Prescribing Information

SINTROM

1 mg and 4 mg tablets

Oral Anticoagulant

Paladin Labs Inc.
6111 Royalmount Avenue, Suite 102
Montreal, Quebec
H4P 2T4

Date of Preparation:
May 22, 2009
Version : 3.0

Control No.: 130073

NAME OF DRUG

SINTROM

1 mg and 4 mg tablets

THERAPEUTIC CLASSIFICATION

Oral Anticoagulant

ACTIONS

Sintrom (acenocoumarol) a 4-hydroxycoumarin derivative, reduces the concentration of prothrombin in blood and increases the prothrombin time by inhibiting the formation of prothrombin (coagulation factor II) in the liver. The drug also interferes with the production of coagulation factors VII, IX, X, as well as protein C, so their concentration in the blood is lowered during therapy.

Coumarin derivatives are vitamin K antagonists. They inhibit the g-carboxylation of certain glutamic acid molecules which are located at several sites near the amino terminal end of vitamin K-dependent coagulation factors. g-carboxylation has a significant bearing on the interaction of the coagulation factors with calcium. Without this reaction, blood clotting cannot be initiated. Precisely how coumarin derivatives prevent vitamin K from bringing about g-carboxylation of the glutamic acid molecules in the coagulation factors has not yet been determined.

Depending on the size of the initial dose, maximal effect on prothrombin time is usually achieved within 36 to 48 hours. Following a single therapeutic dose or cessation of therapy, the prothrombin time usually returns to normal within 48 hours.

Sintrom is rapidly absorbed by the oral route. At least 60% of the dose is systemically available. Peak plasma concentrations are generally attained within 1 to 3 hours of oral administration, with levels of 0.3 ± 0.05 mg/ml observed following a single 10 mg dose. The peak plasma

concentrations and the areas under the blood concentration-time curve (AUC) are proportional to the size of the dose over a range of 8 to 16 mg.

No correlation can be established between the plasma concentrations of Sintrom and the apparent prothrombin level due to variation in plasma concentrations among patients. At any given prothrombin level, patients over 70 years of age generally have higher plasma concentrations than younger patients.

The bulk of the Sintrom administered is found in the plasma fraction of the blood. 98.7% of the drug is bound to plasma proteins, notably to albumin.

The calculated apparent volume of distribution of Sintrom is 0.16 to 0.18 litre/kg for the R(+) enantiomer and 0.22 to 0.34 litre/kg for the S(-) enantiomer.

Sintrom passes into the breast milk, but the quantities are too small to be detected by the usual analytical methods. The drug also crosses the placental barrier.

Sintrom is extensively metabolised. At least two primary pathways are involved. Oxidation of Sintrom results in two hydroxy metabolites. Reduction of the keto group on Sintrom forms two different alcohol metabolites. A major portion of the amino metabolite, produced by reduction of the nitro group, is further transformed to the corresponding acetamido metabolite. An additional unidentified strongly polar metabolite fraction was also noted. These metabolites appear to be pharmacologically inactive in man.

Sintrom is eliminated from the plasma with a half-life of 8 to 11 hours.

Only 0.1% to 0.3% of the dose is excreted unchanged in the urine. Over a period of one week, the cumulative excretion of metabolites and unchanged active substance in the urine and feces is 60% and 29% of the dose respectively.

INDICATIONS

SINTROM is indicated for the prophylaxis and treatment of venous thrombosis and its extension, for the treatment of atrial fibrillation with embolization, for the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion and transient cerebral ischemic attacks.

CONTRAINDICATIONS

SINTROM is contraindicated in all pathological states in which the risk of hemorrhage is greater than the possible clinical benefits, e.g.:

- Hemorrhagic blood diathesis and/or blood dyscrasia
- Recent or contemplated surgery of CNS or eye
- Traumatic surgery resulting in large open surfaces
- Bleeding tendencies associated with active ulceration or overt bleeding of gastrointestinal, genitourinary or respiratory tracts; cerebrovascular hemorrhage; aneurysms: cerebral, dissecting aorta; pericarditis and pericardial effusions; subacute bacterial endocarditis
- Threatened abortion, eclampsia and preeclampsia
- Severe hypertension
- Severe parenchymal lesions of the liver and kidneys
- Increased fibrinolytic activity as encountered after operations on the lung, prostate, uterus, etc.

Pregnancy: Sintrom passes through the placental barrier, and the danger of hemorrhage to the fetus exists to the point of fatal hemorrhage in utero, even within the accepted therapeutic range of maternal prothrombin level. There have been reports of birth malformation in children born to mothers who have been treated with coumarin anticoagulants during the first trimester of pregnancy. Therefore, SINTROM must not be employed during pregnancy. In women of childbearing age, contraceptive measures are necessary during treatment. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus. The possibility of termination of the pregnancy should be discussed in light of those risks.

Known hypersensitivity to Sintrom and related coumarin derivatives.
Intramuscular injections (See PRECAUTIONS / WARNINGS)
Lack of patient cooperation (e.g. unsupervised and senile patients, alcoholics and patients with psychiatric disorders).
Inadequate laboratory facilities.
Miscellaneous: polyarthritis, ascorbic acid deficiency, major regional block anesthesia.

PRECAUTIONS / WARNINGS

SINTROM is a potent drug and its effects tend to be cumulative and prolonged. At the earliest sign of bleeding the drug should be withdrawn.

Treatment of each patient is a highly individualized matter. Dosage can be controlled only by periodic determination of prothrombin time or other suitable coagulation test (see DOSAGE AND ADMINISTRATION). Determinations of clotting and bleeding times are not effective measures for control of therapy.

It is recommended that the blood samples for laboratory tests always be taken at the same time of day.

Since heparin prolongs the one stage prothrombin time when it is given with Sintrom, a period of from 4 to 5 hours after the last I.V. dose and 12 to 24 hours after the last S.C. dose of heparin should elapse before blood is drawn, if a valid prothrombin time is to be obtained.

Elderly patients on anticoagulant medication should be monitored with special care.

Factors which increase or decrease the absorption, storage or utilization of vitamin K may interfere with anticoagulant dosage. It is important that the diet not only be adequate but stable from day to day in order to regulate the dosage.

Caution should be used in patients with hepatic dysfunction since the production of coagulation factors and detoxification of oral anticoagulants can be affected by diseases of the liver.

Patients with impaired renal function do not appear to be subject to unusual risks. However, caution should be exercised in view of the possibility of a compromised state of platelet-mediated hemostasis.

SINTROM may show greater activity in certain conditions or diseases due to reduced protein binding (e.g. thyrotoxicosis, tumours, renal diseases, infections and inflammation). Strict medical supervision is necessary in these situations.

Diagnostic or therapeutic interventions (e.g. angiography, lumbar puncture, minor surgery, tooth extractions, etc.) may require the shortening of thromboplastin time. This should be done with meticulous care.

During treatment with anticoagulants, intramuscular injections may cause hematomas and are therefore contraindicated. There is no evidence that subcutaneous or intravenous injections lead to such complications.

Out-patients should be advised to carry an oral anticoagulant card so that appropriate actions can be taken in the event of injuries or accidents.

Abrupt cessation of anticoagulant therapy is generally not recommended; taper dose gradually over 3 to 4 weeks.

Administration of anticoagulants in the following conditions will be based upon clinical judgement in which the risk of hemorrhage due to anticoagulants is weighed against the risk of thrombosis or embolization in untreated cases:

- Prolonged dietary deficiency (cachexia, vitamin K)
- Moderate to severe hepatic or renal insufficiency (See also CONTRAINDICATIONS)

- Infectious diseases or disturbances of intestinal flora (sprue, antibiotic therapy)
- Severe trauma of head, bones or muscles associated with extreme raw surfaces
- Indwelling catheters
- Spinal punctures
- Moderate to severe hypertension (See also CONTRAINDICATIONS) Miscellaneous: polycythemia vera; vasculitis; severe diabetes; menometrorrhagia; severe allergic and anaphylactic disorders.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

- **Endogenous**: hepatic disorders; vitamin K deficiency (hypoprothrombin-emia) of obstructive jaundice, steatorrhea and infectious hepatitis; poor nutritional state; diarrhea; elevated temperature; congestive heart failure; carcinoma; collagen disease.

- **Exogenous**: drug interactions (see below); carbon tetrachloride; alcohol; dietary deficiencies in protein, ascorbic acid, choline or cystine; narcotics with prolonged use; drugs affecting the blood elements; hepatotoxic drugs; anesthetics; prolonged hot weather, anticoagulant overdosage; unreliable prothrombin determinations.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

- **Endogenous**: edema; hyperlipemia; diabetes mellitus; hereditary resistance to coumarin therapy; hypothyroidism.
- **Exogenous**: drug interactions (see below); vitamin K in polyvitamin preparations; diet high in vitamin K; anticoagulant underdosage; unreliable prothrombin determinations.

N.B.: A patient may be exposed to a combination of the above factors, some of which may increase and some decrease sensitivity to Sintrom. Because the net effect on prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Lactation: Sintrom passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected. As a precaution, however, it is recommended that the infant be given 1 mg of vitamin K_1 per week for prophylactic purposes. Clinical monitoring of the infant for signs of prothrombin abnormalities is also advised.

Drug Interactions: Coumarin anticoagulants have been involved in a number of serious adverse drug interactions. Important mechanisms associated with these interactions include disturbances of absorption, reduced availability of vitamin K necessary for g-carboxylation of prothrombin-complex factors, inhibition or induction of metabolising enzymes and interference with plasma protein binding. The anticoagulant effects may be increased or decreased by drug interactions. It is therefore essential to monitor the patient's response with additional prothrombin time determinations (e.g. twice weekly), and adjust dosage of SINTROM appropriately, whenever other medications are initiated, discontinued or taken haphazardly.

The anticoagulant effect may be potentiated by concurrent treatment with the following drugs: acetaminophen, allopurinol, androgens, antiarrhythmic agents (e.g. amiodarone, quinidine), antibiotics (e.g. erythromycin, tetracyclines, neomycin, chloramphenicol), chloral hydrate*, clofibric acid as well as its derivatives and structural analogues, diazoxide, disulfiram, ethacrynic acid, glucagon, histamine H_2-receptor antagonists (e.g. cimetidine), imidazole derivatives (e.g. metronidazole and, even when administered locally, miconazole), mefenamic acid, mercaptopurine, MAO inhibitors, nalidixic acid, oral hypoglycemics (e.g. tolbutamide), phenyramidol, quinine, sulfonamides (including co-trimoxazole), sulfinpyrazone, thyroid hormone (including dextrothyroxine**).**
*Increased and decreased prothrombin time responses have been reported.

During treatment with drugs which affect hemostasis, the anticoagulant effect may be potentiated, thereby increasing the risk of gastro-intestinal haemorrhage. Chief among these drugs are heparin and platelet-aggregation inhibitors such as salicylic acid and its derivatives (e.g. acetylsalicylic acid, paraaminosalicylic acid or PAS, diflunisal) and phenylbutazone or other pyrazolone derivatives (e.g. sulfinpyrazone). Use of SINTROM together with these substances is therefore highly unadvisable.

Increased risk of haemorrhage has been reported with the combined use of oral anticoagulants and non-steroidal anti-inflammatory agents. It is therefore recommended that more frequent coagulation tests be performed.

The anticoagulant effect may be diminished by concurrent treatment with the following drugs: aminoglutethimide, barbiturates, carbamazepine, cholestyramine (see below), corticosteroids, diuretics*, ethchlorvynol, griseofulvin, meprobamate, oral contraceptives, rifampin.
*Increased and decreased prothrombin time responses have been reported.

Cholestyramine reduces intestinal absorption, notably by interrupting the enterohepatic circulation; for this reason, it can be recommended as treatment for overdosage of a coumarin derivative.

A two-way interaction between Sintrom and phenytoin has been suggested. Phenytoin has been reported to decrease the serum concentrations of Sintrom and to increase the plasma prothrombin-proconvertin concentrations. Presumably, phenytoin acts as a stimulator of Sintrom metabolism. Conversely, Sintrom has been reported to increase the serum concentrations and prolong the serum half-life of phenytoin by inhibiting its metabolism. Patients receiving Sintrom and phenytoin concurrently should be closely observed for signs of phenytoin toxicity. Frequent monitoring of the prothrombin time is also essential. Other hydantoin anticonvulsants may interact with Sintrom in a manner similar to that of phenytoin.

During concomitant treatment with sulphonylurea derivatives, their hypoglycemic effect may be potentiated.

Since neither the severity nor the early signs of interactions can be predicted, patients taking Sintrom, especially if they also suffer from hepatic dysfunction, should refrain from consuming alcohol.

ADVERSE EFFECTS

Depending on the intensity of therapy, the patient's age and nature of the underlying disease, the complications most frequently reported with anticoagulants have been haemorrhage at various site. Prospective studies give no indication that the incidence of bleeding depends on duration of treatment. If haemorrhage occurs in a patient whose thromboplastin time is within the therapeutic range, the case must be clarified diagnostically (in view of such possibilities as ulceration, tumour and congenital coagulation disorders). Predilection sites of heamorrhage include the gastrointestinal tract (melena), the brain, the urogenital tract (macroscopic and microscopic hematuria), the uterus (metrorrhagia and menorrhagia), the liver and gall bladder (hematobilia), and the eye. Usually, heamorrhage is evident but the possibility of intestinal heamorrhage must be considered when a patient has abdominal symptoms.

Gastrointestinal disorders (loss of appetite, nausea, diarrhea, vomiting), allergic reactions (urticaria, dermatitis and fever) and reversible loss of hair (alopecia) have rarely been noted with similar coumarin derivatives.

Isolated cases of hemorrhagic skin necrosis have been reported, even when the prothrombin time was within apparently safe limits. This adverse reaction is usually associated with congenital protein C deficiency. Isolated cases of liver damage have also occurred.

OVERDOSE

Signs and symptoms:

The patient's individual sensitivity to oral anticoagulants, the size of the overdosage and the duration of anticoagulant administration have a decisive bearing on the onset and severity of the effects.

Heamorrhages in the region of various organs are the most prominent clinical feature. Depending on the size of the dose and the patient's reaction to it, haemorrhage set in 1 to 5 days after ingestion.

Effects of overdosage may take the form of nose-bleed, hematemesis, hemoptysis, gastrointestinal heamorrhage, vaginal bleeding, hematuria (with renal colic), cutaneous haemorrhage, bleeding into the joints and menorrhagia.

Tachycardia, hypotension, and peripheral circulatory disorders due to loss of blood, as well as nausea, vomiting, diarrhea, and colicky pains in the abdomen are further signs and symptoms of poisoning.

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

Antidote:
Phytomenadione (vitamin K_1) is capable of counteracting, within 3 to 5 hours, the inhibitory effect ofSINTROM on hepatic-carboxylation of the vitamin K-dependent coagulation factors.

Treatment:
If at the time of taking a single overdose the patient's thromboplastin time is normal, the drug can be partly eliminated by inducing vomiting or gastric lavage. Administration of activated charcoal or a rapid-acting laxative may also prevent or reduce absorption of the ingested anticoagulant. Cholestyramine may increase the drug's elimination.

In the event of clinically insignificant haemorrhages, such as brief nose-bleed or small isolated hematoma, a temporary reduction of the dose of SINTROM is often sufficient.

In cases of mild to severe haemorrhage administer 1 to 10 mg Vitamin K_1 by slow I.V. infusion (rate not to exceed 1 mg/minute). Vitamin K_1 should not be injected I.M. Additional doses (up to a maximum of 40 mg daily) should be administered at 4 hour intervals. It should be noted that doses in excess of 5 mg can cause resistance to oral anticoagulants lasting several days. Should an anticoagulant prove necessary, heparin may be employed as a temporary measure while resuming

oral anticoagulant therapy. Heparin should be subsequently withdrawn when the therapeutic range has been reached.

Only rarely is whole blood needed. If life-threatening haemorrhage has occurred, the effect of treatment with SINTROM can be abolished by intravenous infusion of deep-frozen plasma concentrates or fresh whole blood in order to substitute for the missing coagulation factors II, VII, IX and X.

DOSAGE AND ADMINISTRATION

Sensitivity to anticoagulants varies from patient to patient and may also fluctuate in the course of treatment. It is therefore essential to carry out regular coagulation tests in adequate facilities for standardized laboratory control and to adapt the dosage accordingly. If this is not possible, SINTROM should not be used.
The daily dose should be prescribed as a single dose and always taken at the same time of day.

Initial Dose:
First Day: 8 - 12 mg
Second Day: 4 - 8 mg
If the thromboplastin time is initially abnormal, treatment must be commenced with great caution.

Maintenance Therapy and Coagulation Tests:

In view of the marked individual differences encountered, the maintenance dose should be established and adjusted by reference to the results of periodically performed laboratory tests to determine the patient's blood coagulation time. The Quick value (or INR value, see below) should be carefully maintained within the therapeutic range. Such values should be determined daily from the beginning of treatment until the maintenance dose is established, then repeated at regular intervals (e.g. once a month), so that possible fluctuations outside the therapeutic range can be avoided. Depending on the Quick value (or INR value), as well as on the individual patient and nature of the disease, the maintenance dose is usually 1 to 10 mg daily.

As a routine test procedure, measurement of thromboplastin time yields good results. For the purpose of standardization, an "International Normalised Ratio" (INR) has been introduced. International comparability is made possible with the help of calibrated thromboplastins. An "International Sensitivity Index" value is determined for the reference thromboplastin using the WHO procedure.

To obtain the INR value, the ratio between the test thromboplastin time and the normal thromboplastin time is raised to the power of the specified "International Sensitivity Index" value of the reference thromboplastin. As the Quick value decreases, the thromboplastin time for the patient's blood increases; thus the IND value increases.

Depending on the clinical picture, the therapeutic range to be aimed, at generally lies between INR values of 2 to 4.5; within this range the majority of the patients treated develop neither a recurrence of thrombosis nor any severe hemorrhagic complications.

AVAILABILITY

1 mg tablet: Peach colored, round, biconvex tablet.

4 mg tablet: White, round flat-faced tablet debossed with Paladin shield on one side and double scored on the other.