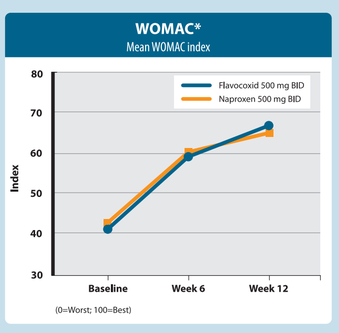
Clinically Effective

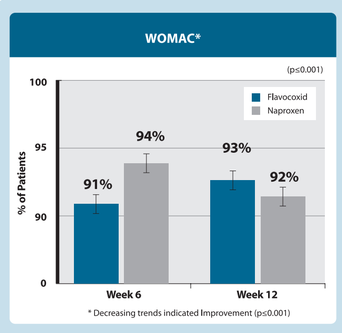
... for the Dietary Management of Osteoarthritis

Limbrel 500
(flavocoxid and citrated zinc bisglycinate) 500 mg/50 mg

The Efficacy of an NSAID with a Superior GI Safety Profile

Limbrel has been shown in clinical trials to have the efficacy of naproxen with a superior GI safety profile





- **Double-blind, multicenter, comparator trial shows that Limbrel works as well as naproxen in managing knee osteoarthritis** [1]
- **93% of Limbrel patients showed significant management of OA by WOMAC Index** [1]

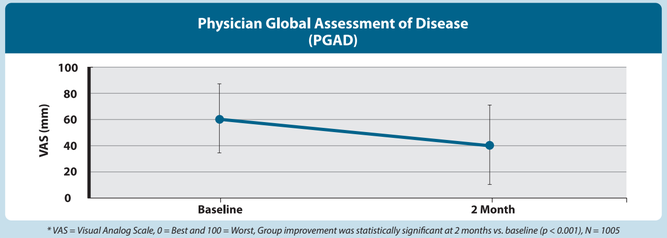
*WOMAC = Western Ontario and McMaster's University Osteoarthritis Index

STUDY DESCRIPTION: 220 subjects with moderate to severe knee osteoarthritis participated in a 12-week multicenter, randomized, double-blind, comparator trial using Limbrel 500 mg BID and naproxen 500 mg BID.

GOAL: Gauging OA with Limbrel

A post market, multi-center real world survey of more than 1000 patients using Limbrel

VAS scores improved for 65.8% of all patients using Limbrel [3]



** VAS = Visual Analog Scale, 0 = Best and 100 = Worst, Group improvement was statistically significant at 2 months vs. baseline (p < 0.001), N = 1005*

Study Description: GOAL open label survey conducted at 41 multi-center, rheumatology practices. Patients with osteoarthritis (OA) of any joint (n=1067) were administered Limbrel 500 mg BID for 60 days. Patients who had used NSAIDs and/or gastro protective medication were not excluded from the study.

A non-NSAID prescription for osteoarthritis patients †

- **Dual modulator of COX-1 and COX-2 with activity on 5-LOX**
  - Effectively manages inflammation and increases functional mobility
  - Minimizes overall side effects
  - Critical for long-term GI safety
- **Clinically shown to be equal to naproxen**

Highlights of Limbrel safety profile:

- **Limbrel has been clinically shown to have a superior GI safety profile for OA patients**
- **Preclinical CYP450 inhibition studies suggest no major drug interaction** [2,5,6]
- **No black box warning**
- **Limbrel may take up to 2-4 weeks of use to see initial result and up to 6-8 weeks for optimal results**
- **LD50: >5000 mg/kg po (rat)**[9t]

Prescribe Limbrel for your Osteoarthritis patients

**Also in 250-50 mg BID.*

Limbrel 500
(flavocoxid and citrated zinc bisglycinate) 500 mg/50 mg

Tough on Osteoarthritis Easy on Your Stomach

References:

1. Levy R, Khokhlov A, Kopenkin S, Bart B, Ermolova T, Kantemirova R, Mazurov V, Bell M, Caldron P, Pillai L, Burnett BP. Efficacy and safety of flavocoxid, a novel therapeutic, compared with naproxen: a randomized multicenter controlled trial in subjects with osteoarthritis of the knee. Advances in Therapy. 2010; 27:731-42. **2.** Data on file, Primus Pharmaceuticals. **3.** Pillai L, Burnett BP, Levy RM for the GOAL Study Cooperative Group. Open-label, post-marketing study of flavocoxid, a novel dual pathway inhibitor anti-inflammatory agent of botanical origin: the GOAL study. Current Medical Research and Opinion. 2010; 26(5):1055-1063. **4.** Burnett BP, Bitto A, Sqadrito F, Levy RM, Pillai L, 2011. Flavocoxid Inhibits Phospholipase A2, Peroxidase Moieties of the Cyclooxygenases (COX), 5-Lipoxygenase, Modifies COX-2 Gene Expression and Acts as an Antioxidant. Mediators Inflamm. 2011:385780, published online June 22, doi: 10.1155/2011/385780. **5.** Burnett BP, et al. Safety Evaluation of a Combination, Defined Extract of Scutellaria baicalensis and Acacia catechu. *J Food Biochem.* 2007;31:797-825. **6.** Data on file, Post-marketing surveillance report, March 2012. **7.** Pillai L, Levy R, Yimam M, Zhao Y, Jia Q, Burnett BP. Flavocoxid, an anti-inflammatory agent of botanical origin, does not affect coagulation or interact with anticoagulation therapies. *Advances in Therapy*. 2010; 27(6):400-11. **8.** Richy F, Bruyere O, et al Time-dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory use: a consensus statement using a meta-analytic approach. *Ann Rheum Dis.* 2004; 63:759-766. **9.** Young Chul Lee, Eujin Hyun, Mesfin Yimam, Lidia Brownell, Qi Jia, Acute and 26-Week Repeated Oral Dose Toxicity Study of UP446, a Combination of Scutellaria Extract and Acacia Extract in Rats, Food and Nutrition Sciences, 2013, 4, 14-27.
doi:10.4236/fns.2013.47A003

PRIMUS PHARMACEUTICALS

Tough on Osteoarthritis Easy on Your Stomach

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(flavocoxid and citrated zinc bisglycinate) 500 mg/50 mg

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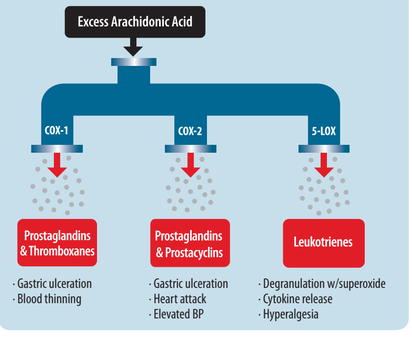
Unique MOA that Balances Efficacy and Safety

Limbrel provides a safer, broader-spectrum inhibition of the COX-1, COX-2 and 5-LOX pathways making it a long-term solution for patients with Osteoarthritis

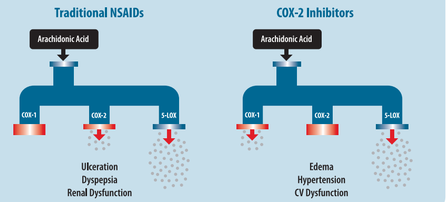
Limbrel Advantage: Unique MOA balances key metabolites[4]



- Limbrel is currently the only prescription product that has any activity on 5-LOX
- Flavocoxid (500mg BID) showed statistically fewer upper GI adverse events compared to naproxen (500mg BID) over a 12-week period [1]
- Flavocoxid also had better overall tolerability in previously NSAID GI-intolerant patients over an 8-week administration and a reduction or cessation in gastroprotective medication use in these same patients [1]

NSAIDs and COX-2 inhibitors completely block the COX-1 and COX-2 enzymes, which can lead to dangerous side effects

MOA of Traditional OA Therapies



Traditional OA therapies block COX-1 and COX-2 enzyme conversion of arachidonic acid (AA), which results in shunting excess AA metabolism down other pathways[1]. All NSAIDs have characteristic as well as overlapping side effects.

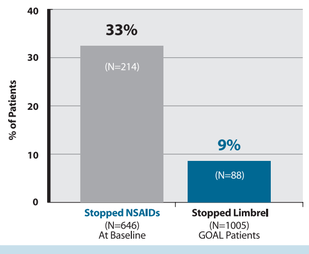
Manages Osteoarthritis with Fewer Side Effects

Limbrel delivers excellent safety profile without compromising efficacy

COX Selectivity	Safety Implications
flavocoxid	**Dual Inhibition of COX and LOX:** · Minimal side effects overall · Strengthened GI safety profile
COX-1	**Traditional NSAID Inhibition:** · GI ulcers · Renal toxicity · Blood thinning · Elevated hypertension
COX-2	**COX-2 Selective Inhibition:** · Cardiovascular events · Elevated hypertension · Renal toxicity · GI ulcers (from chronic use)

World Health Organization (WHO) claims 30 million patients in the US are affected with NSAID induced gastrophy [8]

Patients stopped therapy due to GI tolerability issues



Upper GI tolerability

% of Baseline NSAID Users (N=646)	Upper GI Tolerability
Better or Much Better	48%
About the Same	43%
Worse or Much Worse	7%

**Totals do not add up to 100% due to a small percentage of "not reported" for this question.*

- Limbrel was tolerated in 90% of patients with a prior history of NSAID induced GI events [3]
- 48% of patients who had GI problems on NSAIDs tolerated Limbrel better [3]

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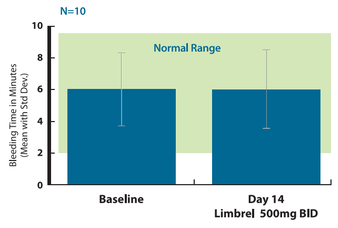
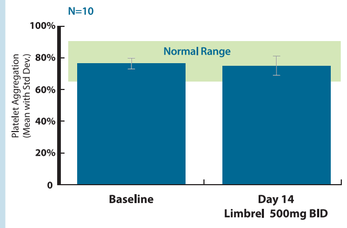
No Significant Effect On Bleeding Time and Blood Thinning

No effect on platelet function – confirmed in human study [7]

Bleeding Time



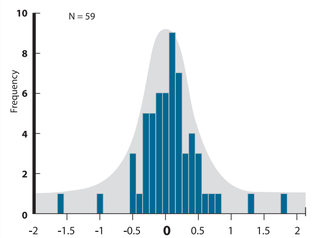
Arachidonic Acid Induced Platelet Aggregation



Limbrel has little or no effect on Pro Times in patients taking warfarin [7]

Routine check of Pro Time 2 weeks after starting Limbrel is recommended

No Significant Change in Pro Times Among Warfarin Patients Taking Limbrel



In multi-center, open-label research, physicians who intended to start Limbrel in patients who were taking warfarin obtained a prothrombin time (PT) prior to initiating Limbrel and 2 weeks after starting Limbrel therapy. Data were collected on 59 patients of both genders, without special selection, during routine office calls. No adverse events were noted. No tendency toward spontaneous bleeding or prolonged minor capillary bleeding (i.e. minor cuts or scrapes) was reported.

The prothrombin time changes are evenly and tightly distributed around the mean of zero change in PT value suggesting that Limbrel has little or no effect on PT in warfarinized patients.

There are a few outliers on both sides of the mean. These probably represent normal variations in the lab test, or genetic polymorphism in CYP450 enzyme system responsible for warfarin metabolism. Obtaining prothrombin times 2 weeks after starting Limbrel in warfarinized patients is recommended.