European Medicines Agency
Evaluation of Medicines for Human Use

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'COMMUNITY HERBAL MONOGRAPH ON *RUSCUS ACULEATUS* L., RHIZOMA' (EMEA/HMPC/261938/2007)

Table 1: Organisations providing comments on the draft 'Community herbal monograph on *Ruscus aculeatus* L., rhizoma' as released for consultation on 7 September 2007 until 15 December 2007

	Organisation
1	The Association of the European Self-Medication Industry (AESGP)
2	European Scientific Cooperative on Phytotherapy (ESCOP)
3	Kooperation Phytopharmaka, Germany

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Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.1. Therapeutic indications	**Well-established use in CVI**	
	The dry extract (15-20:1;60% V/V methanol) has a proven well-established medicinal use as 'supportive therapy for symptoms of chronic venous insufficiency, such as painful, tired and heavy legs, tingling and swelling'.	**Not endorsed** We still consider that the well-established use has not been demonstrated for Ruscus aculeatus used to relieve symptoms of heavy legs. The study of Vanscheidt et al[1] is deserving of being the first clinical study performed with a Ruscus extract alone. Nevertheless, it is always rather difficult to appreciate the real quality of a study through a publication. Several methodological problems remain not resolved information is missing such as, the protocol with modalities of randomisation, sample calculation and power of the study. Moreover, the respect of the double-bind procedure can not be evaluated. 18 patients have been excluded from the analysis for insufficient data and we have no more information. All the missing data, after 12 weeks, have been replaced by last observation carried forward; we don't know how many data are missing. Finally, the study has been conducted in 10 centres in Germany, but we cannot judge the homogeneity of the centres in term of recruitment or clinical practises. Thus, the results should be interpreted with caution.
	We suggest to add under "well-established use": "supportive therapy for symptoms of chronic venous insufficiency, such painful, tired and heavy legs, tingling and swelling." Because the above-mentioned herbal medicinal preparation fulfils the requirements for the well-established medicinal use as defined in the respective HMPC Guideline.	
	We propose to add the following under the "well-established medicinal use": "Supportive therapy for symptoms of chronic venous insufficiency, such as painful, tired and heavy legs, tingling and swelling." From our point of view, the above-mentioned herbal preparation fulfils the requirements for the well-established medicinal use as defined in the mentioned guideline.	

4. CLINICAL PARTICULARS		
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	According to the Guideline EMEA/HMPC/104613/2005 (1) a well-established medicinal use of a substance may be established by factors, such as: - the time over which a substance has been used (not less than one decade) - quantitative aspects of the use of the substance - the degree of scientific interest in the use of the substance (reflected in the published scientific literature) - the coherence of scientific assessments First, it should be mentioned that Rusci aculeati rhizoma preparations meet these factors as they are established in the treatment of chronic venous insufficiency (CVI) since several decades. Experts on the field of herbal medication as well as CVI trust in the safety and efficacy of Rusci aculeati rhizoma (2-5). Second, the available data on Rusci aculeati rhizoma extract reveal one well-conducted, randomized, placebo-controlled trial and supportive pharmacological data consistent with the intended therapeutic use. Therefore Rusci aculeati rhizoma preparations are to be evaluated as substance with "Grade A of recommendation" according to the above mentioned guideline. **[…]** To demonstrate the WEU of Rusci aculeati preparations in the therapy of CVI we presented one placebo-controlled, randomized, double-blind study (level I) supported by consistent pharmacological results in humans that substantiates the efficacy and safety of Butcher's broom Extract in the treatment of CVI symptoms.	According to the author, the study was designed in accordance with the guidelines[2] for testing drugs for chronic venous insufficiency (CVI), i.e. study design with oedema reduction as the primary variable. It has to be noted that these guidelines were written by the author himself and published in "Phlebologie" after the beginning of this study i.e. April 1999. Although we can agree with most of its propositions (e.g. inclusion and exclusion criteria, duration of the study), the clinical relevance of the primary criterion is debatable. Even if oedema reduction as a primary variable can be considered a reliable quantitative primary end-point to evaluate one of the pharmacological effects of Ruscus aculeatus, the clinical relevance of this primary variable is questionable. In the opinion of the assessor, improvement in subjective symptoms such as sensation of heaviness or tiredness, tingling or pain should be of more clinical relevance. As stated by the author himself, any reduction of oedema is only regarded as clinically relevant if it is accompanied by an improvement in patient's quality of life. Thus, despite significative results regarding the primary variable and the positive correlation shown between leg oedema and all the subjective symptoms except pain, the clinical relevance of these results remains questionable. Indeed, the positive effect relative to the subjective symptoms is very limited. The difference between the two groups for the subjective symptoms "tingling sensation" and "pain" are not statistically significant and the significativity of the difference for the two other subjective symptoms "heaviness and tiredness" and "sensation of tension" is debatable taking into account the multiplicity of the analyses. Moreover, the treatment response measured by the disease specific questionnaire on the quality of life appeared negative at the end of this study (quality of life didn't reveal any changes in both arms).

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	The study was conducted according to the relevant scientific guideline, showing leg volume reduction as well as improvement of subjective symptoms. Overmore, as specified by the relevant guidelines, a clear relationship between volume reduction and subjective improvement was shown. The effects found in this study were similar to the results achieved in former studies with horse chestnut extract that has been proven to be effective in comparison with compression stockings. Additionally human pharmacological data support the well-established use of Rusci aculeati rhizoma preparations. Placebo-controlled studies, which investigated the effects of Ruscus extract and TMHC alone, and in combination, revealed the Ruscus extract to be the main or even the only effective ingredient of the combination. Therefore the results of a meta-analysis of 20 placebo-controlled randomised double-blind studies with Cyclo 3 Fort, a widely used Ruscus extract/TMHC-combination, can be attributed to the Ruscus component, as well. Over and above the evaluation should consider, that the well-established use of Rusci aculeati rhizoma preparations is also ascertained by the criteria specified in the Guideline EMEA/HMPC/104613/2005, such as "use over time", "quantitative aspects", the "degree of scientific interest" and the "coherence of scientific assessment", that has been recently assured by international experts on phlebology, who have classified Rusci aculeati rhizoma extract equivalent to horse chestnut extract.	The credit that we can attribute to this study is to have tested a Ruscus extract alone. The posology of the extract used in the study is in adequacy with the one recommended by the available monographs i.e. a daily dose equivalent to an amount of 7 to 11 mg of total ruscogenins. However, the level of evidence of Ruscus extract efficacy in relieving symptoms of chronic venous insufficiency given by this study is low. It has to be noted that the efficacy was not evaluated in men. Another study to confirm these results is deemed necessary. Evaluation of a sustained efficacy over a longer period (up to 1 year) has not been studied at it is recommended in the guideline used by the authors[2]. 1. On the other hand, the conclusions of the meta-analysis by Boyle et al[3] cannot be taken into account. Indeed, this publication is about Cyclo 3 which contains Ruscus aculeatus extract, hesperidine chalcone and ascorbic acid and not Ruscus extract alone so the demonstration of the clinical efficacy cannot be attributed to Ruscus. 2. The results of the randomised placebo-controlled three-armed study with oral horse chestnut extract[4], which demonstrated that edema protection (leg volume reduction) with vaso-active herbal drugs is comparable to the effect of leg compression stockings, cannot be extrapolated to Ruscus aculeatus extract. 3. The International Consensus symposium5, held during the 13th Congress of European Society for Clinical Hemorheology (ESCH) in Siena (Italy), 2005, concluded that vaso-active drugs (VAD) are effective and may be applied in chronic venous disease (CVD), when symptomatic, at any class of CEAP. The Consensus statement of the international experts also declares, that "in some cases VAD may replace compression and/or complement its effects".

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	Considering the entirety of available data the well-established use of Rusci aculeati rhizoma extract in the treatment of CVI complaints is clearly supported. As for other vaso-active drugs, such as horse chestnut extract, it is recommended by experts on the basis of the currently existing evidence.	The experts classified, based on the available data, both the horse chestnut extract and Ruscus extract to "Grade B" of their recommendation explained in the statement published by Ramelet et al. Despite this conclusion, we consider that the efficacy of Ruscus aculeatus to relieve symptoms of chronic venous insufficiency is not demonstrated due to the lack of relevance, for this procedure, of the study and the meta-analysis. Moreover, the French National Authority for Health had recently reassessed the benefice of all veinotonics in the treatment of chronic venous insufficiency. All the veinonotics with marketing authorization in France such as Cyclo 3, Diosmin, Troxerutin had been studied. The conclusions of the Authority were that the efficacy of all the medicines was minor and the proofs given to demonstrate the efficacy were poor.
	<u>Traditional use in CVI</u>	
	We consider the following wording appropriate to be included under "traditional use": "Herbal medicinal product traditionally used for supportive therapy for symptoms of chronic venous insufficiency, tired, tingling and swelling."	**Not endorsed** The wording of the indication, in traditional use, for chronic venous insufficiency has already been discussed at HMPC and the data are not sufficient to detail the indication such as it is claimed.
	The following indication should be added: "Herbal medicinal product traditionally used for supportive therapy for symptoms of chronic venous insufficiency, such as painful, tired and heavy legs, tingling and swelling."	
	Traditional use: "Herbal medicinal product traditionally used for supportive therapy for symptoms of chronic venous insufficiency, such as painful, tired and heavy legs, tingling and swelling."	

4. CLINICAL PARTICULARS		
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	<u>Traditional use in the treatment of haemorrhoids</u>	
	Ruscus aculeatus also has an extensive experience of use in relieving symptoms of haemorrhoids. The use during 30 years in Europe is attested by the following publication / marketing authorisations: o European and national monographs o Scientific publications: see References 1 to 20 o Marketing authorisations in the EU: see references We thus propose to add: "herbal medicinal product traditionally used to relieve symptoms of haemorrhoids such as itching and burning	**Partially endorsed** No clinical studies are available in the treatment of haemorrhoids with *Ruscus aculeatus* extract alone (see assessment report). In the treatment of haemorrhoids, no clinical data are available with Ruscus aculeatus alone; only pharmacological effects, data provided by studies with Ruscus in combination and the long-term use suggest that Ruscus extract is effective to relieve symptoms of haemorrhoids. This indication should be read "*traditional use for symptomatic relieve of itching and burning associated with haemorrhoids*". This indication is limited to oral use.
	We proposed to add the supportive therapy for symptoms of haemorrhoids under traditional use: "supportive therapy for symptoms of haemorrhoids, such itching and burning." From our point of view, this indication is justified by the long-term use of ruscus extract-containing products; a previous diagnosis by a medicinal doctor could be addressed in the patient information.	
4.2 Posology and method of administration	Well-established use: **Posology** *Adults, elderly* Dry extract (15-20:1; 60% V/V methanol): 37 mg 2 times daily equivalent to 7-11 mg ruscogenins daily as determined by the total amount of ruscogenin and neoruscogenin. *Children, adolescents* There is no relevant indication for children and adolescent.	**Not endorsed** Well-established use not endorsed. See comments above.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.2 Posology and method of administration	There is no relevant indication for children and adolescent. **Duration of use** No restriction; long-term administration may be advisable. If the symptoms persist for more than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. **Method of administration** Oral use	**Not endorsed** Well-established use not endorsed. See comments above.
	In accordance with our proposals under 2 and 4.1., we suggest to add the following under the "well-established medicinal use": "Dry extract (15-20:1; 60% V/V methanol): 37 mg 2 times daily equivalent to 7-11 mg ruscogenins daily as determined by the total amount of ruscogenin and neoruscogenin." "Dry extract (15-20:1; 60% V/V methanol): 37 mg 2 times daily. Recommendations given for dry extracts (7-11 mg daily) of quantified ruscogenins as determined by the total amount of ruscogenin and neoruscogenin." Concerning the traditional use, we suggest: In accordance with the data of the study of Kiesewetter et al. [1989; see chapter 5.1. below], we suggest to add to the mentioned aqueous extract the dosage of 2 x 75 mg or 150 mg three times daily.	**Not endorsed** Well-established use not endorsed. See comments above. **Not endorsed** The data of the study of *Kiesewetter et al.* are not relevant; only the data provided from study with ruscus extract alone can be used.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	It is recommended that for dried powdered root or dry extracts 7 - 11 mg daily of total ruscogenins as determined by the total amount of ruscogenin and neoruscogenin are to be applied. For this reason, 7-11 mg ruscogenins daily should be added. The dosage of 7-11 mg ruscogenins is in accordance with the Commission E monograph. However, the basis has been standardised extracts while today quantified extracts with a constant amount of extract (native) is required. For this reason the additionally required range given for ruscogenins (7-11 mg) is too narrow, additionally taking into account that the range can only be achieved by blending batches. Furthermore the posology of 7-11 mg ruscogenins for the extracts described requires extracts with a very high content of ruscogenins which is derived in the following: a) Dry extract 5 - 8,5 : 1 ; 80 % V/V ethanol : 86 mg; 1-2 times daily: (86 mg extract containing 7 mg ruscogenins = 8.1% 86 mg extract containing 11 mg ruscogenins = 12,8% = average 10.5 %) b) Dry extract 6 – 9 : 1 ; primary extraction solvent 96 % ethanol: 45 mg; 1-2 times daily: (45 mg extract containing 7 mg ruscogenins = 15.6 % 45 mg extract containing 11 mg ruscogenins = 24.4 % = average 20.0 %)	

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	c) Dry extract 15 – 20 : 1 ; 60 %V/V methanol: 37 mg; 1-2 times daily (37 mg extract containing 7 mg ruscogenins = 18.9 % 37 mg extract containing 11mg ruscogenins = 29.7 % ≡ average 24.3 %) (45 mg extract containing 7 mg ruscogenins = 15.6 % 45 mg extract containing 11 mg ruscogenins = 24.4 % ≡ average 20.0 %) c) Dry extract 15 – 20 : 1 ; 60 %V/V methanol: 37 mg; 1-2 times daily (37 mg extract containing 7 mg ruscogenins = 18.9 % 37 mg extract containing 11mg ruscogenins = 29.7 % ≡ average 24.3 %)	
	For symptoms of heavy legs and haemorrhoids, based on the posology described in the marketing authorisations of products on the market: - Elusane Fragon, hard capsule (Ruscus extract, dry extract water 200 mg) [1 to 2 hard capsules daily] - Petit Houx Boiron, hard capsule (Ruscus extract, dry extract 143,2 mg) [1 to 3 hard capsules daily] - Veinobiase® tablet (Ruscus extract 60 mg, cassis extract, ascorbic acid) [2 tablets daily] -Arkogelule Fragon®, hard capsule (Ruscus powdered root, 350 mg) [3 to 6 hard capsules daily] We propose to add for the aqueous extract the corresponding posology for oral use: 143.2 mg to 200 mg 1 to 3 times daily. For rectal use, we propose to indicate the posology “2 times daily”.	**Partially endorsed see 4.1** **Not endorsed for rectal use**

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Posology Adults, elderly - oral use, to relieve symptoms of heavy legs Dry extract (4.5-6.5:1 2.5-6.5 : 1 ; water): 143.2 mg to 200 mg 1 to 3 times daily - Oral use to relieve symptoms of haemorrhoids: Dry extract (2.5-6.5 : 1 ; water): 143.2 mg to 200 mg 1 to 3 times daily - Rectal use, to relieve symptoms of haemorrhoids Dry extract (7-18:1; 85% V/V ethanol): twice daily	**Partially endorsed see 4.2** **Not endorsed for rectal use**
	Duration of use There is no restriction. A long-term administration may be advisable.	**Not endorsed** due to the lack of any carcinogenicity study performed with Ruscus extracts.
4.3 Contraindications	Well-established use and traditional use: According to ESCOP's literature search, there is no data available which support the statement "Hypersensibility to the active substance" as a contraindication.	**Not endorsed** Well-established use is not endorsed. See comments above Traditional Use: "Hypersensibility to the active substance" is the appropriate wording for this section in accordance with "TEMPLATE FOR A COMMUNITY HERBAL MONOGRAPH" (EMEA/HMPC/107436/2005 Rev. 2)
4.4 Special warnings and precaution for use	Well-established use: If there is inflammation of the skin or subcutaneous indurations, ulcers, sudden swelling of one or both legs, cardiac or renal insufficiency, a doctor should be consulted.	**Not endorsed** Well-established use is not endorsed. See comments above.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Traditional use: For oral use, diarrhoea could be an undesirable effect. Treatment should be discontinued in order to avoid aggravation into microscopic colitis. We propose adding: 'if diarrhoea develops, discontinue treatment'	**Endorsed**
4.5 interaction with other medicinal products and other forms of interaction	Well-established use "none reported"	**Not endorsed** Well-established use is not endorsed. See comments above.
4.6 Pregnancy and lactation	Well-established use "Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended".	**Not endorsed** Well-established use is not endorsed. See comments above.
4.7 Effects on ability to drive and use machines	Well-established use No studies on the effect on the ability to drive and use machines have been performed.	**Not endorsed** Well-established use is not endorsed. See comments above.
	Traditional use: In accordance with the HMPC template for a Community herbal monograph, we suggest replacing the actual statement by 'not relevant'.	**Not endorsed**

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.8 Undesirable effects	Well-established and traditional use (oral use): Nausea, gastrointestinal complaints, diarrhoea **sometimes severe but rapidly reversible upon discontinuation of treatment**, **very rare cases of microscopic** lymphocytic colitis may occur mainly **lymphocytic have occurred in the absence of treatment discontinuation after occurrence of diarrhoea**. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted. Reason: The analysis of the data collected worldwide on ruscus extract-containing products, and more particularly following the reports in France of occurrence of colitis, we propose to clarify the latter: 'Rare local reaction reversible on discontinuation of the treatment' should be added. Reason: we suggest adding mention of possible local reactions reversible upon discontinuation of the treatment. Traditional use (for rectal use): 'Rare local reaction reversible on discontinuation of the treatment' should be added. Reason: we suggest adding mention of possible local reactions reversible upon discontinuation of the treatment.	**Not endorsed** Well-established use is not endorsed. See comments above **Not endorsed** for traditional use. **Not endorsed**: The rectal use is not endorsed.

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
	Well-established use "Nausea, gastrointestinal complaints, diarrhoea, lymphocytic colitis may occur. The frequency is not known. If another adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted	**Not endorsed** Well-established use not endorsed. See comments above.
	We agree with the statement under "undesirable effects" for traditional use, for the following reasons: - 5 cases reports of diarrhoea have been described in the French literature following administration of Cyclo 3 fort (150 mg butcher's broom dry extract + 150 mg hesperidin methylchalcone + 100 mg ascorbic acid per capsule) - A case report of collagenous colitis following administration of Cyclo 3 fort has been recently been published. This observation allowed the regional pharmacological centre of Besançon (France) to compile 13 lymphocitic colitis - The present undesirable effects are already included in the SPC of the mentioned medicinal product. Although this product is a mixture of a herbal preparation and chemical substances, it can be reasonable to consider that the herbal preaparation is responsible of the undesirable affects based on its composition (presence of saponins)	**Endorsed**
4.9 Overdose	Well-established use "No case of overdose has been reported".	**Not endorsed** Well-established use not endorsed. See comments above.

5. PHARMACOLOGICAL PROPERTIES		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
5.1 Pharmacodynamic properties	In vitro and in vivo experiments showing the effect of Ruscus on vasoprotection, vasoconstriction, permeability, lymph vessels and elastase activity have been described in details in the ESCOP monograph.	**Not endorsed.** In vitro studies, as well as in vivo studies performed in animals were taken into account in the assessment report. However, results of preclinical pharmacodynamic studies are not included in section 5.1 of the SPC of pharmaceuticals.
	With regard to in vitro and in vivo effects, […] we would like to refer to the ESCOP monograph [2003].	
	With regard to in vitro and in vivo data, […] we would like to refer to the ESCOP monograph.	
5.2 Pharmacokinetic properties	Detailed data on pharmacokinetics in animals […] are available in the ESCOP monograph.	**Not endorsed.** Results of preclinical pharmacokinetic studies are not included in section 5.2 of the SPC of pharmaceuticals. In addition, it was considered that the pharmacokinetic studies performed in animals with an extract of Ruscus could not be taken into account for regulatory purposes (see assessment report).
	Detailed data on pharmacokinetics in animals […] are available in the ESCOP monograph.	
5.3 Preclinical safety data	Detailed preclinical and clinical safety data can be found in the ESCOP monograph.	**Not endorsed.** Studies mentioned in the ESCOP monograph were reviewed and present serious limitations as detailed in the assessment report. Therefore, they cannot be taken into consideration for regulatory purposes. Clinical safety data should not be mentioned in section 5.3.
	Detailed preclinical and clinical safety data can be found in the ESCOP monograph.	

References:

[1] **Vanscheidt W, Jost V, Wolna P, Lucker PW, Muller A, Theurer C et al.** Efficacy and safety of a Butcher's broom preparation (Ruscus aculeatus L. extract) compared to placebo in patients suffering from chronic venous insufficiency. *Arzneimittelforschung* 2002; 52: 243-50.

[2] **Vanscheidt W, Heidrich H, Junger M, Rabe E.** Guidelines for testing drugs for chronic venous insufficiency. *Vasa* 2000; 29: 274-8.

[3] **Boyle P, Diehm C, Robertson C.** Meta-analysis of clinical trials of Cyclo 3 Fort in the treatment of chronic venous insufficiency. *Int Angiol* 2003; 22: 250-62.

[4] **Diehm C, Trampisch HJ, Lange S, Schmidt C.** Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. *Lancet* 1996; 347: 292-4.

[5] **Ramelet AA, Boisseau MR, Allegra C, Nicolaides A, Jaeger K, Carpentier P et al.** Veno-active drugs in the management of chronic venous disease. An international consensus statement: current medical position, prospective views and final resolution. *Clin Hemorheol Microcirc* 2005; 33: 309-19.