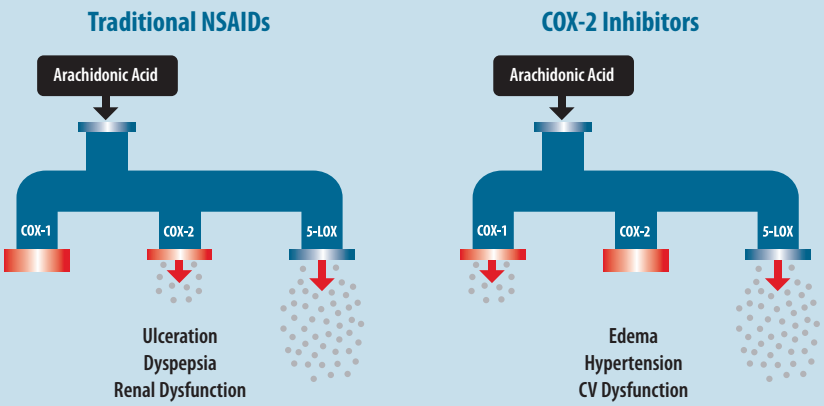
Limbrel® 500
(flavocoxid and citrated zinc bisglycinate) 500 mg/50 mg

Balanced Mechanism of Action

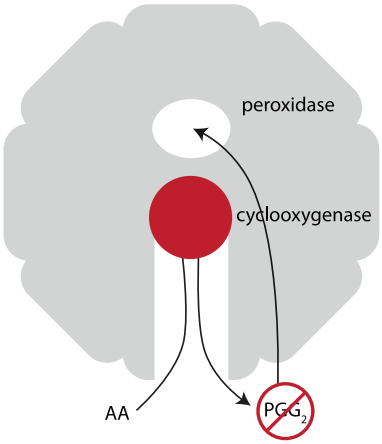
... for the dietary management of osteoarthritis

Arachidonic Acid Metabolism



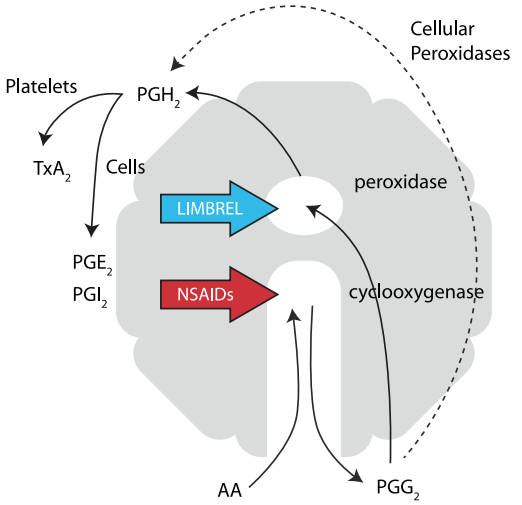
Traditional OA therapies block COX-1 and COX-2 enzyme conversion of arachidonic acid (AA) which results in shunting excess AA metabolism down other pathways[1]. All NSAIDs have characteristic as well as overlapping side effects.

How NSAIDs Work on the COX Enzymes



- NSAIDs bind to and inhibit the *cyclooxygenase* moiety in the COX enzymes [1]
- This inhibition limits the conversion of AA to prostaglandin (PGG_2) and prevents further conversion to thromboxane, prostaglandin (PG) and prostacyclin. Inhibition of PG synthesis contributes to gastric ulceration.[1,4]

How Limbrel Works on the COX Enzymes



- Limbrel modulates the *peroxidase* site [1]
- Limbrel permits production of PGG_2 intermediate which can be converted to prostaglandin H2 by other cellular peroxidases [1]

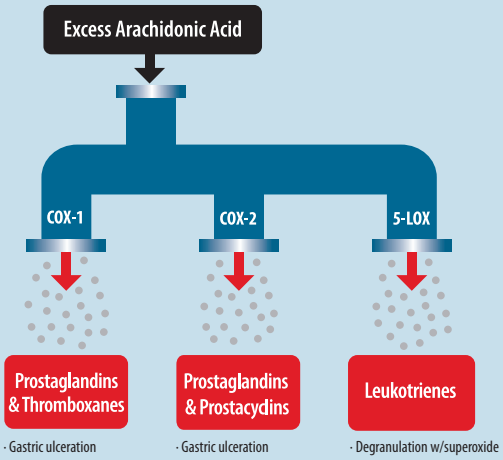
Results in Fewer Side Effects

... for the dietary management of osteoarthritis

Adverse Event	MOA Dependent
Gastrointestinal	**Yes**
Renal	**Yes**
Cardiovascular	**Yes**
Clotting	**Yes**
Hepatic	**No** (Chemical or immune mediated toxicity)

MOA for Limbrel allows for the production of thromboxane, prostaglandins and prostacyclin at reduced levels for fewer GI, renal, cardiovascular, and clotting system side effects [1,2,3,4,5]

Limbrel Advantage: Unique MOA balances key metabolites



- Limbrel works differently on the COX enzymes and also modulates 5-LOX to minimize upper GI and renal side effects [1,6]
- 5-LOX modulation and COX-1/COX-2 balanced inhibition are necessary to avoid hemodynamic changes such as reduced urine volume, hypertension, peripheral edema and myocardial ischemia [4]
- Limbrel does not interact with baby aspirin because it does not prevent aspirin's access to the COX-1 *cyclooxygenase* site [1]

Rx

LIMBREL500
500-50 mg #60 Sig. † BID
Refill x3
DISPENSE AS WRITTEN

**Also in 250-50 mg BID.*

Prescribe Limbrel for your Osteoarthritis patients

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

Free to Move Again

References: 1. Burnett BP et al. Flavocoxid inhibits phospholipase A2, peroxidase moieties of the cyclooxygenases (COX), and 5-lipoxygenase, modifies COX-2 gene expression, and acts as an antioxidant. Mediators Inflamm. 2011;2011:385780. Epub 2011 Jun 19. **2.** 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. **3.** Data on file, post-marketing surveillance report, March 2012. **4.** Burnett BP, Levy RM. 2012. 5-Lipoxygenase Metabolic Contributions to NSAID-Induced Organ Toxicity. Adv Ther. 29(2):79-98. Burnett BP, Levy R, Cole BJ. 2006. Metabolic mechanisms in the pathogenesis of osteoarthritis. A review. J Knee Surg. 19(3):191-197. **5.** 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. **6.** Levy RM, Khokhlov A, Kopenkin S, Bart B, Ermolova T, Kantemirova R, Mazurov V, Bell M, Caldron P. Pillai L, Burnett BP. 2010a. Efficacy and safety of flavocoxid, a novel therapeutic, compared with naproxen in subjects with osteoarthritis of the knee. Adv Ther. 27(10):731-42.

PRIMUS PHARMACEUTICALS