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MIRADON®

brand of anisindione

Tablets

FPO

DESCRIPTION MIRADON Tablets contain a synthetic anticoagulant, anisindione, an indanedione derivative. Each tablet contains 50 mg anisindione. They also contain: corn starch, FD&C Red No. 3, gelatin, lactose, and hydrogenated cottonseed oil.

ACTIONS Like phenindione, to which it is related chemically, anisindione exercises its therapeutic action by reducing the prothrombin activity of the blood.

INDICATIONS Anisindione is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

CONTRAINDICATIONS All contraindications to oral anticoagulant therapy are relative rather than absolute. Contraindications should be evaluated for each patient, giving consideration to the need for and the benefits to be achieved by anticoagulant therapy, the potential dangers of hemorrhage, the expected duration of therapy, and the quality of patient monitoring and compliance.

Hemorrhagic Tendencies or Blood Dyscrasias: In general, oral anticoagulants are contraindicated in patients who are bleeding or who have hemorrhagic blood dyscrasias or hemorrhagic tendencies (eg, hemophilia, polycythemia vera, purpura, leukemia) or a history of bleeding diathesis. They are contraindicated in patients with recent cerebral hemorrhage, active ulceration of the gastrointestinal tract, including ulcerative colitis, or open ulcerative, traumatic, or surgical wounds. Oral anticoagulants may be contraindicated in patients with recent or contemplated brain, eye, or spinal cord surgery or prostatectomy, and in those undergoing regional or lumbar block anesthesia or continuous tube drainage of the small intestine. Oral anticoagulants may be contraindicated in patients who have severe renal or hepatic disease, subacute bacterial endocarditis, pericarditis, polyarthritis, diverticulitis, visceral carcinoma, or aneurysm. Other conditions in which the oral anticoagulants may be contraindicated include severe or malignant hypertension, eclampsia or preeclampsia, threatened abortion, emaciation, malnutrition, and vitamin C or K deficiencies. Since a high degree of patient cooperation is required for the outpatient use of oral anticoagulants, a lack of such cooperation is a relative contraindication to their use.

Pregnancy: Anisindione is contraindicated in pregnancy because the drug crosses the placental barrier. Oral anticoagulants may cause fetal damage when administered to pregnant women. Fetal or neonatal hemorrhage and intrauterine fetal death have occurred even when maternal prothrombin times were within the therapeutically accepted range. Maternal use of warfarin and anisindione during the first trimester of pregnancy has been reported to cause hypoplastic nasal structures or other signs of the Conradi-Hunermann syndrome in the offspring. These patients received other drugs in addition to anticoagulants and a positive causal relationship has not been established. If oral anticoagulants must be used during pregnancy, or if the patient becomes pregnant while taking one of these drugs, the patient should be apprised of the potential hazard to the fetus. The possibility of termination of the pregnancy should be considered in light of these risks.

As an alternative to the use of oral anticoagulants in pregnant patients, the use of heparin, which does not cross the placenta, should be considered.

WARNINGS Anisindione should be reserved for patients who cannot tolerate the coumarins.

Oral anticoagulants are potent drugs with prolonged and cumulative effects. Treatment must be individualized according to patient response, and the benefit expected from anticoagulant therapy should be weighed against the possible hazards associated with the use of these drugs.

Oral anticoagulants should not be used in the treatment of acute completed strokes due to the risk of fatal cerebral hemorrhage (see **INDICATIONS**).

Because agranulocytosis and hepatitis have been associated with the use of anisindione, liver function and blood studies should be performed periodically. Patients should be instructed to report to the physician symptoms such as marked fatigue, chills, fever, or sore throat; the drug should be discontinued promptly since these symptoms may signal the onset of severe toxicity. If leukopenia or evidence of hypersensitivity occurs, the drug should be discontinued. Because of the possibility of renal damage associated with the use of phenindione, the urine should be tested periodically for albumin whenever phenindione or any indanedione anticoagulant is used.

Relatively minor bleeding episodes and hemorrhage occur in 2% to 10% of patients treated with oral anticoagulants. Bleeding will vary in intensity, and may be related to the quality of patient monitoring, compliance on the part of the patient, the incidence of potentially hemorrhagic lesions, or the extent of anticoagulation induced. Severe and moderate hypertension, severe to moderate hepatic and renal insufficiency, and infectious diseases or disturbances of intestinal flora as in sprue, or with antibiotic therapy may increase the risks associated with anticoagulant therapy.

Occasionally, fatal hemorrhages can occur. Massive hemorrhage from organ systems may involve cerebral, pericardial, pulmonary, adrenal, hepatic, spinal, gastrointestinal, or genitourinary sites. Gastrointestinal hemorrhage may be secondary to peptic ulceration or silent neoplasm and is responsible for 25% of all deaths due to oral anticoagulant therapy. Bleeding complications in the genitourinary tract may range in severity from microscopic hematuria to gross hematuria to extensive uterine hemorrhage.

Hemorrhagic necrosis and/or gangrene of the skin and subcutaneous tissue, petechial and purpuric hemorrhage, ecchymosis, epistaxis, hematemesis, or hemoptysis, may also occur. Hemorrhage and necrosis have in some cases been reported to result in death or permanent disability. Necrosis appears to be associated with local thrombosis and usually appears within a few days of the start of anticoagulant therapy. In severe cases of necrosis, treatment through debridement or amputation of the affected tissue, limb, breast, or penis has been reported. Careful diagnosis is required to determine whether necrosis is caused by an underlying disease. MIRADON therapy should be discontinued when anisindione is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation. Although various treatments have been attempted, no treatment for necrosis has been considered uniformly effective. (See below for information on predisposing conditions.) The risks of anticoagulant therapy may be increased in patients with known or suspected hereditary, familial, or clinical deficiency in protein C. This condition, which should be suspected if there is a history of recurrent episodes of thromboembolic disorders in the patient or in the family, has been associated with an increased risk of developing necrosis following warfarin administration, and may be expected following anisindione therapy. Skin necrosis may occur in the absence of protein C deficiency. It has been reported that initiation of anticoagulation therapy with heparin for 4 to 5 days before initiation of therapy with anisindione may minimize the incidence of this reaction. Anisindione therapy should be discontinued when it is suspected to be the cause of developing necrosis and heparin therapy may be considered for anticoagulation.

Concurrent use of anticoagulants with streptokinase, urokinase, or alteplase (recombinant tissue plasminogen activator) is not recommended and may be hazardous. (Consult the product information accompanying those preparations.)

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

PRECAUTIONS **General:** Periodic determination of prothrombin time or other suitable coagulation test is essential. The availability of suitable laboratory facilities to monitor therapy accurately with oral anticoagulants is mandatory, both to assure adequate anticoagulation and to avoid toxicity due to overdosage. The dosage of oral anticoagulants depends on the clinical response as monitored by prothrombin time determinations (see **DOSAGE AND ADMINISTRATION**). Since heparin prolongs the one-stage prothrombin time, a period of at least 5 hours should elapse after the last intravenous dose and after the last subcutaneous dose of heparin before drawing blood to determine the prothrombin time when heparin and anisindione have been given together. In addition to adequate laboratory facilities, a supply of oral or parenteral phytonadione (vitamin K_1) and a source of whole blood or plasma should be available when emergency treatment of acute overdosage is required (see **OVERDOSAGE**).

A number of factors including environmental, mental, medical, and nutritional states may affect an individual's response to anticoagulant therapy. Factors which increase sensitivity to the drug and lengthen prothrombin time include: initial hypoprothrombinemia, increased age, poor nutritional status, vitamin K deficiency or malabsorption, congestive heart failure or vascular damage, hepatic disorders including hepatitis or obstructive jaundice, biliary fistula, febrile states, hyperthyroidism, preparatory bowel sterilization, recent surgery, and X-ray therapy.

Factors which may decrease the response to oral anticoagulants and shorten the prothrombin time include: pregnancy, diabetes mellitus, hyperlipidemia, hypothyroidism, hypercholesterolemia, and hereditary or acquired resistance.

Information for Patients: The physician should instruct patients:

- To follow carefully the physician's directions for taking this drug and not to alter these directions without authorization.
- To follow carefully the physician's directions for the periodic blood test (prothrombin time) required to assure that the correct dose of the drug is being used.
- To discuss with the physician any other medication (prescription or nonprescription) to be used.
- To report to the physician any abnormal bleeding, such as blood in the urine, blood in the stool (a black, tarry appearance); bleeding from the gums or nose; patches of discoloration or bruises on the arms, legs, or toes; or excessive bleeding following minor cuts (eg, while shaving).
- To discuss with the physician any plan to become pregnant or to report any pregnancy promptly.

Laboratory Tests: The need for careful control of the degree of anticoagulation, as determined by changes in prothrombin activity, cannot be overemphasized. It should be noted, however, that bleeding during anticoagulant therapy may not always correlate with prothrombin activity.

The stool guaiac test should be used to detect occult gastrointestinal bleeding.

In long-term therapy with anticoagulants, periodic laboratory evaluation of organ systems, including hematopoietic, renal, and hepatic studies, should be performed (see **WARNINGS**).

Drug Interactions: Addition or deletion of any drug from the therapeutic regimen of patients receiving oral anticoagulants may affect patient response to the anticoagulant. Frequent determination of prothrombin time and close monitoring

of the patient is essential to ascertain when adjustment of dosage of anticoagulant may be needed.

Because of the variability of individual patient response, multiple interacting mechanisms with some drugs, the dependency of the extent of the interaction on the dosage and duration of therapy, and the possible administration of several interacting drugs simultaneously, it is difficult to predict the direction and degree of the ultimate effect of concomitant medications on anticoagulant response. For example, since cholestyramine may reduce the gastrointestinal absorption of both the oral anticoagulants and vitamin K, the net effects are unpredictable. Chloral hydrate may cause an increased prothrombin response by displacing the anticoagulant from protein binding sites or a diminished prothrombin response through increased metabolism of the unbound drug by hepatic enzyme induction, thus leading to interpatient variation in ultimate prothrombin effect. An interacting drug which leads to a decrease in prothrombin time necessitating an increased dose of oral anticoagulant to maintain an adequate degree of anticoagulation may, if abruptly discontinued, increase the risk of subsequent bleeding.

Drugs that have been reported to diminish oral anticoagulant response, ie, decreased prothrombin time response, in man significantly include: adrenocortical steroids; alcohol*; antacids; antihistamines; barbiturates; carbamazepine; chloral hydrate*; chlordiazepoxide; cholestyramine; diet high in vitamin K; diuretics*; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; ranitidine*; rifampin; unreliable prothrombin time determinations; vitamin C; warfarin sodium underdosage.

Drugs that reportedly may increase oral anticoagulant response, ie, increased prothrombin response, in man include: alcohol*; allopurinol; aminosalicylic acid; amiodarone; anabolic steroids; antibiotics; bromelains; chloral hydrate*; chlorpropamide; chymotrypsin; cimetidine; cinchophen; clofibrate; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diflunisal; diuretics*; disulfiram; drugs affecting blood elements; ethacrynic acid; fenoprofen; glucagon; hepatotoxic drugs; ibuprofen; indomethacin; influenza virus vaccine; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; miconazole; monoamine oxidase inhibitors; nalidixic acid; naproxen; oxolinic acid; oxyphenbutazone; pentoxifylline; phenylbutazone; phenyramidol; phenytoin; prolonged hot weather; prolonged narcotics; pyrazolones; quinidine; quinine; ranitidine*; salicylates; sulfinpyrazone; sulfonamides, long acting; sulindac; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations; warfarin sodium overdosage.

Oral anticoagulants may potentiate the hypoglycemic action of hypoglycemic agents, eg, tolbutamide and chlorpropamide, by inhibiting their metabolism in the liver. Because oral anticoagulants may interfere with the hepatic metabolism of phenytoin, toxic levels of the anticonvulsant may occur when an oral anticoagulant and phenytoin are administered concurrently.

Drugs that reduce the number of blood platelets by causing bone marrow depression (such as antineoplastic agents) or drugs which inhibit platelet function (eg, aspirin and other nonsteroidal anti-inflammatory drugs, dipyridamole, hydrochloroquine, clofibrate, dextran) may increase the bleeding tendency produced by anticoagulants without altering prothrombin time determinations. The beneficial effects on arterial thrombus formation from combined therapy with antiplatelet and anticoagulant medication must be weighed against an increased risk of inducing hemorrhage.

*Increased and decreased prothrombin time responses have been reported.

Drug/Laboratory Test Interferences: Dicumarol and indanedione anticoagulants, including anisindione, or their metabolites may color alkaline urine red-orange, which may interfere with spectrophotometrically determined urinary laboratory tests. The color reverses when the test sample is acidified *in vitro* to a pH below 4.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term dosing studies to determine the carcinogenic potential of oral anticoagulants, including anisindione, have not been done. Information on mutagenesis is unknown.

Pregnancy: Teratogenic and other effects – Pregnancy Category X: (See **CONTRAINDICATIONS**.)

Labor and Delivery: Anisindione is contraindicated in pregnancy. If oral anticoagulants are used in pregnant women, they should not be administered during the first trimester, and should be discontinued prior to labor and delivery.

Some clinicians suggest the replacement of oral anticoagulants with heparin therapy before term. Heparin is withheld during early labor and reinstituted 6 hours postpartum. After 5 to 7 days, therapy with oral anticoagulants may be resumed if indicated.

See **CONTRAINDICATIONS** for the use of oral anticoagulants in pregnancy.

Nursing Mothers: Oral anticoagulants or their metabolites are excreted in the milk of nursing mothers, possibly in amounts sufficient to cause a prothrombopenic state and bleeding in the newborn. As a general rule, nursing should not be undertaken while a patient is receiving an oral anticoagulant.

Pediatric Use: The use of oral anticoagulants in pediatric patients is not well documented. However, they may be beneficial in pediatric patients with rare thromboembolic disorder secondary to other disease states such as the nephrotic syndrome or congenital heart lesions. Heparin is probably the initial anticoagulant of choice because of its immediate onset of action.

ADVERSE REACTIONS Multisystem adverse reactions have been reported, and some may be serious enough to warrant hospital admission. In general, they may be divided into 2 categories: those which involve abnormal bleeding and other effects which do not. Hemorrhage and/or necrosis are among the hazards of treatment with any anticoagulant and are the main serious complications of therapy. For additional discussion of possible hemorrhagic complications following oral anticoagulant therapy see **WARNINGS**. Although most of the adverse reactions for oral anticoagulant drugs have been reported for warfarin, dicumarol, and phenindione, all the drugs within this class have similar pharmacologic and clinical properties, and require the same degree of caution in monitoring adverse reactions regardless of the drug administered.

Some indanediones (phenindione) have been associated with undesirable reactions which have not been reported with the coumarins and are not counterbalanced by advantages, thus perhaps favoring the use of the coumarin-type anticoagulants. Changing from one chemical type of oral anticoagulant to the other may eliminate an adverse reaction, such as rash or diarrhea. Dermatitis is the only untoward reaction consistently associated with anisindione therapy.

Adverse reactions reported following therapy with either coumarin or indanedione anticoagulants include: nausea, diarrhea, pyrexia, dermatitis or exfoliative dermatitis, urticaria, alopecia, and sore mouth or mouth ulcers.

Side effects which have additionally been reported for coumarin derivatives include: vomiting, abdominal cramps, anorexia, priapism, erythema and necrosis of the skin and other tissues, manifesting as purple toes and cutaneous gangrene. There is no reason to expect that some or all of these adverse reactions might not occur in patients receiving anisindione.

Additional side effects attributed to the indanedione anticoagulants include: headache, sore throat, blurred vision, paralysis of accommodation, steatorrhea, hepatitis, jaundice, liver damage, renal tubular necrosis, albuminuria, anuria, myeloid immaturity, agranulocytosis, leukocyte agglutinins, red cell aplasia, atypical mononuclear cells, leukopenia, leukocytosis, anemia, thrombocytopenia, and eosinophilia.

Phenprocoumon-induced delayed callus formation following bone fracture has been reported.

DOSAGE AND ADMINISTRATION *Initial dosage* of MIRADON Tablets is 300 mg the first day, 200 mg the second day, and 100 mg the third day. With initiation of treatment, prothrombin activity decreases rapidly to 50 percent of baseline values within 6 hours; thereafter it decreases slowly until it reaches 15 to 30 percent of baseline values in 48 to 72 hours. *Maintenance dosage* is established from daily prothrombin-time determinations for each patient, although with MIRADON Tablets, the uniform, predictable action of the drug makes it possible to reduce the frequency of prothrombin-time determinations in some cases. Maintenance dosage will vary between 25 to 250 mg a day and should be set to keep the prothrombin time one and one-half to two times the normal value. The dose may be repeated for many days; anisindione does not accumulate in the body.

Prothrombin activity returns to normal within 24 to 72 hours after treatment when the drug is discontinued. Some studies suggest that gradual reduction of dosage over a 2-week period may decrease the frequency of recurrence of thromboembolic disease by preventing a rapid rise in prothrombin activity.

OVERDOSAGE Vitamin K_1 is a specific antidote for anticoagulants, such as anisindione, which reduce prothrombin activity in the blood. Vitamin K_1 may be administered orally or by injection, if the patient is not bleeding or if bleeding is slight. A few hours after administration of vitamin K_1 preparations, such as phytonadione, prothrombin activity increases and clotting time decreases. In the presence of more active hemorrhage, however, transfusions of whole blood or plasma are required until the desired level of prothrombin activity is achieved. Treatment with vitamin K_1 preparations is only adjunctive in such cases.

HOW SUPPLIED MIRADON Tablets, 50 mg, pink, scored, compressed tablets impressed with the Schering trademark and product identification numbers 795; bottle of 100 (NDC 0085-0795-05).

Store at Controlled Room Temperature 20°-25°C (68°-77°F) [See USP].

MIRADON®
brand of anisindione
Tablets

Schering Corporation
Kenilworth, NJ 07033 USA

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