PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

DIATRIM CAPSULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains diacerein 50 mg.
This product contains 240 mg lactose per capsule.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Opaque No. 1 hard gelatin capsule with dark blue cap and white body.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

Symptomatic treatment of functional symptoms of osteoarthritis.

4.2. Posology and Method of Administration

ADULTS (aged over 15 years).
As some patients may experience loose stools or diarrhea, the recommended starting dose is 50 mg once daily with evening meal for the first 2 to 4 weeks of treatment, after which the recommended daily dose is 50mg twice daily .
The treatment should be taken with food, one capsule with breakfast and the other capsule with evening meal. The capsules must be swallowed intact, without opening them, together with a glass of water.
In patients older than 65 years, caution should be exercised during use of this medicine; close supervision and monitoring of adverse reactions should be performed.
In the elderly, and in moderate renal impairment, there is no need to change the dosage.
In severe renal insufficiency (creatinine clearance below 30 ml/min), the daily dosage are to be halved.

4.3. Contraindications

- Inflammatory organic bowel disease (ulcerative colitis, Crohn’s disease).
- Intestinal obstruction or partial obstruction.
- Abdominal pain syndromes of indeterminate etiology.
- Known allergy to rhein (substance in the anthraquinone group) and substances with similar activity.
- Known hypersensitivity to any excipient.
- Current and/or history of liver disease.

4.4. Special warnings and precautions for use

Diarrhea

Intake of diacerein frequently leads to diarrhea (see chapter 4.8) that can consequently lead to dehydration and hypokalemia.
In case of diarrhea, patients should be advised to stop diacerein treatment and contact their doctor to discuss treatment alternatives.
In patients receiving diuretics, caution should be exercised because dehydration and hypokalemia may occur.
Particular caution should also be exercised in case of hypokalemia in patients treated with cardiac glycosides (digitoxin, digoxin). (See chapter 4.5)
Concomitant intake of laxatives should be avoided.

Hepatotoxicity

Elevated serum hepatic enzyme levels and symptomatic acute hepatic injury have been reported with diacerein in the post-marketing phase. (See chapter 4.8).
Before treatment with diacerein is initiated, the doctor should question the patient about any possible comorbidities, and past or current liver disease and screen for major causes of active hepatic disease. A diagnosis of liver disease is a contraindication to diacerein use. (See chapter 4.3)
Signs of hepatic injury should be monitored and caution should be exercised when diacerein is used concomitantly with other medicinal products associated with hepatic injury. Patients should be advised to limit their alcohol intake while on treatment with diacerein.
Treatment with diacerein should be stopped if elevation of hepatic enzymes or suspected signs or symptoms of liver damage are detected.
Patients should be advised about the signs and symptoms of hepatotoxicity and must be advised to immediately contact their physician in case of appearance of symptoms suggestive of liver damage.
In patients older than 65 years, caution should be exercised during use of this medicine; close supervision and monitoring of adverse reactions should be performed.

Other Warnings

Diacerin capsules should not be given to children under 15 years.
This medicine is not recommended during pregnancy and lactation.
This product contains lactose. This medicine must not be administered in the event of congenital galactosemia, glucose or galactose malabsorption syndrome or lactase deficiency.

4.5. Interactions with other medicinal products and other forms of interactions

Combinations requiring precautions for use

- *Antacids (aluminum, calcium, and magnesium salts, oxides or hydroxides):*

Decreased of digestive absorption of diacerein.
Antacids should be taken separately from diacerein, allowing for an interval of greater than 2 hours if possible.

- *Diuretic and/or cardiac glycosides:*

Intake of diacerein can lead to diarrhea and hypokalemia. Caution must be exercised in the concomitant administration of diuretics (high-ceiling loop and thiazides) and/or cardiac glycosides (digitoxin, digoxin), as the risk of arrhythmia is increased (see chapter 4.4).

4.6. Pregnancy and lactation

Pregnancy

In animals, an experimental study showed delayed ossification in the fetus due to maternotoxic effect in high doses.
Clinically, there is currently no adequate data to assess a potential teratogenic or foetotoxic effect of diacerin when administered during pregnancy.
Accordingly, the use of this medicine is not recommended during pregnancy.

Lactation

It is not recommended to administer the product to women during lactation, the passage of the anthraquinone derivatives in breast milk in minimal proportions were highlighted in the literature.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Gastrointestinal disorders

Very common (> 1/10): diarrhea, abdominal pain.
Common (> 1/100 and < 1/10): frequent bowel movements, flatulence.
As a rule, these effects abate with continuing treatment. In some cases, diarrhea was severe with complications such as dehydration and disorders of fluid and electrolyte balance.
Pigmentation of the colorectal mucosa (melanosis coli) was rarely observed.

Hepatobiliary disorders

Uncommon (≥ 1/1000 and < 1/100): Cases of elevated hepatic enzymes in serum.

Skin and subcutaneous tissue disorders:

Common (> 1/100 and < 1/10): pruritus, rash, eczema.

Other:

Dark urine related to the structure of the molecule and without pathological value can be observed.

Post-marketing surveillance

Cases of acute liver injury, including elevated serum hepatic enzymes and cases of hepatitis have been reported in the post-marketing phase with diacerein. Most of them occurred during the first months of treatment. Patients should be monitored for signs and symptoms of hepatic injury.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic @moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL)

4.9. Overdose

Profuse diarrhea may occur in the event of overdose. Symptomatic treatment should then be instituted and electrolyte disorders and dehydration corrected if necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Anti-Osteoarthritic.
ATC Classification: M01AX21, Other Anti-inflammatory and Antirheumatic agents, Non-Steroids.
Diacerein is an anthraquinone derivative which has moderate anti-inflammatory activity. It is anti-inflammatory at high doses and devoid of any irritant effect on the stomach.
Action onset is slow, beginning towards day 30 of treatment and becoming significant after about 45 days. It has an additive effect in combination with NSAIDs.

In vitro, diacerein has the following properties:

- inhibition of phagocytosis and macrophage migration

- inhibition of interleukin-1 synthesis

- reduction of collagenolytic activity

In some models, diacerein stimulates production of proteoglycans, glycosaminoglycans and hyaluronic acid.
A positive effect on cartilage has been demonstrated in a number of animal models.
A multicentre, randomized, double-blind, placebo-controlled (ECHODIAH study) to evaluate the effect of diacerein on the progression of Joint Space narrowing (JSN) was preformed for a period of 3 years in 507 patients with hip osteoarthritis. Patients received either 50 mg of diacerein (n=255) or placebo (n=252) twice a day, i.e. in the morning and in the evening.

Efficacy was evaluated using the following two main criteria:

- Percentage of the patients with a radiological impairment (radiological joint space width decreased more than 0.5 mm).
- Annual rate of Joint Space Narrowing (JSN) rate per year (mm/year).

269 patients completed the trial.

At 3 years, the Intend-To-Treat (ITT) analysis shows that:

- The percentage of patients with a radiological impairment of more than 0.5 mm is significantly lower with diacerein group compared to placebo (50.7% versus 60.4 for placebo, p=0.036).
- JSN rate (0.39 mm/year) is not statistically different between the 2 groups.

The clinical significance of these results in terms of prognosis is unknown.

5.2. Pharmacokinetic properties

- Orally administered diacerein undergoes a hepatic first-pass effect and is totally deacetylated to rhein, the sulphoconjugated metabolite.
- After a single 50 mg dose, plasma diacerein concentrations peak arises at a mean 2.5 hours and the maximal concentration (Cmax) is of the order of 3 mg/l.
- Diacerein 50 mg capsule intake with food increases the bioavailability (the area under the curve increases by nearly 25%) and delays absorption.
- For dose ranging from 50 to 200 mg of diacerin capsules in single dose, the pharmacokinetic parameters are dose-independent.

- Protein binding is very strong (99%) and mainly consists in high-affinity binding to albumin.
- The elimination half-life ($t_{1/2}$) of rhein is approximately 4.5 hours. The total quantity excreted in the urine is around 30%. 80% of the rhein excreted in urine is in sulpho- and glucuroconjugated form and 20% is excreted in unchanged form.
- Repeated administration of diacerein (50 mg twice daily) results in slight accumulation.
- In patients with severe kidney failure (creatinine clearance less than 30 ml/min), the area under the curve and elimination half-life are doubled and urinary elimination halved.
- In the elderly, given the good tolerance of the product, it is no necessary to change the dose, despite the slower elimination.

5.3. Preclinical safety data
Not applicable.

6. PHARMACEUTICALS PARTICULARS

6.1. List of excipients
Lactose (anhydrous), magnesium stearate, gelatin capsule (Indigo carmine, erythrosine, titanium dioxide, water, gelatin).

6.2. Incompatibility
Not applicable.

6.3 Shelf life
3 years.

6.4. Special precautions for storage

Store in a dry and cool place, below 25°C

6.5. Nature and contents of container
Blister packs of 30 capsules.

7. Registration number
132.16.30996.00

8. Manufacturer
Trima Israel Pharmaceutical Prouducts Maabarot Ltd., Kibbutz Maabarot 4023000, Israel.