Secondary prophylaxis in patients with antiphospholipid syndrome	2.0 – 3.0
Antiphospholipid syndrome patients with venous thromboembolism on therapeutic vitamin K antagonist	2.0 – 3.5
Mechanical heart valves	2.0 – 3.5

\*The PT, which reflects the reduction of Vitamin K dependent clotting factors VII, X and II, is dependent on the responsiveness of the thromboplastin used for PT-testing. The responsiveness of the respective local thromboplastin compared to World Health Organisation international reference preparations is reflected by its International Sensitivity Index (ISI).

The “International Normalised Ratio” (INR) was introduced for the purpose of standardisation of the PT. The INR is the ratio of the patient’s anticoagulated plasma PT to the normal plasma PT using the same thromboplastin in the same test system raised to the power of a value defined by the International Sensitivity Index.

### **Treatment discontinuation**

Generally, after withdrawal of Sinthrome, there is usually no danger of reactive hypercoagulability and therefore it is not necessary to give gradually diminishing doses. However, in extremely rare cases, in some high risk patients (e.g. after myocardial infarction), withdrawal should be gradual.

### **Missed dose**

The anticoagulant effect of Sinthrome persists beyond 24 hours. If the patient forgets to take the prescribed dose of Sinthrome at the scheduled time, the dose should be taken as soon as possible on the same day. The patient should not double the daily dose to make up for a missed dose, but should refer back to his or her doctor.

### **Conversion from heparin therapy**

In clinical situations which require rapid anticoagulation, initial treatment with heparin is preferred since the anticoagulant effect of Sinthrome is delayed. Conversion to Sinthrome may begin concomitantly with heparin therapy or may be delayed depending on the clinical situation. To ensure continuous anticoagulation, it is advisable to continue to prescribe full dose heparin therapy for at least 4 days after initiation of Sinthrome and to continue heparin therapy until the INR has been in the target range on at least two consecutive days. During the transition phase close monitoring of anticoagulation is necessary.

### **Treatment during dentistry and surgery**

Patients on Sinthrome, who undergo surgical or invasive procedures require close surveillance of their coagulation status. Under certain conditions, e.g. when the operation site is limited and accessible to permit effective use of local procedures for haemostasis, dental and minor surgical procedures may be performed during continued anticoagulation, without undue risk of haemorrhage. The decision to discontinue Sinthrome, even for a short period of time, should carefully consider individual risks and benefits. The introduction of bridging anticoagulant treatment, e.g. with heparin should be based on careful assessment of the expected risks of thromboembolism and bleeding.

### **Special populations**

#### **Renal impairment**

Sinthrome is contraindicated in patients with severe renal impairment due to an increased risk of haemorrhage. Caution should be exercised in patients with mild to moderate renal impairment (see section 4.3 Contraindications, Section 4.4 Special warnings and precautions and Section 5.2 Pharmacokinetic properties).

#### **Hepatic impairment**

Sinthrome is contraindicated in patients with severe hepatic impairment due to an increased risk of haemorrhage. Caution should be exercised in patients with mild to moderate hepatic impairment. (see -Section 4.3 Contraindications, Section 4.4 Special warnings and precautions and Section 5.2 Pharmacokinetic properties).

#### **Paediatric population**

Experience with oral anticoagulants including acenocoumarol in children remains limited. Caution and more frequent monitoring of PT/INR is recommended (see Section 4.4 Special warnings and precautions for use).

*Elderly:* A dose lower than the recommended adult dose may be sufficient in elderly patients. Caution and more frequent monitoring of PT/INR is recommended (see Section 4.4 Special warnings and precautions for use and Section 5.2 Pharmacokinetic properties).

### **Method of administration**

The daily dosage should always be taken at the same time of day. The tablet should be swallowed whole with a glass of water.

### **4.3 Contraindications**

#### *Pregnancy*

Hypersensitivity to acenocoumarol and related coumarin derivatives or to the excipients of Sinthrome, and in patients unable to co-operate (e.g. unsupervised patients with dementia, alcoholics and patients with psychiatric disorders).

All conditions where the risk of haemorrhage exceeds possible clinical benefit e.g. haemorrhagic diathesis and/or haemorrhagic blood dyscrasia; immediately prior to, or after surgery on the central nervous system or eyes and traumatising surgery involving extensive exposure of the tissues; peptic ulceration or haemorrhage in the gastro-intestinal tract, urogenital tract or respiratory system; cerebrovascular haemorrhages; acute pericarditis; pericardial effusion; infective endocarditis; severe hypertension (due to occult risks); severe hepatic impairment or severe renal impairment (see also section 4.2 Posology and method of administration) and in cases of increased fibrinolytic activity following operations on the lung, prostate or uterus etc.

### **4.4 Special warnings and precautions for use**

#### *Hepatic impairment*

Caution should be exercised in patients with mild to moderate hepatic impairment since the synthesis of blood coagulation factors may be impaired or there may be an underlying platelet dysfunction (see Section 4.2 Posology and method of administration and Section 5.2 Pharmacokinetic properties).

#### *Renal impairment*

Due to the possibility of accumulation of metabolites in impaired renal function, caution should be exercised in patients with mild to moderate renal impairment. (see Section 4.2 Posology and method of administration and Section 5.2 Pharmacokinetic properties).

#### *Heart failure*

In severe heart failure, a very cautious dosage schedule must be adopted, since hepatic congestion may reduce the activation of gamma-carboxylation of coagulation factors. However with reversal of the hepatic congestion, it may be necessary to raise the dosage.

#### *Haematological*

Caution should be exercised in patients with known or suspected (e.g. abnormal bleeding after injury) protein C or protein S deficiency (see Section 4.8 Undesirable effects).

#### *Special populations*

In paediatric and elderly patients ( $\geq 65$  years), caution and more frequent monitoring of PT/INR is recommended (see Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

#### *Miscellaneous*

Strict medical supervision should be given in cases where the disease or condition may reduce the protein binding of Sinthrome (e.g. thyrotoxicosis, tumors, renal disease, infections and inflammation).

Disorders affecting gastro-intestinal absorption may alter the anticoagulant activity of Sinthrome.

During treatment with anticoagulants, intramuscular injections may cause haematomas and should be avoided. Subcutaneous and intravenous injections may be given without such complications.

Meticulous care should be taken where it is necessary to shorten the PT/INR (thromboplastin time) for diagnostic or therapeutic procedures (eg angiography, lumbar puncture, minor surgery, tooth extractions etc).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

There are many possible interactions between coumarins and other drugs; those of clinical relevance are given below. Many of these are isolated reports only or have been reported with warfarin rather than acenocoumarol; for

completeness, all have been included. The mechanisms of these interactions include disturbances of absorption, inhibition or induction of the metabolising enzyme system (mainly CYP2C9), see Section 5.2 Pharmacokinetic properties), and reduced availability of vitamin K<sub>1</sub>, necessary for gamma-carboxylation of prothrombin–complex factors. It is important to note that some drugs may interact by more than one mechanism. Every form of therapy may involve the risk of an interaction, although not all will be significant. Thus careful surveillance is important and frequent coagulation tests (e.g. twice weekly) should be carried out when initially prescribing any drug in combination with Sinthrome, or when withdrawing a concomitantly administered drug.

### **Interactions resulting in concomitant use not being recommended**

The following drugs potentiate the anticoagulant activity of acenocoumarol and/or alter haemostasis and thereby increase the risk of haemorrhage:

Drugs altering haemostasis may potentiate the anticoagulant activity of Sinthrome and thereby increase the risk of haemorrhage. Consequently, Sinthrome should not be prescribed with such drugs, which include:

- heparin (including low-molecular-weight heparin) (except in situations which require rapid anticoagulations; see Section 4.2 Posology and method of administration);
- antibiotics (e.g. clindamycin);
- platelet-aggregation inhibitors (e.g. dipyridamole, clopidogrel), salicylic acid and its derivatives, (e.g. acetylsalicylic acid, para-aminosalicylic acid, diflunisal);
- clopidogrel, ticlopidine, phenylbutazone or other pyrazolone derivatives (e.g. sulfinpyrazone), and other non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors (e.g. celecoxib), high dose IV methylprednisolone.

The risk of gastrointestinal haemorrhage is increased if Sinthrome is prescribed in combination with these substances. In the case of unavoidable concurrent use, coagulation tests should be performed more frequently.

### **Interactions to be considered**

The anticoagulant effect may be potentiated by concomitant administration of the following drugs:

- allopurinol;
- anabolic steroids;
- androgens;
- anti-arrhythmic agents (e.g. amiodarone, quinidine);
- antibiotics:
  - broad spectrum antibiotics (e.g. amoxicillin, co-amoxiclav) macrolides (e.g. erythromycin, clarithromycin);
  - cephalosporins second and third generation;
  - metronidazole;
  - quinolones (e.g. ciprofloxacin, norfloxacin, ofloxacin);
  - tetracyclines;
  - neomycin;
  - chloramphenicol.
- imidazole derivatives, including topical administration (e.g. econazole, fluconazole, ketoconazole, miconazole);
- sulfonamides (including co-trimoxazole);
- fibrates (e.g. clofibrac acid), its derivatives and structural analogues (e.g. fenofibrate, gemfibrozil);
- disulfiram;
- etacrynic acid;
- glucagon;
- oral antidiabetics (e.g. glibenclamide);
- sulphonylureas (such as tolbutamide and chlorpropamide);
- H<sub>2</sub> antagonists (e.g. cimetidine);
- paracetamol;
- thyroid hormones (including dextrothyroxine);
- sulfinpyrazone;
- statins (e.g. atorvastatin, fluvastatin, simvastatin);

- selective serotonin re-uptake inhibitors (e.g. citalopram, fluoxetine, sertraline, paroxetine);
- tamoxifen;
- 5-fluorouracil and analogues;
- tramadol;
- proton pump inhibitors (e.g. omeprazole);
- plasminogen activators (e.g. urokinase; streptokinase and alteplase);
- thrombin inhibitors (e.g. argatroben);
- prokinetic agents (e.g. cisapride);
- antacids (e.g. magnesium hydroxide);
- viloxazine.

Inhibitors of CYP2C9 may potentiate the anticoagulant effect of acenocoumarol.

The anticoagulant effect may be diminished by concomitant administration of the following drugs:

- aminoglutethimide;
- antineoplastic drugs (e.g. azathioprine, 6-mercaptopurine);
- barbiturates (e.g. Phenobarbital);
- carbamazepine;
- cholestyramine (see Section 4.9 "Overdose");
- griseofulvin;
- oral contraceptives;
- rifampicin;
- HIV protease inhibitors (e.g. ritonavir, nelfinavir);
- thiazide diuretics;
- St. John's Wort/*Hypericum perforatum*;
- Inducers of CYP2C9, CYP2C19 or CYP3A4 may diminish the anticoagulant effect of acenocoumarol.

Vitamin E and corticosteroids (e.g. methylprednisolone, prednisone) may diminish the anticoagulant effect of coumarin derivatives.

Unpredictable effect on anticoagulation, including both increase and decrease in anticoagulant activity have been reported with the following drugs:

- protease inhibitors (e.g. indinavir, nelfinavir, ritonavir, saquinavir).

#### **Effects of acenocoumarol on other drugs:**

During concomitant treatment with hydantoin derivatives (such as phenytoin), the serum hydantoin concentration may rise.

Sinthrome may potentiate the hypoglycaemic effect of sulphonylurea derivatives e.g. glibenclamide, glimepiride.

Patients being treated with Sinthrome (especially those suffering from hepatic dysfunction) should limit their alcohol intake, since it is not possible to predict the severity of any drug interactions, nor identify any early signs of such interactions.

Cranberry juice should be avoided in patients receiving Sinthrome due to a theoretical risk of enhanced anti-coagulation. Increased medical supervision and INR monitoring should be considered for any patient receiving Sinthrome and regularly drinking cranberry juice. It is not known whether other cranberry products, such as capsules or concentrates, might also interact with Sinthrome. Therefore similar caution should be observed with these products.

## **4.6 Fertility pregnancy and lactation**

### **Pregnancy**

Sinthrome, like other coumarin derivatives, may be associated with congenital malformations of the embryo, therefore Sinthrome is contra-indicated for use in pregnancy (see Section 4.3 Contraindications). Women of child-bearing potential should take contraceptive measures during treatment with Sinthrome.

### **Lactation**

Acenocoumarol passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected. However, as a precaution, the infant should be given 1mg vitamin K<sub>1</sub> per week as a prophylactic measure.

The decision to breast-feed should be carefully considered and may include coagulation tests and vitamin K status evaluation in infants before advising women to breast-feed. Women who are breast-feeding and treated with Sinthrome should be carefully monitored to ensure that recommended PT/INR values are not exceeded.

### Fertility

There are no data available on the use of Sinthrome and its effect on fertility in humans.

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

Sinthrome has no influence on the ability to drive and use machines.

### 4.8 Undesirable effects

Undesirable effects are ranked under headings of frequency, the most frequent first, using the following convention: Very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1000$ ,  $< 1/100$ ); rare ( $\geq 1/10,000$ ,  $< 1/1000$ ); very rare ( $< 1/10,000$ ), including isolated reports.

Haemorrhage, in various organs, is the most common side-effect associated with Sinthrome; its occurrence is related to the dosage of the drug, the patient's age and the nature of the underlying disease (but not the duration of treatment). Fatalities have been reported. Possible sites of haemorrhage include the gastro-intestinal tract, brain, urogenital tract, uterus, liver, gall bladder and the eye. If haemorrhage occurs in a patient with a thromboplastin time within the therapeutic range, diagnosis of their condition must be clarified.

<b>Immune system disorders</b>	
Rare:	Hypersensitivity (e.g. urticaria, rash, dermatitis and fever)
<b>Vascular disorders</b>	
Common:	Haemorrhage
Very rare:	Vasculitis
<b>Gastrointestinal disorders</b>	
Rare	Decreased appetite, nausea, vomiting
<b>Hepatobiliary disorders</b>	
Very rare:	Liver injury
<b>Skin and subcutaneous tissue disorders</b>	
Rare:	Alopecia
Very rare:	Skin necrosis (haemorrhagic)*

\*Usually associated with congenital deficiency of protein C or its cofactor protein S.

### 4.9 Overdose

Clinical manifestations of overdosage are unlikely with large single doses, but more likely following prolonged use of daily doses exceeding those required therapeutically.

Hospital referral is recommended for any amount of Sinthrome taken above the therapeutic dose.

#### Symptoms:

The onset and severity of the symptoms are dependent on the individual's sensitivity to oral anticoagulants, the severity of the overdose and the duration of treatment.

Haemorrhage is the prominent feature of an overdose and may occur within 1 to 5 days after ingestion. Nose-bleeds, haematemesis, haemoptysis, gastro-intestinal haemorrhage, vaginal bleeding, haematuria (with renal colic), cutaneous haemorrhages, gingival bleeding, haematomata, and bleeding into the joints or menorrhagia may be experienced.

Further symptoms include tachycardia, hypotension, peripheral circulatory disorders due to loss of blood, nausea, vomiting, diarrhoea and abdominal pains.

Laboratory tests will show an extremely low Quick value (or high PT/INR value), pronounced prolongation of the recalcification time or thromboplastin time and disturbed gamma-carboxylation of factors II, VII, IX and X.

### *Treatment:*

The necessity or desirability of the treatment by gastric lavage in addition to the activated charcoal and cholestyramine administration is controversial. The benefits of these treatments should be balanced against the risk of bleeding in each patient.

### *Emergency and supportive measures:*

In emergency situations of severe haemorrhage, clotting factors can be returned to normal by administering fresh whole blood or fresh frozen plasma, complex concentrate or recombinant factor VIIa supplemented with vitamin K1.

### *Antidote:*

Vitamin K<sub>1</sub> (phytomenadione) may antagonise the inhibitory effect of Sinthrome on hepatic gamma-carboxylation of the vitamin K-dependent coagulation factors within 3 to 5 hours. In cases of clinically insignificant haemorrhages, such as a brief nose-bleed or small isolated haematomas, a temporary reduction or omission of the dose of Sinthrome is often sufficient. In cases of moderate to severe haemorrhage, Vitamin K<sub>1</sub> can be given orally.

Doses of Vitamin K<sub>1</sub> in excess of 5mg can cause resistance to further anticoagulant therapy for several days. If an anticoagulant is required, heparin may be used temporarily, although oral anticoagulant therapy should be resumed at the same time and heparin withdrawn once the therapeutic range has been reached.

In the case of life-threatening haemorrhage, intravenous transfusions of fresh frozen plasma or whole blood, complex concentrate or recombinant factor VIIa supplemented with vitamin K1 can abolish the effects of Sinthrome.

Sinthrome should be resumed when INR is in target range in case of moderate to severe haemorrhage.

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antithrombotic, vitamin K antagonists. ATC code: B01AA07

Acenocoumarol is a coumarin derivative and functions as vitamin K antagonist. Vitamin K antagonists produce their anticoagulant effect by inhibition of the vitamin K-epoxide-reductase with a subsequent reduction of the gamma-carboxylation of certain glutamic acid molecules which are located at several sites near the terminal end both of coagulation factors II (prothrombin), VII, IX, and X and of protein C or its cofactor protein S. This gamma-carboxylation has a significant bearing on interaction of the aforementioned coagulation factors with Calcium ions. Without this reaction, blood clotting cannot be initiated.

Depending on the initial dosage, Sinthrome prolongs the thromboplastin time within approximately 36 to 72 hours. Following withdrawal of Sinthrome, the thromboplastin time usually reverts to normal after a few days.

### **5.2 Pharmacokinetic properties**

#### Absorption

Acenocoumarol, is a racemic mixture of the optical R(+) and S(-) enantiomers.

Following oral administration, Sinthrome is rapidly absorbed; at least 60% of the administered dose is systemically available. Peak plasma concentrations are achieved within 1 to 3 hours after a single dose of 10mg and AUC values are proportional to the size of the dose over a dosage range of 8 to 16mg.

No correlation between plasma concentrations of acenocoumarol and the apparent prothombin levels can be established, due to the variation of plasma drug concentrations between patients.

#### Distribution

Over 98% of acenocoumarol is protein-bound, mainly to albumin. The calculated apparent volume of distribution is 0.16-0.18 L/kg for the R(+) enantiomer and 0.22-0.34 L/kg for the S(-) enantiomer.

#### Biotransformation

Acenocoumarol is extensively metabolised, 6- and 7-hydroxylation of both enantiomers of acenocoumarol are the major metabolites and the cytochrome P450 2C9 is the major catalyst for the formation of these four metabolites. Other enzymes involved in the metabolism of (R)-acenocoumarol are CYP1A2 and CYP2C19. By reduction of the keto group two different carbinol metabolites are formed. Reduction of the nitro group results in an amino metabolite. None of these metabolites contribute to the anticoagulant activity of the parent drug in man, but they are all active in an animal model. CYP2C9-related genetic variability accounts for 14% of the inter-individual variability in acenocoumarol pharmacodynamics response.

#### Elimination

The elimination half-life of acenocoumarol from the plasma is 8 to 11 hours. The apparent plasma clearance amounts to 3.65 L/h after oral administration. The total plasma clearance of the (+) enantiomer of acenocoumarol, which possesses

significantly higher anticoagulant activity, is much lower than that of the S(-) enantiomer.

29% is excreted in the faeces and 60% in the urine, with less than 0.2% of the dose renally excreted being unchanged.

### Special Populations

#### Geriatric Patients

Plasma drug concentrations are generally higher in patients of 70 years or over when compared with younger patients, after the same dose.

#### Renal impairment

No clinical pharmacokinetic information of acenocoumarol in renal impairment is available. Based on the urinary excretion of acenocoumarol, the possibility of accumulation of metabolites in impaired renal function cannot be excluded. Therefore usage of acenocoumarol is contraindicated in patient with severe renal impairment and caution should be exercised in patients with mild to moderate renal impairment (see section 4.2 Posology and method of administration, section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

#### Hepatic impairment

No clinical pharmacokinetic information of acenocoumarol in hepatic impairment is available. Based on the metabolism of acenocoumarol, and possible reduced enzyme activities, CYP2C9, CYP1A2 and CYP3A4, clearance is likely to be reduced. Therefore usage of acenocoumarol is contraindicated in patients with severe hepatic impairment and caution should be exercised in patients with mild to moderate hepatic impairment (see section 4 Posology and administration, section 4.3 Contraindications and section 4.4 Special warnings and precautions for use).

#### Ethnicity

CYP2C9 enzyme systems are polymorphically expressed and the frequency of these in population differs. In Caucasians, occurrence of CYP2C9\*2 and CYP2C9\*3 frequencies are 12 and 8%, respectively. Patients with one or more of these variant CYP2C9 alleles have decreased clearance of S-acenocoumarol. In African patients, CYP2C9\*2 and CYP2C9\*3 occur at much lower allele frequencies 1-4% and 0.5-2.3%, respectively compared to Caucasians. Japanese population had lower allelic frequencies of 0.1% and 1-6% for CYP2C9\*2 and CYP2C9\*3, respectively].

The maintenance dose of acenocoumarol differs based on the genotype.

Detailed information of mean and median maintenance dose based on CYP2C9 genotype is given in the table below:

**Table 1 CYP2C9 genotype and maintenance dose of acenocoumarol**

<b>Genotype</b>	<b>N</b>	<b>Mean dose (mg/week)</b>	<b>SD</b>	<b>Median dose (mg/week)</b>	<b>Range</b>
CYP2C9*1	169	17.1	8.7	15.8	2.3- 61
CYP2C9*2	90	14.4	6.3	13.5	3.5- 37.5
CYP2C9*3	48	11.0	5.1	10.5	2.3- 22

### **5.3 Preclinical safety data**

#### **Toxicity**

After a single (acute) oral and/or intravenous dose, acenocoumarol showed a low degree of toxicity in mice, rats, and rabbits. In dogs, high acute oral toxicity was seen.

In repeated-dose studies, the liver is suggested to be the main target organ in the toxicity of coumarin derivatives including acenocoumarol. The administration of these substances at excessive pharmacological doses can cause haemorrhages.

#### **Reproduction toxicity, teratogenicity**

No reproductive toxicity studies were performed with acenocoumarol. However, placental and transplacental interference with vitamin K dependent coagulation factors may give rise to embryonic or foetal anomalies and neonatal haemorrhages both in animals and in humans (see section 4.6 Fertility, pregnancy and lactation).

#### **Mutagenicity**

From investigations on bacterial and mammalian cell systems in vitro, including a DNA repair assay on rat hepatocytes, it can be concluded that acenocoumarol and/or its metabolites did not exert any mutagenic effects. An in vitro study on human lymphocytes has shown some mild mutagenic activity at a concentration of acenocoumarol, 500 to 1000 times higher than concentrations determined in human plasma after medication with acenocoumarol.



## **Carcinogenicity**

No lifetime-exposure studies were carried out in animals with acenocoumarol.

Coumarin, induced an increase in the incidence of lung and benign liver tumours in mice, and liver and benign kidney tumours in rats. Liver tumours in rats and lung tumours in mice are understood to be associated with species-specific metabolic pathways in these species. Hepatotoxicity of coumarin and its derivatives in the rat is understood to be associated with enzyme induction and the metabolic pathway of coumarin and/or its metabolites peculiar to this rodent species. Renal tumours observed in male mice are considered to be a species-specific effect.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Aerosil 200 (silica aerogel)

Hypromellose

Lactose

Magnesium stearate

Maize starch

Talc

### **6.2 Incompatibilities**

None stated.

### **6.3 Shelf life**

3 years.

### **6.4 Special precautions for storage**

None stated.

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

Blister packs of 100 tablets.

### **6.6 Special precautions for disposal and other handling**

None stated.

## **7. Marketing authorisation holder**

Merus Labs Luxco II S.à.R.L.

26-28, rue Edward Steichen

L-2540 Luxembourg

## **8. Marketing authorisation number(s)**

PL 44374/0001

## **9. Date of first authorisation/renewal of the authorisation**

08/08/1972 / 25/02/2005

## **10. Date of revision of the text**

08/10/2015

## **Legal category**

POM

## **Company Contact Details**

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