COMPOSITION
ARTRODAR® 50 mg capsules: Each capsule contains Diacerein 50 mg.

DESCRIPTION
Diacerein belongs to the class of other non-steroidal anti-inflammatory and anti-rheumatic products. It is used in the treatment of inflammation and rheumatism.

PHARMACOLOGICAL PROPERTIES
Mode Of Action
Due to its specific mode of action, which does not involve the inhibition of prostaglandin synthesis, Diacerein has been shown to have anti-osteoarthritic and cartilage stimulating properties in vitro and in animal models, together with anti-inflammatory properties.

Diacerein has shown disease-modifying properties in animal models of osteoarthritis.

In clinical trial, Diacerein significantly improved osteoarthritis symptoms such as pain and joint dysfunction.

The beneficial effects of Diacerein are observed after 2-4 weeks of treatment, with significant improvement appearing after about 4-6 weeks of treatment, and are still present for about 2 months after treatment has stopped (carry-over effect). A combination therapy with an analgesic or a NSAID may be recommended during the first 2-4 weeks of treatment.

Pharmacokinetics
After oral administration, Diacerein is hydrolyzed before entering the systemic circulation and is absorbed, metabolized and excreted as rhein and its conjugates.

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 (Cmax) were 8-10 mg/ml of free rhein. The values for Tmax 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 Tmax, together which results in a higher bioavailability (increase of about 25% in the AUC). Given this behavior, 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 is steady state, Vss/F, was approximately 17.1 liters.

Metabolism
Diacerein is very rapidly metabolized (mainly pre-systematically) to rhein and this is conjugated to different extents in each species.

Elimination
The elimination half-life from plasma (t1/2) 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 glucu-conjugated forms of rhein.

Pharmacokinetics in special groups of patients
In cirrhotic patients with mild to moderate hepatic insufficiency, no statistically significant changes were observed in any of the pharmacokinetic parameters of rhein as determined from plasma or urine concentrations in comparison to a reference group of healthy subjects of a similar age.

Consequently, it is not necessary to modify the Diacerein dose in these patients. On the other hand, 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 (t1/2) 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. 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, the dose for elderly patients is the same as that for younger adults.

INDICATIONS
Treatment of degenerative joint diseases (osteoarthritis & related diseases) and also symptomatic relief in long-term treatment of osteoarthritis.

DOSAGE AND ADMINISTRATION
The usual dosage regimen for Diacerein in one capsule taken orally twice a day with the main meals for prolonged periods (not less than 6 months). However, as Diacerein may cause acceleration in intestinal transit time during the first 2 weeks of treatment, it is recommended that treatment be started with one capsule of Diacerein per day taken orally with evening meal for 4 weeks. Once the patient has become accustomed to the medication, the dose should be increased to 2 capsules per day, taken orally with meals. The duration of treatment should not be less than 6 months. As with prolonged treatment with any other medication, a complete blood test, including liver enzymes, and urinalysis should be conducted every 6 months. Due to its late onset of action (after 2-4 weeks of treatment), Diacerein may be associated with a non-steroidal anti-inflammatory drug or analgesic for the first 2-4 weeks of treatment.

Children
No clinical studies have been conducted in children. As the safety and efficacy on the product have not been established in this age group, its use is not recommended.

Elderly
No change in the usual recommended dose is necessary in elderly subjects.

Renal insufficiency
In subjects with moderate renal insufficiency, the daily dose should be decreased by 50% of the recommended dose for adults. Diacerein is contraindicated in subjects with severe renal insufficiency.

Hepatic insufficiency
No significant deviations were observed in any of the pharmacokinetic parameters in cirrhotic with mild or moderate hepatic insufficiency and therefore no dose adjustment is required.
CONTRAINDICATIONS
Diacerein should not be administered to patients with known hypersensitivity to the drug itself or to those with previous episodes of hypersensitivity to anthraquinone derivatives. Temporary treatment suspension must be considered in cases of antibiotic therapy, which may affect intestinal flora and kinetics. The benefit/risk ratio of administering Diacerein to patients with previous episodes of enterocolic disturbances, especially irritable colon, must be considered.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Renal insufficiency modifies the pharmacokinetics of Diacerein and therefore a dose reduction is recommended in such cases (creatinine clearance < 30 ml/min). When Diacerein is taken with food, there is an increase (about 24%) in its absorption on the other hand, severe nutritional deficiencies decrease the bioavailability of Diacerein.

As the incidence of collateral effect, such as accelerated intestinal transit time, is directly proportional to the amount of unabsorbed Diacerein, the intake of the product in a fasting state or after very small amounts of food could cause an increased incidence of collateral effects.

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

Effect on ability to drive and use machines
No sedative effect, which may affect the ability to handle machines, is known for Diacerein. Laxatives should not be taken concomitantly with Diacerein.

DRUG INTERACTIONS
Diacerein must not be administered at the same time as drugs that modify intestinal transit and/or the quality of the intestinal content (e.g. excess fibers or phytates). The concomitant administration of products containing aluminium hydroxide and/or magnesium hydroxide should be avoided in order to maximize the bioavailability of Diacerein. Treatment with Diacerein may cause an increase in enterocolic events in patients undergoing antibiotic and/or chemotherapy which could affect the intestinal flora.

UNDESIRABLE EFFECTS
Accelerated intestinal transit is the most frequently reported side-effect (7%) associated with Diacerein treatment. The symptoms may appear within the first few days of treatment. In most cases these symptoms resolve spontaneously with continuing treatment.

Diarrhoea and epigastric pain and disturbances were reported in 3-5% of the treated patients, with nausea and vomiting reported in less than 1% of the patients. Pigmentation of the recto-colic mucosa (melanosis coli) has been observed rarely. The intake of Diacerein may sometimes result in a more intense yellow coloring of the urine. This is typical of the type of compound and is of no clinical significance. Some cases of pruritus, eczema and cutaneous eruptions have been reported (1-10% of the patients).

OVERDOSAGE
The accidental or voluntary ingestion of high doses of Diacerein could produce diarrhoea. No specific antidotes exist. If diarrhoea persists, please see your doctor. Emergency treatment consists of restoring the hydro-electrolytic balance if necessary.

STORAGE
Store below 25°C in dry place. Protect from light.

PRESENTATION
ARTRODAR® 50mg capsules: Pack of 30 capsules.

TO BE SOLD ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.