EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/HMPC/354205/2016
Committee on Herbal Medicinal Products (HMPC)

Overview of comments on European Union herbal monograph on *Harpagophytum procumbens* DC. and /or *Harpagophytum zeyheri* Decne., radix (EMA/HMPC/627057/2015)

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Harpagophytum procumbens* DC. and /or *Harpagophytum zeyheri* Decne., radix as released for public consultation on 15 February 2016 until 15 May 2016.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	A.Vogel Biohorma NL

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	We refer to our comments submitted during the consultation phase January – April 2008 with regard to the well-established medicinal use. In our view, sufficient clinical data are available for some defined Harpagophyti radix preparations to reclassify them under the category of well-established medicinal use. Our comments refer not only to the Monograph but also to the Assessment Report since the latter contains relevant background information for the Monograph.	
Biohorma A.Vogel NL	We refer to the limitation of use in the now to be peer reviewed HMPC monograph on *Harpagophytum* which restricts the duration of use of preparations from *Harpagophytum* to 4 weeks.	

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
Assessment report 3.1.5. Conclusions	AESGP	In the first sentence "The traditional use of *Harpagophytum …" the word "traditional" should be replaced by "medicinal" because there is a long-term use for medicinal purposes.* The use of registered devil's claw products before final publication of the HMPC monograph in 2008 was not termed to be "traditional".	Endorsed
Assessment report	AESGP	From our point of view, the classification and interpretation of the study from "Göbel et al. Effects of *Harpagophytum*	Not endorsed In the revised Assessment Report, the Gobel's trial is

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4.2.2. Clinical studies (case studies and clinical trials)		*procumbens* LI174 (devil's claw) on sensory, motor and vascular reagibility in the treatment of unspecific back pain. Schmerz 2001, 15:10-18" is not in line with the HMPC *Guideline on the assessment of clinical safety and efficacy*. In contrast to the classification under *II.3.2.3 Open Studies* in the Assessment Report, Göbel *et al.* performed a randomised, double-blind, placebo controlled study with 63 patients (31 verum and 32 placebo) to investigate the effects of *Harpagophytum* dry extract (LI174) on sensory, motor and vascular mechanism of muscle pain. It remains unclear why the study population is regarded as an inhomogeneous group, although there were several inclusion and exclusion criteria which appear plausible for the recruitment of a homogeneous patient group for this indication. It also remains unclear why the assessor rates the results from the placebo group as doubtful and not being in accordance with other references. To this effect it should be mentioned that the results from this study exclusively reflect the safety and efficacy of the tested *Harpagophytum* dry extract (4-5:1; 60% V/V ethanol). We suggest re-assessing this extract for evidence level 1b and recommendation grade A for well-established use of *Harpagophytum* dry extract for the treatment of unspecific back pain.	reclassified as randomised, double-blind, placebo controlled study. HMPC keeps its view: it is difficult to reach any conclusion, taking into account the weaknesses of the study: (1) inclusion of the heterogeneous (mixed) musculoskeletal pain conditions (2) small sample size; (3) no sufficient information to judge baseline similarity; actually in the per-protocol analysis the verum group had less pain than the placebo group and the distribution of sites of pain appeared to differ between the verum and placebo groups (back pain 96.5% in verum vs. 75% in placebo); (4) no data about additional analgesic treatments that might have been received. In the same time the results from the placebo group are doubtful because the well-known placebo effect in the treatment of this condition is lacking (e.g VAS is practical constant in the placebo group). HMPC opinion is in line with other three published reviews already included in the Assessment report (Chrubasik *et al*., 2003; Brendler *et al*., 2006; Gagnier *et al*., 2004)

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Monograph 4.2. Posology and method of administration	AESGP	This comment relates to the posology of the Herbal preparation e) Dry extract (DER 1.5-2.5:1), extraction solvent water used in Indication 1) Traditional herbal medicinal product for relief of minor articular pain. For the indication 1) the listed posology e) ~~Single dose: 750-800 mg, 3 times daily~~ ~~Daily dose: 2.25-2.4 g~~ should be replaced by either Single dose: 100 mg – 1.2 g, 2-3 times daily; maximum daily dose: 2.4 g or by retaining the posology given in the HMPC monograph from 2008: Daily dose: 300 mg to 2.4 g divided in 2 to 3 doses Comment The revised posology of the herbal preparation e) in the indication articular pain does not seem to be justified. Single dose The traditional herbal medicinal products registered in the Community since 2007 show single doses in the range of 100 mg to 1.2 g of the aqueous extract (refer to table 1 in the annex). Traditionally used herbal medicinal product containing the	Endorsed

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		aqueous extract in question which have been in the German market for 14 to 40 years are listed in table 2 in the annex. The single dose is in the range of 100 mg to 1.2 g dry extract, too. In summary, the traditionally used single dose is in the range of 100 mg to 1.2 g extract. <u>Daily dose</u> The traditional herbal medicinal products registered in the Community show daily doses in the range of 200 mg to 2.7 g of the aqueous extract (table 1 in the annex). The traditionally used herbal medicinal products which have been in the German market for 14 to 40 years show daily doses in the range of 200 mg to 2.4 g of the extract (table 2 in the annex). In summary, the traditionally used daily dose is in the range of 200 mg to 2.4 g extract. <u>Number of doses per day</u> The number of doses of the traditional herbal medicinal products granted a registration in the Community is 2 times or 2 to 3 times per day (table 1 in the annex). The number of doses of the traditionally used herbal medicinal products which have been in the German market for 14 to 40 years is 2 times or 2 to 3 times or 3 times per day (table 2 in the annex).	

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		In summary, 2 to 3 doses per day of medicinal products containing herbal preparation e) are traditionally given in indication 1).	
4.2. Posology and method of administration	A.Vogel Biohorma NL	Comment The former version of the monograph (EMEA/HMPC/251323/2006) states under 4.2: **Note** to be taken for more than 4 weeks. Whereas the now to be peer reviewed version of the monograph (EMA/HMPC/627057/2015) says: **Not** to be used for more than 4 weeks. We have found that a) there are no data supporting the proposed change contained in the pertaining assessment report, and b) there are the same long term studies* supporting the indication on duration of intake of the former version of the monograph (EMEA/HMPC/251323/2006), and c) this original indication on duration, i.e. to be taken for more than 4 weeks, as reflected in the current use of *Harpagophytum* products, is further corroborated by the fact that clinical studies as well as pharmacological properties alike support that H*arpagophytum* is a slow onset drug with a known latency of two to four weeks before onset of efficacy.	Partially endorsed The duration of use was corrected. According to OoC (Doc. Ref.: EMEA/HMPC/454136/2008) the duration of use up to 4 weeks was proposed for the previous version of the monograph. The duration of use is in line with approved SPC's for traditional medicinal products authorized in DK, FR, ES. The duration of use for indication 1 was changed to: If the symptoms persist longer than 4 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

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		Based on the above we interpret the proposed change as a spelling mistake due to an erroneous translation of «**Note**» in the 2008 HMPC monograph into «**Not**» in the prospective 2016 HMPC Monograph. Rationale Long term studies as contained in the EMA/HMPC/627058/2015 Committee on Herbal Medicinal Products (HMPC) Assessment report on *Harpagophytum procumbens* DC. and/or *Harpagophytum zeyheri* Decne., radix and supporting the indication on duration of use of the previous monograph (EMEA/HMPC/251323/2006), whilst not supporting the corresponding indication of the prospective monograph (EMA/HMPC/627057/2015) are listed in the following: 6 weeks: 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 Chrubasik S, Model A, Black A, Pollak S. A randomized double-blind pilot study comparing Doloteffin® and Vioxx® in the treatment of low back pain. Rheumatology 2003, 2:141-148 Engel S. Rivoltan (Li 174) zur Behandlung von Patienten mit degenarativen Erkrankungen des Bewegungsapparates. Deutsche Apothekar Zeitung 2000, 140:1369	

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		Lienert A, Ruetten S, Kuhn M, Wartenberg-Demand A. A randomised, active-controlled, monocentric 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. Meeting abstract. 54. Jahrestagung der Norddeutschen Orthopâdenvereinigung e.V. Hamburg 2005, 616-618 Schendel UM. Arthrose-Therapie: Verträglich geht es auch. Studie mit Teufelskrallenextrakt. Der Kassernarzt 2001, 29/30:36-39 Schmidt A, Berghol U, Schmidt E. Therapie der unspezifischen Lumbalgie mit Teufelskrallenwurzelextrakt – Ergebnisse einer Klinischen Studie. Effectiveness of Harpagophytum procumbens in treatment of unspecific low back pain. Phys Med Rehab Kuror 2005, 15:317-321 Szczepanski L. Efficacy and tolerability of 'Pagosid' (Harpagophytum procumbens root extract) in the treatment of rheumatoid arthritis and osteoarthritis. Rheumatologia 2000; 38: 67–73 <u>8 weeks:</u> Kloker B, Flammersfeld L. Rheumatherapie mit Teufelskrallenwurzelextrakt: eine multizentrische Praxisstudie. Arztezeitschrift fur Naturheilverfahren 2003, 44:108-111 Laudahn D and Walper A. Efficacy and tolerance of	

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		Harpagophytum Extract LI 174 in patients with chronic non-radicular back pain. Phytother Res 2001, 15:621-624 Lecomte A, Costa JP. Harpagophytum dans l'arthrose: Etudes en doulble insu contre placebo. Le Magazine 1992, 15:27-30 Ribbat JM, Schakau D. Behandlung chronisch aktivierter Schmerzen am Bewegungsapparat. Natura Med 2001, 16:23-30 Pinget M, Lecomte A. Die wirkung der "Harpagophytum Arkocaps" bei degenerativem rheuma. Naturehellpraxis 1997, 2:267-269 Warnock M, McBean D, Suter A, Tan J, Whittaker P. Effectiveness and Safety of Devil's Claw Tablets in Patients with General Rheumatic Disorders. Phytother Res 2007, 21:1228–1233 <u>12 weeks:</u> Wegener T, Lüpke NP. Treatment of patients with arthrosis of hip or knee with an aqueous extract of Devil's Claw (Harpagophytum procumbens DC). Phytother Res 2003, 17:1165-1172 <u>16 weeks:</u> 1. Chantre P, Cappelaere A, Leblan D, Guédon D, Vandermander J, Fournie B. Efficacy and tolerance of Harpagophytum procumbens versus Diacerhein in treatment of osteoarthritis. Phytomedicine 2000, 7:177-183 Leblan D, Chantre P, Fournie B. Harpagophytum procumbens in	

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		the treatment of knee and hip osteoarthritis. Four-month results of a prospective, multicenter, double-blind trial versus Diacerhein. Joint Bone Spine 2000, 67:462-467 <u>20 weeks:</u> 1. Frerick H, Biller A, Schmidt U. Stufenschema bei Coxarthrose. Der Kassenarzt 2001, 5:34-41 <u>54 weeks:</u> 1. Chrubasik S, Künzel O, Tanner J, Conradt C, Black A. A 1-year follow-up after a pilot study with Doloteffin® for low back pain. Phytomedicine 2005, 12:1-9 2. Chrubasik S, Chrubasik C, Künzel O, Black A. Patient-perceived benefit during one year of treatment with Doloteffin. Phytomedicine 2007, 14:371-376 Consistent with the data above the erroneous wording on duration of use Indication 1) ~~Not to be used for more than four weeks.~~ should be replaced by the correct wording Indication 1) Note: To be taken for more than four weeks.	