Diosmin + Hesperidin

Dioxel

450 mg/50 mg Film-Coated Tablet
Venotonic / Vasculoprotective

FORMULATION

Each film-coated tablet contains:
Micronized purified flavonoid fraction ..... 500 mg
(Equivalent to 450 mg diosmin + 50 mg hesperidin)

PHARMACOLOGIC CATEGORY

Venotonic / Vasculoprotective

PRODUCT DESCRIPTION

Brown, film-coated, elliptical, biconvex tablet, plain on both sides

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Micronized purified flavonoid fraction (MPFF) is an oral phlebotropic and vascular protective agent consisting of 90% diosmin and 10% hesperidin. It increases venous tone, improves lymphatic drainage and protects the microcirculation from inflammatory processes and apoptosis. By decreasing the expression of some endothelial adhesion molecules, MPFF inhibits the activation, migration and adhesion of leukocytes at the capillary level. This leads to a reduction in the release of inflammatory mediators such as oxygen-free radicals, prostaglandins and thromboxane resulting in a decrease in capillary hyperpermeability.

PHARMACOKINETICS

Diosmin is rapidly transformed in the intestine by intestinal flora and absorbed as its aglycone, diosmetin, after oral administration.

A study compared the absorption of a single oral dose of radiolabelled MPFF [500 mg tablets containing trace amounts (about 25 nCi) of ^{14}C-diosmin] with that of nonmicronized diosmin in 12 healthy male volunteers. Results showed that about half of an oral 500 mg dose of radiolabelled MPFF was absorbed within 48 hours of administration. Since unabsorbed diosmin was not excreted in the urine, absorption was evaluated based on the urinary elimination of radioactivity. Reduction in the particle size of diosmin led to a significant increase in absorption; mean gastrointestinal absorption of micronized ^{14}C-diosmin was significantly greater than with nonmicronized ^{14}C-diosmin (57.9 vs. 32.7% during 0 to 168 hours postdose; p=0.004).

The time to peak plasma concentration of diosmetin is 1 hour and plasma concentrations decrease slowly after 2 hours; diosmetin is still detectable after 48 hours. The mean volume of distribution of diosmetin is 62.1 liters.

Diosmetin is rapidly and extensively degraded to phenolic acids or their glycine conjugate derivates, which are eliminated in the urine. The predominant metabolite in man is 3-hydroxy-phenylpropionic acid which is mainly eliminated in its conjugated form. Metabolites found in smaller amounts include other phenolic acids corresponding to 3-hydroxy-4-methoxybenzoic acid, 3-methoxy-4-hydroxyphenylacetic acid and 3,4-dihydroxybenzoic acid. It is possible that unidentified metabolites may be responsible for the pharmacological activity of diosmin.

Elimination of micronized diosmin is relatively rapid with » 34% of the radiolabelled dose of ^{14}C-diosmin excreted in the urine and feces over the first 24 hours and » 86% over the first 48 hours. Unmetabolized diosmin and diosmetin are not excreted in the urine. The cumulative excretion of the dose in the urine and feces was 100%. About half of the dose was eliminated in the feces as unchanged diosmin and diosmetin.

INDICATIONS

- Treatment of symptoms related to venolymphatic insufficiency (heavy legs, pain, early morning restless cramps)
- Treatment of functional symptoms related to acute hemorrhoidal attack

DOSAGE AND ADMINISTRATION

INDICATION	RECOMMENDED ORAL DOSE (Should be taken at midday and evening, with meals)
Venolymphatic insufficiency	1 tablet twice a day
Acute hemorrhoidal attack	3 tablets twice a day for the first 4 days, then 2 tablets twice a day for the next 3 days
Or, as prescribed by a physician	

CONTRAINDICATIONS

- Hypersensitivity to any component of the product

WARNINGS AND PRECAUTIONS

Venolymphatic insufficiency

- The most effective way of giving this treatment is in combination with a healthy lifestyle such as diet and exercise.
- Avoid exposure to sun, heat, excessive standing and being overweight.
- Walking and wearing special support stockings stimulate blood circulation.

Acute hemorrhoidal attack

- This medicine is no substitute for the specific treatment of other anal disorders.
- The treatment must be short-term. If the symptoms do not disappear within 15 days, ask your doctor for advice; proctological examination should be performed and the treatment reviewed.

INTERACTIONS WITH OTHER MEDICAMENTS

There are no known drug interactions with this medicine.

Tell your physician about other medicines you are taking.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: Inform your physician if you become pregnant while taking this medicine.

Experimental studies in animals have not demonstrated any teratogenic effect. To date, there have been no reports of adverse effects in humans.

Lactation: Due to lack of information, breastfeeding should be avoided during treatment.

UNDESIRABLE EFFECTS

Autonomic: Anxiety, cramps, drowsiness, feeling of discomfort, headache, hypotension, insomnia, palpitation, tiredness, vertigo
Gastrointestinal: Abdominal pain, diarrhea, dyspepsia, epigastric pain, gastric discomfort, nausea, vomiting

OVERDOSE AND TREATMENT

No overdosage has been reported.

STORE AT TEMPERATURES NOT EXCEEDING 30°C.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Availability : Alu/Clear PVC Blister Pack by 10's; box of 30's

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