European Medicines Agency
Evaluation of Medicines for Human Use

London, 12 March 2009
Doc. Ref.: EMEA/HMPC/251324/2006 *Corr.*[1]

ASSESSMENT REPORT ON *HARPAGOPHYTUM PROCUMBENS* DC. AND/OR *HARPAGOPHYTUM ZEYHERI* DECNE, RADIX

[1] Changes introduced in section II.3.2.3

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

I. REGULATORY OVERVIEW

MA: Marketing Authorisation;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	**Regulatory Status**			
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: Only fixed combination
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:
Greece	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: Healing products
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: Food supplements
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Malta	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify: No products

II. ASSESSMENT REPORT ON HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH TRADITIONAL USE

***Harpagophytum procumbens* DC. and/or *Harpagophytum zeheyri* Decne, radix**

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

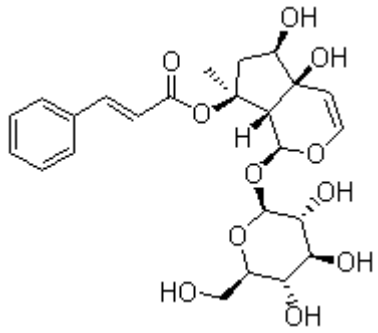
Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne, radix
Herbal preparation(s)	Dry extracts Soft extracts Liquid extracts Powdered herbal substance Comminuted herbal substance
Pharmaceutical forms	Herbal substance or herbal preparation in solid or liquid dosage forms or as herbal tea for oral use.
Rapporteur	Antoine SAWAYA
Assessors	Pharmaceutical: Jacqueline VIGUET POUPELLOZ Non-Clinical: Fabien LAVERGNE Clinical (rheumatology): Sylvain GUEHO Pharmacovigilance: Nathalie DELEAU Interactions: Beatrice SAINT-SALVI

II.1 INTRODUCTION

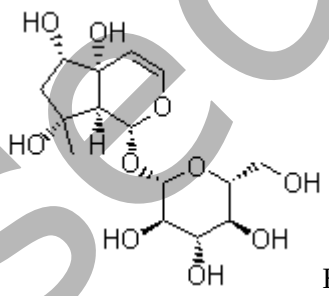
II.1.1 Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)[2,3]: Cut dried tuberous secondary root of *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne
- Herbal preparation(s)[1,2]: Powdered herbal substance, comminuted herbal substance, liquid extract (1 : 1 ; 30% V/V ethanol), soft extract (2.5-4.0 : 1 ; 70% V/V ethanol), dry extract (1.5-2.5 : 1 ; water), dry extract (5-10 : 1 ; water), dry extract (2.6-4 : 1 ; 30% V/V ethanol), dry extract (1.5-2.1 : 1 ; 40% V/V ethanol), dry extract (3-5 : 1 ; 60% V/V ethanol), dry extract (3-6 : 1 ; 80% V/V ethanol), dry extract (6-12 : 1 ; 90% V/V ethanol)

The characteristic constituents are iridoid glucosides (0.5 – 3 %): harpagoside, harpagide, 8-(4-coumaroyl)-harpagide, procumbide, its 6′-4-coumaroyl ester and procumboside. The European Pharmacopoeia prescribes no less than 1.2% of harpagoside.



Harpagoside



Harpagide

The other constituents are principally sugars (stachyose, raffinose and monosaccharides) and phenolic glycosides (verbascoside and isoacteoside).

II.1.2 Information on period of medicinal use in the Community regarding the specified indication

The first herbal medicinal product has been authorized in Germany in 1978. Some products are marketed also in Belgium, in Denmark, in France, in Hungary and in Malta.

The different herbal medicinal products on the market are prepared with powder, aqueous extract or ethanolic extracts (30 - 40% V/V, and 60 - 90% V/V)

II.2 NON-CLINICAL DATA

II.2.1 INTRODUCTION

Harpagophytum procumbens belongs to the *Pedaliacea* family. This perennial herbaceous plant grows naturally in the Kalahari desert and Namibian steppes region of south-west Africa. Its secondary tuberised roots, commonly called “Devil’s claw” because of their shape, have been widely used in

[2] According to “Guideline on quality of herbal medicinal products/traditional herbal medicinal products” (CPMP/QWP/2819/00 Rev. 1)

[3] According to “Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products” (CPMP/QWP/2820/00Rev.1)

traditional medicine for various indications. In Europe, it is used for painful arthritis, tendinitis, loss of appetite and dyspeptic complaint [**Baghdikian *et al.* 1997**].

Studies quoted in this document were not performed in compliance with GLPs. Most of them were conducted to evaluate the pharmacodynamics of *Harpagophytum procumbens* secondary roots extracts referred to as "*Harpagophytum procumbens* extracts" in the following pages. Other non-clinical data (pharmacokinetics, toxicology) are scarce.

II.2.2 PHARMACODYNAMICS

II.2.2.1 Primary pharmacodynamics

II.2.2.1.1 Analgesic effect

Writhing test

An aqueous extract of *Harpagophytum procumbens* (containing 2.2% harpagoside) was tested for its analgesic activity in the writhing test. It was administered intraperitoneally to male Swiss mice at the following dose levels: 100, 400, 800 and 1200 mg/kg [**Baghdikian *et al.* 1997**]. Acetylsalicylic acid (Aspegic®) was used as a reference peripheral analgesic compound at the dose of 68 mg/kg. Control animals received 0.9% NaCl solution under the same experimental conditions. Thirty minutes after these administrations, the animals were injected a 1.2% acetic acid solution by intraperitoneal route. Each animal was then isolated and observed for 30 minutes. During this period, the number of writhings and stretchings was recorded. The percentage of protection against the acetic acid algic effect was then calculated for each group.
The results indicated that *Harpagophytum procumbens* dose-dependently decreased the number of writhings and stretchings from the 400 mg/kg dose (35% protection). The maximal effect was observed at 1200 mg/kg, the percentage of protection reaching 62%. Comparatively, acetyl salicylic acid (68 mg/kg) induced a protection of 59% [**Baghdikian *et al.* 1997**].

Another experiment was performed according to the same protocol, to study the analgesic activity of a standardized aqueous extract of *Harpagophytum procumbens* containing 1.8% harpagoside (50, 100, 200 and 400 mg/kg) and harpagoside (5 and 10 mg/kg). Acetylsalicylic acid (68 mg/kg) and morphine sulphate (1.15 mg/kg) were used as reference peripheral/central analgesic compounds. The results indicated that *Harpagophytum procumbens* dose-dependently decreased the number of writhings and stretchings from the 100 mg/kg dose (47% protection). The maximal effect was observed at 400 mg/kg, the percentage of protection reaching 78%. Harpagoside exerted a protective effect against the painful stimuli at the dose of 10 mg/kg only (10 mg harpagoside corresponding to twice the harpagoside content of 400 mg extract) [**Lanhers *et al.* 1994**].
The acid treatment of the extract and harpagoside (HCl 0.1 N (pH 1) during 3 hours at 38°C), performed to reproduce the physico-chemical conditions found in the stomach, abolished their analgesic activity in the writhing test [**Lanhers *et al.* 1994**].

Hot plate test

The same authors evaluated the protection potential of the extract and harpagoside against heat-induced pain [**Lanhers *et al.* 1994**]. Male Swiss mice were placed in a glass flack bathing in water whose temperature was maintained at 56°C. Reaction times of mice before any treatment were recorded – time to obtain a response to heat stimuli, e.g. licking of the forepaws, jumping. Then, mice were intraperitoneally injected the extract (200 and 400 mg/kg) or harpagoside (10 mg/kg). Acetylsalicylic acid (68 mg/kg) and morphine sulphate (4.6 mg/kg) were used as reference substances. The procedure to measure time reactions was repeated after 30 minutes. Each animal was its own control.
In this test, *Harpagophytum procumbens*, harpagoside and acetylsalicylic acid did not increase the reaction time of mice. On the contrary, morphine sulphate (4.6 mg/kg) exerted a significant protective effect on heat-induced pain, as the reaction time was increased by 46% 30 minutes after its administration.

Assessor's comments

Analgesic activity of Harpagophytum procumbens and harpagoside was evaluated in two murine models. In these models, pain was induced either chemically by intraperitoneal injection of acetic acid (writhing test), or thermally (hot plate test). In these experiments, test articles were administered by intraperitoneal route.
Harpagophytum procumbens had a dose-dependant protective effect against the pain induced by acetic acid. The lowest effective dose varied from 100 to 400 mg/kg, according to the extract used.
In the same animal model, harpagoside was only effective at the dose of 10 mg/kg, which represents twice the harpagoside dose contained in 400 mg of the extract effective at 100 mg/kg. Therefore, the authors concluded that other substances (than harpagoside) are involved in the analgesic activity of Harpagophytum procumbens [**Lanhers *et al.* 1994**]. *However, these substances remain unknown.*
Moreover, the extract and harpagoside were submitted to an acid treatment whose aim was to mimic the physico-chemical conditions found in the stomach. The substances obtained were then evaluated for their analgesic activity in the writhing test, according to the same protocol (i.p. route). The results indicated that their protective effect against chemical-induced pain observed previously was abolished. Although the gastric degradation of active substances involves other phenomena (enzymatic action, absorption, intestinal resorption), this would suggest that Harpagophytum procumbens is not effective in terms of analgesia when administered orally.
In the hot plate test, like acetylsalicylic acid, but contrary to morphine sulphate, Harpagophytum procumbens was ineffective. Therefore, it does not possess any central analgesic properties.
In summary, Harpagophytum procumbens possesses peripheral analgesic properties after intraperitoneal administration, as shown in the writhing test in mice. Studies performed with harpagoside suggest that other unidentified substances are involved in this analgesic effect, but these active substances remain unknown. Effective doses are not accurately defined, as they can change according to the extract used. A study performed after the acid treatment of an extract suggested that Harpagophytum procumbens could be ineffective by oral route in terms of analgesia.

II.2.2.1.2 Anti-inflammatory effect

II.2.2.1.2.1 Isolated substances (harpagoside, harpagogenin)

Three animal models of inflammation were used:

- the carrageenan-induced mouse/rat paw oedema [**Lanhers *et al.* 1994**; **Recio *et al.* 1994**].
- the TPA-induced mouse ear oedema [**Recio *et al.* 1994**].
- the granuloma pouch test [**Eichler and Koch 1970**].

- Carrageenan-induced mouse paw oedema [Recio *et al.* 1994]

This study was designed to evaluate the anti-inflammatory activity of harpagoside (100 mg/kg) and 11 other iridoids administered orally to female Swiss mice. Control animals received the vehicle in the same conditions. Indomethacin at the dose of 7 mg/kg was used as a reference product. Each group was composed of 6 mice.
One hour after these administrations, each mouse was injected a 3% w/v suspension of carrageenan in its right hind paw to induce oedema. The volumes of the injected and contra-lateral paws were measured at 1, 3 and 5 hours after the induction of inflammation.
The values of the oedema volume and the oedema inhibition percentage were calculated for each group. The authors considered that harpagoside administered orally did not exert a notable protective effect in this test.

- Carrageenan-induced rat paw oedema [Lanhers *et al.* 1994]

Male OFA rats were administered harpagoside by intraperitoneal route at the doses of 5 and 10 mg/kg. In the same conditions, indomethacin (2.5, 5 and 10 mg/kg) was used at a reference product and the controls received 0.9% NaCl solution. Twelve rats per harpagoside group were used, as well as

13 control rats and 10 rats per indomethacin group. Thirty minutes after these administrations, each rat received a subplantar injection of a 1% carrageenan suspension in its right back paw.
The average volume of the back paws of each animal were measured before any treatment and at different time points after the injection of the carrageenan suspension (30 min, 1, 2, 3, 4, 5, 6 and 24 hours). For each group, the following data were then calculated: average volumes of the back paws before treatment and at the different time points, and percentages of variation (percentages of oedema).
In control animals, a local oedema was observed 30 minutes after the injection of the carrageenan suspension, and reached a maximal intensity after 3 or 4 hours (% of oedema = 56 to 67%). Then, the oedema progressively decreased but still remained obvious after 24 hours. The intraperitoneal pre-treatment with harpagoside did not induce an inhibitory effect on carrageenan-induced oedema, contrary to indomethacin.

- TPA-induced mouse ear oedema [Recio *et al.* 1994]

Application of a single dose of 12-O-tetradecanoylphorbol-13-acetate (TPA) to mouse ears induces an acute inflammatory reaction consisting of erythema, oedema and polymorphonuclear leukocyte (PMN) infiltration. TPA was applied on the right ear of mice (2 groups, 6 per group).
Then, harpagoside was administered topically at the dose of 1 mg (right ear). The reference substance was indomethacin, 0.5 mg (right ear). Left ears of the animals served as controls, and were applied vehicle (EtOH) or acetone, which was used to dissolve TPA or harpagoside. After 4 hours, animals were sacrificed and the swelling induced by TPA was assessed in terms of the increase in the weight of the right ear biopsy over that of the left ear.
The results indicate that harpagoside 1 mg/kg induced an inhibition of 36.2 % of the oedema, as compared to controls. This oedema inhibition percentage amounted to 87.1% with indomethacin 0.5 mg/kg. Therefore, it was concluded that harpagoside did not exert anti-inflammatory effects in this model.

- Granuloma pouch test [Eichler and Koch 1970]

In this test, an aseptic inflammation with large volumes of haemorrhage is induced. Here, croton oil (0.5 ml, 0.5%) was used as irritant in Wistar rats. Harpagoside (20 mg/kg) and harpagogenin (20 mg/kg) were tested following daily intraperitoneal administration for 12 days. Phenylbutazone (40 mg/kg) was used as a reference substance.
The results indicated that harpagoside and harpagogenin induced a significant inhibition of exudate production (respective values of 33.8% and 28.9%), of granuloma weight (respective values of 29.9% and 24.5%) and of tissue granulation (respective values of 19.2% and 14.6%).

II.2.2.1.2.2 Aqueous extracts of Harpagophytum procumbens (secondary roots)

Various aqueous extracts of *Harpagophytum procumbens* have been evaluated for their anti-inflammatory activity in mice and rats. Three main animal models of inflammation were used:

- the carrageenan-induced rat paw oedema [**Baghdikian *et al.* 1997**, **Lanhers *et al.* 1994**, **McLeod *et al.* 1979**, **Whitehouse *et al.* 1983**, **Soulimani *et al.* 1983**].
- the adriamycine-induced rat paw oedema [**Jadot and Lecomte 1992**].
- the adjuvant-induced arthritis in rats [**McLeod *et al.* 1979**, **Whitehouse *et al.* 1983**].
- the granuloma pouch test [**Erdös *et al.* 1978**].

- Carrageenan-induced rat paw oedema

Aqueous extracts of *Harpagophytum procumbens* were tested in this model by intraperitoneal and oral routes. Due to conflicting results, another study was undertaken to compare directly the anti-inflammatory activity of *Harpagophytum procumbens* by intraperitoneal, oral and intraduodenal routes.

– *Intraperitoneal route*

A standardised aqueous extract of *Harpagophytum procumbens* (containing 1.8% harpagoside) was administered to rats (15 per group) at the following dose levels: 100, 200 and 400 mg/kg – doses expressed in terms of dried plant material [**Lanhers *et al.* 1994**]. As precised in the protocol described above, a carrageenan suspension was injected thirty minutes after in the right back paw of each animal. The average back paw volume of each rat was measured before any treatment and at different time points after the injection of the inflammatory agent (up to 24 hours).
The results showed that the local oedema induced by the carrageenan suspension was reduced dose-dependently by a pre-treatment by *Harpagophytum procumbens* from the dose of 100 mg/kg within 2-3 hours. The intensity of the anti-inflammatory effect was maximal 3 hours after carrageenan injection. Then, it progressively declined, but still remained significant after 24 hours. The oedema inhibition percentages were 38%, 63% and 72% at respectively 100, 200 and 400 mg/kg (3 hours). Compared to indomethacin (2.5 to 10 mg/kg), whose effect reached a maximal intensity 30 minutes after injection of the carrageenan suspension and remained steady for 5 hours, the anti-inflammatory effect of *Harpagophytum procumbens* was more transient [**Lanhers *et al.* 1994**].
The same test was performed to study the influence of acid treatment on the anti-inflammatory effect of *Harpagophytum procumbens*. Therefore, the extract was treated to reproduce the physico-chemical conditions found in the stomach (HCl 0,1 N (pH 1) during 3 hours at 38°C). At the unique dose of 400 mg/kg i.p. used, the anti-inflammatory effects of *Harpagophytum* previously observed were abolished by this treatment [**Lanhers *et al.* 1994**].
Another aqueous extract of *Harpagophytum procumbens* (containing 2.2% harpagoside) was administered to rats at doses of 400, 800 and 1200 mg/kg – doses expressed in terms of dried plant material [**Baghdikian *et al.* 1997**]. Control animals received a 0.9% NaCl solution, and the reference substance used was indomethacin 10 mg/kg. As in the previous study, a 1% carrageenan suspension was injected in the right back paw (subplantar route) 30 minutes after these administrations. The average volumes of each rat back paws were measured before any treatment and at different time points after the injection of the inflammatory agent (up to 24 hours).
In controls, a local oedema was observed 1 hour after the injection of the carrageenan suspension, and reached a maximal intensity after 3 or 4 hours and still remained obvious after 24 hours. The carrageenan-induced oedema was dose-dependently decreased in animals pre-treated with *Harpagophytum procumbens* from 400 mg/kg. This inhibitory effect was significant 3 and 4 hours after the injection of the phlogistic agent in the 400 mg/kg group (percentages of inhibition respectively 43 and 30%); in the 800 and 1200 mg/kg groups, it was more marked and sustained (significant from 1 to 5 hours), the maximal inhibition being reached 3 hours after induction of the oedema (56 and 64% inhibition, respectively). The inhibitory effect of indomethacin was recorded as soon as 1 hour after the injection of carrageenan and reached a maximum at 3 hours (58% inhibition). Then, it remained steady for 5 hours. This effect was still significant after 24 hours [**Baghdikian *et al.* 1997**].

– *Oral route*

Thirty male Wistar rats were administered either an aqueous extract of *Harpagophytum procumbens* (1 g/kg), indomethacin as a reference substance (5 mg/kg), or 0.5% tragacanth. One hour after these administrations, carrageenin 0.1% was injected into the rear right foot of each animal, and volumes of both rear feet were then measured at hourly intervals. The peak reaction was observed 4 hours after the injection of the phlogistic agent. At this time point, the anti-inflammatory effect of the extract and indomethacin were evaluated taking into account the inhibition of the oedema intensity. Respective inhibition percentages were 6% and 63%. Therefore, this extract of *Harpagophytum procumbens* did not exert any anti-inflammatory effect in these conditions [**McLeod *et al.* 1979**].

An extract of *Harpagophytum procumbens* was compared to acetylsalicylic acid (ASA) in terms of inhibition of the oedema induced in male Sprague-Dawley rats injected a 1% solution of carrageenan into the subplantar tissue of the right hind foot. The animals were pre-treated one hour before with either *Harpagophytum procumbens* (20, 200, 2000, 6000 mg/kg, 6 rats per group) or ASA (200 mg/kg, 4 rats) by gastric gavage. Volumes of the hind feet (right and left) were measured before and 3 hours after carrageenan treatment. This study showed that *Harpagophytum* administered up to

6000 mg/kg did not reduce the oedema consecutive to carrageenan injection (max. 20.3% inhibition, 2000 mg/kg) contrary to ASA (51.9% inhibition) [**Whitehouse *et al.* 1983**].

– *Intraperitoneal/oral/intraduodenal routes*

Harpagophytum procumbens exerts an anti-inflammatory effect when administered by intraperitoneal route but not by oral route. Furthermore, this effect is abolished after treatment of the extract in conditions mimicking the physico-chemical conditions found in the stomach. Therefore, some authors conducted a study to investigate the influence of the gastric passage on the anti-inflammatory activity of *Harpagophytum procumbens* in rats [**Soulimani *et al.* 1994**].
The extracts prepared had a total glucoiridoid content 2.72%, and an harpagoside content of 0.44%. Extracts intended to be administered orally and intraduodenally were lyophilized with β-cyclodextrin to promote its bioavailability. The general design of the study is listed below:

- IP route: administration of the extract (100, 200 and 400 mg/kg in terms of dry material) or NaCl 0.9% (controls) followed after 30 minutes by an injection of a 1% carrageenan suspension into the back paw of each animal.
- Oral route: administration of the extract (200, 400, 800, 1600 mg/kg in terms of dry material) or water (controls) followed after 60 minutes by an injection of a 1% carrageenan suspension into the back paw of each animal.
- Intraduodenal route: ketamine anaesthesia followed by the administration of the extract (200, 400, 800, 1600 mg/kg in terms of dry material) or water (controls) and, after 60 minutes, by an injection of a 1% carrageenan suspension into the back paw of each animal.

In control animals belonging to intraperitoneal and oral groups, a local oedema appeared 1 hour after carrageenan injection; its intensity increased to reach a maximum at 3 hours. In control animals of the intraduodenal groups, the local oedema was observed 2 to 3 hours after the injection of carrageenan and reached a maximal intensity at 6-9 hours. This temporal shift was attributed to ketamine administration. In all control groups, the oedema progressively decreased in intensity but remained obvious 24 hours after its induction.
Three hours after intraperitoneal administration of the extract, significant inhibition of the carrageenan-induced oedema was observed from the 100 mg/kg dose (36% inhibition of the oedema). At 400 mg/kg, the effect is maximal (67% inhibition) and was significant from 2 hours to 6 hours after oedema induction. Administered intraduodenally, the extract reduced the carrageenan-induced oedema from the dose of 200 mg/kg 6 to 9 hours after the carrageenan injection (43% inhibition). The effect was maximal at the dose of 400 mg/kg (60% inhibition). By oral route, no inhibitory effect was observed on the carrageenan-induced oedema, whatever the dose of extract administered [**Soulimani *et al.* 1994**].

- Adriamycine-induced rat paw oedema

Harpagophytum procumbens (powder in suspension in arabic gum, 3% glucoiridoids) was administered daily for 5 days to male Wistar rats by oral gavage (0, 37, 370 and 3700 mg/kg/d). Then, all animals were injected in the left hind paw (subplantar injection) 0.2 ml of a solution of adriamycine chlorhydrate (0.5 mg). The volumes of the injected paw were measured before any administration, 1 hour and 5 days after administration of the inflammatory agent.
In a previous study, the authors showed that the injection of adriamycine chlorhydrate in the same conditions caused, after 1 hour, a release of serotonin and histamine. After 5 days, lipid peroxidation and free radicals were identified.
In the present study, one hour after having induced inflammation, the injected paw volume was decreased in all treated groups, but the effect was maximal in the 37 mg/kg dose group (-48.07%). After 5 days, the administration of *Harpagophytum procumbens* did not inhibit the formation of free radicals, the injected paw volumes not significantly differing between control and treated animals. Therefore, it is concluded that *Harpagophytum procumbens*, after 5 days of oral administration, exerts an anti-inflammatory activity from the 37 mg/kg dosage but no anti-oxidant activity at any dose-level [**Jadot and Lecomte 1992**].

- Adjuvant-induced arthritis in rats

Female Sprague-Dawley rats were induced adjuvant arthritis by injection of *Mycobacterium tuberculosis* (0.1 ml, 1 mg/ml) into their rear right feet [**McLeod *et al.* 1979**]. Then, the following drugs were administered orally daily for 21 days: *Harpagophytum procumbens* dried aqueous extract (100 mg/kg – 1 g/kg), indomethacin (3 mg/kg, used as a reference substance), or tap water (controls). The number of animals involved in this experiment totalled 40. During the administration period, the following parameters were measured: body weight and rear foot volumes.
The results of the study indicated that contrary to indomethacin, *Harpagophytum procumbens* administered orally did not produce a significant effect on either the primary or secondary inflammatory reaction. Moreover, when given in the high-dose group (1 g/kg), the volumes of the injected and uninjected feet were greater than controls. This unexpected effect was significant on day 7 (+16%). Therefore, the authors do not exclude the potential of *Harpagophytum procumbens* to potentiate adjuvant arthritis in a manner similar to that seen with levamisole and penicillamine [**McLeod *et al.* 1979**].

In another experiment [**Whitehouse *et al.* 1983**], male Sprague-Dawley rats were injected an oily suspension of *Mycobacterium butyricum* (0.05 ml, 15 mg/ml) into the right hind paw (day 0). An additional group (n = 6) served as a control group and was left uninjected. Oedema in the contra-lateral foot was monitored in each animal. On day 11, all adjuvant-pre-treated animals exhibiting a foot volume of 2 ml or more were randomly divided into 3 treatment groups (6 per group) and received daily until day 17, by oral route, either:

- Water (2 ml/kg).
- *Harpagophytum procumbens* extract (2 g/kg).
- Indomethacin (3 mg/kg), reference substance.

Volumes of the feet were monitored on days 11, 15 and 17 and mean foot volumes were then calculated. The results indicate that *Harpagophytum procumbens* was ineffective in this model of inflammation after 6 days of treatment, whereas indomethacin completely alleviated the adjuvant-induced arthritis after 4 days of treatment (day 15 of the experiment) [**Whitehouse *et al.* 1983**].

- Granuloma pouch test

An experiment similar to the one described above was performed with an aqueous extract containing 2.7% harpagoside given orally and daily for 11 days at the doses of 20 and 200 mg/kg. At the higher dose-level, the granuloma weight was significantly decreased by 69%, as well as the exudate production [**Erdös *et al.* 1978**].

Assessor's comments

In the carrageenan-induced paw oedema model, harpagoside administered either orally to mice at the doses of 100 mg/kg or intraperitoneally to rats at doses up to 10 mg/kg did not prevent the inflammation produced by the injection of the phlogistic agent. Moreover, it did not exert any anti-inflammatory effect when tested in the TPA-induced mouse ear oedema model.
However, some anti-inflammatory effects were reported for harpagoside and harpagogenin in the granuloma pouch test performed in rats, after intraperitoneal administration at higher dose-level (20 mg/kg).
Aqueous extracts of Harpagophytum procumbens showed anti-inflammatory activity in the carrageenan-induced rat paw oedema model after intraperitoneal administration. The lowest effective dose was 100 mg/kg or 400 mg/kg, according to the extract used. When compared to indomethacine, the reference substance, the effect was more transient.
By oral route, Harpagophytum did not exert any anti-inflammatory effect in the same animal model of inflammation, as well as in another model, the adjuvant-induced arthritis (2 studies).
The inefficacy of Harpagophytum procumbens in these models when administered orally, compared to its efficacy in the carrageenan-induced rat paw oedema model when administered intraperitoneally is

amazing. Some studies have shown that this discrepancy could result from the gastric passage of the extract. First, some authors showed that an extract submitted to an acid treatment whose aims was to mimic the physico-chemical conditions found in the stomach abolishes its anti-inflammatory activity previously reported. Secondly, other authors reported that the same extract protected rats against carrageenan-induced paw oedema when given intraperitoneally or intraduodenally, but not orally.
Moreover, in rats injected a suspension of Mycobacterium butyricum to induce arthritis, Harpagophytum procumbens was ineffective but authors evoked its ability to potentiate adjuvant arthritis in a manner similar to that seen with levamisole and penicillamine.

Only two isolated studies reported an anti-inflammatory activity of Harpagophytum procumbens after oral administration (granuloma pouch test and adriamycine-induced rat paw oedema model).

In summary, several points remain unresolved/unclear:
- Isolated compounds (mainly harpagoside) were not or were slightly, effective in animal model of inflammation, whereas Harpagophytum extracts have shown anti-inflammatory activity in the carrageenan-induced rat paw oedema model after intraperitoneal administration. Therefore, harpagoside does not seem to be <u>the</u> active substance/the <u>unique</u> active substance involved in the anti-inflammatory activity claimed for Harpagophytum procumbens. These substances should then be identified.
- The influence of the gastric passage on Harpagophytum procumbens's anti-inflammatory activity should be clarified; presently, available preclinical studies do not support its potential to induce anti-inflammatory effects after oral administration.
- The lowest effective dose should be accurately precised, as it varied according to the extract used (intraperitoneal studies).
- The ability of Harpagophytum procumbens to potentiate adjuvant arthritis in a manner similar to that seen with levamisole and penicillamine should be taken into consideration.

II.2.2.1.3 Mechanism of action

Four mechanisms of action were investigated either in *in vitro* or in *in vivo* studies in order to explain the analgesic and anti-inflammatory activity of *Harpagophytum procumbens* reported in animal and in man. Its possible influence on the arachidonic acid pathway was particularly studied.

- <u>Influence on arachidonic acid pathway</u>

The effects of *Harpagophytum procumbens* on prostaglandin synthetase were examined *in vitro*. Radiolabelled arachidonic acid and prostaglandin synthetase were incubated at 37°C for 4 minutes with various concentrations of indomethacin, acetylsalicylic acid or *Harpagophytum procumbens* extract. The percentage of inhibition of the enzyme was then determined. IC_{50} were then calculated and amounted to 0.376 µg/ml for indomethacin and 437 µg/ml for acetylsalicylic acid. In comparison, the concentration of *Harpagophytum procumbens* causing 50% inhibition of prostaglandin synthetase was superior to 10^5 µg/ml. Therefore, it was concluded that the claimed anti-inflammatory activity of *Harpagophytum procumbens* is not mediated by the inhibition of the prostaglandin synthetase [**Whitehouse *et al.* 1983**].

Other authors have investigated the effects of *Harpagophytum procumbens* (aqueous extract) against LPS-stimulated expressions of COX-2 and iNOS (inducible nitric oxide synthase) in murine fibroblast cell line L929 [**Jang *et al.* 2003**]. The following parameters were measured:

- Cell viability (MTT assay).
- COX-1, COX-2 and iNOS mRNAs expressions (RT-PCR).
- PGE_2 biosynthesis (commercial competitive enzyme immunoassay kit).
- NO biosynthesis (commercial NO detection kit).

The results obtained did not indicate any cytotoxic effect of the extract tested towards L929 cells at concentrations up to 1 mg/ml. In LPS-stimulated cells, compared to controls, the expressions of COX-1, COX-2 and iNOS mRNAs were increased, as well as PGE_2 and NO synthesis. However, when the cells were incubated with LPS and *Harpagophytum procumbens* (up to 1 mg/ml), these parameters were increased compared to controls, but significantly reduced compared to LPS-stimulated cells not incubated with *Harpagophytum procumbens*.
As shown by Salvemini *et al* (1993), NO modulates the activity of COX-2 in a cGMP-independent manner and plays a critical role in the release of PGE_2 by direct activation of COX-2. Therefore, the results obtained in murine cell line L929 suggest that *Harpagophytum procumbens* suppresses COX-2 and iNOS mRNAs expressions, resulting in inhibition of PGE2 synthesis. This mechanism could explain its analgesic and anti-inflammatory activities [**Jang *et al.* 2003**].
This possible inhibitory potential of COX-2 was further investigated *in vivo* in ICR mice. The animals were applied a methanolic extract of *Harpagophytum procumbens* (200 and 400 µg) onto their shaven back. After 30 minutes, TPA (12-O-tetradecanoylphorbol-13-acetate, a prototype tumour inducer) was administered the same way to induce cutaneous COX-2 expression. As an underlying mechanism of COX-2 inhibition, this extract reduced TPA-stimulated catalytic activity of extra-cellular signal-regulated protein kinase (ERK), which is known to regulate the activation of eukaryotic transcription factors mediating COX-2 induction. While TPA-induced activation of nuclear factor-κB remained unaffected by the extract, it inhibited TPA-induced activation of activator protein-1 (AP-1) and attenuated the expression of its key component c-Fos. Furthermore, pre-treatment with the same extract abrogated the DNA binding of cyclic AMP response element binding (CREB) protein induced by topical application of TPA [**Kundu *et al.* 2005**].

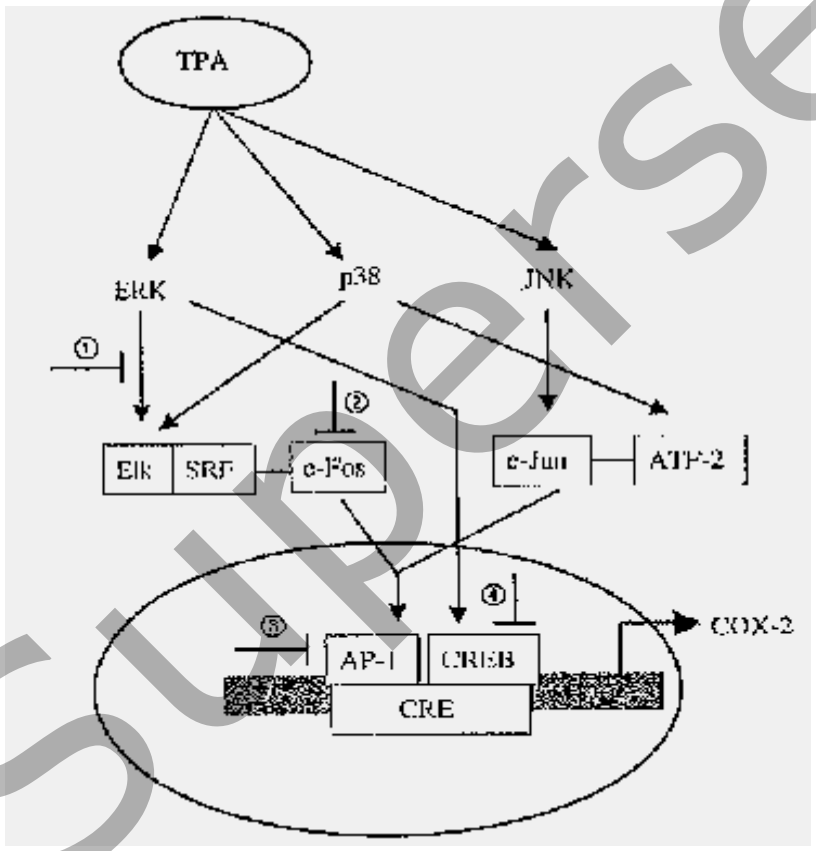


Figure 1: Proposed molecular mechanism of COX-2 down-regulating effects of *Harpagophytum procumbens* [Kundu *et al*. 2005].

The methanol extract of *Harpagophytum procumbens* inhibited TPA-induced COX-2 expression in mouse skin *in vivo* by blocking ERK kinase activity (①), c-Fos expression (②), AP-1 DNA binding (③) and CREB DNA binding (④).

The effects of different fractions of *Harpagophytum procumbens* extracts on ecosanoid biosynthesis were evaluated on human whole blood *in vitro* [**Loew *et al.* 2001**]. A crude aqueous ethanolic extract (80% wt/wt), extract fractions prepared by liquid/liquid extraction with solvent of increasing polarity and 2 other extracts were tested. These extracts were pre-incubated with human whole blood (n=5 volunteers) for 15 minutes. Then, the Ca^{2+} ionophore A23187 was added to stimulate the biosynthesis of Cys-LT (cysteinyl-leukotriene) and TXB_2 (thromboxane B_2) by blood cells. Control

samples were not pre-incubated with any extracts. Cys-LT and TXB_2 were measured by radioimmunoassay.
The results obtained with different fractions of the extract showed that the inhibition of A23187-stimulated Cys-LT and TXB_2 biosynthesis is dependent on the harpagoside content in the extracts (see table 1).

Extract and fraction	*Harpagoside content*	*Effect on Cys-LT biosynthesis*	*Effect on TXB_2 biosynthesis*
Crude aqueous ethanolic extract	2.1%	IC_{50} = 1.45 mg/mL (61.7 µmol/L)*	2.35 mg/mL = –42.7% (no IC_{50})
Heptane fraction (fraction A)	1.3%	1.0 mg/mL = –37.3% ± 7.2% (no IC_{50})	No effect up to 1.0 mg/mL
Ethyl acetate fraction (fraction B)	19.95%	IC_{50} = 0.391 mg/mL (158 µmol/L)*	1.0 mg/mL = –27.8% ± 7.9% (no IC_{50})
Butanol fraction (fraction C)	19.5%	IC_{50} = 0.565 mg/mL (223 µmol/L)*	IC_{50} = 0.203 mg/mL (80.1 µmol/L)*
Water fraction (fraction D)	0%	No effect up to 1.0 mg/mL	No effect up to 1.0 mg/mL
Harpagoside	100%	IC_{50} = 39 µmol/L	IC_{50} = 49 µmol/L
Patented special extract WS1531 (fraction F)	7.3%	IC_{50} = 0.062 mg/mL (9.2 µmol/L)*	IC_{50} = 0.373 mg/mL (55 µmol/L)*
Constituents removed from WS1531 (fraction E)	0.36%	1.0 mg/mL = 170.5% ± 14.9% (no IC_{50})	1.0 mg/mL = 128.7% ± 24.5% (no IC_{50})

Cys-LT, Cysteinyl-leukotriene; TXB_2, thromboxane B_2; IC_{50}, 50% inhibitory concentration.
*Molar IC_{50} values were calculated on the basis of the harpagoside concentration of the extracts and extract fractions.

Table 1: Effect of different *Harpagophytum* extracts and extract fractions on the ionophore A23187-stimulated biosynthesis of Cys-LT and TXB_2 *in vitro* in human whole blood [Loew *et al.* 2001].

This study also showed that the different extract fractions have different pharmacological properties. For example, fraction E stimulates the synthesis of Cys-LT and TXB2 and consequently exerts potentially a pro-inflammatory activity [**Loew *et al.* 2001**].

- Inhibition of TNF-α synthesis

This potential mechanism of action has been investigated by Fiebich *et al* 2001. A *Harpagophytum procumbens* extract was obtained after aqueous ethanolic extraction (60% v/v) and labelled SteiHap69 (Steiner *Harpagophytum procumbens* 69). This extract was then purified from lipopolysaccharides of bacterial origin to obtain PSH69 extract (Purified SteiHap 69). Studies were also conducted with LPS-free harpagide and harpagoside.
Human monocytes were incubated with either PSH69, harpagide or harpagoside and then LPS 10 ng/ml were added in the culture medium. After 24 hours, IL-1β, IL-6, TNF-α and PGE_2 concentrations were measured in the supernatants. Controls were only incubated with LPS 10 ng/ml.
The results show that the LPS-stimulated excretion of TNF-α is inhibited dose-dependently when cells are pre-treated with PSH69 (IC_{50} = 100 µg/ml). Furthermore, IL-1β, IL-6, and PGE_2 were decreased with PSH69 concentrations superior to 100 µg/ml. On the contrary, pre-treating cells with harpagide or harpagoside up to 10 µg/ml did not influence the TNF-α synthesis, compared to control.
Therefore, PSH69 inhibits inflammatory processes by preventing the release of TNF-α from human monocytes *in vitro*. However, harpagide and harpagoside had no activity in the same pharmacological model.

- Inhibition of human leukocyte elastase

Boje *et al.* performed an *in vitro* study to evaluate the inhibiting activity of *Harpagophytum procumbens* towards the elastase from human leukocytes [**Boje *et al.* 2003**].
An aqueous extract (2.35% harpagoside) or 5 of the main components of *Harpagophytum procumbens* were incubated with human neutrophile elastase for 1 hour. At the end of the enzymatic reaction, inhibition rates were calculated and corresponding IC_{50} were then determined.
IC_{50} of the aqueous extract was 542 µg/ml. The more potent active substances in this test were 6′-O-acetyllacteoside and isoacteoside, with respective IC_{50} values of 47 and 286 µg/ml (70 and 286 µM). Other compounds, including harpagoside, had IC_{50} greater than 500 µg/ml (800 µM).

The elastase inhibiting potency of the aqueous extract *Harpagophytum procumbens* and its main components, with IC50 > 50 μM, is mediocre [**Boje *et al.* 2003**].

- Anti-oxidant activity

An ethanolic extract (53% w/v) of *Harpagophytum procumbens* was administered to male Wistar rats by intraperitoneal route for 1, 7 or 14 days in doses of 100 and 200 mg/kg. Control animals received NaCl 0.9% in the same conditions. Selegiline (Deprenyl®) 2 mg/kg was used intraperitoneally as a reference substance.
At the end of the treatment period, the frontal cortex and the striatum were dissected out and the following parameters were measured:

- Super-oxide dismutase (SOD) activity.
- Catalase (CAT) activity.
- Glutathione peroxidase (GPX) activity.
- Lipid peroxidation.
- Protein estimation.

In animals pre-treated at least 7 days with either *Harpagophytum procumbens* or Selegiline, the activities of SOD, CAT and GPX were dose-dependently increased, and lipid peroxidation was decreased. The authors concluded that the extract tested exerts an anti-oxidant activity at the dosages tested [**Bhattacharya and Bhattacharya 1998**].

Assessor's comments

Several in vitro and in vivo studies were conducted to investigate, on a mechanistic basis, the analgesic and anti-inflammatory activities of Harpagophytum procumbens.

A first series of experiments explored its influence on the arachidonic acid pathway. Two studies showed that Harpagophytum procumbens can interfere with arachidonic acid metabolism by acting on the COX-2 mRNA expression. The first study was performed with an aqueous extract in vitro, and the second with a methanol extract in mice, after cutaneous application.
In an in vitro model of A23187-stimulated biosynthesis of ecosanoids on human whole blood, it was reported that a crude aqueous ethanolic extract inhibits the release of Cys-LT and TXB_2. Assays performed with different fractions of this extract showed that this activity depends on the harpagoside content. However, a fraction stimulated the release of Cys-LT and TXB_2, underlying the need of standardized extracts. Another in vitro study showed that Harpagophytum procumbens does not act by inhibiting the prostaglandin synthetase.

A LPS-free aqueous ethanolic extract of Harpagophytum procumbens prevented the in vitro release of TNF-α from human monocytes. In the same experimental conditions, harpagide and harpagoside did not exert any activity. Furthermore, other authors showed that an aqueous extract of Harpagophytum procumbens and its main components have a mediocre elastase-inhibiting potency in human leukocytes.

In rats, an ethanolic extract administered by intraperitoneal route exerted an anti-oxidant activity after 7 and 14 days of treatment at 100 and 200 mg/kg. This result is not consistent those of a previous study, which showed that an orally administered suspension of Harpagophytum procumbens (doses up to 3700 mg/kg) did not induce any anti-oxidant activity 5 days after adriamycine injection. This raises the previously highlighted question about Harpagophytum procumbens efficacy variability according to the route of administration.

Therefore, some points remain unresolved/ unclear:

- *Mechanistic studies were performed with aqueous, aqueous alcoholic or alcoholic extracts of Harpagophytum procumbens. As qualitative and quantitative composition of the extracts differs according to the extraction process, the relevance of these data is uncertain. For example, although*

a crude ethanolic extract exerted anti-inflammatory activity by inhibiting LPS-stimulated release of Cys-LT and TXB2 in vitro, a fraction of this extract had the opposite effect.

II.2.2.2 Other studies

- Cardiovascular activity [Circosta *et al.* 1984]

The cardiovascular activity of *Harpagophytum procumbens* and harpagoside was evaluated in rats, and in Langendorff preparations of rabbit heart.

Single doses of a methanolic extract (2.09% total glucoiridoids/1.70% harpagoside) or harpagoside were administered either orally or intraperitoneally to conscious normotensive rats (5 per group). By *i.p*. route, the extract was administered from 25 to 100 mg/kg and harpagoside at 5 and 10 mg/kg. By oral route, the extract was administered from 100 to 400 mg/kg and harpagoside at 20 and 30 mg/kg. Controls received water in the same experimental conditions. Sixty minutes after these administrations (30 minutes for *i.p.* route), anesthetized rats were injected a pro-arythmogenic drug (either aconitine, $CaCl_2$ or epinephrine-chloroform) by *i.v.* route.
A dose-dependent bradycardic effect was reported after *Harpagophytum procumbens* administration. At higher dose-levels (300-400 mg/kg oral and 75-100 mg *i.p.*), the effect became significant 30 and 15 minutes after the administration of the extract, by oral and *i.p*. routes respectively. It lasted up to 120 minutes. ECG records also showed P-wave changes (decreased voltage and long-lasting increased) at these higher dose-levels. Moreover, a dose-dependant reduction of arterial blood pressure was noted. Significant responses were obtained 15 minutes after an oral dose of 400 mg/kg and *i.p.* doses of 50 and 100 mg/kg. This hypotensive effect lasted 75 minutes. In experiments conducted with harpagoside, the same effect on arterial blood pressure was noted by both routes of administration, and was more long-lasting compared to the extract. However, the intensity of the effect is lower, compared to the extract containing corresponding quantities of harpagoside. A protective effect of the extract against chemically-induced arrhythmias was observed from 300 mg/kg oral and 25 mg/kg *i.p*. doses. With harpagoside, a protective effect was reported too, but its intensity was lower than that of the extract containing corresponding quantities of harpagoside.

Single doses of either the methanolic extract of *Harpagophytum procumbens*, harpagoside or harpagide, were injected in the coronary circulation of rabbit hearts – Langendorff preparations. Pro-arythmogenic drugs were added before, together with or after.
The results indicate that in this model, *Harpagophytum procumbens* caused a mild positive inotropic effect at lower doses but a marked negative inotropic effect at higher dose, with a concomitant decrease in coronary flow. A mild decrease in heart rate was also reported. In the same model, the negative chronotropic and positive inotropic effects of harpagoside were comparatively higher than that of the extract. Harpagide had slight negative chronotropic and considerable negative inotropic effects. A protective effect of the extract against chemically-induced arrhythmias was observed.

From this study, it is concluded that the extract of *Harpagophytum procumbens* might interfere with penetration of calcium into the myocardial cells – protection against arrhytmias induced by calcium chloride. This could explain the anti-arrhythmic effects reported in this study, in two animal models [**Circosta *et al.* 1984**].

- Effects on hyperkinetic ventricular arrhythmias (HVA) by reperfusion [de Pasquale *et al.* 1985]

A methanolic extract of *Harpagophytum procumbens* (2.09% total glucoiridoids/1.70% harpagoside) was evaluated for its protective potential against ischemic reperfusion-induced HVA in Langendorff preparations of rat heart.

Isolated rat hearts were perfused by Langedorff method up to stabilization of ECG. Then, the coronary flow was reduced to provoke an ischemic perfusion. After 30 minutes, the perfusion was brought to basal conditions. In the same time, the extract and harpagoside were added to the perfusion medium through a cannula connected to the aorta. Seven rat hearts per dose-level were used.

In control hearts, polytope extrasystoles occurred 1 minute after the reperfusion. One minute later (2^{nd} minute of reperfusion), ventricular tachycardia occurred. The treatment with *Harpagophytum*

procumbens extract reduced the HVA observed in control animals from 1 mg (= 0.085 mg harpagoside) but this protective effect was improved at the dose of 2 mg. With harpagoside, a protective effect was reported too, at 0.170 mg. However, its intensity was lower than that of the extract containing corresponding quantities of harpagoside (2 mg of extract).

The methanolic extract (2 mg) and harpagoside (0.170 mg) impeded the insurgence of hyperkinetic arrhythmia set off by 100 µg digitoxin, limiting this latter's toxic effects to disturbances of conduction and of the repolarisation phase. It is hypothesized by the authors that *Harpagophytum procumbens* might inhibit HVA due to a verapamil-like mechanism (calcium antagonistic effect) [**de Pasquale *et al.* 1985**].

Assessor's comments

These studies were conducted in the same laboratory and most of their authors took part in both studies. Therefore, the methanolic extracts used, containing the same amount of total glucoiridoids and harpagoside, are supposed to be identical.
This methanolic extract of Harpagophytum procumbens exerts hypotensive and bradycardic effects in conscious rats. In isolated rabbit heart a marked negative inotropic effect with a concomitant decrease in coronary flow was reported at the higher dose tested. Moreover, this extract had a protective effect against chemically-induced arrhythmia in conscious rats and in isolated rabbit hearts, and against HVA induced by reperfusion in isolated rat hearts. The effects were observed with harpagoside, but their magnitude was lower than that of the extract containing corresponding quantities of harpagoside. This suggests that harpagoside is not the unique active substance in the extract of Harpagophytum procumbens, as previously underlined in various primary pharmacodynamics studies.
From the results of these studies, it is also concluded that Harpagophytum procumbens could have a verapamil-like mechanism on calcium currents. Therefore, caution should be taken and Harpagophytum procumbens should not be administered to patients affected by cardiovascular disorders.

In summary:

- Decreased heart rate and arterial blood pressure were reported in exposed conscious rats, and marked negative inotropic effect with a concomitant decrease in coronary flow was noted in a model of isolated rabbit heart. The authors hypothesized that it might have a verapamil-like effect on calcium currents.

- The potential of Harpagophytum procumbens to induce QT prolongation is unknown.

- Potential pharmacodynamic interactions have not been investigated.

- Therefore, Harpagophytum procumbens should not be administered to patients affected by or treated for cardiovascular disorders.

II.2.3 PHARMACOKINETICS

Van Haelen conducted *in vitro* studies with harpagoside and harpagide to obtain the corresponding genin resulting form acid hydrolysis (harpagogenin). Optimal conditions were: pH 2 and 6 hours incubation in a saturated butanol-1 aqueous solution. Those conditions were chosen to mimic the physico-chemical conditions found in the stomach. The author reports that harpagogenin has not been isolated *in vivo* probably because of its high reactivity and of its high protein-binding rate [**van Haelen 1983**].

Another study was performed to study the metabolism of 3 iridoid glycosids from *Harpagophytum procumbens* by human intestinal bacteria: harpagoside, harpagide and 8-o-p-coumaroylharpagide.
Those iridoids were incubated aerobically at 37°C for 24 hours with either almond β-glucosidase or a bacterial mixture from human faeces (18 strains). In these two tests, aucubinine B was obtained from

the 3 iridoids, the amount recovered being higher with human intestinal bacteria than with β-glucosidase. Seventeen of the 18 bacterial strains were involved in this reaction. Furthermore, the highest formation rate was observed with harpagoside, as 12.5% harpagoside were converted to aucubinine B by human bacterial mixture [**Baghdikian *et al.* 1999**].

Assessor's comments

Information about the pharmacokinetics of Harpagophytum procumbens is scarce. In vitro studies showed that harpagoside and harpagide can be transformed into harpagogenin in physico-chemical conditions mimicking those found in the stomach. However, harpagogenin has not been isolated in vivo, so that the relevance of this data remains uncertain. In a in vitro second study, harpagoside, harpagide and another iridoid (8-o-p-coumaroylharpagide) were metabolised to aucubinine B by a bacterial mixture from human faeces. However, previous studies have shown that harpagoside could be denatured in the stomach. As this transformation of iridoids to aucubinine B has not been shown in vivo, the relevance of this data remains uncertain too.

In summary:

- The pharmacokinetic profile of Harpagophytum procumbens or its main constituents has not been established.

- In particular, the outcome of the gastric passage could be of interest as pharmacodynamics studies have shown that Harpagophytum procumbens extract exerts anti-inflammatory and analgesic activities by i.p. route, but not after oral administration.

II.2.4 TOXICOLOGY

II.2.4.1 Single-dose toxicity

The acute oral LD_0 and intravenous LD_0 in mice of aqueous, methanolic and butanolic extracts of *Harpagophytum procumbens* were greater than 4.6 g/kg and 1.0 g/kg, respectively. A purified extract containing 85% harpagoside showed an acute oral LD_0 greater than 4.6 g/kg and acute and LD_{50} of 395 mg/kg and 511 mg/kg, respectively [**Erdös *et al.* 1978**]. The intraperitoneal LD_{50} of harpagoside in mice amounted to 1 g/kg, whereas the LD_{50} of harpagide was greater than 3.2 g/kg in the same conditions [**van Haelen 1983**].

In another study, the LD_0 of an extract of *Harpagophytum procumbens* was superior to 13.5 g/kg. However, the mode of extraction was not described by the authors [**Whitehouse *et al.* 1983**].

Assessor's comments

Oral LD_0 of Harpagophytum procumbens were determined in mice with extracts obtained by various modes of extraction. The results show that their acute toxicity in mice is low.

II.2.4.2 Repeated-dose toxicity

In male Wistar rats, no significant haematological or gross pathological findings were evident following 21 days of sub-acute oral treatment with 7.5 g/kg of *Harpagophytum procumbens*. No hepatotoxic effects were observed with respect to liver weight or levels of microsomal protein and six liver enzymes after 7 days of oral treatment with 2 g/kg [**Whitehouse *et al.* 1983**].

Assessor's comments

The relevance of this study remains uncertain. Indeed, it is briefly described in the publication of Whitehouse et al. 1983. *The aim of this paper was to report studies exploring the anti-inflammatory activity of Harpagophytum procumbens. Therefore, very few details are given about the 21- and 7- day toxicity studies. The nature of the extracts, the materials and methods, and detailed results of this study are not described. Therefore, no conclusion can be drawn from these data.*

II.2.4.3 Genotoxicity

No data.

II 2.4.4 Carcinogenicity

No data.

II 2.4.5 Reproduction toxicity

No data.

II.2.4.6 Local tolerance

No data.

II.2.4.7 Other studies

No data.

Assessor's comments on toxicology

Harpagophytum procumbens has a low toxic potential after a single administration in mice. However, its toxicological profile after repeated administrations is not established, as studies are lacking. Moreover, its genotoxic potential has not been investigated and its toxic potential to reproduction has not been studied.
Therefore, in view of the toxicological data available, the safety of Harpagophytum procumbens in human is not guaranteed.

II.2.5 ASSESSOR'S OVERALL CONCLUSIONS ON NON-CLINICAL DATA

Harpagophytum procumbens is claimed to exert analgesic and anti-inflammatory activities in humans. Several pharmacodynamics studies were performed in animals to support these assumptions.
In the writhing test, *Harpagophytum procumbens* showed peripheral analgesic properties after intraperitoneal administration. Unfortunately, similar studies were not performed by the oral route.
In various animal models of inflammation (carrageenan-induced rat paw oedema, adjuvant-induced arthritis), *Harpagophytum procumbens* showed anti-inflammatory properties when administered by intraperitoneal route only. However, this activity was abolished in the same models after oral administration. The inefficacy of *Harpagophytum procumbens* by oral route is amazing. Some authors have hypothesized that this discrepancy could result from the gastric passage of the extract. Indeed, the acid treatment of an extract, whose aims was to mimic the physico-chemical conditions found in the stomach, was reported to abolish its anti-inflammatory activity previously reported by *i.p*. route. Other authors reported that the same extract protected rats against carrageenan-induced paw oedema when given intraperitoneally or intraduodenally, but not orally.
Most of these studies included the testing of the supposed active substances of *Harpagophytum procumbens*, harpagoside or harpagide. Harpagoside exerted a peripheral analgesic activity (*i.p.* route) at a dose level representing twice the harpagoside dose contained in the dose of extract needed to obtain a maximal analgesic effect. Therefore, the authors concluded that other substances are involved in the analgesic activity of *Harpagophytum procumbens*. In the carrageenan-induced paw oedema model, harpagoside administered either orally to mice or intraperitoneally to rats did not prevent the inflammation produced by the injection of the phlogistic agent. Moreover, it did not exert any anti-

inflammatory effect when tested in the TPA-induced mouse ear oedema model. Some anti-inflammatory effects were reported for harpagoside and harpagogenin in the granuloma pouch test performed in rats, after intraperitoneal administration.

Several *in vitro* and *in vivo* studies were conducted to investigate, on a mechanistic basis, the analgesic and anti-inflammatory activities of *Harpagophytum procumbens*. Two studies showed that *Harpagophytum procumbens* can interfere with arachidonic acid metabolism by acting on the COX-2 mRNA expression. One was conducted in vitro and the other *in vivo* after cutaneous application. A LPS-free aqueous ethanolic extract of *Harpagophytum procumbens* prevented the *in vitro* release of TNF-α from human monocytes. In the same experimental conditions, harpagide and harpagoside did not exert any activity. In addition, an ethanolic extract administered to rats by intraperitoneal route exerted an anti-oxidant activity after 7 and 14 days of treatment. This result is not consistent those of a previous study, which showed that an orally administered suspension of *Harpagophytum procumbens* did not induce any anti-oxidant activity 5 days after adriamycine injection.

Studies conducted with a methanolic extract have shown that *Harpagophytum procumbens* could have a verapamil-like mechanism on calcium currents.

Scarce information is available on the pharmacokinetics and toxicology of *Harpagophytum procumbens*.

Therefore, the assessor's current opinion on the subject is:

1. **Toxicological data available do not guarantee the safety of *Harpagophytum procumbens* in humans. In particular, adequately conducted repeated-dose toxicity studies, genotoxicity studies and reproduction toxicity studies are lacking.**
2. **Decreased heart rate and arterial blood pressure were reported in exposed conscious rats, and a marked negative inotropic effect with a concomitant decrease in coronary flow was noted in a model of isolated rabbit heart. It has been hypothesized that *Harpagophytum procumbens* might have a verapamil-like effect on calcium currents. Its influence on QT prolongation remains unknown and potential pharmacological interactions have not been investigated. Therefore, it may be relevant to include a warning for patients affected by or treated for cardiovascular disorders especially with drugs known to prolong QT interval.**
3. Available studies were performed with extracts differing in their mode of preparation, qualitative and quantitative composition. Extracts are not adequately standardised.
4. *Harpagophytum procumbens* has been shown to possess peripheral analgesic and anti-inflammatory properties after intraperitoneal administration. However, effective dose (*i.p*. route) differs from one study to another and is not accurately defined.
5. When administered intraperitoneally, harpagoside exerted analgesic effects at high-dose levels. The results concerning its anti-inflammatory properties are conflicting. Various authors suggested that other substances present in the extract are involved in its claimed activities. However, these compounds are not identified.
6. Neither *Harpagophytum procumbens*, nor harpagoside, possessed any analgesic or anti-inflammatory activity by oral route in animal models of inflammation. It seems that the gastric passage inactivates some compounds present in the extract. However, pharmacokinetic data are lacking and the influence of the gastric passage on *Harpagophytum procumbens* activity is not clarified.
7. The ability of *Harpagophytum procumbens* to potentiate adjuvant arthritis in a manner similar to that seen with levamisole and penicillamine should be taken into consideration **[McLeod *et al.*, 1979**].
8. Mechanistic studies were performed with aqueous, aqueous alcoholic or alcoholic extracts of *Harpagophytum procumbens*. As the qualitative and quantitative composition of the extracts differs according to the extraction process, the relevance of these data is uncertain. For example,

although a crude ethanolic extract exerted anti-inflammatory activity by inhibiting LPS-stimulated release of Cys-LT and TXB2 *in vitro*, a fraction of this extract had the opposite effect.

II.3 CLINICAL DATA

II.3.1 CLINICAL EXPERIENCE

The assessment is based on the documentation provided by the European Scientific Cooperative on Phytotherapy (ESCOP) and the Association of the European Self-Medication Industry (AESGP).
Different kind of preparations of *Harpagophytum procumbens* were traditionally used for the treatment of various diseases, mostly musculoskeletal complaints. *Harpagophytum* products were various: powder, aqueous and ethanolic extracts.

The monograph of the ESCOP recommends *Harpagophytum procumbens* preparation for painful osteoarthritis and low back pain. The assessment is therefore focused on the potential effectiveness of *Harpagophytum* products in both pathologies. No other rheumatic disease has been examined.
For *Harpagophytum* products, the ESCOP monograph recommends that the daily dose should contain up to 100 mg of the coactive constituent harpagoside, twice the dose recommended by the German Monograph.

Based on the empirical recommendations of the ESCOP monograph for *Harpagophytum* clinical use, study selection was made in the field of osteoarthritis and low back pain. In order to establish a sufficient scientific basis, clinical trials should met criteria of randomisation. For safety, open label studies are acceptable.
For a well-established concept, herbal medicine must do embracing the formalities and the technicalities of the current "state of the art" for these pathologies. The chosen bibliographical documentation is therefore focused on clinical trials in recent years (last past decade).

II.3.2 ASSESSMENT OF EFFICACY AND SAFETY

II.3.2.1 Dose finding studies

The recommended daily dose of harpagoside is not supported by clinical evidence.
According to the provided literature references, no dose-finding studies have been conducted in the treatment of osteoarthritis or low back pain. The choice of daily doses of *Harpagophytum*/harpagoside is mainly empirical.
It should be mentioned that a detailed clinical trial by Chrubasik *et al.* 1999 compares two doses of *Harpagophytum* (600 mg and 1200 mg, containing 50 and 100 mg of harpagoside, respectively) but no conclusion about a dose related effect resulted.

II.3.2.2 Randomised Controlled clinical trials

Effectiveness of *Harpagophytum procumbens* in treatment of acute low back pain.[Chrubasik *et al.* 1996]

This trial can be considered as a starting point in the assessment of the efficacy of *Harpagophytum* in patients with low back pain and it was a four-week randomised double-blind study. Patients between 18 and 75 years of age were recruited when they had experienced at least six months of low back pain that could not be attributed to identifiable causes. 118 patients were randomised in the treatment and placebo groups. Patients in the treatment group received two tablets of *Harpagophytum* 400 mg, three times daily, corresponding to harpagoside consumption of 50 mg.
The only rescue medication allowed was tramadol. In fact, cumulative requirements for tramadol, over the last three weeks of the study period, were taken as the principal outcome measure of efficacy. Secondary end-points, were the number of pain-free patients and global assessment with the Arhus low back pain index.

No difference was observed in the analgesic rescue medication sparing measurement between placebo and treatment groups. A greater number of pain-free patients were observed in the treatment group, than in placebo group but that difference did not show statistical significance.
Overall, negative clinical results as compared to placebo were observed in this clinical study.
The conclusion of the authors, was the need of further clinical trials. Future studies may also assess the effect of dose in order to obtain clinical dose-response if applicable.

Effectiveness of *Harpagophytum* extract WS 1531 in the treatment of exacerbation of low back pain: a randomised, placebo-controlled, double-blind study. [Chrubasik *et al.* 1999]

This second trial is in direct line with the previous one. The design of the study is identical, but two doses of *Harpagophytum* (600 and 1200 mg daily containing 50 and 100 mg of harpagoside, respectively) were assessed *versus* placebo. The principal outcome measure was the proportion of patients free of pain, without rescue medication (tramadol) for at least 5 days, in the fourth week. Secondary outcome measure use Arhus Index to assess pain and functional disability. Of the 197 included patients, 183 completed the trial.
The number of patients free of pain in the last week of treatment (primary analysis) was small. A greater number of responders was significantly observed ($p = 0.027$) in the treatment groups (9% and 15% for 600 mg and 1200 mg respectively) than in the placebo group (5%) However, inconsistency in the direction of any dose related effect was observed between primary and secondary analyses, in particular for the pain component. Stratification tends to indicate that only some subgroups (shorter exacerbations, less pain, no radiation) could be improved by the treatment. Due to the contradictory results, no clear conclusion could be drawn regarding the efficacy of *Harpagophytum* in the treatment of low back pain.

Efficacy and tolerance of *Harpagophytum procumbens* versus Diacerhein in treatment of osteoarthritis. [Chantre *et al.* 2000]

***Harpagophytum procumbens* in the treatment of knee and hip osteoarthritis. Four-month results of a prospective, multicenter, double-blind trial versus Diacerhein. [Leblan *et al.* 2000]**

A four month clinical trial, published two times in different journals but in similar terms, assessed the efficacy of *Harpagophytum* in the symptomatic treatment of osteoarthritis. This was a double blind, randomised, parallel group, multicentre trial. Patients were recruited with radiologically proven osteoarthritis of the knee or the hip; the clinical criteria of the activity of the disease was a spontaneous pain of at least 50 mm on a 100 mm Visual Analogue Scale (VAS). The Lequesne Index was also used to assess activity.
The clinical study compared the efficacy of *Harpagophytum* capsule (435 mg of powder containing 50 mg of harpagoside) to another active medication, diacerrhein, considered as a symptomatic slow acting drug for osteoarthritis. There was no placebo group. Rescue medications allowed were acetaminophen associated with caffeine and, if response was inadequate, diclofenac.
Primary efficacy endpoint was defined by the level of spontaneous pain using VAS. Primary analysis was to demonstrate the non-inferiority of both treatments after 4 months of treatment.
Lequesne Index, functional disability of movement assessed on a VAS, amount of taken rescue medication were used as secondary efficacy endpoints. Overall 122 patients were randomised and 92 patients completed the trial in accordance with the protocol. No differences were found between both treatment in terms of pain relief and algo-functional parameters. The relevance of this clinical trial is nevertheless very limited; the absence of a placebo group is questionable as it is necessary for the design of a non-inferiority study and all the more regrettable as diacerrhein is not a reference drug in the treatment of osteoarthritis.

A randomised double-blind pilot study comparing Doloteffin® and Vioxx® in the treatment of low back pain. [Chrubasik *et al.* 2003]

A 1-year follow-up after a pilot study with Doloteffin® for low back pain [Chrubasik *et al.* 2005]

The initial clinical trial is a double-blind study comparing an aqueous extract of *Harpagophytum* (containing 60 mg of harpagoside) and rofecoxib (12.5 mg per day) in the symptomatic treatment of chronic low back pain. The aim of the exploratory study was to estimate effect sizes for a number of outcome measures (number of pain-free patients, decrease in averaged daily pain score, percentage change from baseline in Arhus Low Back Pain index, requirement for rescue medication, etc.). Patients were recruited when they had experienced at least six months of low back pain that could not be attributed to identifiable causes and with current exacerbation that had lasted for at least 8 weeks. A score of 5 out of 10 on a visual analogue scale was needed. Patients were allowed to take tramadol as a rescue medication up to 400 mg per day. 88 patients were randomised in the two groups of treatment. There was no placebo group. The number of pain-free patients without taking rescue medication increased progressively during the course of treatment and more or less in both groups.
No statistically significant difference was observed between the two treatments neither for pain-free patients, nor for Arhus Low Back Pain and Health Assessment Questionnaire.
The interest for this clinical trial is very limited, in particular for efficacy assessment. The absence of a placebo group is questionable as for the choice of active comparator. Rofecoxib can not be considered as a reference in the treatment of chronic low back pain. In the European Union, rofecoxib was principally indicated for symptomatic relief in osteoarthritis and rheumatoid arthritis, and for some countries in the relief of pain and the treatment of dysmenorrhoea. Furthermore, the number of patients was small. No definitive clinical conclusions can be drawn from this study.

Remaining patients from the pilot study (79 of the initial 88 patients) were invited to participate in a follow-up study. The aim of the study was to assess the long-term effectiveness and safety of a one-year treatment with the aqueous extract of *Harpagohytum*. 73 patients were included in the trial. The clinical measures to be evaluated were the Arhus Index and Health Assessment Questionnaire. The tolerability of the treatment was assessed with a verbal rating scale. Any additional analgesic treatment was allowed. A total of 30 patients dropped out before the 54 weeks of the follow-up study. Thirteen did so because of insufficient pain relief. As stated previously, the small number of patients and the open design of the study preclude any conclusion on the efficacy and safety of *Harpagophytum.*

A randomised, active-controlled, mono-centric study of the herbal drug Devil's claw (*Harpagophytum procumbens*) (ALLYA® tablets), Voltaren® and Vioxx® indicates equal efficacy in the treatment of patients with unspecific lumbar pain.
[Lienert A *et al.* 2005]

There is only a meeting abstract of the 54th annual conference of the north German orthopaedic organisation available with poor information. This study does not seem to have been published. The authors themselves conclude to an equivalent efficacy of the three treatments (ethanolic extract of devil's claw, Voltaren, Vioxx), but small sample size and data variability make a definitive interpretation difficult. Furthermore, it is not sure whether the North American Spine Society (NASS) Instrument (German version) is valid to show change for the factor "impairment" for a study duration of six weeks.

A stepweise scheme in coxarthrosis: Double-blind study with *Harpagophytum*.
[Frerick *et al.* 2001]

In this randomised double-blind study in a group of 46 patients with activated coxarthrosis, the successive reduction of an ibuprofen dose of 400 mg twice daily was investigated over a period of 20 weeks, under the concomitant treatment with either *Harpagophytum* extract Lo-Har-45 (flexi-loges) or placebo. The WOMAC (Western Ontario and McMaster Universities) Arthrosis Index fell from a score of 5.01 to 3.61 in the *Harpagophytum* group and from 4.39 to 3.31 in the placebo group. An increase in pain score by a maximum of 20% in the period without ibuprofen (which was

regarded as a clinically relevant response) was fulfilled by 70.8% of patients of the *Harpagophytum* group, but by only 40.9% of patients in the placebo group. This paper gives some suggestions on a possible mild therapeutic effect of *Harpagophytum* in coxarthrosis patients, however the low number of patients (22 to 24 per group) and the study design in which *Harpagophytum* was given just as an add-on therapy to decreasing doses of ibuprofen precludes further conclusions on the proof of clinical efficacy.

II.3.2.3 Open Studies

Efficacy and tolerance of *Harpagophytum* Extract LI 174 in patients with chronic non-radicular back pain [Laudahn and Walper, 2001]

This open-label, multicentre study was to assess the clinical effectiveness and safety of *Harpagophytum* extract on a period of 8 weeks. This was a non comparative trial – there was no placebo or standard medication group to compare with. Patients were recruited with lumbar pain at rest and on motion over a period of at least 6 months. Rescue medication in the form of acetaminophen was allowed for the first 4 weeks. Multidimensional Pain Scale and Arhus Back Pain Index were used as outcome clinical measure. Pain and mobility improvement were observed during the overall period of the study. This trial could only be supportive for safety due to its open design. As mentioned by the authors, further rigorous studies (i.e. against placebo, active treatment) will be needed to clarify the therapeutic value of *Harpagophytum* for chronic back pain patients.

Comparison of outcome measures during treatment with the proprietary *Harpagophytum* Extract Doloteffin® in patients with pain in the lower back, knee or hip. [Chrubasik *et al.* 2002]

This open study was conducted to examine various outcome measures of effect during treatment with aqueous extract of *Harpagophytum* (containing 60 mg of harpagoside). Patients were recruited on the basis of non specific low back pain or osteoarthritic pain in the knee or hip with current exacerbations, requiring at least 8 weeks of symptomatic treatment. Patients were allowed to continue their concomitant treatments and to supplement *Harpagophytum* with other analgesics as necessary.
Assessment of pain and disability included established instruments (Arhus Low Back Pain Index, WOMAC,) and other non-validated measures. This trial could only be supportive for safety due to its open design. The effectiveness of the herbal product was not the primary endpoint of the study.

***Harpagophytum*-Extrakt LI 174 (Teufelskralle) bei der Behandlung unspezifischer Rûckenschmerzen. [Göbel *et al.* 2001]**

The study population was an inhomogeneous group. Subpopulations were not evaluated. The results show a significant improvement of muscle pain in the verum group in comparison to the placebo group, but the results of the placebo group are not in accordance with other references and therefore these results seem to be doubtful. In summary, the study is insufficient to prove the efficacy of devil's claw (ethanolic extract) in the treatment of low back pain.

Therapie der unspezifischen Lumbalgie mit Teufelskrallenwurzelextrakt – Ergebnisse einer klinischen Studie. Effectiveness of *Harpagophytum procumbens* in treatment of unspecific low back pain. [Schmidt *et al.* 2005]

This open prospective study shows no significant advantage of a mono therapy or a combination therapy of *Harpagophytum procumbens* (ethanolic extract) with conventional therapy. Without further information these data are insufficient to support a well-established indication like unspecific low back pain.

Treatment of patients with arthrosis of hip or knee with an aqueous extract of Devil's Claw (*Harpagophytum procumbens* DC).[Wegener and Lüpke 2003]

The aim of this open study is to assess the efficacy of a coated tablet containing 400 mg of an aqueous extract in the osteoarthritis of the knee or hip. However, the results of this study can not support a well- established indication.

Patient-perceived benefit during one year of treatment with Doloteffin [Chrubasik *et al.* 2007]

This open study was conducted to examine various outcome measures of effect during treatment with aqueous extract of *Harpagophytum* (containing a daily dose of 60 mg of harpagoside). 114 patients were recruited on the basis of non-specific low back pain or osteoarthritic pain in the knee or hip. All patients received four-week prescriptions of Doloteffin renewable at four-weekly assessment visits until week 12, and then at six-weekly intervals for up to 54 weeks. Six 400 mg tablets of Doloteffin per day contain a total of 2400 mg of aqueous extract of *Harpagophytum procumbens*. This is equivalent to 4.5 g of crude drug per day (1.5-2.5:1). Patients were allowed to supplement *Harpagophytum* with other analgesics as necessary. Initially, and at each subsequent visit, the assessments consisted of a series of established and non-validated measures. Of the 15 patients that dropped out, 9 did so because of insufficient pain relief. About a third of the 114 patients used additional analgesic medications.
This trial could only be supportive of safety due to its open design. As there was no placebo control group, the documented improvements cannot be attributed confidently to the designated treatment Doloteffin.

Rivoltan (Li 174) zur Behandlung von Patienten mit degenerativen Erkrankungen des Bewegungsapparates [Engel 2000]

This open study was conducted to assess the clinical effectiveness and safety of *Harpagophythum* extract (480 mg twice/day) on a period of 6 weeks.
Patients with degenerative disease of the musculoskeletal system were recruited. Rescue medications (analgesics) and physical therapies were allowed. Pain and mobility improvement were observed during the overall period of the study.
This study could only be supportive for safety due to its open design and absence of control group.

***Harpagophytum procumbens* ist effizient bei degenerativen Erkrankungen des Bewegungsapparates [Müller *et al.* 2000]**

This open prospective study aimed to assess the clinical effectiveness of *Harpagophythum* extract (400 mg 3 times/day) on a period of 4 weeks.
Patients with non acute diseases of the musculoskeletal system were enrolled.
An average improvement of symptoms was reported to be 45% but only minor anti-oedematous and anti-inflammatory effects were found. The ratio of adverse events was reported to be 0.9% and 5 patients suffered from severe adverse effects (abdominal symptoms).
This open study with no control group is insufficient to prove the efficacy of *Harpagophytum* extract.

Behandlung chronisch aktivierter Schmerzen am Bewegungsapparat [Ribbat and. Schakau 2001]

The study population was an inhomogeneous group. The results of the treatment (480 mg of *Harpagophytum* dry extract once or twice/day up to 8 weeks) show an improvement in the examined parameters of all symptoms. Five treatments were stopped because of adverse events.
This open study is insufficient to prove the efficacy of *Harpagophytum* extract due to the absence of a control group and to the subjective estimation of the degree of the pain and of the efficacy by the patients and the physicians.

Arthrose-Therapie: Verträglich geht es auch [Schendel 2001]

This open prospective study was conducted with patients suffering from arthrosis of the knee or the hip. A twice daily dose of 480 mg of *Harpagophytum* extract was tested over a period of 8 weeks.

The aim of the study was to examine whether Non-steroidal anti rheumatics (NSAR) can be replaced by *Harpagophytum*.
Therefore patients were told that they will be able to and should reduce or even discontinue the intake of NSAR.
At the end of the study 27.9% of the patients had reduced their daily intake of NSAR while 61.4% of the patients had discontinued the treatment with NSAR. An improvement of 52.5% in the intensity of pain and an improvement of 49.68% in the rigidity was reported.
Six cases of adverse events were reported. No severe adverse events occurred.
This study is not conclusive due to its open design and the absence of a control group.

Analgetische Wirkung eines Teufelskrallenwurzel [Schmelz *et al.* 1997]

This placebo-controlled pilot study was conducted to assess the effectiveness of *Harpagophytum* root (3 times/day equivalent to a 4.92 g daily dose) over a period of 30 days. The results of this study can not support a well-established use due to the three different indications assessed with a small number of patients per group, the lack of statistical interpretation and the assessment of symptoms by patients in a completely subjective way. The authors interpret the outcome of the study as a hint for a possible antiphlogistic and analgesic activity which should be confirmed by further studies.

Wirksamkeit und Wirtschaftlichkeit von Teufelskrallenwurzelextrakt bei Rückenschmerzen: Erste Ergebnisse einer therapeutischen Kohortenstudie [Chrubasik *et al.* 1997]

This open prospective study was conducted to evaluate the effectiveness and economy of *Harpagophytum* extract (equivalent to 30 mg harpagoside/day) in the treatment of acute low back pain.
The results of this study cannot support a well-established medication. The authors state that due to its efficacy and economy the oral administration of *Harpagophytum* extract should gain more importance in the treatment of acute low back pain. They also conclude that however an equivalence study has to be performed to confirm these results.

Review

***Harpagophytum procumbens* for osteoarthritis and low back pain: a systematic review [Gagnier *et al.* 2004]**

The quality of twenty studies of treatment with various *Harpagophytum* products for exacerbations of chronic musculoskeletal pain was examined.
Among the twenty, ten were double-blind, randomised controlled comparisons. The conclusion of this systematic review is that further clinical trials are needed, to properly define the place of *Harpagophytum* preparations in the treatment of osteoarthritis and low back pain. Numerous questions remain on the potential efficacy, the safety (in particular for long-term) and the doses. None of the studies contribute to make categorical recommendation for treatment with *Harpagophytum* products.

II.3.2.4 Other properties

Like other bitter herbals, *Harpagophytum* is used for loss of appetite and mild digestive disorders. Several EU Member States validate such indications for *Harpagophytum* based on the long-standing use. Moreover, the above-mentioned properties are the oldest known in Europe for H*arpagophytum*; its use in articular pain is more recent. The link between bitterness of herbals (including *Harpagophytum*) and their use as appetite stimulating agent and to relieve digestive disorders is described in several references in literature [**Hänsel *et al.* 1993**; **Zimmerman**, **1976**; **Schilcher H 1999**; **Braun and Frohne 1987**; **Czygan 1987**; **Bisset 1994**; **Weiss 1991**].

II.3.3 OVERALL CONCLUSION ON CLINICAL DATA

There is not sufficient evidence of any consistent clinically relevant effect, especially pain relief, as can be judged from selected studies. The provided evidence of efficacy and safety in osteoarthritis and

low back pain is thus insufficient to implement marketing authorisations for a well-established use for *Harpagophytum* products.
Despite the lack of adequately conducted toxicological studies the safety of the use of *Harpagophytum* products is, however, reassuring based on safety data in the clinical trials and lack of serious signals on pharmacovigilance. No clear conclusion of efficacy in osteoarthritis and low back pain can be drawn from the varying doses and kind of *Harpagophytum* extract.

This is based on the following considerations:

- The numbers of patients included in randomised clinical trials were too small for any definitive conclusion about clinical significant efficacy in the treatment of osteoarthritis or low back pain and the safety.
- The studied populations and the chosen endpoints are variable from one study to another, which makes comparison difficult. Endpoints are generally not in line with those used at present time for assessing clinical efficacy in the treatment of osteoarthritis or low back pain,
- Information on the safety of *Harpagohytum* product is very sparse and limited, in particular for long-term treatment.
- There are inconsistent results when *Harpagohytum* is compared with placebo. For some comparative clinical trials, the absence of placebo group is highly questionable.
- Therapeutic effects are very doubtful as there is no direct comparison between *Harpagophytum* products and the known reference therapy (NSAIDs, acetaminophen) in the symptomatic treatment of osteoarthritis or low back pain.
- Analysis of therapeutic efficacy over time (during the first days/weeks) is not presented, therefore, the onset of response cannot be assessed (all studies). This is especially relevant for the target population that needs rather quick pain relief.
- Proper dose-finding studies are still needed to find the minimal dose required for efficacy.

Based on the requirements given in the clinical guidance for the treatment of osteoarthritis, there is no sufficient scientific basis to recommend a well-established use for *Harpagophytum* products.

II.3.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

During some clinical studies, data on gastric or duodenal side effects have been reported [**Chantre *et al.* 2000**], [**Chrubasik *et al.* 1999**], [**Frerick *et al.* 2001**]. Harpagophyti radix is contraindicated in case of gastric or duodenal ulcer in the British Herbal Compendium, in the ESCOP monograph and by the German Commission E [**Blumenthal *et al.* 2000**].
On the basis of non clinical data, *Harpagophytum* might have a verapamil-like effect on calcium currents. Consequently, a special warning should be included in the corresponding section of the monograph.

II.3.5 DRUG INTERACTIONS

Among clinical data available for *Harpagophytum*, we could not find any study or reported cases suggesting an interaction between *Harpagophytum* and oral anticoagulants, or sulfonylureas for instance.
Harpagophutym was sometimes quoted as part of phytotherapy in general reviews but no specific publications examined its interactive potential so far. Additionally, no signal, even weak, has emerged from the literature to date [**Izzo *et al.* 2005**; **Heck *et al.* 2000**].

II.4. ASSESSOR'S OVERALL CONCLUSIONS

The clinical data are not sufficient to support a well-established use whether it is in low back pain treatment or in osteoarthritis treatment. A monograph for traditional herbal medicinal products is proposed, based on the existing herbal products in the European Countries and the ESCOP monograph.