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HEALTH PROFESSIONAL SUMMARY INFORMATION - DROXANOL™

INDICATIONS AND CLINICAL USE

Droxanol™ is indicated for the **treatment of chronic and acute pain.**

The major clinical uses of Devil's claw are as an anti-inflammatory or analgesic in joint diseases, back pain, and headache. In Europe, standardized Devil's claw formulations are widely used as a mild analgesic for joint pain. Experimental studies demonstrated that Devil's claw has anti-inflammatory properties, including COX-2 inhibition. The COX-2 inhibition has not been shown to be selective.

Over 23 clinical trials have been performed in patients with osteoarthritis, rheumatoid arthritis or low back pain with Devil's claw. This data led the Natural Standard database[1], an independent organization, to conclude that *there is a growing body of scientific evidence suggesting that devil's claw is safe and beneficial in the short-term management of pain related to degenerative joint disease or osteoarthritis. It may be equally effective as drug therapies, such as non-steroidal anti inflammatory drugs (or may allow for dose reductions or cessation of these drugs in some patients)*.

The body of clinical evidence has led to the following recommendations/observations[2,3]:

1. Administer between 50 and 100 mg of harpagosides per day for the management of Osteoarthritis, Rheumatoid arthritis and Low back pain.
2. Important to take for at least 1 month to obtain optimal benefits.
3. Has a slower onset of action than prescription NSAIDs.

Use 1 tablet of Droxanol twice a day (morning and evening).

Pediatrics (18 < years of age): The product is only approved for use in adults.

COMPOSITION

Route of Administration	Dosage Form / Strength	Active Ingredient	Nonmedicinal Ingredients
oral	Tablet. 468 mg extract equivalent to 3.7 g of the dried secondary root of Devil's claw	Extract standardized to 5% harpagoside (based on HPLC analysis). Contains 23.4 mg harpagoside per tablet.	Alginate, anhydrous dibasic calcium phosphate, cellulose, croscarmellose sodium, colloidal silicon dioxide, vegetable magnesium stearate

Enteric coating:

Harpagoside is considered unstable in gastric juices[4]. Experimental studies demonstrated that the anti inflammatory effects could not be obtained by oral administration, but dose-dependent effects were obtained with intraperitoneal and intraduodenal administration. Gastric digestion has been shown to decrease the potency of Devil's claw (i.e., inactivated after acid hydrolysis). Enteric-coated tablets are used to maintain efficacy despite exposure to gastric acids.

ACTION AND CLINICAL PHARMACOLOGY

Droxanol™ is a natural NSAID. It inhibits COX-2 and is a potent inhibitor of the release of cytokines[1,5].

MECHANISM OF ACTION[1]

Anti inflammatory properties:

Extracts demonstrated anti-inflammatory properties in animals' models of acute inflammation/pain, such as carrageenan-induced edema and adriamycin-induced edema in rats, and in the acute and chronic treatment of Freund's adjuvant-induced arthritis in rats. Studies using the active medicinal ingredients of Devil's claw demonstrated that Aucubin inhibits LCT4-release in studies on the stimulated release of inflammatory mediators from mouse peritoneal macrophages. Most active ingredients (except harpagoside) demonstrated significant inhibition of stimulated TXB2 release. Harpagoside inhibited both arachidonic acid

metabolism pathways. Downregulation of iNOS expression in rat mesangial cells by *Harpagophytum* extracts has been reported. Extract prevented TNF-alpha synthesis; the latter, however, having a greater inhibitory effect on COX-2 pathway products. Extract was able to suppress enhanced production of matrix-degrading enzymes (matrix metalloproteinases) via the inhibition of the synthesis of inflammatory cytokines has also been reported.

5-Lipoxygenase biosynthesis inhibition activity:
Experimental studies demonstrated that extracts totally inhibited 5-lipoxygenase biosynthesis.

Analgesic properties:
Administration of 20mg/kg harpagoside produced an analgesic effect similar to that of phenylbutazone at 50mg/kg. Writhings and stretchings induced in rats by 1.2% acetic acid was significantly reduced after administration of an aqueous Devil's claw extract (2.2% harpagoside).

PHARMACODYNAMICS/PHARMACOKINETICS[6]
In a blood sample taken from a human two hours after ingesting a Devil's claw extract containing 44mg harpagoside, the harpagoside level was 15.4ng/mL. Oral administration of a 600mg extract containing 25% harpagoside led to plasma harpagoside levels of 32.2ng/mL after 1.3 hours, which subsequently rapidly decreased. A second peak was observed after eight hours. Harpagoside elimination half-life has been reported as 5.6 hours.

THERAPEUTIC INFORMATION

GENERAL:

Hematology-Coagulation[7]:
European Medical Agency (EMA) performed a detailed assessment of the safety information and could not find any study or reported cases suggesting an interaction with oral anticoagulants, or sulfonylureas. The EMA stated that no signal, even weak, has emerged from the literature to date supporting a potential interaction.

Drug Interactions[1]:
No cytochrome P450 induction or inhibition.

CONTRAINDICATIONS[1,7,8]

Pregnancy
Do not use during pregnancy. Lack of evidence to recommend safe use.

Allergy
Known allergy/hypersensitivity to Devil's claw.

PRECAUTIONS

Cardiovascular[1,7]:
Use cautiously in patients with heart disease, especially patients with arrhythmias or taking antiarrhythmic agents, due to potential negative inotropic effects of Devil's claw. In rabbits, Devil's claw has been associated with negative chronotropic, as well as positive and negative inotropic effects. However, these effects have not been clearly documented in humans.

SIDE EFFECTS

Gastrointestinal[1]:
Side effects have been reported in some individuals in studies, including mild gastrointestinal upset, diarrhea, or anorexia. There is no reported incident of gastrointestinal bleeding. As a general precaution, the EMA recommends not to use in patients with a history of gastric or duodenal ulcer.

STORAGE AND STABILITY

Droxanol™ tablets should be stored at room temperature. The medicinal ingredient is stable for 2 to 3 years.

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[1] **Natural Standard database**. *Evidence-based Systematic Reviews of herbs* by the Natural Standard Research Collaboration. Copyright ® 2011.
[2] Gibofsky A et al. Comparing the efficacy of cyclooxygenase 2-specific inhibitors in treating osteoarthritis. Arthritis & Rheumatism 2003; 48(11):3102-3111.
[3] Laudahn D et Walper A. Efficacy and tolerance of Harpagophytum extract LI 174 in patients with chronic non-radicular back pain. Phytother. Res. 2001; 15:621-624.
[4] Soulimani, R., Younos, C., Mortier, F., and Derrieu, C. *The role of stomachal digestion on the pharmacological activity of plant extracts, using as an example extracts of Harpagophytum procumbens*. Can.J Physiol Pharmacol 1994;72(12):1532-1536.
[5] Chrubasik S et al. Treating low back pain with an extract of Harpagophytum that inhibits cytokine release. Eur J Anaesthesiol 2002, 19:209.
[6] Loew, D., Mollerfeld, J., Schrodter, A., Puttkammer, S., and Kaszkin, M. Investigations on the pharmacokinetic properties of Harpagophytum extracts and their effects on eicosanoid biosynthesis in vitro and ex vivo. Clin.Pharmacol.Ther. 2001;69(5):356-364.
[7] Assessment report on Harpagophytum procumbens DC and/or Harpagophytum zeyheri decne, radix. European Medicines Agency, Evaluation of Medicines for Human Use, 2009.
[8] **Health Canada**. Monographs prepared by the Natural Health Products Directorate, Health Canada.