Osteoarthritis (OA) is currently defined by the American College of Rheumatology as a “heterogeneous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins.” Until recently, osteoarthritis was classified as a mechanical wear–and–tear disorder of articular cartilage, for which only pain–modifying therapies such as nonaddictive analgesics were prescribed. However, OA represents an advanced stage of disease progression caused in part by injury, loss of cartilage structure and function, and an imbalance in inflammatory and non–inflammatory pathways.

Its prevalence after the age of 65 years is about 60% in men and 70% in women. The burden of this disease will increase in direct proportion to the increase in the older adult population.

The etiology of OA is multifactorial, with inflammatory, metabolic, and mechanical causes. A number of environmental risk factors, such as obesity, occupation, and trauma, may initiate various pathological pathways. The principal treatment objectives are to control pain adequately, improve function, and reduce disability.

Nonpharmacological interventions are frequently and widely used in the management of OA patients, but there is little evidence that they are effective: the best studied and most successful nonpharmacological interventions are patient education, self–management, and exercise.

There is some evidence for the pain–relieving efficacy of thermotherapy and transcutaneous electrical nerve stimulation (TENS) but not of electrotherapy, acupuncture, homeopathy, or manual therapy. The value of interventions aimed at improving function and maximizing independence (occupational therapy, walking aids, workplace adaptation) is also unclear.

The disease course and patient’s requirements often change over time, thus requiring a periodic review and readjustment of therapy rather than the rigid continuation of a single treatment.

Recently, new research identified interleukin 1–beta, collagenase and other matrix metalloproteinases, and signal transduction pathways as important pathobiologic targets in OA. Cartilage agonists such as recombinant human growth factors and gene therapy constructs that stimulate the chondrocyte are being studied in animal models and in humans. Orthopedic approaches, including cartilage regeneration and joint resurfacing techniques with or without biomaterials, are being developed.

Acetaminophen is frequently used for symptomatic OA with mild to moderate pain. Nonsteroidal antiinflammatory drugs (NSAIDs) are more effective in the case of moderate–severe pain, but they have an increased risk of serious upper gastrointestinal adverse events. The newer cyclooxygenase COX–2 specific inhibitors (Coxibs) are as efficacious as traditional NSAIDs, and have a better gastrointestinal safety profile.

Treatment with NSAID or selective anti–COX–2 agents appears to
have a beneficial effect during acute phases of inflammation but their use in long–term regimens appears to have less favorable effects.¹

**DIACEREBIN**

Diacerein is a slow acting symptomatic treatment of OA which has demonstrated efficacy on functional manifestations of OA and on the structural component. OA generally occurs in a context of an overloaded normal cartilage matrix or normal loading of a vulnerable cartilage matrix. Interleukin–1 appears to be principally indicated in degradation phenomena while transforming growth factor (TGF–beta) is mainly implicated in phenomena of excessive synovial and chondrocyte repair observed at the same time as degradation.

Compounds such as diacerein have a symptomatic effect that is slower and less than that of NSAIDs. The structure–modifying effects of diacerein have been evaluated, and diacerein has been shown in some trials to have a beneficial structural effect.²

Data obtained from several clinical trials have demonstrated that relief of joint pain obtained with the interleukin–1 inhibitor, diacerein is comparable with that observed with NSAIDs after four to six weeks of treatment and that relief persists after treatment withdrawal. Patients taking diacerein are less handicapped, use less NSAID and/or analgesics, and have lower demands for care as well as an improved quality of life. Drug watch data and clinical trials have confirmed the safety and tolerance of diacerein, so there is no limitation on the duration of its use.³

**CLINICAL PHARMACOKINETICS**

Diacerein is entirely converted into rhein before reaching the systemic circulation. Rhein itself is either eliminated by the renal route (20%) or conjugated in the liver to rhein glucuronide (60%) and rhein sulfate (20%); these metabolites are mainly eliminated by the kidney.

The pharmacokinetic characteristics of diacerein are about the same in young healthy volunteers and elderly people with normal renal function, both after a single dose (50 mg) or repeated doses (25 to 75 mg twice daily).⁴

Rhein kinetics after single oral doses of diacerein are linear in the range 50 to 200 mg. However, rhein kinetics are time–dependent, since the non–renal clearance decreases with repeated doses. This results in a moderate increase in maximum plasma concentration, area under the plasma concentration–time curve and elimination half–life. Nevertheless, the steady–state is reached by the third administration and the mean elimination half–life is then around 7 to 8 hours. Taking diacerein with a standard meal delays systemic absorption, but is associated with a 25% increase in the amount absorbed.

Mild–to–severe (Child Pugh’s grade B to C) liver cirrhosis does not change the kinetics of diacerein, whereas mild–to–severe renal insufficiency (creatinine clearance < 2.4 L/h) is followed by accumulation of rhein, which justifies a 50% reduction of the standard daily dosage.

Rhein is highly bound to plasma proteins (about 99%), but this binding is not saturable so that no drug interactions are likely to occur, in contrast to those widely reported with nonsteroidal anti–inflammatory drugs.

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**Efficacy and Safety of Diacerein**

To determine whether the efficacy of diacerein persists at 2 months after the end of a 3–month treatment period, compared with placebo, in patients with painful knee osteoarthritis (OA) a study was done.

In this study, after a 1–week NSAID washout period, patients received either diacerein or placebo for 3 months, followed by an off–treatment period of 3 months to determine the carry–over effects of the drug. Although patients were followed up through month 6, the primary efficacy end point was the percent change from baseline in pain (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] A) at month 5 (i.e., 2 months after the end of treatment) compared with placebo. The co–primary efficacy end point was the percent change from baseline in the total WOMAC score, also at month 5 versus placebo.

At month 5, diacerein showed statistically significant superiority versus placebo, as assessed with both the WOMAC A (P < 0.0001) and the total WOMAC (P < 0.0001), demonstrating the carry–over effect of the drug. This superiority was already evident from month 2 for pain (P = 0.001) and month 1 for total WOMAC (P = 0.0021).

This is the first published study of a symptomatic slow–acting OA drug in which the time of assessment of the primary outcome end points was 2 months after the end of a 3–month treatment period. The results show that diacerein is safe and effective for the treatment of knee OA and has a long carry–over effect.⁵

**THE ECHODIAH TRIAL – THE DIACEREBIN CHONDROPROTECTIVE EFFECT**

The principal objective of ECHODIAH study conducted in patients with hip osteoarthritis was to evaluate the chondroprotective potential of diacerein compared with placebo. The study was conducted over a 3–year period using progression of joint space narrowing as the assessment criterion.

For aggravation, expressed as joint space narrowing of at least 0.5 mm, there were significantly fewer patients in the diacerein group than in the placebo group; aggravation came significantly later in the diacerein group.

In the population of patients who completed at least 3 months treatment, the sparing effect on joint space narrowing was 32% in the diacerein group compared with the placebo group. In addition, the mean progression of joint space narrowing was significantly less in patients treated with diacerein; the mean progression decreased from 0.18 mm/year at the end of the first year to 0.13 mm/year at the end of the third year.⁶

**PHARMACOLOGIC EFFECT OF DIACEREBIN VS A COX–2 INHIBITOR**

During the process of inflammation, COX–2 activity appears to occur at two specific time points, with a peak at 2 hours, associated with maximal activity of PGE(2) synthase (pro–inflammatory

<table>
<thead>
<tr>
<th>Drug</th>
<th>Composition</th>
<th>Packing</th>
<th>Administration</th>
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<tbody>
<tr>
<td>DYAserin</td>
<td>Diacerein 50 mg</td>
<td>10 Tablets</td>
<td>1 BD</td>
</tr>
</tbody>
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Except for moderate and transient digestive disturbances, diacerein is well tolerated and seems neither responsible for gastrointestinal bleeding nor for renal, liver or haematological toxicity.

**Finecure Update**
Efficacy, Safety and Carry-over Effect of Diacerein vs Piroxicam

This was a double-blind, randomized, piroxicam-controlled, parallel-group study. A 7-day NSAID washout period was followed by a 16-week treatment period with either diacerein 100mg/day or piroxicam 20mg/day, and an 8-week treatment-free observation period.

Of 171 randomized patients, 150 completed the study and 161 were analysed in the intent-to-treat population (diacerein: 82, piroxicam: 79). Pain, as assessed by (WOMAC); A score decreased to a similar extent in both groups at week 16 (diacerein: $-69.7\% \pm 31.5\%$; piroxicam: $-74.1\% \pm 26.2\%$; P=ns.).

On treatment discontinuation, pain increased in the piroxicam group at weeks 20 ($-47\% \pm 47.8\%$) and 24 ($-26.8\% \pm 60.6\%$), while improvements persisted in the diacerein group at weeks 20 ($-66.9\% \pm 35.9\%$) and 24 ($-69.5\% \pm 33.7\%$), with a significant difference in favour of diacerein at weeks 20 and 24, demonstrating the carry-over effects of the drug. The incidence of adverse events was similar in both groups but more patients from the piroxicam group dropped out of the study due to these events.

Diacerein vs Glucosamine in OA

The purpose of this study was to compare the chondroprotective effect of diacerein and glucosamine regarding degenerative changes and articular stiffness in an experimental model of arthritis. It was concluded that:

- Prophylactic use of diacerein leads to lower degree of articular stiffness when compared to glucosamine;
- The prophylactic chondroprotective effects of diacerein and glucosamine are histologically similar.

- The prophylactic chondroprotective effects of diacerein and glucosamine are histologically similar.

HIGHLIGHTS

- Until recently, osteoarthritis was classified as a mechanical wear-and-tear disorder of articular cartilage, for which only pain-modifying therapies such as nonaddictive analgesics were prescribed. However, OA represents an advanced stage of disease progression caused in part by injury, loss of cartilage structure and function, and an imbalance in inflammatory and noninflammatory pathways
- Diacerein is a slow acting symptomatic treatment of OA which has demonstrated efficacy on functional manifestations of OA and on the structural component
- Two mechanisms of action have been validated for diacerein: in vitro inhibition of interleukin-1 (IL-1) synthesis, the main cytokine involved in cartilage destruction, and activity on the synthesis of proteoglycans, and hyaluronic acid, the principal component of cartilage
- Use of long-action symptomatic treatments without any apparent effect on COX-2, for example diacerein, could protect against the potentially deleterious effects of COX-2 inhibition. Specific COX-2 inhibitors could thus be beneficially combined with disease modifying osteoarthritides drugs such as diacerein.
- In the population of patients who completed at least 3 months treatment, the sparing effect on joint space narrowing was 32% in the diacerein group. In addition, the mean progression of joint space narrowing was significantly less in patients treated with diacerein
- Diacerein was as effective as piroxicam in reducing pain and improving function but, unlike piroxicam, displayed a carry-over effect and a better safety profile
- Drug watch data and clinical trials have confirmed the safety and tolerance of diacerein, so there is no limitation on the duration of its use.

REFERENCES

Anti-Osteoarthritis Drug with Cartilage Stimulating Properties

Dyaserin
Diacerein 50 mg. Tab

- Unique action on Cytokine Cascade
- Unique mode of action (inhibition of IL-1)
- Halts Degeneration: Stimulates Regeneration
- Retards Progression of Osteoarthritis
- Reduces Consumption of NSAID and Analgesics
- Improves Knee Bending Significantly
- Excellent Long Term Tolerability and Safety Profile
- As effective as an NSAID in respect to analgesia & restoration of functionality
- Significant Structure modifying effect
- Good Safety Profile
- No GI Side Effects
- Disease modifying effect on TNF driven chronic

Ref:
The Cochrane Database of Systematic Reviews 2006 Issue 1.

Rx Dyaserin,

Effective in treatment of painful episodes of osteoarthritis
Stimulating new ray of hope in Osteoarthritis

Dosage:
50 mg. once daily after the meals for first four weeks (after meals at night) thereafter 50 mg. BID (Preferably with food)