

[2002] [THU0189] FIRST CLINICAL RESULTS OF LICOFELONE (ML3000), AN INHIBITOR OF COX-1, COX-2 AND 5-LOX, FOR THE TREATMENT OF OSTEOARTHRITIS

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Background: Licofelone (ML3000) is the first in a new class of drugs that suppresses inflammation and pain by competitively inhibiting three enzymes: cyclooxygenase (COX)-1, COX-2 and 5-lipoxygenase (5-LOX). There is increasing evidence that NSAID-induced GI toxicity may involve alternative processing of arachidonic acid by 5-LOX to form leukotrienes. It was postulated that inhibition of leukotriene formation by an inhibitor of both 5-LOX and both COX isoenzymes can provide anti-inflammatory effects without GI toxicity and without the negative effects of selective COX-2 inhibition. As leukotriene-modulated mechanisms are involved in the pathogenesis of osteoarthritis (OA) licofelone may offer additional benefits for the treatment of OA.

Objectives: The innovative mechanism of action and the anti-inflammatory and analgesic efficacy of licofelone was shown in a full series of preclinical studies. The GI, renal, hepatic and general tolerability was excellent. In clinical phase II and phase III studies in patients with osteoarthritis the efficacy/tolerability profile was studied in comparison with placebo and active treatment.

Methods: In an endoscopic study, 121 subjects with normal gastric and duodenal mucosa were treated for 4 weeks with licofelone 200 mg bid or 400 mg bid, placebo or naproxen 500 mg bid. The mucosa was evaluated with modified Lanza scores. Ulcers (3 mm or more in diameter) were assessed. In another study, 148 patients with OA were treated for 12 weeks with licofelone 200 mg bid or naproxen 500 mg bid. Efficacy was evaluated using the WOMAC index. Responders were defined to show a 30% improvement versus baseline.

Results: In the endoscopic study, the gastric mucosa was completely normal after 4 weeks in 93% (200 mg bid), 89% (400 mg bid), 90% (placebo) and 37% (naproxen) of subjects. No ulcers were present in either licofelone group or the placebo group. In the naproxen group 6 ulcers (20%) were observed (5 GU, 1 DU). In the 12-week study the efficacy of licofelone 200 mg bid was comparable or slightly better than in the naproxen group. With licofelone, the mean WOMAC index was improved by 23.3 mm (VAS) and with naproxen there was an improvement by 21.5 mm. For the WOMAC index, 69.4% of licofelone-treated patients were responders (68.4% with naproxen). GI adverse events were reported by 13.9% (licofelone) and by 26.3% (naproxen) of patients.

Conclusion: Treatment of OA patients with Licofelone was shown to have a comparable efficacy as conventional NSAIDs but to have an excellent GI and general tolerability. The combined inhibition of both COX-isoenzymes and of 5-LOX avoids the obvious disadvantages of selective COX-2 inhibitors (e.g. thromboembolic risk) but spares also the GI mucosa. Phase III clinical studies are already completed. The innovative mechanism of action may offer a new alternative for the treatment of OA with an optimal benefit/risk ratio.

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