Rhein, the active metabolite, is highly bound to plasma proteins (about 99%), the binding however is not saturable therefore drug interactions are unlikely.

In vitro, rhein has shown to inhibit the production and activity of IL-1β in the superficial and deep layers of the cartilage, in the synovial membrane and synovial fluid. In the same time, rhein stimulates the production of transforming growth factor (TGF-β) and extracellular matrix components (Leeb, 2010).

Rhein additionally reduces cytokine production in inflammatory cells (Sanchez et al, 2003) and the production and phagocytic activity of macrophages (Mian et al, 1989).

All of the mentioned effects of rhein contribute to the cartilage sparing activity observed in animal models of osteoarthritis (Brandt et al, 1997; Smith et al, 1999). No evidence of mutagenicity was observed in the different test systems used (Heidemann, 1991; TRB Artrodar monograph, 1999; Longo, 2002). Concerning the gastrointestinal tract, diarrhoea was observed relatively high daily doses (TRB Artrodar monograph, 1999; Mengs, 1992). Ingestion of diacerein with a standard meal results in delayed absorption (reduction in Cmax and increase in tmax) but increased total amount absorbed. The oral bioavailability of rhein increased by 13% as estimated from the change in the AUC (TRB Artrodar monograph, 1999). Mild to severe liver dysfunction does not affect diacerein pharmacokinetics, as opposed to mild to severe renal failure (Magnard et al, 1993; Debord et al, 1993).

Pharmacokinetics

1. Absorption and plasma concentrations:

Diacerein is well-absorbed following oral dosing. Once absorbed, diacerein is rapidly broken down and completely de-acetylated into its active metabolite, rhein, which is