

# Artrodar®

**Diacerein 50 mg**

## **COMPOSITION**

Each capsule of ARTRODAR contains Diacerein 50 mg; Lactose monohydrate, Croscarmellose sodium, Polyvidone K30, Colloidal silicon dioxide, Magnesium stearate.

## **MODE OF ACTION**

### **PHARMACOLOGICAL PROPERTIES**

Anti-osteoarthritis and anti-inflammatory drug in degenerative joint disease (osteoarthritis and related diseases).

Due to its specific mode of action, which does not involve the inhibition of prostaglandin synthesis, Diacerein has been shown to have anti-osteoarthritis 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, ARTRODAR significantly improved osteoarthritis symptoms such as pain and joint dysfunction.

The beneficial effects of ARTRODAR 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.

### **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 pharmacokinetics 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 mg/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 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 in steady state,  $V_{ss}/F$ , was approximately 17.1 litres.

#### Metabolism

Diacerein is very rapidly metabolised (mainly pre-systemically) to rhein and this is conjugated to different extents in each 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<sub>max</sub> and AUC of free and total rhein were proportional to the doses administered.

### 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 (*see-Posology and method of administration*)

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 (t<sub>1/2</sub>) 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 Contraindication*).

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 has already been 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**

Symptomatic relief in long-term treatment of osteoarthritis.

## **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 case of antibiotic therapy, which may affect intestinal flora and kinetics.

The benefit / risk ratio of administering ARTRODAR to patients with previous episodes of enterocolic disturbances, especially irritable colon, must be considered.

Severe hepatic or renal insufficiency.

Use in children

Pregnancy and lactation

Intestinal obstruction or pseudo-obstruction

Inflammatory intestinal disease (ulcerative colitis, Crohn disease)

## **UNDESIRABLE EFFECTS**

Accelerated intestinal transit is the most frequently reported side-effect (7%) associated with ARTRODAR 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.

A pigmentation of the recto-colic mucosa (melanosis coli) has been observed rarely (1-10%) of the patients.

The intake of ARTRODAR may sometimes result in a more intense yellow colouring of the urine. This is typical of the type of compound and is of no clinical significance.

Effects on the skin and subcutaneous tissue.

Some cases of pruritus, eczema and cutaneous eruptions have been reported (1-10% of the patients).

## **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. 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.

### *Effect on ability to drive and use machines*

No sedative effect, which may affect the ability to handle machines, is known for Diacerein. ARTRODAR should not be prescribed to children below 15 years old as no clinical studies have been undertaken in this age-group.

Laxatives should not be taken concomitantly with ARTRODAR.

### *Overdose*

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 consist of restoring the hydroelectrolytic balance if necessary.

## **DRUG INTERCATIONS**

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 fibres or phytates).

The concomitant administration of products containing aluminium hydroxide and/ or magnesium hydroxide should be avoided in order to maximise 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.

## **POSODOLOGY AND METHOD OF ADMINISTRATION**

The usual dosage regimen for ARTRODAR 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 intestinal transit time during the first 2 weeks of treatment, it is recommended that treatment be started with one capsule of ARTRODAR 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 doctor should decide the duration of treatment as a function of the outcome. However this 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 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 not recommended (see-*Contraindications*).

#### 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-*Contraindication*)

#### 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 in these patients (see-*Pharmacokinetic Properties*).

However, the use of diacerein is contraindicated in patients with a severe deterioration of hepatic function (see-*Contraindication*).

### **SHELF LIFE AND SPECIAL PRECAUTION FOR STORAGE**

#### **Shelf-life**

If stored as indicated below, this medication can be used until the date stated on the packaging. The shelf life of the tablets is 3 years.

#### **Special precautions for storage**

Store in a dry place, protected from light and at room temperature (150-250C) in a well closed packaging.

### **PACKAGING**

Box, 3 Blister @ 10 Capsules

ON MEDICAL PRESCRIPTION ONLY

**HARUS DENGAN RESEP DOKTER**

<b>COMBIPHAR</b>	Manufactured by :
	<b>TRB Pharma S.A.</b> , Argentina
	Under license from:
	<b>TRB Chemicica International S.A.</b> , Geneva, Switzerland
	Imported by:
	<b>PT. COMBIPHAR</b> , Bandung, Indonesia