JOINCERIN M

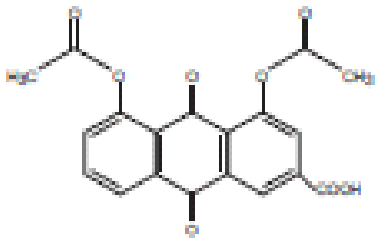
(Diacerein 50 mg, Glucosamine Sulfate Potassium Chloride 250 mg & Methylsulfonylmethane 750 mg Tablets)

COMPOSITION

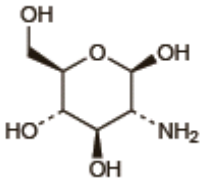
Each film coated tablet contains:
Diacerein I.P. 50 mg
Glucosamine sulfate Potassium chloride U.S.P. 750 mg
Methylsulfonylmethane U.S.P. 250 mg
Colour: Yellow oxide of iron

DESCRIPTION

Diacerein is a low-molecular-weight heterocyclic compound designated as (4,5-bis (acetyloxy)- 9,10-dioxo-2-anthracene carboxylic acid). Following oral administration, it is rapidly metabolized to the deacetylated active metabolite, rhein. Rhein is an anthraquinone found in plants of the Genus Cassia and has moderate anti-inflammatory and analgesic activity.



Glucosamine Sulfate Potassium Chloride
$(C_6H_{14}NO_5)_2SO_4$, 2KCl = 605.5.



Glucosamine is a natural substance found in chitin, mucoproteins, and mucopoly saccharides. It is involved in the manufacture of glycosaminoglycan, which forms cartilage tissue in the body; glucosamine is also present in tendons and ligaments. Glucosamine must be synthesised by the body but the ability to do this declines with age. Glucosamine and its salts have therefore been advocated in the treatment of rheumatic disorders including osteoarthritis. Glucosamine may be isolated from chitin or prepared synthetically; glucosamine sulfate have been used.

Methylsulfonylmethane

C2H6O2S = 94.13.

Methylsulfonylmethane is an oxidation product of dimethyl sulfoxide and has been used similarly as an organic solvent. It may be responsible for some of the pharmacological actions of dimethyl sulfoxide and has been tried in disorders including osteoarthritis, allergic rhinitis, and interstitial cystitis. It has also been used as a nutritional supplement.

CLINICAL PHARMACOLOGY

Mechanism of action

The mechanism of action defers from the nonsteroidal anti-inflammatory drugs since it is not related to the inhibition of the synthesis of the prostaglandins. Anti-osteoarthritic and cartilage-stimulating properties have been demonstrated in vitro and in animals models. Diacerein and rhein have been shown to inhibit the production of interleukin-1 beta by human monocytes and the effects of the cytokine on chondrocytes in vivo. They exert chondroprotective effects in cultured articular cartilage and reduce severity of cartilage, bone, and synovial membrane damage in osteoarthritis. There appear to be some inhibitory effects on leucocyte migration and activation, contributing to the weak anti-inflammatory activity of the drug. Studies indicate that diacerein does not block the synthesis of prostaglandins, thromboxanes, or leukotrienes but may actually stimulate prostaglandin synthesis, especially PGF-2 alpha, a prostaglandin with cytoprotective effect on the gastric mucosa.

Diacerein in therapeutic doses inhibits the stimulation of interleukin-1beta production and production of nitrous oxide. It also significantly reduces severity of pathological changes of osteoarthritis compared to placebo and increases the expression of transforming growth factor (TGF)-beta1 and (TGF)-beta2, with potential cartilage repairing properties. Diacerein does not alter renal or platelet cyclo- oxygenase activity and may therefore be tolerated by patients with prostaglandin- dependent renal function.

Pharmacokinetics

Absorption

Oral bioavailability of Diacerein is 35% to 56%. Concurrent intake of food delays the time to peak concentration from 2.4 hours to 5.2 hours, but is associated with a 25% increase in absorption. Therefore, diacerein is best given with food.

Distribution

Total protein binding of rhein is about 99% to plasma albumin and in a lesser percentage to lipoproteins and gamma-immunoglobulins. It achieves synovial fluid concentration of 0.3 to 3.0 milligrams/liter.

Metabolism

Diacerein is metabolized extensively (100%) in liver following oral dosing, prior to entering systemic circulation. Major active metabolites include rhein glucuronide and rhein sulfate with half life being 7 to 8 hours.

Excretion
Urinary excretion of diacerein in the form of its metabolites has ranged between 35% and 60%, with approximately 20% as free rhein and 80% as conjugates of rhein.

Glucosamine Sulfate Potassium Chloride
Effects on glucose metabolism.
Glucosamine has a role in glucose metabolism, increasing insulin resistance in skeletal muscle which has raised concerns about its safety profile in diabetic patients. However, alteration of glycaemic homoeostasis was not found in a 3-year randomised controlled study in patients without diabetes.4 A review5 of the literature found limited data on diabetic patients taking glucosamine supplements, and recommended close monitoring of blood glucose levels in this group until more data are available.

Special Populations
Geriatric patients:
Doses exceeding 100 milligrams diacerein daily may warrant close clinical monitoring in geriatric patients.

Pediatric patients:
Pharmacokinetics of diacerein are not studied in pediatric population and its administration is not recommended in pediatric population.

Hepatic Insufficiency:
Pharmacokinetics was unchanged in patients with severe cirrhosis after receiving a single oral dose of diacerein 50 milligrams. However, since cirrhosis may influence drug accumulation after multiple doses, close clinical monitoring is advised for patients with hepatic insufficiency.

Renal Insufficiency:
In patients with mild to severe renal insufficiency, there was a significant increase in the area-under the-curve and a decrease in the total apparent clearance in renal insufficiency patients compared to the healthy adults. Severe renal failure (creatinine clearance 10 to 27 milliliters/minute) showed a significantly decreased renal clearance of rhein.

INDICATIONS
JOINCERIN M is indicated as initial therapy in adult patients with osteoarthritis of knees and hip joints

DOSAGE AND ADMINISTRATION
50 milligrams (mg) administered orally BID for the treatment of OSTEOARTHRITIS of the hip or knee. Initiate the treatment with one tablet night time for 2 to 4 weeks;

gradually adjust the dose to two tablets twice daily. Oral absorption is greatest when administered with food.

USE IN SPECIAL POPULATIONS

Pregnancy

The use of diacerein is not recommended in women attempting to conceive. No clinical data on exposed pregnancies are available for diacerein. The potential for human risk in pregnancy is unknown.

Lactation

Pharmacokinetics of diacerein has not been studied in lactating women and its administration is not recommended.

Pediatric Use

Pharmacokinetics of diacerein has not been studied in pediatric population and its administration is not recommended in pediatric population.

Geriatric Use

Doses exceeding 100 milligrams diacerein daily may warrant close clinical monitoring in geriatric patients.

Hepatic Insufficiency

No significant difference in pharmacokinetic parameters of rhein between patients with liver impairment and healthy volunteers was observed either in plasma or in urine assessments. However, since cirrhosis may influence drug accumulation after multiple doses, close clinical monitoring is advised for patients with hepatic insufficiency

Renal Insufficiency

In patients with mild-to-severe renal insufficiency, there was a significant increase in the area-under the-curve and a decrease in the total apparent clearance compared to the healthy adults. Severe renal failure (creatinine clearance 10 to 27 milliliters/minute) showed a significantly decreased renal clearance of rhein; therefore, a 50% reduction in the dose of diacerein should be made in patients with severe renal insufficiency. Diacerein dose should be reduced by half in patients with a creatinine clearance less than 2.4 liters/hour

CONTRAINDICATIONS

Hypersensitivity to diacerein or any components of this product.

WARNINGS

- It is recommended to initiate use of a tablet at night for initial 2 to 4 weeks since the use of the drug initially can produce an acceleration of the time of intestinal transit.

- It is recommended to prolong the treatment by at least 6 months: the clinical studies have demonstrated that the drug can be used for 2 years without serious problems.

- As with any other prolonged treatment, it is recommended to monitor laboratory parameters, including hepatic enzymes, every 6 months.
- Combined use with laxatives is contraindicated.

ADVERSE EFFECTS
Generally, the drug has been well tolerated. The commonest reported adverse reaction was acceleration of the time of intestinal transit (diarrhea 37% of patients). Few cases of abdominal pains have been described .The modification of the dose in the initial periods of the treatment (2 to 4 weeks) has allowed to surpass or to diminish these adverse events.

Other adverse events reported are urine discoloration in 14.4% cases and a single case of hypokalemia, hepatotoxicity resulting into acute hepatitis and fatal toxic epidermal necrolysis (Lyell's syndrome).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
No data regarding carcinogenesis, mutagenesis, impairment of fertility is available

DRUG INTERACTIONS
The clinical studies have demonstrated the absence of interaction between the drugs such as: warfarin, tolbutamide, aspirin (acetylsalicylic acid), chlorpromazine and indomethacin.

OVERDOSAGE
In cases of overdose it can produce a profuse diarrhea. The treatment must be symptomatic with correction of any electrolyte imbalance which may be necessary.

Expiry date
Do not use later than the date of expiry.

Storage
Store in a dry and dark place at a temperature not exceeding 25°C.

Presentation
JOINCERIN M is available as Blister strip of 10 tablets

MARKETED BY

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