European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *HARPAGOPHYTUM PROCUMBENS* DC. AND/OR *HARPAGOPHYTUM ZEYHERI* DECNE, RADIX' (EMEA/HMPC/251323/2006)

Table 1: Organisation(s) that commented on the draft 'Community herbal monograph on *Harpagophytum procumbens* D.C. and/or *Harpagophytum zeyheri* Decne, radix' as released for consultation on 10 January 2008 until 15 April 2008.

	Organisation
1	The European Scientific Cooperative on Phytotherapy (ESCOP)
2	The Association of the European Self-Medication Industry (AESGP)
3	Kooperation Phytopharmaka, Germany
4	PhytoLab, Germany
5	Phytopharm Klęka S.A., Poland
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Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT
We appreciate the opportunity to comment on this draft Community Herbal Monograph. In our view, sufficient clinical data are available to qualify certain Harpagophyti radix preparations for the category of Well-established medicinal products, fulfilling the requirements for well-established use defined in the ***Guideline on the assessment of clinical safety and efficacy in the preparation of community herbal monographs*** *for well-established and of community herbal monographs / entries to the community list for traditional herbal medicinal products / substances / preparations* **(EMEA/HMPC/104613/2005)'). Accordingly, this should be reflected in the monograph.** In the following text we endeavour to provide suitable wording for the "well-established use" column, as well as offering comments with respect to the "traditional use" column.
We appreciate the above-mentioned draft document prepared by the Herbal Medicinal Products Committee (HMPC) as it provides harmonised and sound criteria which should facilitate the granting of marketing authorisation of product containing this plant in Europe. However, we consider that some modifications are necessary. As outlined in the 'Guideline on the Assessment of Clinical Safety and Efficacy in the Preparation of Community Herbal Monographs for well-established and of Community Herbal Monographs/Entries to the Community List for Traditional Herbal Medicinal Products/Substances/Preparations' (EMEA/HMPC/104613/2005), *"…the results of pre-clinical tests or clinical trials are not required if it can be demonstrated that the active substances of the herbal medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety …"* In the following, the guideline mentions *"factors which have to be taken into account in order to establish a well-established medicinal use"*. For defined preparations of Devil's claw root, these requirements are fulfilled, for the following reasons: • The time over which a substance has been used: Devil's claw root extracts/preparations have been used since the early 1960's. • Quantitative aspects of the use of the substance: Data on the amounts of herbal drug and herbal drug preparations brought into the market are available. • The degree of scientific interest in the use of the active substance: This is reflected in the published scientific literature where a great number of scientific papers on various aspects on Devil's claw are available. • The coherence of scientific assessments: This requirement is also fulfilled because most authors support and/or recommend the medicinal use.

Moreover, the guideline clearly states that *"with respect to the provisions on 'well-established medicinal use' it is in particular necessary to clarify that 'bibliographic reference' to other sources of evidence such as post marketing studies, epidemiological studies, appropriate monographs, etc. and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a herbal medicinal product if the use of these sources of information is satisfactorily explained and justified"*.

Chapter 4.1 mentions that *"In addition to published controlled clinical trials, the assessment of safety and of efficacy may be based on non-controlled clinical studies, epidemiological studies such as cohort or observational studies, etc."* Clinical data available for Devil's claw root products are considered sufficient to support the application of some of them as well-established use products, with respect to the definition on page 7 of this guideline: *"In general, at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy."*

Most of the studies had been conducted in Germany. Most of the reported controlled clinical studies were conducted according to the GCP guidelines and most of the reported open studies were conducted according to the guidance of the German Medicines Law (section 67 para 6) as well as according to the published recommendations of the BfArM (1998) and the German Society of Phytotherapy (Kraft et al. 1997, Wegener et al. 2003). Therefore, most of these studies have been planned and conducted according to modern requirements and are of "good quality". From our point of view, a level of evidence Ib is justified. As examples, we would like to mention the studies of Chrubasik 1999, Chrubasik 2003 and Wegener 2003 for the aqueous extract and the studies of Frerick 2001, Ribbat 2001 and Laudahn 2001 for the extract prepared with ethanol 60%.

In contrast to this, it is stated that *"data relating only to in-vitro pharmacology or general pharmacology in animals will not deliver sufficient supportive evidence to allow a marketing authorisation. Such data may, however, contribute to the plausibility of a "traditional use""* (see page 7 of the mentioned guideline). For traditionally used products *"according to WHO, a "long history of medical use" may be defined"*, which *"… will, in most cases, provide the basis for acceptance of an indication."* As outlined in the enumerative listing on page 9 of the guideline, the basis of acceptance of such an indication relies on *"i) Excerpts from archives of national competent authorities …; ii) A comprehensive literature search…; … iiI) Official expert committee reports or monographs …; iv) A monograph in Ph. Eur. or an official national pharmacopoeia...", and v) Product related documentation..."* Such data is (only) available for those extract preparations which are suggested to be listed for a traditional use (see below).

In conclusion, taking into account the above comments, we recommend the following amendments for the "well-established use" and "traditional use" columns (suggestions for addition appear in light blue).

Well-established use

For these herbal drug preparations sufficient data is available to support the WEU

Dry extract (1.5-2.5 : 1; extraction solvent: **water**)

Referenced by the HMPC

Chrubasik et al. 1996

Chrubasik et al. 1999

Chrubasik et al. 2002

Chrubasik et al. 2003

Chrubasik et al. 2005

Wegener and Lüpke 2003

Not referenced by the HMPC / missing

Chrubasik et al., 1997

Chrubasik et al., 2007

Schmelz und Hämmerle 1997

Müller et al, 2000

Dry extract (4-5 : 1 ; 60% V/V ethanol)

(Note: For reasons of clarity, the DERnative is given in integral numbers, e.g. 4-5:1 covers 4.4-5.0:1 as well)

Referenced by the HMPC

Göbel et al., 1999??2001?

Laudahn 1999?? 2001?

Not referenced by the HMPC / missing

Engel 2000

Schendel 2001

Frerick et al. 2001

Ribbat und Schakau 2001

Traditional use

For these herbal drugs/herbal drug preparations available data support only a use as THMP

Dried powdered root

Referenced by the HMPC

Chantre et al. 2000

Not referenced by the HMPC / missing

Lecomte und Costa 1992 ; Lecomte und Costa 1997 ; Moussard et al., 1992 ; Pinget und Lecomte 1990, ; Pinget und Lecomte 1997

Herbal substance : cut dried tuberous secondary root

Used as an infusion

Referenced by the HMPC

None

Not referenced by the HMPC / missing

Schmidt 1978 ; Schmidt 1983 ; Wilhelmer 1976 ; Zimmermann 1977

Other extracts/studies not listed by the HMPC

Aqueous extract, 2-3:1

Schrüffler 1980 ; Grahame und Robinson 1981 ; Belaiche 1982

Extracts, listed by the HMPC, without any/clinical data (according to available information)

Liquid extract (1 : 1; extraction solvent 30% V/V ethanol)

Soft extract (2.5-4.0 :1 ; extraction solvent 70% V/V ethanol)

Dry extract (5-10 : 1; extraction solvent water)

Dry extract (2-4 : 1; 30% m/m 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)

*This extract covers dry extracts of 2.8-3.4 : 1; extraction solvent 30% V/V ethanol, 1.9-3.4:1 extraction solvent 30% V/V ethanol , 2-3:1 extraction solvent 30% V/ V ethanol and of 2.6-3.1 : 1; 30% m/m ethanol as well

- Parts of the mentioned clinical studies which have already been quoted in the ESCOP monograph have not been taken into account in the HMPC draft monograph. They should be added to the reference list.

We welcome the preparation of the Community herbal monograph on Harpagophyti radix which may contribute to the creation of harmonised assessment criteria for herbal medicinal products in Europe.

The HMPC accepted the use of preparations made from Harpagophyti radix only for a traditional use.

In our opinion, however, some Harpagophyti radix preparations fulfill the requirements for a well - established use as outlined in the guideline EMEA/HMPC/104613/2005 (ON THE ASSESSMENT OF CLINICAL SAFETY AND EFFICACY .
There are published results of clinical controlled and open, uncontrolled clinical trials available demonstrating that some extract preparations have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety. Within the above referenced guideline it is stated, that in addition to controlled clinical trials, the assessment of safety and of efficacy may be based on non-controlled clinical studies,

epidemiological studies such as cohort or observational studies etc. There are several clinical controlled studies, which had been planned and conducted to address specific questions as e.g. to address the mode of action of Harpagophyti radix and to evaluate the efficacy by explorative rather than confirmative methods. However, these studies reflect the interest on the drug in the sense of a well-established medicinal use.

Most data are available from "epidemiological studies such as cohort or observational studies" which had been conducted in Germany under respect of specific regulations for the planning, conducting and reporting of open studies according to the German Drug Law as outlined in the chapter on the methodic particulars. These regulations and recommendations had been published by the Federal Institute for Drugs and Medical Devices (BfArM 1998) as well as by the German Society of Phytotherapy (Kraft et al. 1997, Wegener et al. 2003). These data contribute to the overall documentation of a well-established medicinal use of the specific drug preparations.

We thereforesuggest to include the use of herbal preparations containing an aqueous and aqueous-ethanolic extract for a well-established medicinal as can be justified by clinical studies and bibliographic data.
For this reason, the following amendments are suggested for the table columns "well-established use" and "traditional use" in the draft community herbal monograph.

Propositions for changes are written in bold letters.

References:

- Bundesinstitut für Arzneimittel und Medizinprodukte. Bekanntmachung über die Zulassung und Registrierung von Arzneimitteln. Empfehlungen zur Planung und Durchführung von Anwendungsbeobachtungen. BAnz Nr. 229 vom 04.12.1998.
- Kraft K, Loew D, Schneider B, Kemper FH. Planung, Durchführung und Auswertung von Anwendungsbeobachtungen. Empfehlungen der Gesellschaft für Phytotherapie (GPHY). Arzneim-Forsch/Drug Res 1997; 47: 990-994.
- Wegener T, Schneider B; Working Party of the German Society of Phytotherapy. Proposals to enhance the quality of observational cohort studies. Phytomedicine. 2003; 10: 700-707.

In the present draft released for consultation on 10. January 2008, only the traditional use of *Harpagophyti radix* for relief of minor articular pain or the relief of mild digestive disorders such as bloating and flatulence and loss of appetite is provided, whereas the well-established use of *Harpagophyti radix* is not included in the monograph.

We do not agree with this proposal of the HMPC and strongly believe that a well-established use of *Harpagophyti radix* is justified due to the available clinical data:
Ten studies on the treatment of chronic or exacerbated (low) back pain were published so far (Chrubasik et al. 1996, Chrubasik et al. 1997 cited in ESCOP 2003, Chrubasik et al. 1999, Chrubasik et al. 2002, Chrubasik et al. 2003, Chrubasik et al. 2005, Göbel et al. 2001, Laudahn and Walper 2001, Ribbat and Schakau cited in ESCOP 2003, Schmidt et al. 2005, Stange and Schulze 1997, Pinget and Lecomte 1997 cited in Wegener 2000).
6 studies thereof were randomised, controlled clinical trials. In 2 studies verum controls (diacerhein = diacetylrhein (ART50®) and NSAID standard therapy) were used.
Fourteen studies addressed painful osteoarthritis (Biller 2002, Chantre et al. 2000, Frerick et al. 2001 cited in ESCOP 2003, Grahame and Robinson 1981, Kloker

and Flammersfeld 2003, Wegener 2003, Bélaiche 1982 cited in ESCOP 2003, Guyader 1984 cited in ESCOP 2003, Lecomte and Costa cited in ESCOP 2003, Ribbat and Schakau cited in ESCOP 2003, Schmelz et al. 1997 cited in ESCOP 2003, Schrüffler 1980 cited in ESCOP 2003).
Of these, 7 were randomised, controlled clinical trials. Verum controls were used in 2 of them (rofecoxib, phenylbutazone).

Harpagophytum preparations proved efficacy in the majority of studies. Although not all studies are of good methodological quality, the overall assessment of the efficacy and usefulness of *Harpagophytum* for the treatment of painful rheumatic and arthritic disorders is unanimously acknowledged by the majority of authors and confirmed in various recent reviews (Ernst 2004, Brien et al 2006, Gagnier et al 2007, Gagnier et al. 2004, Grant et al 2006).
Harpagophytum preparations have both immediate (analgesic) and sustained (anti-inflammatory) effects. The sustained efficacy of *Harpagophytum* was systematically investigated by Chrubasik et al. (2005), who performed a one year follow-up trial in patients from a 6-week double-blind controlled study versus rofecoxib (Chrubasik et al. 2003). This study demonstrated that the efficacy of *Harpagophytum* extract is maintained during long-term treatment of acute exacerbations of chronic low back pain and is generally considered to be as powerful as rofecoxib.

A variety of *Harpagophytum* preparations was used in the above-mentioned studies, whereas most studies were conducted either with aqueous extracts (DER 1.5-2.5:1) or 60% V/V ethanolic extracts (DER 4.4-5.0:1).
Harpagophytum preparations were very well tolerated in the clinical trials and post-marketing surveillance studies. The study durations ranged from 4 weeks to up to 1 year. Severe side effects associated with the use of *Harpagophytum* preparations were not reported so far. Mild gastrointestinal symptoms such as diarrhea and nausea as well as allergic reactions may occur particularly in sensitive individuals at higher dosages.

The "well-established use" of *Harpagophyti radix* is further supported by the wide range of herbal medicinal products with *Harpagophytum* extracts that are available on the German market:
4 products thereof contain aqueous extracs of *Harpagophyti radix* with a DER of 1.5-2.5:1 (Bomarthros® Harpagophytum Filmtabletten, Doloteffin® Filmtabletten, Harpagoforte® 375 mg Kapseln, Rheuma-Sern® Kapseln), whereas 11 products with 60% V/V ethanolic extracts (DER 4.4-5.0:1) are available (Cefatec® 480 BT Brausetabletten, Cefatec® 480 FT Filmtabletten, flexi-loges® Filmtabletten, Jucurba® 240 mg Hartkapseln, Jucurba® forte 480 mg Filmtabletten, PASCOE®-Agil 240 mg Filmtabletten, Rivoltan® Teufelskralle 480 mg Filmtabletten, Teltonal® 480 FT Filmtabletten, Teltonal® dispers Brausetabletten, TEUFELSKRALLE-ratiopharm® Filmtabletten, Teufelskralle STADA® 480 mg Filmtabletten).
In contrast to the therapeutical alternatives in the respective indications (mainly NSAIDs) which are known to possess considerable gastrointestinal side effects, *Harpagophytum* preparations can be used over a long-term period without a noteworthy safety risk which is particularly important for the treatment of osteoarthritic and rheumatic conditions. As mentioned in the respective SPCs (see attachment), *Harpagophytum* preparations can be used until the disappearence of symptoms.
Thus, compared to the therapeutical alternatives such as NSAIDs with their frequent and in part severe side effects, *Harpagophytum* extracts show a comparable efficacy along with a clearly superior safety profile.

Conclusion
Since both the efficacy and safety were convincingly proven in a large number of clinical studies, the well-established use of aqueous extracts (DER 1.5-2.5:1) or 60% V/V ethanolic extracts (DER 4.4-5.0:1) of *Harpagophyti radix* in the indications

- symptomatic treatment of painful osteoarthritic conditions and
- relief of low back pain

should be compulsory included in the Community herbal monograph.

We can not agree with that proposal of the HMPC and its approach to Devil 's claw root as a traditional herbal substance and herbal preparations only. Please take into consideration a well-established use of *Harpagophyti radix* what is justified by "recognized efficacy and an acceptable level of safety... " (EMEA/HMPC /104613/2005) and literature data on many clinical studies (see attached the references). Many of these studies demonstrating safety of treatment over the long-term period comply with modern requirements. Especially aqueous extracts (DER 1.5-2.5) and 60% V/V ethanolic extracts (DER 4.4-5.0) were well tolerated in the clinical trials and post-marketing surveillance studies. Conclusions : Both mentioned extracts should be classified as well-established use due to enough literature data on safety and clinical studies and many examples of medicinal products existing within the Community
Outcome: Not endorsed. None of the references can clearly support a "well-established use" (see Assessment Report)

SPECIFIC COMMENTS ON TEXT		
2. QUALITATIVE AND QUANTITATIVE COMPOSITION		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Traditional use Under ii) Herbal preparations. "Dry extract (4.4-5.0 : 1 : 60% V/V ethanol)" should be deleted as it is only relevant to well-established use. Well-established use The following herbal preparation quilify for **well-established use** category : - Dry extract (1.5-2.5 : 1 ; water) - Dry extract (4.4-5.0 : 1 ; 60% V/V ethanol). **Justifications are provided under 5.1. Pharmacodynamic properties**.	Not endorsed. « well-established use » is not accepted

	With regard to the information on the DER native we would like to suggest taking into consideration the use of integral numbers, e.g. 4-5:1 (which covers e.g. also 4.4-5.0:1), except a DER native of 1.5-2.5:1 which should not be changed in order to maintain the mean value of 2.0 with a defined range. According to the above-referred available data, we believe that the following list of preparations reflects the scientific evidence: Well-established use **With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended** **Herbal preparations** **Dry extract (1.5-2.5 : 1 ; extraction solvent water)** **Dry extract (4-5 : 1 ; extraction solvent 60% V/V ethanol)** New references to support the well-established medicinal use are: Chrubasik et al., 1997 ; Chrubasik et al., 1999 ; Schmelz und Hämmerle, 1997 ; Engel, 2000 ; Schendel, 2001 ; Frerick et al., 2001 ; Ribbat und Schakau, 2001 ; Chrubasik et al., 2007 ; Müller et al, 2000	Not endorsed. « well-established use » is not accepted
	<u>Well-established use</u> For these extract preparations sufficient data are available to support the well-established use: **Dry extract (1.5-2.5 : 1 ; water)** References considered already by the HMPC: Chrubasik et al., 1996, Chrubasik et al. 2002, Chrubasik et al. 2003, Chrubasik et al. 2005, Wegener and Lüpke 2003.	Not endorsed. « well-established use » is not accepted

	Further, so far unconsidered references: Chrubasik et al., 1997, Chrubasik et al., 2007, Schmelz und Hämmerle 1997 (open studies). **Dry extract (4.4-5.0 : 1 ; 60% V/V ethanol)** References considered already by the HMPC: Göbel et al., 1999, Laudahn 1999. Further, so far unconsidered references: Frerick et al. 2001 (controlled study); Engel 2000, Schendel 2001, Ribbat und Schakau 2001 (open studies). Almost all of these studies are available only in German language; the controlled study of Frerick et al. 2001 is summarized below: In this randomised, double-blind study, the effects of the ethanolic extract (1 coated tablet with 480 mg twice daily, DER 4,4-5,0:1, extraction solvent ethanol 60% v/v) were tested for 20 weeks in 46 patients with articular hip pain. Each group received concomitantly, a stepwise-decreasing dose of ibuprofen. For the first 8 weeks, patients received 800 mg ibuprofen daily and Harpagophyti radix extract (n = 24) or placebo (n = 22). For the second 8 week period, ibuprofen was reduced to 400 mg daily and, in the last 4 weeks of study, no ibuprofen was administered. The clinical effects were evaluated using the WOMAC index (Western Ontario and McMaster Universities Arthrose index), a scale of self-assessment of factors such as pain, stiffness and physical mobility. The main criterion for determining responder rate was defined as the percentage of patients who reported an increase in pain in the last 4 weeks of not more than 20 % and did not use more than 10 times the rescue medication (ibuprofen 400 mg) during the last 4 weeks (therapy responders). At the end of study, the responder rates were calculated as 70.8% and 40.9% for Harpagophyti radix extract and placebo (p=0.041) respectively. Significant differences in favour of Harpagophyti radix were also	

	calculated for the decrease of the WOMAC total score (p=0.039), for the difference of the WOMAC total score of week 4 to 12 (p=0.031) and for the subscore of stiffness. All other parameters showed a tendency to improve. Tolerability was considered as good and was comparably well evaluated by physicians and patients in both groups (Frerick et al. 2001). References: • Chrubasik S, Chrubasik C, Kunzel O, Black A. Patient-perceived benefit during one year of treatment with Doloteffin. Phytomedicine 2007; 14: 371-376. • Chrubasik S, Schmidt A, Junck H, Pfisterer M. Wirksamkeit und Wirtschaftlichkeit von Teufelskrallenwurzelextrakt bei Rückenschmerzen: Erste Ergebnisse einer therapeutischen Kohortenstudie. Forsch Komplementärmed 1997; 4: 332 – 336. • Engel S. Rivoltan (Li 174) zur Behandlung von Patienten mit degenerativen Erkrankungen des Bewegungsapparates Dtsch. Apoth. Ztg. 2000, 140, 1369. • Frerick H, Biller A, Schmidt U. Stufenschema bei der Coxarthrose. Doppelblindstudie mit Teufelskralle. Der Kassenarzt 2001; 5: 34-41. • Müller B, Deitelhoff P, Petrowicz O. Harpagophytum procumbens ist effizient bei degenerativen Erkrankungen des Bewegungsapparates. NaturaMed 2000; 15: 21-29. • Ribbat JM, Schakau D. Behandlung chronisch aktivierter Schmerzen am Bewegungsapparat. NaturaMed 2001; 16: 23-30. • Schendel UM. Arthrose-Therapie: Verträglich geht es auch. Studie mit Teufelskrallenextrakt. Der Kassenarzt 2001; 29/30: 36-39. • Schmelz H, Hämmerle HD, Springorum HW. Analgetische Wirksamkeit eines Teufelskrallenwurzel-Extraktes bei verschiedenen chronisch-degenerativen Gelenkerkrankungen. In: Chrubasik S, Wink M (Hrsg.): Rheumatherapie mit	

	Phytopharmaka. Hippokrates, Stuttgart 1997: 86 - 89. In summary, our text proposal is: **<u>Well-established use</u>** **With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended** ***Harpagophytum procumbens* D.C. and / or *Harpagophytum zeyheri* Decne, radix (devil's claw root)** **Herbal preparations** **Dry extract (1.5-2.5 : 1 ; water)** **Dry extract (4.4-5.0 : 1 ; 60% V/V ethanol)** <u>Well-established use</u> ii) Herbal preparations Dry extract (1.5-2.5:1; water) Dry extract (4.4.-5.0; 60% V/V ethanol) <u>Traditional use</u> With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended i) Herbal substance : cut dried tuberous secondary root ii) Herbal preparations Dried powdered root Liquid extract (1 : 1; extraction solvent 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 (2.8-3.4 : 1; 30% V/V ethanol)~~	

	~~Dry extract (2.6-3.1 : 1; 30% m/m ethanol)~~ Dry extract (2-4 : 1; 30% m/m ethanol) * Dry extract (1.5-2.1 : 1; 40% V/V ethanol) Dry extract (3-5 : 1; 60% V/V ethanol) ~~Dry extract (4.4-5.0 : 1; 60% V/V ethanol)~~ Dry extract (3-6 : 1; 80% V/V ethanol) Dry extract (6-12 : 1; 90% V/V ethanol) **Tincture (ethanol 45% V/V)** (this correspond to a product marketed in France by Boiron since 1965) *This extract covers dry extracts of 2.8-3.4 : 1; extraction solvent 30% V/V ethanol, 1.9-3.4:1 extraction solvent 30% V/V ethanol , 2-3:1 extraction solvent 30% V/ V ethanol and of 2.6-3.1 : 1; 30% m/m ethanol as well New references to document the traditional use are: Schmidt 1978 ; Schmidt 1983 ; Wilhelmer 1976 ; Zimmermann 1977 ; Schrüffler 1980 ; Grahame und Robinson 1981 ; Belaiche 1982 ; Lecomte und Costa 1992, 1997 ; Moussard et al., 1992 , Pinget und Lecomte 1990, 1997 As an alternative to the list of preparations (DER native and extraction solvent), **we would like to strongly recommend, for consistency reasons, adopting the same approach as the one used for Valerianae radix i.e. listing the equivalents of the herbal substance.** (http://www.emea.europa.eu/pdfs/human/hmpc/valerianae_radix/34071905fin.pdf). **Traditional use** As the aqueous and the 60% ethanolic extract are considered as well-established use preparations, the list of traditional use is as follows:	Not endorsed. *No evidence of medicinal use in France has been submitted* Not endorsed. It doesn't correspond to the current approach adopted for other monographs

	Traditional use **With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended** ***Harpagophytum procumbens* D.C. and / or *Harpagophytum zeyheri* Decne, radix (devil's claw root)** i) Herbal substance : cut dried tuberous secondary root ii) Herbal preparations Dried powdered root 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 (2.8-3.4 : 1 ; 30% V/V ethanol) Dry extract (2.6-3.1 : 1 ; 30% m/m ethanol) Dry extract (3-4 : 1 ; 30% m/m ethanol) Dry extract (1.5-2.1 : 1 ; 40% V/V ethanol) Dry extract (3-5 : 1 ; 60% V/V ethanol) ~~Dry extract (4.4-5.0 : 1 ; 60% V/V ethanol)~~ Dry extract (3-6 : 1 ; 80% V/V ethanol) Dry extract (6-12 : 1 ; 90% V/V ethanol)	Not endorsed. « well-established use » is not accepted

3 PHARMACEUTICAL FORM		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use Herbal preparations in solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term. Well-established use **Herbal preparations in liquid and solid dosage forms for oral use.** **The pharmaceutical form should be described by the European Pharmacopoeia full standard term.** To be added: **Well-established use** **Herbal preparation in solid dosage form for oral use.** **The pharmaceutical form should be described by the European Pharmacopoeia full standard term.**	Not endorsed. « well-established use » is not accepted

4.1 Therapeutic indications		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use We propose inclusion of the following indications : “Symptomatic treatment of painful osteoarthritis” and “Relief of low back pain”.	Not endorsed. « well-established use » is not accepted

	These indications appear in the ESCOP monograph (2003) and are supported by a number of clinical studies summarized in the updated ESCOP monograph (February 2006) and fulfilling the criteria for well-established use (see 5.1 Pharmacodynamic properties) Well-established use **Symptomatic treatment of painful osteoarthritis, relief of low back pain and muscular pain.** The proposed indications are justified by the following clinical studies: Symptomatic treatment of painful osteoarthritis Dry extract (1.5-2.5 : 1; water) Chrubasik et al., 2002 ; Chrubasik et al., 2007 ; Müller et al., 2000 ; Schmelz und Hämmerle, 1997 ; Wegener and Lüpke, 2003 Dry extract (4-5 : 1 ; 60% V/V ethanol) Engel, 2000 ; Schendel, 2001 ; Frerick et al., 2001 ; Ribbat und Schakau, 2001 Relief of low back pain Dry extract (1.5-2.5 : 1; water) Chrubasik et al. 1996 ; Chrubasik et al. 1999 ; Chrubasik et al. 2003 ; Chrubasik et al. 2005 ; Chrubasik et al., 1997 ; Chrubasik et al., 2007 ; Müller et al., 2000 Dry extract (4-5 : 1 ; 60% V/V ethanol Göbel et al., 2001 ; Laudahn, 2001 ; Ribbat und Schakau, 2001	

	Relief of muscular pain Dry extract (4-5 : 1 ; 60% V/V ethanol) Göbel et al., 2001 Taking into consideration the large amount of clinical data, a level of evidence Ib is justified. Well-established use As outlined under ch. 2, the well-established use is documented by available data for the aqueous and the 60% ethanolic extract for following indications: i) Symptomatic treatment of painful osteoarthritis Dry extract (1.5-2.5 : 1; water) References: Chrubasik et al. 2002, Chrubasik et al., 2007, Müller et al. 2000, Schmelz und Hämmerle 1997, Wegener and Lüpke 2003 Dry extract (4-5 : 1 ; 60% V/V ethanol) References: Engel 2000, Schendel 2001, Frerick et al. 2001, Ribbat und Schakau 2001 ii) Relief of low back pain and muscular pain Dry extract (1.5-2.5 : 1; water) References: Chrubasik et al. 1996, Chrubasik et al. 1999, Chrubasik et al. 2003, Chrubasik et al. 2005, Chrubasik et al., 1997, Chrubasik et al., 2007, Müller et al. 2000 Dry extract (4-5 : 1 ; 60% V/V ethanol) References: Göbel et al., 1999, Laudahn 1999, Ribbat und Schakau 2001	

	In summary, our text proposal is: Well-established use **i) Symptomatic treatment of painful osteoarthritis** **ii) Relief of low back pain and muscular pain** We propose to include the well-established use of herbal preparations as above for treatment of chronic or exacerbated back pain and painful osteoarthritic conditions. **Traditional use** Data for the traditional use as a herbal substance are only in some elder references (not quoted by the HMPC) and sparcely available. However, there are several papers which document the clinical use as e.g. in epidemiological studies; some of them had not been referenced yet (Lecomte und Costa 1992, 1997, Moussard et al., 1992, Pinget und Lecomte 1990, 1997, Belaiche 1982). Therefore, the wording should be: The product is a traditional herbal medicinal product for use in specified indications ~~exclusively based on long-standing use~~. In summary, our text proposal is: Traditional use **a) Traditional herbal medicinal product for relief of minor articular pain.** **b) Traditional herbal medicinal product used for the relief of mild digestive disorders such as bloating and flatulence and where there is loss of appetite.** **The product is a traditional herbal medicinal product for use in specified indications.**	Not endorsed. The statement should be maintained in conformity with the requirements of the EU Directive.

4.2 Posology and methode of administration		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-establihed use Posology We propose the following text: Daily dose i) Herbal substance Not applicable. ii) herbal preparations Dry extract (1.5-2.5:1; water): 2.4g divided into 2 to 3 doses Dry extract (4.4-5.0:1; 60% V/V ethanol): 960mg divided into 2 doses Justifications are given under 5.1 Pharmacodymanic properties. Duration of use Clinical data support a treatment duration of at least 2-3 months; clinical studies lasting for at least 8 weeks and up to 5 months have been reported [Frerick 2001: Chantre 2000, Lecomte 1992, Wegener 2003; Laudahn 2001; Kloker 2003; Chrubasik 2002]. These studies demonstrated a progressive and continous reduction of symptoms during the course of treatment (e.g. improvements in VAS-pain, WOMAC total score, stiffness score, physical function). The following comment summarizes the observations. As the drug was slow in taking effect , Harpagophytum extract does not seem to have immediate analgesic potency. I n clinical use, the patient should be told about the slow onset of action so that treatment is not stopped prematurely" [Laudhan 2001]. Moreover, safety of devil's claw preparations has recently been reviewed [Vlachojannis,2008], showing an overall adverse event rate	Not endorsed. « well-established use » is not accepted

	of around 3%. In none of the double-blind studies was the incidence of adverse events during treatment with devil's claw root higher than that durind placebo treatment (10 studies). Two observational studies carried out over a year of surveillance, corresponding to 189 patients, confirmed the good tolerance of devil's claw root (adverse events were few and none were serious) [Chrubasik, 2007; Wegener 2003] We propose that the text should read : "This herbal preparation takes effect gradually and progressively during a course of treatment. For optimum benefit it should be taken for a period of 2 to 3 months. If symptoms persist thereafter, a doctor or qualified health care practitioner should be consulted" Method of administration We propose "Oral use" Well-established use **Posology** *Adults* Daily dose herbal preparations Dry extract (1.5-2.5 : 1 ; water): 1.2 to 2.4 g divided in 2 to 3 doses Dry extract (4-5 : 1 ; 60% V/V ethanol) : 960 mg divided in 2 to 4 doses **Duration of use** **No restriction.**	

	Method of administration Oral use. <u>Well-established use</u> As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). The dosage range of the aqueous dry extract is documented in the available clinical controlled and open trials and is Dry extract (1.5-2.5 : 1 ; water): 1.2 g to 2.4 g divided in 2 to 3 doses. The safety of a long-term use for up of the addressed herbal preparations is documented in several long-term studies (Dry extract 1.5-2.5:1; water: e.g. Wegener and Lüpke 2003, Chrubasik et al., 1997, Chrubasik et al., 2007; dry extract 4.4-5.0:1; 60% V/V ethanol: Frerick et al. 2001, Schendel 2001, Ribbat und Schakau 2001). Moreover, the study reported by Belaiche, 1982 (cited in ESCOP 2003) has to be highlighted. A total of 630 patients were treated for 3 4 months with an aqueous *Harpagophytum* extract (3 – 9 g/day). 42 – 85% of the patients showed an improvement, depending on the localisation of the arthrosis. 238 patients of the total collective were treated for up to 3 further months (corresponding to a total of 6 months) with a daily dose of 9 g extract. The only obvious adverse reaction was diarrhoea. Therefore, the duration of use should be prolonged up to 3 months to ensure a clinical sufficient effect. In summary, our text proposal is:	

	Well-established use **Posology** **Adults** **Daily dose** **herbal preparations** **Dry extract (1.5-2.5 : 1 ; water): 1.2 g to 2.4 g divided in 2 to 3 doses** **Dry extract (4.4-5 : 1 ; 60% V/V ethanol) : 960 mg divided in 2 to 4 doses** **Not recommended for use in children and adolescents under 18 years of age (see section 4.4 Special warnings and precautions for use).** **Duration of use** **Up to 3 months. If symptoms persist, a doctor should be consulted.** **Method of administration** **Oral use.** Traditional use **Posology** *Adults* Indication a) (minor articular pain) Daily dose i) herbal substance Dried root : 4.5 g in 500 ml water as herbal tea divided in 3 doses ii) herbal preparations Dried powdered root : **1.0-2.6 g** divided in 3 doses Liquid extract (1 : 1; extraction solvent 30% V/V ethanol) : 15 ml	Not endorsed. The posology of the Monograph is based on the products curerntly marketed.

	Soft extract (2.5-4.0 : 1; extraction solvent 70% V/V ethanol) : 10 ml Dry extract (5-10 : 1; extraction solvent water) : 600 to 800 mg divided in 2 to 3 doses Dry extract (2-4 : 1; extraction solvent 30% m/m ethanol) : 400 to 1600 mg divided in 2 to 4 doses Dry extract (1.5-2.1 : 1; extraction solvent 40% V/V ethanol): 600 mg to 2.7 g divided in 2 to 3 doses Dry extract (3-5 : 1; extraction solvent 60% V/V ethanol) : 960 mg divided in 2 doses Dry extract (3-6 : 1; extraction solvent 80% V/V ethanol): 300 mg divided in 3 doses Dry extract (6-12 : 1; extraction solvent 90% V/V ethanol): 90-**400** mg divided in 2 doses **Tincture (ethanol 45% V/V): 20 to 50 drops** Indication b) Daily dose i) herbal substance Dried root: 1.5 g in water divided in several doses ii) herbal preparations Soft extract (2.5-4.0 : 1 ; extraction solvent 70% V/V ethanol) : 10 ml **Indications a) and b)** Not recommended for use in children and adolescents under 18 years of age (see section 4.4 Special warnings and precautions for use). **Duration of use** **No restriction.** ~~Indication a)~~ ~~Note to be taken for more than 4 weeks.~~	Posolgy of tincture is not accepted since this product is not included (See 2.) Not endorsed.

	~~Indication b)~~ ~~Duration of use should be restricted to a maximum of two weeks.~~ If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Method of administration** Oral use. Not recommended for use in children and adolescents under 18 years of age (see section 4.4 Special warnings and precautions for use). <u>Comment:</u> Modified posology (1.0-2.6 g instead of 1.35 g) covers present daily doses of the registered herbal preparations in EU containing dried powdered root. A limitation of the duration of use of preparations for which data on a long-term use is available does not seem justified. Many studies have been conducted for up to several months of treatment without significant adverse effects. Therefore, a longer duration of therapy is justified. <u>Traditional use</u> The suggested well-established use extract preparations should be de-listed and the duration for the use in minor articular pain should be prolonged up to 3 months as data are available which document a safe therapeutic use (see above). In summary, our text proposal is: <u>Traditional use</u> **Posology** *Adults*	The duration of use should be limited to 4 weeks as for the same indication (minor articular pain) adopted in other monographs. Compared with the symptoms of indication b), posology should be restricted to a maximum of 2 weeks

	Indication a) Daily dose i) herbal substance Dried root : 4.5 g in 500 ml water as herbal tea divided in 3 doses ii) herbal preparations Dried powdered root : 1.35 g divided in 3 doses Liquid extract (1 : 1 ; 30% V/V ethanol) : 15 ml Soft extract (2.5-4.0 : 1 ; 70% V/V ethanol) : 10 ml ~~Dry extract (1.5-2.5 : 1 ; water): 300 mg to 2.4 g divided in 2 to 3 doses~~ Dry extract (5-10 : 1 ; water) : 600 to 800 mg divided in 2 to 3 doses Dry extract (2.8-3.4 : 1 ; 30% V/V ethanol) : 460 mg divided in 2 doses Dry extract (2.6-3.1 : 1 ; 30% m/m ethanol) : 1.6 g divided in 2 to 4 doses Dry extract (3-4 : 1 ; 30% m/m ethanol) : 1.35 g divided in 3 doses Dry extract (1.5-2.1 : 1 ; 40% V/V ethanol): 600 mg to 2.7 g divided in 2 to 3 doses Dry extract (3-5 : 1 ; 60% V/V ethanol) : 960 mg divided in 2 doses ~~Dry extract (4.4-5.0 : 1 ; 60% V/V ethanol) : 960 mg divided in 2 to 4 doses~~ Dry extract (3-6 : 1 ; 80% V/V ethanol): 300 mg divided in 3 doses Dry extract (6-12 : 1 ; 90% V/V ethanol): 90 mg divided in 2 doses Indication b) Daily dose i) herbal substance Dried root: 1.5 g in water divided in several doses ii) herbal preparations Soft extract (2.5-4.0 : 1 ; 70% V/V ethanol) : 10 ml Indications a) and b) Not recommended for use in children and adolescents under 18 years of age (see section 4.4 Special warnings and precautions for use).	

	Duration of use Indication a) **Up to 3 months at maximum. If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.** ~~Note to be taken for more than 4 weeks.~~ Indication b) Duration of use should be restricted to a maximum of two weeks. If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Method of administration** Oral use. Duration of use – indication a) Comment: The following text is suggested: Note**:** To be taken for more than 4 weeks. Rationale: A misprint is assumed. Alternatively, the following text is suggested: At least 2 to 3 months or until symptoms disappear. Rationale: According to the ESCOP monograph Harpagophyti radix (1996) treatment for at least 2 to 3 months is recommended in the case of arthrosis, which is a main therapeutic indication for extract from Harpagophytum. In addition, various clinical trials were identified, which confirmed that preparations containing Harpagophytum are well tolerated, safe and effective, when taken for several months (e. g. Chantre P et al., 2000; Chrubasik S, et al. 2002; Laudahn D and Walper A, 2001; Warnock M et al. 2007; Wegener T and Lüpke NP, 2003; Frerick H et al., 2001; Belaich P, 1982). No serious intoxications have been described to date.	

4.3 Containdications		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use : “Hypersensitivity to the active substance” Well-established use **Hypersensitivity to the active substance. In case of biliary disorders, medical advice should be sought.** Comment: The contraindication “biliary disorders” is derived from the choleretic effect of the active substance Well-established use As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided. Our text proposal is: Well-established use **Hypersensitivity to the active substance** Traditional use Hypersensitivity to the active substance. **In case of biliary disorders, medical advice should be sought.** Comment: The contraindication “biliary disorders” is derived from the choleretic effect of the active substance	Not endorsed. « well-established use » is not accepted Not endorsed. The choleretic effect of Harpagophyti radix is not documented .

4.4 Special warning and precautions for use		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use We propose the same warning and precautions for use as stated in the draft monograph under "Traditional use" except for the exclusion of : - "caution should be taken when devil's claw is administrered to patients affected by cardiac disorders"(see comments above) - "For liquid extracts containing ethanol, the appropriate laballing for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use, must be included" (since only solid dosage forms are relevant here) Traditional use The warning "caution should be taken when devil's claw is administered to patient affected by cardiac disorders" is derived from in vitro studies and studies in animals which demonstrated antiarrhythmic effects (Circosta 1984 ; Costa de Pasquale 1985) and reduction in arterial blood pressure (Circonsta 1984). A methanolic dry extrac given to rats by gavage caused a significant reduction in artirial blood pressure and a decrease in heart rate only at a high dose (400 mg/kg). The extration solvent (methanol) used to prepare texted dry extract does not correspond to any of those used to manufacture commercial extracts (see 2. Qualitative and quantitative composition). The same extract showed a protective action toward hyperkinetic ventricular arrhythmias induced by reperfusion in perfused isolated ta heart [Costa de Pasquale, 1985]. The methanolic dry extract also afforded protection against induced arrhytmis following gavage at doses of 300-400 mg/kg [Circosta. 1984]. Cardiac effects have not been documented in humans. Only one case has been describd in the literature corresponding to a patient who withdrew from a double blind clinical study for tachycardia. Nevertheless, it occurred suddenly just after a climatic change due to vacation. After returning, the patient took once more the medication and	Not endorsed. « well-established use » is not accepted Not endorsed. (See 5.3)

	tolerated it without any complaints (Chrubasik, 1996). Therefore we propose inclusion of a statement only under 5.3 Preclinical safety data (see 5.3). The warning *"caution should be taken when devil's claw is administered to patient affected by cardiac disorders"* is derived from *in vitro* studies and studies in animals which demonstrated antiarrhythmic effects (Circosta 1984; Costa de Pasquale 1985) and reduction in arterial blood pressure (Circosta 1984). A methanolic dry extract given to rats by gavage caused a significant reduction in arterial blood pressure and a decrease in heart rate only at a high dose (400 mg/kg). The extraction solvent (methanol) used to prepare the dry extract tested does not correspond to any of those used to manufacture commercial extracts (see 2. Qualitative and quantitative composition). The same extract showed a protective action toward hyperkinetic ventricular arrhythmias induced by reperfusion in perfused isolated rat heart [Costa de Pasquale, 1985]. The methanolic dry extract also afforded protection against induced arrhytmias following gavage at doses of 300-400 mg/kg [Circosta, 1984]. These cardiac effects have not been documented in humans. Only one case has been described in the literature corresponding to a patient who withdrew from a double-blind clinical study for tachycardia. Nevertheless, it occurred suddenly just after a climatic change due to vacation. After returning, the patient took once more the medication and tolerated it without any complaints (Chrubasik, 1996). Such effects have never been observed in post-marketing experience and have never been reported in open studies which included patients with common concomitant diseases such as cardiovascular diseases	

	(e.g. Ribbat und Schakau 2001). Therefore we propose the inclusion of a statement only under 5.3 Preclinical safety data (see 5.3). Further information listed in chapters 4.4 - 4.9 has to be included to the well-established medicinal use section. <u>Well-established use</u> As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). The special warning: "Caution should be taken when devil's claw is administered to patient affected by cardiac disorders" is not justified. We assume that this warning derives exclusively from the experimental studies reported by Circosta et al. (1984), Occhiuto et al. (1985), de Pasquale et al. (1985) and Occhiuto and De Pasquale (1990). All the experimental studies were initiated and conducted in the context of systematic (morphological, chemical and biological) researches on this drug. There are no historical, traditional or ethnomedicinal rationale on a cardiovascular pharmacodynamic action. Any direct or related effects have never been observed in post-marketing experience and have never been reported in open studies which included patients with concomitant diseases including also cardiovascular diseases (e.g. Ribbat und Schakau 2001, Wegener and Lüpke 2003, Schendel 2001, Chrubasik et al. 1997). In controlled studies vital parameters blood pressure and hear rate were not affected (e.g. Chrubasik et al. 1996, Goebel et al. 2001). Our text proposal is:	

	Well-established use **The use in children and adolescents under 18 years of age is not recommended because of the lack of available experience.** **Articular pain accompanied by swelling of joint, redness or fever should be examined by a doctor.** **As a general precaution, patients with gastric or duodenal ulcer should not use devil's claw preparations.** **If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.** **For liquid extracts containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.** Traditional use (See the comments on the cardiac disorders above). Our text proposal is: Traditional use **The use in children and adolescents under 18 years of age is not recommended because of the lack of available experience.** **Articular pain accompanied by swelling of joint, redness or fever should be examined by a doctor.** **As a general precaution, patients with gastric or duodenal ulcer should not use devil's claw preparations.** **If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.**	

	For liquid extracts containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.	
4.5 Interactions with other medicinal products and other forms of interaction		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use "Not known". Further information listed in chapters 4.4 - 4.9 has to be included to the well-established medicinal use section. Well-established use As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). Our proposal is to use the same wordings as listed already in the chapters on the traditional use section.	Not endorsed. « well-established use » is not accepted

4.6 Pregnancy and lactation		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use We propose the same wording as that for Traditional use : "Safety during pregnancy and lactation has not been established. In the absence of sufficient data, use during pregnancy and lactation is not recommended." Further information listed in chapters 4.4 - 4.9 has to be included to the well-established medicinal use section. Well-established use As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). Our proposal is to use the same wordings as listed already in the chapters on the traditional use section.	Not endorsed. « well-established use » is not accepted
4.7 Effects on ability to drive and use machines		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use We propose the same wording as that for Traditional use : "No studies of the effect on the ability to drive and use machines have been performed." Further information listed in chapters 4.4 - 4.9 has to be included to the well-established medicinal use section.	Not endorsed. « well-established use » is not accepted

	Well-established use As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). Our proposal is to use the same wordings as listed already in the chapters on the traditional use section.	
4.8 Undesirable effects		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Traditional use The undesirable effect "central nervous system desorders : headache, dizziness" is cited, according to our knowledge, only very rarely in the scientific leterature : - one patient withdrew after four days of therapy due to a throbbling frontal headache and innitus (Graham; 1981). It is not clear that these symtoms were caused by devil's claw root ; - among patients reciving a daily dose of 2.4 g dry aqueous extract for 6 weeks, three cases of dizainess have been described which were evaluated as being possible (1 case), likely (1 case) and certain (1 case). Also, 1 case of somnolence possibly due to the dry aqueous extract has been described (Chrubasik, 2003). We propose to read : "Rarely central nervous system disorders : headache, dizziness". Well-established use We propose the following text : "Gastrointestinal disorders : diarrhoea, nausea, vomiting, abdominal pain."	Not endorsed. Not endorsed. "well-established use" is not accepted.

	"Rarely central nervous system disorders : headache, dizziness". Skin disorders : allergic skin reactions. The frequency is not known. If other adverse reactions not mentioned above accur, a doctor or qualified health care practitioner should be consulted" Further information listed in chapters 4.4 - 4.9 has to be included to the well-established medicinal use section. With regard to headache and dizziness as undesirable effects, we are wondering on which reference this statement is based. The ESCOP monograph does not include such a statement. <u>Well-established use</u> As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). Our proposal is to use the same wordings as listed already in the chapters on the traditional use section.	

4.9 Overdose		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use : "No case of overdose has been reported" Further information listed in chapters 4.4 - 4.9 has to be included to the well-established medicinal use section. Well-established use As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). Our proposal is to use the same wordings as listed already in the chapters on the traditional use section.	Not endorsed. "well-established use" is not accepted.
5.1 Pharmacodynamic properties		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use : With regard to in vitro and in vivo effects, pharmacological studies in humans and clinical data, we would like to refer to the undated ESCOP monograph [February 2006]. Controlled clinical studies and observational studies have been performed with various devil's claw preparations in adults suffering form pain due to osteoarthritis or low back pain. Only controlled clinical studies on good quality are summarized in the table below. Six studies are described, three investigating osteoarthritis and three investigating low back pain. The table includes 4 randomized controlled studies and 2 equivalence studies. They	Not endorsed. "well-established use" is not accepted.

include 3 types on preparation, each used in two studies: dry extract (4.4-5.0:1; water) and dried powdered root.

Author, year	Type of preparation (daily dosage)	Study design (N)	Condition	Comments
Frerick 2001	Dry extract (4.4-5.0:1; ethanol 60% V/V (960 mg)	Randomized, placebo-controlled, double-blind (n = 46)	Degenerative joint disease/osteoarthiris	Significant improvement during the final ibuprofen-free period (pain score).
Lecomte 1992	Dried powered root (2010 mg)	Placebo-controlled, double-blind (n=89)	Degenerative joint disease/osteoarthiris	Significant improvement in devil's claw group (severity of pain, spinal and cofexomoral mobilility).
Chanter 2000	Dried powered root (2610 mg) Diacerhein (100 mg)	Randomized, placebo-controlled, double-blind. Equivalence (vs.diacerhein) (n = 122)	Degenerative joint disease/osteoarthiris	Equivalent therapeutic response in both groups (spontaneous pain. Functional joint disability).

Chrubasik 1996	Dry extract (1.5-2.5-1:water) (2400 mg)	Placebo-controlled, double-blind (n= 118)	Low back pain	No significant intergroup Artus global index differences but significant difference in pain index.
Chrubasik 1996	Dry extract (1.5-2.5-1:water) (2400 mg) Rofecoxib, 12.5 mg	Randomized, placebo-controlled, double-blind. Equivalence (vs.diacerhein) (n = 88)	Low back pain	No significant intergroup differences.
Göbel 2001	Dry extract (4.4-5.0:1; ethanol 60% V/V) (960 mg)	Randomized, placebo-controlled, double-blind (n =65)	Pain and tension of back, shoulder and neck.	Significant criteria: muscular pain intensity, muscular pain intensity, muscle stiffness and muscu-lar ischa emia tests.

Devil's claw root preparations appeared effective in the reduction of the

	main clinical symptom of pain based on good scientific evidence. Note: other placebo-controlled double-blind studies or randomized comparator trials have not been mentioned here because either the herbal preparation has not been properly described (Guyader 1984; Chrubasik 1999) or the quality of the study is not considered good enough (Srüffer 1990; Pinget 1990; Schmelz 1997). The guideline EMEA/HMPC/104613/2005 states that well-established use is not restricted to indications proven by placebo-controlled trials. According to the guideline, not only controlled trials but also "other clinical trials, cohort or longitudinal studies, observational (non-interventional) studies, case-control studies, other collections of single cases allowing a scientific evaluation, scientifically documented medical experience "have to be taken in consideration for evaluation of clinical evidence. Observational and open studies supporting the efficacy of herbal preparations previously mentioned are also available. They are described in the updated ESCOP monograph [February 2006]: • 60 ù V/V ethanolic dry extract (4.4-5.0:1) at a daily dosage of 960 mg for symptomatic treatment of painful osteoarthritis (Ribbat 2001; Schendel 2001) or relief of low back pain (Laudhan 2001; Klober 2003) • Water dry extract (1.5-2.5:.) at a daily dosage of 2.4 g for relief of low back pain (Chrubasik 1997), symptomatic treatment of painful osteoarthritis (Wegener 2003) or mixed-pain conditions (Chrubasik 2002; Chrubasik 2007). Thus, these two preparations of devil's claw root have been the subject on controlled and uncontrolled clinical studies demonstrating beneficial effects in the alleviation of pain and improvement of motility in a variety of musculoskeletal conditions (non-specific back pain, arthrosis of the knee and hip, general arthritic complaints and muscle soreness). Based on the Guideline EMEA/HMPC/104613/2005, the two different	

	herbal preparationsfulfil the criterai for “well-established use”,i.e “at least one controlled clinical of good quality” with additional uncotrolled clinical studies in the symptomatic treatment of painful osteoarthritis or relief of low back pain, or both : - Aqueous dry extract (1.5-2.5 : 1) at a daily dosage of 2.4 g (relief of low back pain). - 60% V/V ethanolic dry extract (4.4-5.0 : 1) at a daily dosage of 960 mg (symptomatic treatment of painful osteoarthrictis or relief of low back pain). Furthermore, information on the well-established medicinal use with regard to chapters should be included under 5.1, 5.2 and 5.3. For a respective wording for these chapters we would recommend taking over the wording from the ESCOP monograph. <u>Well-established use</u> As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). Our text proposal referencing the data listed in the ESCOP monograph of 2003 is: <u>Well-established use</u> Harpagophyti radix preparations are reported to exert anti-inflammatory and analgesic effects. In clinical studies, patients reported a reduction of pain and stiffness.	
5.2 Pharmacokinetic properties		

Paragraph no. line no.	Comment and Rationale	Outcome
	Well-established use : Detailed data on pharmacokinetics in animals and in humans are available in the ESCOP monograph (2003) and the updated ESCOP monograph [february 2006] Furthermore, information on the well-established medicinal use with regard to chapters should be included under 5.1, 5.2 and 5.3. For a respective wording for these chapters we would recommend taking over the wording from the ESCOP monograph. Well-established use As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). Our text proposal referencing the data listed in the ESCOP monograph of 2003 is: Well-established use Some studies showed a absorption of harpagoside; systematic studies are not available.	Not endorsed. "well-established use" is not accepted. Moreover, results of preclinical pharmacokinetic studies are not usually included in section 5.2 of the SPC of pharmaceuticals.
5.3 Preclinical safety data		

Paragraph no. line no.	Comment and Rationale	Outcome
	Traditional use We propose inclusion of the following text : "Data from in vitro and animal studies indicated that a methanolic extract from devil's claw root had antiarrhytmic and hypotensive effects. The clinical relevance of these findings is not knwn and no such effects have been reported in humans". Well-established use Detailed preclinical as well as clinical safety data con be found in the ESCOP monograph (2003) and the updated ESCOP monograph [febuary 2006]. Tests on genotoxicity, carcinogenicity, and reproductive toxicity hace not been performed. We propose inclusion of the following text : "Data from in vitro and animal studies indicate that the methanolic extract of devil's claw root have antiarrhytmic and hypotensive effects. The clinical relevance of these findings is not known". We propose the inclusion of the following text (in the right column): "Data from *in vitro* and animal studies indicated that a methanolic extract from devil's claw root had antiarrhytmic and hypotensive effects. The clinical relevance of these findings is not known and no such effects have been reported in humans." Furthermore, information on the well-established medicinal use with regard to chapters should be included under 5.1, 5.2 and 5.3. For a respective wording for these chapters we would recommend taking over the wording from the ESCOP monograph. Well-established use	Not endorsed. These data are not usually included in section 5.3 of the SPC of pharmaceuticals... Not endorsed. "well-established use" is not accepted.

	As two extract preparations are considered as justified to be listed in the well-established use section, information has to be provided (see text proposal below). Our text proposal referencing the data listed in the ESCOP monograph of 2003 is: <u>Well-established use</u> Some data showed a low acute toxicity in rodents. Other data is not available	