ARTRODAR® 50 MG
Diacerein

Capsules

PHYSICAL CHARACTERISTICS
ARTRODAR® is presented as hard gelatin capsules each containing 50 mg diacerein as the active ingredient and excipients.

PHARMACOLOGY INFORMATION (PHARMACODYNAMICS/PHARMACOKINETICS)
Pharmacodynamic properties
In vitro and *in vivo* studies have shown that diacerein:
- inhibits the production of interleukin 1,
- decreases collagenolytic activity.

The anti-osteoarthritis properties of diacerein are due to its capacity to inhibit the pro-inflammatory, pro-catabolic cytokines such as interleukin 1 which plays an important role in the degradation of articular cartilage, for example, it inhibits cartilage production and stimulates the liberation of cartilage degrading enzymes (collagenase and stromelysin).
Clinical studies of 2 to 6 months duration demonstrate that diacerein is effective in improving the signs and symptoms of osteoarthritis (pain and joint function). These studies show that the drug has a slow onset of action which becomes significant after 30-45 days and which is maintained once treatment is interrupted. Diacerein has a good gastric tolerance.

Pharmacokinetic properties
After oral administration, diacerein is hydrolysed before entering the systemic circulation and is absorbed, metabolised and excreted as rhein and its conjugates. All the pharmacokinetic data that follow refer to this active principle.
Absorption
After oral administration diacerein undergoes a first hepatic passage and is totally deacetylated to rhein. After the intake of a single dose of 100 mg, the peak plasma levels (C_{max}) were 8-10 µg/ml of free rhein. The values for T_{max} were 1.8-2.0 hours after administration to fasting healthy volunteers. The simultaneous intake of a standard meal induces a delay in the absorption process and prolongs the T_{max} together which results in a higher bioavailability (increase of about 25% in the AUC). Given this behaviour, it is advisable to take the drug with meals.
Distribution
Nearly all the non-conjugated rhein (more than 99%) is bound to plasma proteins, mainly albumin, and is not displaced by the usual drugs at their therapeutic concentrations. The mean distribution volume in steady state, V_{ss}/F, was approximately 17.1 litres.
Metabolism
Diacerein is very rapidly metabolised (mainly pre-systematically) to rhein and this is conjugated to different extents in different species.
Elimination
The elimination half-life of plasma ($t_{1/2}$) is about 5-7 hours. Excretion is mainly renal as rhein and as conjugates of rhein (glucuronide and sulphate). Following oral administration of doses of 50-100 mg, about 50% of the total dose of diacerein is recovered in the urine as rhein, mainly (more than 90%) as the sulpho- and gluco-conjugated forms of rhein.
Linearity
In linearity studies using doses between 50 and 200 mg diacerein, the C_{max} and AUC of free and total rhein were proportional to the doses administered.
Pharmacokinetics in special groups of patients
A comparison between healthy subjects and patients with renal insufficiency shows that there is a highly significant increase in the AUC and terminal half-life ($t_{1/2}$) with a simultaneous decline in renal clearance of rhein in subjects with severe renal insufficiency (creatinine clearance less than 30 ml/min). Consequently diacerein is contraindicated in this type of patients. In patients with moderate renal insufficiency, a 50% reduction in the daily dose is recommended (see *Posology and method of administration and Contraindications*).
Finally, when elderly patients are compared to a control group of younger healthy volunteers, an increase in the AUC proportional to age and a prolongation of the terminal plasma half-life of free rhein are observed. However, these findings did not reach the necessary significance to require a modification of the dose in these patients. Therefore, as stated in the dosage and administration section, the dose for elderly patients is the same as that for younger adults (see *Posology and method of administration*).

INDICATIONS
Treatment of symptoms in patients with osteoarthritis of the hip or knee, with delayed effect. Treatment with diacerein is not recommended in patients with rapidly progressive hip osteoarthritis, as they may have a weaker response to diacerein.

POSOLOGY AND METHOD OF ADMINISTRATION
The treatment should be initiated by specialists experienced in the treatment of osteoarthritis.
For Adults only
As some patients may experience loose stools or diarrhoea, 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 50 mg twice daily. The treatment should be taken with food, one with breakfast and the other with evening meal. The capsules must be swallowed intact, without opening them, together with a glass of water. Diacerein is not recommended in patients older than 65 years. ARTRODAR® has a slow onset of action but its beneficial effects persist for at least 2 months after treatment is stopped. In fact, as a consequence of the delay in the onset of initial activity (30 to 45 days to attain an analgesic effect), the product should be taken continuously for a minimum period of one month in order to observe its beneficial effects. In addition, it may be necessary to start treatment with the usual rapid acting analgesics/anti-inflammatory drugs. The doctor should decide the duration of treatment as a function of the outcome. Clinical studies have shown that there is a significant decrease in pain and an improvement in joint function after 2 months treatment with ARTRODAR®. These effects are still present for about 2 months after treatment is stopped (carry-over effect).
As no clinical studies have been conducted in children, its use is not recommended in children.
Elderly
No change in the usual recommended dose is necessary in elderly subjects (see *Pharmacokinetic properties*).
Renal insufficiency
In subjects with moderate renal insufficiency, the daily dose should be decreased by 50% of the recommended dose for adults (see *Pharmacokinetic properties*).
ARTRODAR® is contraindicated in subjects with severe renal insufficiency (see *Contraindications*).

SIDE EFFECTS
The safety of ARTRODAR® has been evaluated in over 5,000 patients in clinical studies. 6% of the patients stopped treatment due to adverse reactions.
Gastrointestinal effects:
Diarrhoea, abdominal pain, frequent bowel movements and flatulence are the most frequently reported side effects associated with ARTRODAR® treatment. As a rule, these effects abate with continuing treatment. In some cases, diarrhoea was severe with complications such as dehydration and disorders of fluid and electrolyte balance. The intake of the drug with meals or starting treatment with half the recommended daily dose (50 mg/day) could decrease the incidence of these events. A pigmentation of the recto-colic mucosa (melanosis coli) has been observed rarely (1-10% of the patients).
Renal and urinary changes:
A dark colouration of the urine may be observed. This is due to the structure of the molecule and is of no clinical significance (> 10% of the patients).
Hepatobiliary disorders:
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 (see *Warnings and Precautions*).
Effects on the skin and subcutaneous tissue:
Some cases of pruritus, eczema and cutaneous eruptions have been reported (1-10% of the patients).

OVERDOSE
In case of overdose, severe diarrhoea may occur. As an immediate measure, correct the hydroelectrolytic problems.

WARNINGS AND PRECAUTIONS
ARTRODAR® has a slow onset of action but its effects persist for at least 2 months after treatment is stopped. In fact, due to this delay in the onset of action (30 to 45 days to attain an analgesic effect) it may be necessary not only to begin treatment with the usual analgesics/anti-inflammatory drugs whose onset of action is immediate, but also to take ARTRODAR® without interruption for a minimum of one month to be able to observe its beneficial effects (see *Posology and method of administration*).
Patients with moderate renal insufficiency should be followed as a precaution. In addition, the doses of diacerein should be decreased in accordance with that stated in the "*Posology and method of administration*" section and tests of renal function carried out periodically.
To assure the tolerability of the preparation (for example, loose stools), clinical experience suggests that treatment should be started with half the recommended daily dose (50 mg/day diacerein) for the first 2 to 4 weeks and then, the dose can be increased to the recommended dose of 100 mg/day (see *Posology and method of administration*).
Diarrhoea:
Intake of diacerein frequently leads to diarrhoea that can consequently lead to dehydration and hypokalaemia. Patients should be advised to stop diacerein treatment in case of diarrhoea and contact their physician to discuss treatment alternatives. As elderly patients are more vulnerable to complications associated with severe diarrhoea, diacerein is not recommended in patients older than 65 years.
Caution should be exercised in patients receiving diuretics, because dehydration and hypokalaemia may occur. Particular caution should also be exercised in case of hypokalaemia in patients treated with cardiac glycosides (digitoxin, digoxin).

Laxatives should not be taken concomitantly with ARTRODAR®.

Hepatotoxicity:

Elevated serum hepatic enzyme levels and symptomatic acute hepatic injury have been reported with diacerein in the post-marketing phase.

Before treatment with diacerein is initiated, the patient should be questioned about possible comorbid conditions and past or concurrent liver disease and screened for major causes of active hepatic disease. A diagnosis of liver disease is a contraindication to diacerein use.

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. (see *Side Effects*).

Due to the presence of lactose, this medicine is contraindicated in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Pregnancy and lactation:

Although animal studies did not reveal any toxic effects on fertility or foetal development, ARTRODAR® should not be administered during pregnancy. In addition, ARTRODAR® should not be prescribed to lactating women due to reports that small amounts of diacerein derivatives pass into the maternal milk.

Effects on ability to drive and use machines:

No sedative effect, which may affect the ability to handle machines, is known for diacerein.

Keep out of reach of children.

CONTRAINDICATIONS

- Hypersensitivity to diacerein and substances with a similar structure or any of the excipients.
- Inflammatory intestinal disease (ulcerative colitis, Crohn disease).
- Intestinal obstruction or pseudo-obstruction.
- Current and/or history of liver disease.
- Severe renal insufficiency.
- Use in children.
- Pregnancy and lactation.

DRUG INTERACTION

Antacids derived from magnesium, aluminium and calcium can decrease the digestive absorption of diacerein. In case of concomitant use, there should be a minimum time interval of 2 hours between the intake of any of these preparations and ARTRODAR®.

No pharmacological interactions have been described with warfarin, phenytoin, indomethacin, salicylic acid, glibenclamide, hydrochlorothiazide and NSAIDs. In addition, no interaction was observed in interaction studies with cimetidine and paracetamol. Intake of diacerein can lead to diarrhoea and hypokalaemia. 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.

PRE-CLINICAL SAFETY

In acute toxicology studies following oral administration of the drug in rodents the LD_{50} was greater than 2,000 mg/kg. The main clinical symptom was diarrhoea. The laxative action, proportional to the dose administered, was also the most frequently observed adverse effect after repeated administration to rats and dogs. Diacerein had no effects on reproduction and was not teratogenic in the species studied. Both the drug and its metabolite rhein showed an absence of genotoxicity under the conditions of *in vitro* and *in vivo* studies. In longer-term studies carried out in rats and mice, there was no evidence of a carcinogenic potential.

Therefore, the results of the pre-clinical studies do not reveal any particular risks to humans if we consider the results of the safety pharmacology studies, repeated dose toxicity studies, genotoxicity, carcinogenicity and reproduction studies.

HOW SUPPLIED

ARTRODAR® capsules are packed in a thermoformed PVC blister and heat-sealed in a lacquered aluminium foil. Each blister contains 10 capsules. Each box contains 30 capsules (3 blisters).

INSTRUCTIONS FOR HANDLING

No special requirements.

SHELF LIFE

3 years if stored in its intact package at a temperature of 30° C and below. Do not use after expiry date printed on the box.

STORAGE

Do not store above 30° C.

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