NICOUMALONE/ ACENOCOUMAROL

Indications/Uses

Thromboembolic disorders.

Dosage/Direction for Use

Adult : PO Initial: 2-4 mg/day for 2 days, or 6 mg on 1st day, followed by 4 mg on 2nd day. Subsequent dose adjusted according to response. Maintenance: 1-8 mg/day.

Dosage Details

Oral

Thromboembolic disorders

Adult: Initially: 2-4 mg daily for 2 days. Alternatively, 6 mg on the 1st day as loading dose, followed by 4 mg on the 2nd day. Subsequent dose adjusted according to response. Maintenance: 1-8 mg daily. Administer at the same time each day.

Elderly: Reduce dose if necessary.

Renal Impairment

Severe: Contraindicated.

Hepatic Impairment

Severe: Contraindicated.

Contraindications

Haemorrhagic diathesis and blood dyscrasia (e.g. haemophilia, thrombocytopenic purpura, leukaemia), peptic ulcer or haemorrhage of the GI tract, urogenital tract or resp system; cerebrovascular haemorrhage, acute pericarditis, pericardial effusion, infective endocarditis, severe HTN. Recent or potential surgery of the eyes/CNS. Recent surgery resulting in increased fibrinolytic activity (e.g. surgery of the lung, prostate, uterus). Uncooperative patient (e.g. unsupervised senile, alcoholic, psychotic, w/ dementia). Severe hepatic and renal impairment. Pregnancy.

Special Precautions

Patient w/ severe heart failure, known or suspected protein C or S and vit K deficiency. Mild to moderate hepatic and renal impairment. Elderly. Lactation.

Adverse Reactions

Rarely, urticaria, rash, dermatitis, purpura, skin necrosis; fever, decreased appetite, nausea, vomiting, diarrhoea; alopecia; hepatic dysfunction, jaundice, pancreatitis; purple toe syndrome.

Potentially Fatal: Haemorrhage.

MonitoringParameters

Determine prothrombin time (PT)/INR (daily or on alternate days in early days of treatment, then at longer intervals depending on response). Monitor CBC, hepatic and renal function.

Overdosage

Symptoms: Haemorrhage, haematemesis, haemoptysis, haematuria (w/ renal colic), haematoma, menorrhagia, GI and cutaneous haemorrhage, vaginal, gingival, joint, and nose bleeding; tachycardia, hypotension, peripheral circulatory disorder, nausea, vomiting, diarrhoea, abdominal pain, high PT/INR value, prolonged thromboplastin time. Management: Oral vit K1 (phytomenadione) may be given for moderate to severe haemorrhage. Administer fresh blood/frozen plasma, complex concentrate/recombinant factor VIIa supplemented w/ vit K1 for severe and life-threatening haemorrhage.

Drug Interactions

Increased effect w/ antiarrhythmics (e.g. amiodarone, quinidine), antibiotics (e.g. broad spectrum antibiotics, tetracyclines, chloramphenicol), antifungal (e.g. metronidazole), SSRIs (e.g. citalopram, fluoxetine, sertraline, paroxetine), antigout (e.g. allopurinol), lipid-regulating drugs (e.g. atorvastatin, fluvastatin, simvastatin), and inhibitors of CYP2C9 isoenzyme. Reduced anticoagulant effect w/ antineoplastics (e.g. azathioprine, 6-mercaptopurine), antivirals (e.g. ritonavir, nelfinavir), thiazide diuretics, oral contraceptives, and inducers of CYP2C9, CYP2C19, and CYP3A4 isoenzymes. May increase the serum hydantoin concentration of phenytoin. May potentiate the hypoglycaemic effect of sulphonylurea derivatives (e.g. glibenclamide, glimepiride).

Potentially Fatal: Increased risk of haemorrhage w/ other anticoagulants (e.g. warfarin, heparin, LMWH), antiplatelets (e.g. dipyridamole, clopidogrel, ticlopidine), antibiotics (e.g. clindamycin), analgesics (e.g. salicylates, pyrazolone derivatives, COX-2 inhibitors), high dose IV methylprednisolone.

Food Interaction

Reversed anticoagulant effect w/ foods high in vit K (e.g. beef and pork liver, green tea, green leafy vegetables). Increased metabolism and reduced PT/INR w/ chronic alcohol consumption; conversely, acute ingestion reduces metabolism and increases PT/INR. Increased INR and may cause severe bleeding w/ cranberry juice. Reduced effect w/ St. John’s wort.

Action

Description: Acenocoumarol, a coumarin derivative, is a vitamin K-epoxide-reductase complex 1 (VKORC1) antagonist, depleting functional vit K reserves, thus, reducing the synthesis of coagulation factors II (prothrombin), VII, IX, and X, as well as proteins C and S. It also reduces γ-carboxylation of certain glutamic acid molecules, important for blood clotting initiation.

Pharmacokinetics:

Absorption: Rapidly absorbed from the GI tract. Bioavailability: 60%. Time to peak plasma concentration: 1-3 hr.

Distribution: Crosses the placenta; enters breast milk (small amounts). Volume of distribution: 0.16-0.34 L/kg. Plasma protein binding: 99%, mainly to albumin.

Metabolism: Both S- and R- isomers are metabolised in the liver by CYP2C9 isoenzyme via oxidation; R-isomer is also metabolised by CYP1A2 and CYP2C19. Undergoes nitro-reduction by gut flora.

Excretion: Via urine (approx 60%, as inactive metabolites) and faeces (29%, as metabolites). Elimination half-life: 8-11 hr.

Chemical Structure

Click on icon to see table/diagram/image

Storage

Store between 15-30°C.

MIMS Class

Anticoagulants, Antiplatelets & Fibrinolytics (Thrombolytics)

ATC Classification

B01AA07 - acenocoumarol ; Belongs to the class of vitamin K antagonists. Used in the treatment of thrombosis.