1. NAME OF THE MEDICINAL PRODUCT

ALDOCUMAR 1 mg tablets
ALDOCUMAR 3 mg tablets
ALDOCUMAR 5 mg tablets
ALDOCUMAR 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1. General description

ALDOCUMAR are tablets for oral use contained in a blister pack.

2.2. Qualitative and quantitative composition

ALDOCUMAR 1 mg: each tablet contains warfarin sodium, 1 mg. Excipients: lactose monohydrate, colorant E-123 and others, qs
ALDOCUMAR 3 mg: each tablet contains warfarin sodium, 3 mg. Excipients: lactose monohydrate and others, qs
ALDOCUMAR 5 mg: each tablet contains warfarin sodium, 5 mg Excipients: lactose monohydrate and others, qs
ALDOCUMAR 10 mg: each tablet contains warfarin sodium, 10 mg. Excipients: lactose monohydrate and others, qs

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL DATA

4.1. Therapeutic indications

ALDOCUMAR is indicated for the prophylaxis and / or treatment of venous thrombosis, and in pulmonary embolism. Prophylaxis and / or treatment of thromboembolic complications associated with atrial fibrillation and / or replacement of heart valves.
After a myocardial infarction, ALDOCUMAR reduces the risk of death from recurrent myocardial infarction as well as from thromboembolic events such as stroke or systemic embolization.

4.2. Dosage and method of administration

The dosage and administration of ALDOCUMAR should be individualized for each patient according to the patient's particular response to the drug.
The dosage should be adjusted based on the INR (International Normalized Ratio) value. The INR is the quotient between the patient's plasma thromboplastin time and the normal thromboplastin time, raised to the International Sensitivity Index (ISI), determined by the WHO method for reference thromboplastin. The therapeutic margin to be achieved is, in general, between INR values of 2.0 and 3.5, depending on the clinical picture.

- Venous thromboembolism (including pulmonary embolism):

The available clinical evidence indicates that an INR of 2.0-3.0 is sufficient for the prophylaxis and treatment of venous thromboembolism and minimizes the risk of bleeding associated with higher INR values.

- Atrial fibrillation:

An INR of 2.0-3.0 is recommended for long-term warfarin therapy in patients with atrial fibrillation.

- Post myocardial infarction treatment:

In patients with myocardial infarction post, warfarin therapy should be initiated early (2-4 weeks after infarction) and the dosage should be adjusted to maintain an INR of 2.5- 3.5 to long term. In patients at increased risk of bleeding complications or receiving acetylsalicylic acid, maintenance therapy with warfarin is recommended to be around an INR of 2.5.

- Mechanical and bioprosthetic heart valves:

In patients with mechanical heart valves, long-term prophylaxis with warfarin at an INR of 2.5-3.5 is recommended. In patients with bioprosthetic heart valves, warfarin therapy is recommended at an INR of 2.0-3.0 for 12 weeks after valve insertion. In patients with additional risk factors such as atrial fibrillation or previous thromboembolism, longer term therapy should be considered.

- Recurrent systemic embolism:

In cases where the risk of thromboembolism is high, such as in patients with recurrent systemic embolism, a higher INR may be necessary.
An INR greater than 4.0 does not appear to provide any additional therapeutic benefit in most patients and is associated with an increased risk of bleeding.
Initial dosage:
The use of a large starting dose can increase the incidence of bleeding, does not offer faster protection against thrombus formation and is therefore not recommended. In elderly and / or debilitated patients and those who may show a response to warfarin greater than expected, low starting doses are recommended.
In general, it is recommended to initiate therapy with 2 to 5 mg of warfarin daily with dose adjustments based on the results of INR determinations.

Maintenance:
Most patients are satisfactorily maintained with a dose of 2 to 10 mg daily. The individual dose and interval should be adjusted according to the patient's response.

Duration of therapy:
The duration of therapy in each patient must be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.
It is essential that the prothrombin time (INR) is determined before starting treatment and every 24 hours until the maintenance dose is established. Then it is recommended once a week until the first month and then a monthly control for the duration of the treatment.

Missed dose:
The anticoagulant effect of ALDOCUMAR persists for more than 24 hours. If the patient forgets to take the prescribed dose of warfarin within the specified time, the dose should be taken as soon as possible on the same day.
The patient should not take the forgotten dose by doubling the daily dose to make up for the forgotten dose, but should consult their doctor.

Use in children:
There are insufficient clinical data to support the use of the preparation in children.

4.3. Contraindications

- Pregnancy.
- Lack of cooperation on the part of the patient.
- Pathological states in which the risk of bleeding is greater than the possible clinical benefit, for example: bleeding diathesis and / or blood dyscrasia.

- Organic lesions susceptible to bleeding.
- Recent or planned surgery on the central nervous system, ophthalmic operations and traumatic procedures that expose large areas of tissue.
- Gastroduodenal ulcer or overt bleeding in the gastrointestinal, urogenital or respiratory tracts, cerebrovascular hemorrhages, pericarditis and pericardial effusions, slow endocarditis.
- Severe hypertension; severe lesions of liver and kidney parenchyma.
- Increased fibrinolytic activity (for example, after lung, prostate, etc. operations).
- High doses of NSAIDs, miconazole (general route and oral gel), phenylbutazone (general route), high dose of acetylsalicylic acid and by extrapolation other salicylates to high doses.
- Hypersensitivity to the active principle or to any of the excipients.

4.4. Special warnings and precautions for use

The most serious risks associated with anticoagulant therapy with warfarin sodium are bleeding in any tissue and organ and, less frequently, necrosis and / or gangrene of the skin and other tissues. A proper diagnosis is necessary to determine if the necrosis is caused by an underlying disease. Warfarin therapy should be stopped if warfarin is suspected to be the cause of the development of necrosis and heparin therapy should be instituted.
In situations of high risk of bleeding and predisposition to necrosis, warfarin sodium should be administered with caution.
Anticoagulant therapy with warfarin can increase the release of emboli and atheromatous plaques, therefore increasing the risk of complications from the microembolization of systemic cholesterol. When this phenomenon is observed, warfarin therapy should be discontinued.

Calciphylaxis is a rare syndrome of vascular calcification with skin necrosis associated with high mortality. This condition mainly develops in patients with end-stage renal disease undergoing dialysis or in patients with known risk factors such as lack of protein C or S, hyperphosphatemia, hypercalcemia, or hypoalbuminemia. Rare cases of calciphylaxis have been reported in patients taking warfarin also in the absence of kidney disease. If calciphylaxis is diagnosed, appropriate treatment should be instituted and discontinuation of warfarin should be considered.

In the following conditions, the risks of anticoagulant therapy must be weighed against the possible benefits:

- Moderate to severe kidney or liver failure.
- Infectious diseases or alterations of the intestinal flora.
- Trauma that can result in internal bleeding.
- Surgery or trauma of large exposed surfaces.
- Catheters
- Severe to moderate hypertension.
- Known or suspected deficiency in protein C-mediated anticoagulant response: Inherited or acquired deficiencies of protein C or its cofactor, protein S, have been associated with tissue necrosis after warfarin administration. Concomitant anticoagulant therapy with heparin for 5 to 7 days during the initiation of warfarin therapy may minimize the incidence of tissue necrosis.

Periodic determination of prothrombin time (INR) is essential. Numerous factors, alone or in combination, physical condition, or concomitant medication can modify the patient's response to anticoagulants. It is generally good practice to monitor the patient's response with additional INR measurements in the period immediately after discharge from the hospital, and when other medications are started, interrupted, or taken irregularly.

Closer INR monitoring is recommended for patients who, due to the marketing of the new 1, 3 and 5 mg doses, substitute the 10 tablet fractions for the new 1, 3 and 5 tablets, as these allow more precise dosing.

These medicines contain lactose. Patients with hereditary galactose intolerance, Lapp lactase deficiency (deficiency seen in certain Lapland populations) or glucose or galactose malabsorption should not take this medicine.

ALDOCUMAR 1 mg tablets:
This medicine can cause allergic reactions because it contains amaranth dye (E-123).
May cause asthma, especially in patients allergic to acetylsalicylic acid.

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

Oral anticoagulants are drugs that can lead to a large number of interactions, among which those of clinical relevance will be described. The mechanisms related to these interactions are absorption disorders, inhibition or induction of the metabolizing enzyme system, displacement of plasma protein binding, and reduced availability of vitamin K. Rigorous control of coagulation is required when administered a drug in combination with a coumarin anticoagulant or its concomitant administration is discontinued.

- Enzyme inducers: they can produce inhibition of the anticoagulant effect, by inducing their hepatic metabolism, when it is administered together with: aminoglutethimide, carbamazepine, phenazone, griseofulvin, barbiturates (phenobarbital, secobarbital), rifampicin, hypericum perforatum (St. John's wort).
- Enzyme inhibitors: they can potentiate the anticoagulant effect, with risk of bleeding, due to an inhibition of their hepatic metabolism, when administered together with: allopurinol, analgesics (dextropropoxyphene, tramadol), antiarrhythmics (amiodarone), antibacterials (ciprofloxacin, clarithromycin, erythromycin , norfloxacin, ofloxacin, perfloxacin, chloramphenicol), antiulcer drugs (cimetidine, omeprazole, ranitidine), cisapride, disulfiram, statins (fluvastatin, lovastatin, simvastatin), fluconazole, fluorouracil, fluoxetine, alphaconazole and itxicam, betaconazole, interferon and itxicam , metronidazole, saquinavir, tamoxifen, viloxazine, inactive influenza viruses.

Drugs that displace anticoagulants from their binding to plasma proteins, with potentiation of anticoagulant activity: ethacrynic acid, nalidixic acid, non-steroidal anti-inflammatory drugs (diclofenac, phenylbutazone, feprazone, ibuprofen, ketoprofdarine, mefenamic acid, sulindacidene, carnitine, benzylamide, carnitine) , gemfibrozil, chloral hydrate, miconazole, valproic. There are some studies with chlorpropamide in which an increase in its half-life has been recorded, with possible potentiation of the antidiabetic effect, due to displacement of its binding to plasma proteins.

- Decreased availability of vitamin K, with the consequent enhancement of anticoagulant activity: thyroid hormones (levothyroxine), neomycin.
- Drugs that decrease the synthesis of coagulation factors, with the consequent potentiation of the anticoagulant effect: danazol, paracetamol, quinidine, quinine, vitamin E (tocopherol).

Other mechanisms:

- Ethyl alcohol: there is some study in which an alteration in the response to the anticoagulant has been recorded, especially at large doses of alcohol or in patients with some liver disorder, due to a decrease in coagulation factors and / or induction of liver metabolism.
- Oral contraceptives: they can reduce the anticoagulant effect, although in others this effect has been enhanced. This seems to be due to the balance between various effects of the estrogenic component of contraceptives, its procoagulant effect may predominate through an increase in the synthesis of coagulation factors, or its anticoagulant effect by inhibiting the hepatic metabolism of the anticoagulant.
- Ascorbic, acid: high doses of ascorbic acid (2 g / day or more) can decrease the absorption of the anticoagulant, with possible inhibition of its effect, due to the probable production of diarrhea.
- Benzbromarone: can enhance the action and / or toxicity of the anticoagulant. The mechanism is not known.
- Cephalosporins (cefamandol): may enhance the anticoagulant effect with risk of bleeding, with antivitamin K action.
- Clindamycin: may increase anticoagulant activity with increased values of coagulation tests (TP / INR) and / or bleeding.

- Clofibrate: can enhance the anticoagulant effect. There are several mechanisms such as decreased availability of vitamin K, displacement of the anticoagulant from its binding to plasma proteins, or inhibition of its hepatic metabolism.
- Disopyramide: there may be a possible inhibition or potentiation of the anticoagulant action, due to the action of disopyramide.
- Diuretics (chlorthalidone, spironolactone): may cause a reduction in prothrombin time, due to possible hemoconcentration of coagulation factors, due to the diuretic effect.
- Stanozolol: can enhance the anticoagulant effect, with risk of bleeding, due to possible increase in coagulation factors and decreased availability of vitamin K or increased sensitivity of receptors to the action of anticoagulants.
- Phenytoin: can produce variations in the plasma levels of the anticoagulant. there may be induction of its hepatic metabolism, displacement of plasma protein binding and even phenytoin can lengthen the prothrombin time in some of the patients.
- Flutamide: can increase prothrombin time. The mechanism is unknown.
- Ginseng: can produce a possible inhibition of the anticoagulant effect. The mechanism is unknown.
- Piracetam: can produce potentiation of the anticoagulant effect, with the presence of bleeding. The mechanism is unknown.
- Propranolol: can cause an increase in plasma warfarin levels, with possible potentiation of its effect. The mechanism is not known.
- Ion exchange resins (cholestyramine): can cause decreased levels of the anticoagulant and risk of bleeding. There are two opposite mechanisms: inhibition of warfarin absorption and decreased availability of vitamin K.
- Salicylates (acetylsalicylic acid, diflunisal): can produce a possible potentiation of the anticoagulant effect, with a risk of bleeding.
- Sucralfate: it can produce a possible inhibition of the effect by reducing the absorption of the anticoagulant, as the intestinal tract becomes alkaline.
- Sulfamethoxazole, can cause an increase in prothrombin time, with risk of bleeding, due to possible alteration of the warfarin receptor, increasing its sensitivity.
- Tetracyclines (doxycycline, tetracycline): can enhance the anticoagulant effect, with the risk of bleeding, by adding its hypothrombinemic effects.
- Vitamin K (phytomenadione, menadione): can inhibit the anticoagulant effect, by antagonizing its actions on the synthesis of coagulation factors.

Nutritional interactions:
Foods rich in vitamin K (cereals, broccoli, cabbage, carrots, poultry giblets, etc.)

4.6. Fertility, pregnancy and lactation

Pregnancy

Coumarin-derived oral anticoagulants, such as warfarin, cross the placenta and are not recommended for use during pregnancy. Congenital malformations and other adverse effects on fetal development, including severe nasal hypoplasia, chondrodysplasia punctata, optic atrophy, microcephaly, and mental and growth retardation have been reported in children born to mothers undergoing this medication during the first trimester. Oral anticoagulants cross the placenta with risk of fetal or placental hemorrhage when administered weeks before delivery. In the case of essential anticoagulant therapy, the use of heparin is recommended, especially during the first trimester, since it does not cross the placenta.
Patients should be informed to contact their physician as soon as they suspect that they may be pregnant. Those who become pregnant while receiving this medication should be informed of the potential risks to the fetus .

Lactation

Warfarin is practically not detected in breast milk, therefore unwanted effects on the infant are not to be feared. Children fed milk from mothers treated with warfarin do not have changes in prothrombin times.

4.7. Effects on ability to drive and use machines

The influence of ALDOCUMAR on the ability to drive and use machines is zero or negligible.

4.8. Adverse reactions

The following adverse reactions are listed according to MedDRA system organ class and by frequency.

Vascular and nervous system disorders
Common (> 1/100, <1/10)
Fatal or non-fatal hemorrhage from any tissue or organ, as a consequence of the anticoagulant effect. The signs, symptoms and severity will vary according to the location and degree or extent of the bleeding. Bleeding complications can present as paralysis, paraesthesia, headache, chest, abdomen, muscles, dizziness, shortness of breath, difficulty in breathing or swallowing, unexplained swelling, weakness, hypotension, or unexplained shock. Bleeding during anticoagulant therapy does not always correlate with prothrombin time / INR.

Bleeding that occurs when the prothrombin time / INR is within the therapeutic range warrants diagnostic investigation, as it can mask a previously unsuspected lesion, eg, tumor, ulcer, etc.

Uncommon (? 1 / 1,000 to <1/100): Vasculitis. Purple foot syndrome. Microembolization of systemic cholesterol. Cold intolerance and paresthesia.

Immune system disorders
Uncommon (? 1 / 1,000 to <1/100): Hypersensitivity, allergic reactions, edema.

Hepatobiliary disorders
Uncommon (? 1 / 1,000 to <1/100): Hepatitis, cholestatic liver damage, jaundice, elevated liver enzymes.

Gastrointestinal disorders
Uncommon (? 1 / 1,000 to <1/100): Abdominal pain, nausea, vomiting, diarrhea, fatigue, asthenia, lethargy.

Skin and subcutaneous tissue disorders
Uncommon (? 1 / 1,000 to <1/100): Alopecia.
Very rare (<1 / 10,000): Necrosis of the skin and other tissues, dermatitis, itching.
Frequency 'not known' : Calciphylaxis

4.9. Overdose

Biological monitoring of an overdose without clinical repercussions requires an adequate dose reduction and constant monitoring.

The steps to follow are the following, depending on whether or not there are bleeding complications:

- In case of overdose with INR <6 and in the absence of bleeding: temporarily interrupt the anticoagulant and restart therapy with a lower dose, depending on the INR.
- In the event of overdose with INR> 6 and in the absence of severe bleeding: administer 0.5 mg of injectable vitamin K_1 in continuous infusion for 20 to 30 minutes. Increase the dosage to 1 mg if the INR ? 10.

- In case of overdose with severe bleeding: administer 10 to 20 mg of injectable vitamin K_1 in a continuous slow infusion of 1 hour, together with a transfusion of fresh frozen plasma or whole blood or a commercial Factor IX complex.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Therapeutic group: Oral anticoagulants B01AA03.
Warfarin prevents the formation of active coagulation factors II, VII, IX, and X in the liver by inhibiting vitamin K-mediated gamma carboxylation of precursor proteins.
Full therapeutic action is not manifested until circulating clotting factors are eliminated by normal catabolism, which occurs at different rates for each factor. Although prothrombin time (PT) can be prolonged when factor VII (which has the shortest half-life) is depleted, it is believed that maximum antithrombotic effects are not achieved until all four factors disappear. Warfarin does not have a direct thrombolytic effect, although it can limit the extent of existing thrombi.

5.2. Pharmacokinetic properties

Orally administered warfarin is rapidly and completely absorbed and peak plasma concentrations are reached within 1 to 9 hours.
The volume of distribution of warfarin approaches the albumin space and more than 97% of the total drug is bound to proteins, with only free drug being active.

Elimination of warfarin is almost exclusively by hepatic metabolism through the cytochrome $P_{450\ system}$, and the metabolites have weak anticoagulant activity.

The isomers of warfarin are metabolized differently (the warfarin present in the preparation ALDOCUMAR 1, 3, 5 and 10 mg is a racemic mixture of the two isomers), with the half-lives of approximately 48 and 31 hours for the R and isomers. Yes, respectively. Metabolism is primarily by keto-reduction to warfarin alcohols (R-warfarin) and hydroxylation (S-warfarin) .

5.3. Preclinical safety data

The oral LD_{50} in male rats is 323 mg / Kg, in female rats 58 mg / Kg, in mice 374 mg / Kg and in rabbits 800 mg / Kg.
By IV route the LD_{50} in male and female rats is 186 mg / Kg, in rabbits it is 100-200 mg / Kg, in dogs 200-300 mg / Kg and in chickens 200-225 mg / Kg.

6. PHARMACEUTICAL INFORMATION

6.1. List of excipients

ALDOCUMAR 1 mg: Lactose monohydrate (63.63 mg / tablets) , microcrystalline cellulose, sodium carboxymethyl starch (Primojel), colloidal silica dioxide, magnesium stearate, amaranth red dye (E-123) .

ALDOCUMAR 3 mg: Lactose monohydrate (61.63 mg / tablet) , microcrystalline cellulose, sodium carboxymethyl starch (Primojel), colloidal silica dioxide, magnesium stearate, brilliant blue colorant (E-131) .

ALDOCUMAR 5 mg: Lactose monohydrate (59.50 mg / tablet) , microcrystalline cellulose, sodium carboxymethyl starch (Primojel), colloidal silica dioxide, magnesium stearate, quinoline yellow dye (E-104) .

ALDOCUMAR 10 mg: Lactose monohydrate (151.87 mg / tablet), microcrystalline cellulose, sodium carboxymethyl starch (Primojel), colloidal silica dioxide, magnesium stearate .

6.2. Incompatibilities

Patients receiving warfarin anticoagulant therapy should not take other medications without first consulting their doctor.

6.3. Period of validity

ALDOCUMAR 1, 3 and 5 mg tablets : 3 years.
ALDOCUMAR 10 mg tablets : 5 years.

6.4. Special precautions for storage

Store in the outer carton to protect from light.

6.5. Nature and contents of container

A LDOCUMAR 1, 3 and 5 mg tablets: Blister pack (aluminum and PVC). Box containing 2 platelets with 20 tablets scored on one side and the anagram 1, 3 and 5 respectively.

ALDOCUMAR 10 mg tablets : Blister pack (aluminum and PVC). Box containing 2 platelets with 20 double-scored tablets.

CLINICAL PACKAGING (1, 3, 5 and 10 mg): Box containing 500 tablets in blister platelets of 2 tablets each (aluminum and PVC).

Only some pack sizes may be marketed.

6.6. "Special precautions for disposal <and other handling>"

Disposal of unused medicine and all materials that have been in contact with it will be done in accordance with local regulations .

7. HOLDER OF THE MARKETING AUTHORIZATION

ALDO-UNION Laboratory, S. L .
Baroness of Maldá, 73
08950 Esplugues de Llobregat (Barcelona)
e-mail: info @ aldo-union. com (mailto:info@aldo-union.com)

8. MARKETING AUTHORIZATION NUMBER (S)

ALDOCUMAR 1 mg tablets, Registration Number: 63,062

ALDOCUMAR 3 mg tablets, Registration Number: 63,063

ALDOCUMAR 5 mg tablets, Registration Number: 63,064

ALDOCUMAR 10 mg tablets, Registration Number: 32,864

9. DATE OF THE FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

ALDOCUMAR 1 mg, 3 mg and 5 mg tablets : Authorization, M ay 2000 / Renewal, November 2009

ALDOCUMAR 10 mg tablets : Authorization, November 1959 / Renewal, May 2009.

10. DATE OF REVISION OF THE TEXT

July 2016

Top