European Medicines Agency
Evaluation of Medicines for Human Use

London, 16 July 2009
Doc. Ref.: EMEA/HMPC/262723/2009

OVERVIEW OF COMMENTS RECEIVED ON COMMUNITY HERBAL MONOGRAPH ON *AESCULUS HIPPOCASTANUM* L., SEMEN

This document was valid from 16 July 2009 until 15 January 2020.

Table 1: Organisations that commented on the draft Community herbal monograph on '*Aesculus hippocastanum* L., semen' as released for public consultation on 4 September 2008 until 15 January 2009.

	Name of organisation or individual
1	Association of the European Self-Medication Industry (AESGP)
2	A.Vogel Group / Bioforce AG, Switzerland
3	European Scientific Cooperative on Phytotherapy (ESCOP)
4	Kooperation Phytopharmaka, Germany
5	Dr. Willmar Schwabe GmbH & Co. KG

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Table 2: Discussion of comments

GENERAL COMMENTS	
Comment and Rationale	**Outcome**
Well-established use We suggest to modify and add: Well-established use ~~Dry extract (4.5-5.5:1, 50 % aqueous ethanol) quantified to contain 16-20% triterpene glycosides, calculated as aescin~~ **Dry extract (40-80% (V/V) ethanol), standardised to contain a defined content between 16% and 28% triterpene glycosides, calculated as aescin.** Extracts prepared from *Aesculus hippocastani* semen are standardised to contain a defined content of triterpene glycosides, calculated as aescin. Due to the fact that the main active component is known and a standardisation is defined in the Pharm. Eur. monograph, a DER has not to be given. A new Cochrane review (2007) summarised the clinically efficacy of different dry extracts, standardised to contain a defined content of triterpene glycosides, calculated as aescin. The extracts included contain 50 mg up to 75 mg triterpene glycosides calculated as aescin in a single dose, with a daily dosage of 100 mg up to 150 mg aescin. Slightly different extraction agents are used. Extracts have a DER of 5-7:1. The above mentioned dry extracts fulfil the clinically used and tested single dosages of 50 mg or 75 mg triterpene glycosides calculated as aescin. Bearing in mind that there are different dry extracts in the marked containing the same amount of the therapeutically relevant triterpene glycosides calculated as aescin, we recommend to include all these extracts in this monograph.	Following the proposal of several interested parties, the extract for well-established use should be defined as: Dry extract (40-80% (v/v) ethanol), standardised to contain a defined content between 16% and 28% triterpene glycosides, calculated as aescin. The posology of the extract should be adjusted to correspond to 50 mg aescin 2 times daily. The data in support of aescin as responsible for the therapeutic effect of horse chestnut seed extract is very weak, but the extracts used in most clinical trials appear to be produced as a standardized extracts.

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AESGP welcomes, in principle, the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for *Aesculus hippocastanum*-containing products, should facilitate mutual recognition in Europe. However, the HMPC draft monograph limits the well-established use of this plant, which is extensively studied, to only one specific preparation and leaves out other preparations which qualify for the traditional use. **Important note: Hydroethanolic dry extracts, used in a daily dosage calculated as 50 mg aescin 2 times daily, have been on the European market for over 30 years and have been subject to clinical studies justifying their well-established use. For this reason the mentioned extracts, i.e. the dry extract (ethanol 40-80 % (V/V)), standardised to contain between 16 and 20 % triterpene glycosides, calculated as aescin, as well as the dry extract (ethanol 68 % (V/V)), standardised to contain between 24 and 28 % triterpene glycosides, calculated as aescin, should be allocated to the well-established medicinal use category.** **In case this is not accepted in spite of the arguments given below, the respective preparations should be added to the traditional use category, as tradition is undoubtedly proven.**	Extracts made with 40-80% ethanol are now considered well-established (see above).
1. Traditional use For this section Bioforce AG recommends to consider the evidence that is provided for own preparations supporting the use of oral dosage forms and propose to extend the traditional use to this category of products. The preparations to which reference is taken are the following: - A dry extract from fresh horse chestnut seeds (*Aesculus hippocastanum* L., semen rec.) standardised to contain 8% triterpene glycosides, calculated as anhydrous β-aescin (HPLC). The extraction solvent is ethanol 68% V/V, the DER is 4-6:1 (referred to the dried drug). - A tincture from fresh horse chestnut seeds (*Aesculus hippocastanum* L., semen) with a drug to extraction solvent ratio of 1:2.6, quantified to 12.8 - 29.3 mg β -aescin/ml, extraction solvent ethanol 68% V/V. This tincture is also the starting material for the manufacture of the above-described dry extract.	Extracts produced by 68% ethanol are now included in the well-established use monograph (see above).

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Bioforce AG / A.Vogel group has marketed the horse chestnut seeds tincture (*Aesculaforce tincture*) for oral medicinal use in Switzerland and EU member states since the early seventies. The extract was first produced as a mother tincture, then towards end of the end of the nineties, as tincture in a fix drug to extraction solvent ratio corresponding to the mean ratio of the mother tincture. On the basis of this tincture a solid dosage form in two strengths was subsequently developed: *Aesculaforce Tablets 20 mg*, standardised to contain 20 mg aescin/tablet and *Aesculaforce Tablets 50 mg*, standardised to contain 50 mg aescin /tablet. The tincture and the solid dosage form are presently still available as medicinal product in Switzerland and in the EU.	
2. Well-Established Use In the draft monograph for the well-established use a dry extract (4.5-5.5:1, 50% aqueous ethanol) quantified to contain 16-20% triterpene glycosides, calculated as aescin, is described. Bioforce AG proposes to include in the scope of the monograph an own extract, for which published clinical data supporting the well-established use indication are available. The Bioforce AG preparation is a dry extract from fresh Horse chestnut seeds (*Aesculus hippocastanum* L., semen rec.) standardised to contain 8% triterpene glycosides, calculated as anhydrous β-aescin (HPLC). The extraction solvent is ethanol 68% V/V, the DER is 4-6:1 (referred to the dried drug). The pharmaceutical for is a gastro-resistant tablet, which is available in 2 strengths: *Aesculaforce Tablets 20 mg*, standardised to contain 20 mg aescin/tablet and *Aesculaforce Tablets 50 mg*, standardised to contain 50 mg aescin /tablet. For the above-mentioned preparations the following references are provided: - Shah D, Bommer S, Degenring FH. Aesculaforce bei chronisch venöser Insuffizienz. Placebokontrollierte Doppelblind-Studie zum Nachweis der Wirksamkeit und Verträglichkeit eines Phytotherapeutikums. [Aesculaforce in chronic venous insufficiency. Placebo controlled double blind trial to demonstrate the efficacy and tolerability of a plant remedy.]Schweiz Z Ganzheitsmed. 1997;9:86-91. - Dickson S, Gallagher J, McIntyre L, Suter A, Tan J. An open study to assess the safety and efficacy of Aesculus hippocastanum tablets (Aesculaforce 50 mg) in the treatment of chronicvenous insufficiency. J Herbal Pharmacother. 2004;4:19-32.	Extracts produced by 68% ethanol are now included in the well-established use monograph (see above).

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SPECIFIC COMMENTS ON TEXT		
2 Qualitative and quantitative composition	**<u>Well-established use</u>** For a well-established medicinal use, a standardised hydroethanolic extract containing 16-20% triterpenglycosides, calculated as aescin, is described. For the sake of completeness it should be clarified that the ethanol content of the extraction solvent is defined in volume <u>(V/V), not mass (m/m)</u>. Following recent discussions on the monograph for horse chestnut dry extract, standardised, published in Pharmeuropa, the method used to determine the content of triterpene glycosides should be mentioned. At present, a photometric method (method A according to Pharmeuropa) is used. According to the Pharmeuropa draft monograph, horse chestnut dry extract is not a quantified, but a **standardised** extract. This is in line with the fact that triterpene glycosides, calculated as aescin, are considered components with known therapeutic activity. This corresponds to the dosage recommendation of the HMPC draft monograph. Furthermore, we propose deleting information on the DER because it is not required according to the Ph. Eur. As the extract is standardised based on aescin, the substance bearing the activity, the amount of aescin is decisive for the therapeutic efficacy and not the DER. However, in case the DER is maintained, we propose to include a DER of 4.5-7:1. The declaration should hence read: ***"Dry extract (4.5 - 7:1, ethanol 40-80% (V/V), standardised to contain 16 - 20 % triterpene glycosides, calculated as aescin, or dry extract (4.5 - 7:1, ethanol 68 % (V/V), standardised to contain 24 - 26 % triterpene glycosides, calculated as aescin"***. This would cover the extract mentioned in the HMPC draft as well as extracts which exist on the	Dry extracts made with ethanol 40-80% (v/v) are now included in the monograph (see above). The photometric method should be mentioned in the monograph. No clinical data on methanol have been provided and these extracts are consequently not included in the monograph. In a standardised extract, the DER could be omitted.

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	European market and which will be described in the European Pharmacopoeia. They have a DER of 5 - 7:1 and are produced with ethanol 40 to 80 % (V/V) to contain 16-20% triterpene glycosides, or with ethanol 68 % (V/V) to contain 24 to 28 % triterpene glycosides. These extracts have been proven equivalent to the extract prepared with ethanol 50 % (see below) and should therefore be included as a "well-established medicinal use" preparation.	
2 Qualitative and quantitative composition	**Well-established use** To be included: *Aesculus hippocastanum* L., semen rec. (fresh horse chestnut seed) Herbal preparations Dry extract (ethanol 68% V/V) standardised to contain 8% triterpene glycosides, calculated as anhydrous β-aescin. Comment: The native dry extract contains 22-32% triterpene glycosides, calculated as anhydrous β-aescin (HPLC). Referring to the requirements of the Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products in the SPC EMEA/HMPC/CHMP/CVMP/287539/05, we suggest omitting the DER as the preparation in question is a standardised extract. However, should it be required to mention the DER, than the declaration would be: Dry extract (4-6:1, ethanol 68% V/V) standardised to contain 8% triterpene glycosides, calculated as anhydrous β-aescin. (The DER of 4-6:1 is referred to the dried drug)	This extract is likely to be covered by the WEU monograph, but it has to be assessed individually in the framework of an application.

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2 Qualitative and quantitative composition	**Well-established use** Well-established use **We propose replacement of the word "quantified" by "standardised"** In the recent draft monograph on "Aesculus extract – horse-chesnut dry extract" published in *Pharmeuropa* (2008;20:478-83),the term "standardised" is used, rather than "quantified". This accords with the general definition of Extracts in the European Pharmacopoeia, on the basis that triterpene glycosides, calculated as aescin, are regarded as constituents with known therapeutic activity. The same amendment is required in Sections 4.2 (Posology) and 5.1 (Pharmacodymanic properties). Traditional use Herbal preparations There are no scientific data to justify such precise definitions of the herbal preparations for traditional and external use, particularly when limits are defined (under Posology) for the aescin content of the ointments/gels into which they are to be incorporated. **We propose the following herbal preparations to introduce a measure of flexibility:** • Dry extract (4.5-8:1, extraction solvent: aqueous ethanol or methanol, 50-80%). • Tincture (1:5, extractions solvent: aqueous ethanol 45-60%). Fluid extract (1:1, extraction solvent: aqueous ethanol 45-60%).	Concerning "standardised " extract, see above. No justification is given why "flexibility" should be introduced in the definition of extracts. Flexibility can be considered within the framework of an individual application.
2 Qualitative and quantitative composition	**Traditional use** Dry extract (~~4.5-5.5:1,~~ 50 % aqueous ethanol)	Extracts that are covered by the well-established use monograph should not be included in the traditional use monograph for a similar indication. Data on traditional use of methanol extracts have not been provided.

[1] Should the data justifying the well-established use of this preparation not be accepted, the preparation should be mentioned under traditional use given its long experience on

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	Dry extract (ethanol 40 - 60 %(V/V)) **Dry extract (ethanol 68 % (V/V))** **Dry extract (methanol 80 % (V/V))** **Dry extract (methanol 40 - 60 %(V/V))** [1] **Liquid extract (ethanol 25% (V/V)** Tincture (1:5, extraction solvent: 50% aqueous ethanol v/v~~), 20 % in an ointment/gel base~~ **Tincture (1:10; ethanol 65% V/V)** We propose to add further dry extracts because they have been traditionally used in Europe, e.g. on the German market. Some of them have already been mentioned under "well-established use". Independently from their clinical proofs of efficacy, however, a tradition of more than 30 years exists in Europe. These extracts correspond to the German Pharmacopoeia (DAB) (ethanol or methanol, approximately 40-60% V/V) or are produced using comparable solvents e.g. ethanol 68%. In case this is not accepted in spite of the arguments given below, the respective preparations should be added to the traditional use category. Further dry extracts can also prove their traditional use. As example of dry extract (ethanol 60% (V/V)) we would like to mention the preparation "Venen Aktiv Kapseln" traditionally used on the German market (one capsule contains 32.4 mg dry extract from horse chestnut seed (5-7:1), extraction solvent ethanol 60% (V/V), 3.0 mg rutoside trihydrate).	Data on the the tincture 1:10 for oral use with a traditional use in France are insufficient for inclusion in the monograph.

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	Methanolic dry extracts are included in the German list according to section 109a of the German Medicines Law for both oral administration and topical application, e.g. a dry extract (5 - 10:1, methanol 80% (V/V)) [List according to section 109a AMG]. As example of liquid extract (ethanol 25% (V/V)) we would like to mention the preparation "Fagorutin Roßkastanien-Balsam N" traditionally used in Germany (100 g emulsion for external use contain liquid extract from horse chestnut seed (1:1; extraction solvent ethanol 25% V/V) 3.000 g; rutosid sulphuric acid ester, sodium salt 0.100 g; levomenthol 0.500 g). The tincture (1:10; ethanol 65% V/V) is marketed in France since 1965 and hence fulfils the 30 years criteria; we would like to have it added to the traditionally used preparations.	
2 Qualitative and quantitative composition	**<u>Traditional use</u>** To be included: *Aesculus hippocastanum* L., semen rec. (fresh horse chestnut seed) <u>Herbal preparations</u> Dry extract (ethanol 68% V/V), standardised to contain 8% triterpene glycosides, calculated as anhydrous β-aescin. and Tincture (drug to extraction solvent ratio of 1:2.6, extraction solvent: ethanol 68% V/V), quantified to 12.8 - 29.3 mg β -aescin/ml	A 68% ethanol extract would now be included in the well-established use monograph.

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	Comment: The above-mentioned dry extract is a standardised extract. Therefore, in line with the requirements of the Guideline on Declaration of Herbal Substances and Herbal Preparations in Herbal Medicinal Products/Traditional Herbal Medicinal Products in the SPC EMEA/HMPC/CHMP/CVMP/287539/05, we suggest omitting the DER. However, should it be required to mention the DER, than the declaration for extract in question would be: Dry extract (4-6:1, ethanol 68% V/V) (The DER of 4-6:1 is referred to the dried drug)	
2 Qualitative and quantitative composition	**<u>Traditional use</u>** <u>Traditional use</u> ~~Dry extract (4.5-5.5:1, 50 % aqueous ethanol)~~ **Dry extract (40-80% (V/V) ethanol)** **Dry extract (40-80% (V/V) methanol)** A more than 30 years tradition exists in Europe for the above mentioned hydroalcoholic dry extracts, extracted with 40-80% ethanol (V/V) and 40-80% methanol (V/V) respectively. In Germany different preparations with a daily dosage of 100 mg up to 150 mg triterpene glycosides calculated as aescin are mentioned in the "Rote Liste 1971". These preparations correspond to the dry and liquid extracts added. Horse chestnut seed methanolic and ethanolic extracts are also registered according to § 109a of the German Medicines Law (AMG), as traditionally used extracts.	Extracts that are covered by the well-established use monograph should not be included in the traditional use monograph for a similar indication. Data on traditional use of methanol extracts have not been provided.

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3. Pharmaceutical form	**Well-established use** ~~Herbal preparations in prolonged release dosage forms for oral use~~ **Herbal preparations in prolonged release or other dosage forms for oral use.** The pharmaceutical form should be described by the European Pharmacopoeia full standard term. According to existing pharmaceutical, clinical and pharmacokinetic data, the prolonged release dosage form is not essential for the therapeutic efficacy. Therefore, other preparations not described as extended release are also effective and can be allocated to the well-established and traditional medicinal use. Reasons From pharmacokinetic, pharmaceutical and clinical data it can be concluded that all these dosage forms are therapeutically equivalent. **See the document**	Dosage forms for immediate release have been included in the monograph.
3. Pharmaceutical form	**Well-established use** As summarized under "Pharmacokinetics in humans" in the ESCOP monograph (2003) on Hippocastani semen [1], human pharmacokinetic studies have failed to demonstrate any significant difference in the bioavailability of aescin from rapid-release and prolonged-release oral dosage forms containing horse-chesnut seed extracts. There is no scientific evidence to support a restriction to prolonged-release dosage forms only. **We propose deletion of the term "prolonged release", so that the sentence reads:** Herbal preparations in dosage forms for oral use.	See above.

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3. Pharmaceutical form	**<u>Well-established use</u>** We suggest to add the following passages: Herbal preparations ~~in prolonged release dosage forms~~ for oral use. As mentioned above, there are different herbal preparations on the European market, which are in line with the well-established use as well as with the traditional use. They are described in §109a of the German Medicines Law, where medications with traditional use are registered. Additionally there are at least two reasons not to restrict the well established use to specific galenic forms. Firstly, the release of the prolonged release form available in the market is not retarded: more than 50% of the active agent is released within 2 hours in an acidic solution [Kolkmann and Böttcher 1994]. Further *in vitr*o dissolution tests confirm that different release dosage forms are pharmaceutical equivalent, because the increase and terminal value of release of all these preparations are comparable [Deffner 1998]. A truly prolonged release dosage form has to release the active agent delayed and continuously over a long period of time. The aim is a prolonged therapeutic effect with a decreased frequency of intake. This is not given her, because the "prolonged" release form has to be taken two times daily as well as the non-prolonged release dosage form with the same content of triterpene glycosides calculated as aescin. Secondly, the retardation is not essential for the therapeutic efficacy, because the elimination of aescin is so slow (terminal half-life of 10 to 19 hours), that a prolonged release will not relevantly influence the aescin concentration in the serum. Serum concentration/time curves and additional pharmacokinetic parameters shown in different studies did not demonstrate any significant differences between absorption rates for the prolonged versus the non-prolonged release preparation [Bässler et al. 2003, Kunz et al. 1998].	See above.

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	The fact that the galenic form is not crucial for the therapeutic efficacy is also supported by a new Cochrane Review, which does not differentiate between different dosage forms. This review came to a positive assessment for the efficacy and also for the safety of horse chestnut seed extracts [Pittler and Ernst 2007].	
3. Pharmaceutical form	**<u>Well-established use</u>** We propose to change: „Herbal preparations in **prolonged-release** dosage forms“ into: „Herbal preparations in **modified-release (prolonged- or delayed-release)** dosage forms“. **Rationale:** The most important well-established use products containing horse chestnut extract and registered for many years are modified release formulations which should meanwhile be described as “prolonged-release” or “delayed-release” dosage forms, referring to the current version of Ph.Eur. (2.9.3.). The basic purpose of modifying (prolonging or delaying) the release of horse chestnut extract in oral herbal medicinal products was to avoid gastric irritations caused by aescin, but not to modify the aescin blood levels from an efficacy perspective. This is in line with the statement in section 5.2 of the draft monograph for well-established use: “The pharmacokinetic parameters of aescin are not considered relevant for the dosing regimen of horse chestnut extract.” Consequently, no dissolution profile is specified in section 5.2. We agree with the HMPC’s assessment that in view of the gastric intolerability of aescin, immediate release dosage forms for oral use should not be covered by the monograph, neither in the well-established nor in the traditional use section.	According to the monograph, the frequency of gastrointestinal side effects is not known.

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3. Pharmaceutical form	**Traditional use** **Solid or liquid herbal preparations for oral use.** Solid or liquid preparations for oral use should be included because they have a long tradition in Europe (e.g. Germany – cf. Rote Liste 1971, France, etc.)	No oral use accepted.
3. Pharmaceutical form	**Traditional use** To be included: Solid and liquid dosage forms for oral use.	No oral use accepted.
3. Pharmaceutical form	**Traditional use** We suggest to add the following passages: Traditional use: **Solid preparations for oral use.**	No oral use accepted.
4.1. Therapeutic indications	**Well-established use** **We propose an *additional* indication:** C) for the symptomatic relief of itching and burning associated with haemorrhoids. The French regulatory guideline, *Médicaments à base de plantes* (1998) [2] and earlier editions back to 1986, accepts the use of horse-chestnut seed (Marron d'Inde) "dans la symptomatologie hémorrhoïdaire" and the above wording has already been adopted in the Community monograph for *Ruscus aculeatus* L., rhizoma.	No medicinal products are avaible in such indication according to the French Authorities. Furthermore, no adequate information on the medicinal use in this indication could be retrieved. Thus, it is not accepted.

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4.1. Therapeutic indications	**<u>Traditional use</u>** **c) Traditional herbal medicinal product used in the treatment of venous insufficiency and haemorrhoids.** Products containing aesculus (alone or in combination with other plants) have been used to treat venous insufficiency and haemorrhoids in Europe (e.g. France) for extensive period of time. Such indication should thus be added to the traditional ones.	No oral use accepted.
4.1. Therapeutic indications	**<u>Traditional use</u>** To be included: Traditional herbal medicinal product for the relief of symptoms associated with venous insufficiency and varicose veins, such as tired heavy legs, aching painful legs, cramps, swelling, restless legs and unsightly veins.	No oral use accepted.
4.2. Posology and method of administration	**<u>Well-established use</u>** **Posology** ***Adolescents**, adults and elderly* 240 - 290 mg of **dry** extract ~~quantified to a content of~~ **(ethanol 40 - 80 % (V/V), standardised to contain 50 mg of triterpene glycosides, calculated as aescin, 2 times daily.** **146 - 203 mg of dry extract (ethanol 68 % (V/V), standardised to contain 50 mg triterpene glycosides, calculated as aescin, 2 times daily.** The product is not intended for **children** ~~and adolescents~~ under ~~18~~ **12** years of age. The proposed dosage recommendations are in line with the types of extracts listed under section 2. and the dosage of the preparations in	The posology of ethanol extracts should correspond to 50 mg aescin twice daily. The 68 % ethanol extract can make reference to the monograph, but it's applicability has to be assessed individually in the framework of an application. No change of the monograph. The products covered by the monograph are not intended for adolescents, but they are neither contraindicated in this patient group. No change of the monograph.

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	the market. The use should not be restricted to adults as preparations on the market are licensed for use from 12 years onwards. There are no differences between adults and adolescents which could be the basis of a different tolerability of these preparations, as is confirmed by pharmacovigilance data. Thus there is no rationale for the exclusion of adolescents from the use.	
4.2. Posology and method of administration	**Well-established use** To be included: 157.5-225.0 mg dry extract (ethanol 68% V/V), corresponding to 50 mg triterpene glycosides, calculated as anhydrous β-aescin, 2 times daily.	See above.
4.2. Posology and method of administration	**Well-established use** We propose replacement of the word "quantified" by "standardised" As explained above for Section 2.	Accepted.
4.2. Posology and method of administration	**Well-established use** We propose the following amendments: **Adolescents**, ~~A~~adults and elderly Well-established use: 240-290 mg of **dry** extract ~~(quantified to a content of 50 mg aescin)~~ **(40% - 80% (V/V) ethanol) or 146-203 mg of dry extract (68% (V/V) ethanol), standardised to contain 50 mg triterpene glycosides,** 2 times daily The product is not intended for children ~~and adolescents~~ under ~~18~~ **12** years of age.	See above.

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	17 clinical studies were recently systematically analysed in a Cochrane review [Pittler and Ernst 2007]. The most common preparations were standardised to 50 mg triterpene glycosides, calculated as aescin, twice daily. The earliest incorporated studies were published in 1976 and 1978 [Neiss and Böhm 1976, Friederich et al. 1978] and document, in addition to the efficacy, also the traditional use of these extracts. Further herbal preparations, which are also traditionally used, are mentioned in the German "Rote Liste 1971" with a daily dosage of 100 up to 150 mg triterpene glycosides, calculated as aescin. The use of these preparations should also include children up to 12 years. There are preparations in the market and registered by the German regulatory agency BfArM for this age group which therefore have been included into the pharmacovigilance system for drugs. There have never been reported any safety concerns due to side effects or adverse events for patients of this age group. Despite the fact, that horse chestnut preparations are used in these age groups comparatively rarely, the decision to use or not to use them in these patients should be left over to the health practitioner or physician, and should not be restricted by this monograph more than necessary.	
4.2. Posology and method of administration	**<u>Traditional use</u>** **Posology** **<u>Oral use (indications A and B)</u>** **Dry extract (ethanol 40 - 60 %(V/V)), dry extract (ethanol 68 % (V/V)), dry extract (methanol 80 % (V/V)), dry extract (methanol 40 - 60 %(V/V)); all corresponding to 100 - 150 mg aescin daily** **Dry extract (ethanol 60% (V/V)):** **2 capsules daily each containing 32.4 mg dry extract *)**	The dry ethanol extracts 40-60% are included in the well-established monograph and should not appear in the traditional use monograph for a similar indication. The posology of the tincture for oral use has been insufficiently documented to be included in the monograph on traditional use. For cutaneous use of the dry extract, a span of 25-50% ethanol as extraction solvent has been introduced and the

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	<u>Oral use (indication C)</u> **Tincture: 100-150 drops of tincture in ethanol 65% V/V (1:10) up to 3-4 times daily, as a single dose.** **<u>Topical use</u>** Dry extract (~~4.5-5.5:1 aqueous~~ ethanol 50 % V/V) in a strength … **Liquid extract (ethanol 25% (V/V)) a semi-solid preparation: 1-2 times daily**)** **Method of administration** For **oral and** cutaneous use. We suggest adding dry extracts corresponding to 100 - 150 mg aescin daily. These products are included in the list according to section 109a of the German Medicines Law. *) Note: as an example for a dry extract (ethanol 60% (V/V)) the preparation "Venen Aktiv Kapseln" is mentioned with a daily dose of 2 capsules corresponding to a daily dose of 64.8 mg dry extract. **) Note: the mentioned liquid extract (ethanol 25% (V/V)) in "Fagorutin Roßkastanien-Balsam N" is topically applied 1-2 times daily in a 3% emulsion. The posology of the tincture corresponds to products on the market. As mentioned above, we suggest leaving out the DER because it is not required according to Ph.Eur.	DER has been omitted.
4.2. Posology and method of administration	**<u>Traditional use</u>** To be included: Adults and elderly: Dry extract (ethanol 68% V/V), corresponding to a daily dose of 100 mg aescin.	Dry extracts made with 68% ethanol are included in the well-established use monograph.

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4.2. Posology and method of administration	**<u>Traditional use</u>** We propose *additional* definitions for ointments/gels: • Dry extract (4.5-8:1, extraction solvent: aqueous ethanol or methanol, 50-80%) in a strength corresponding to 0.7-2.0% aescin in an ointment/gel base. • Tincture (1:5, extraction solvent: aqueous ethanol 45-60%) in a strength corresponding to 0.7-2.0% aescin in an ointment/gel base. • Fluid extract (1:1, extraction solvent: aqueous ethanol 45-60%) in a strength corresponding to 0.7-2% aescin in an ointment/gel base. The efficacy of a 2% aescin gel for the treatment of haematoma has been demonstrated [3]. Duration of use: We propose that the heading "Indication A) be extended to read: Indication A) and C).	This broadening of the spans has not been adequately substantiated by the documentation for traditional use. No further change of the monograph in this respect.
4.2. Posology and method of administration	**<u>Traditional use</u>** <u>Traditional use:</u> Posology **Oral use** **Indication A) and B)** **All extracts corresponding to 100 – 150 mg triterpene glycosides, calculated as aescin, daily** **• Dry extract (40-80% (V/V) ethanol)** **• Dry extract (40-80% (V/V) methanol)** **Topical use** • Dry extract (~~4.5-5.5:1 aqueous~~ ethanol 50 % v/v**)** in a	See above.

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	strength corresponding to 0.7-1.5 % triterpene glycosides, calculated as aescin in an ointment/gel base • Tincture (~~1:5; extraction solvent:~~ 50% ~~aqueous~~ ethanol v/v), 20% **triterpene glycosides, calculated as aescin** in an ointment/gel base Indication A) **Adolescents**, ~~Aa~~adults and elderly **For oral use: 2 times daily, up to maximum daily dose of 100 – 150 mg triterpene glycosides calculated as aescin** **For topical use:** Apply a thin layer on the affected area 1-3 times per day. Indication B) Adolescents, adult and elderly **For oral use: maximum daily dosage of 100 – 150 mg triterpene glycosides calculated as aescin** **For topical use:** Apply a thin layer on the affected area 1-3 times per day.	
4.4. Special warnings and precautions for us	**Traditional use** We suggest including the following modification: "*The products should not be used on broken skin, around the eyes or on mucous membranes* ***(only applies to topical use)***" because this is not relevant for the oral use.	Indication B is cutaneous use, only. No change required.
4.4. Special warnings and precautions for use	**Well-established use** We propose to delete the statement "The diagnosis should be established by a doctor" in the well-established use section.	Proposal accepted.

Superseded

	Rationale: For the well-established use indication, it is required that the diagnosis should be established by a doctor, whereas for the traditional use indication A), a doctor or a qualified health care practitioner should be consulted only, if the symptoms persist for more than 2 weeks during the use of the medicinal product, if there is inflammation of the skin, thrombophlebitis, varicosis or subcutaneous induration, ulcers, sudden swelling of one or both legs, cardiac or renal insufficiency, or if symptoms worsen or signs of skin infections occur during the use of the medicinal product. The well-established use indication („*treatment of chronic venous insufficiency, which is characterised by swollen legs, varicose veins, a feeling of heaviness, pain, tiredness, itching, tension and cramps in the calves*“) and the traditional use indication A) („*relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances*“) are worded in a way that an average patient cannot be expected to distinguish whether he suffers from „*minor venous circulatory disturbances*“ or from „*chronic venous insufficiency*“ on symptoms alone. The need for consulting a health care professional is not based on compound-related risks but on prevention of risks from delayed medical treatment of chronic venous insufficiency or other diseases that can result in comparable symptoms, like deep vein thrombosis or renal failure. This need is identical for both, the well-established use indication and the traditional use indication A). The HMPC deemed it adequate to recommend consultation of a health care professional only under certain, clearly described circumstances for traditional use indication A), and we agree. Therefore the identical recommendation should apply for the well-established use indication, too. There is no obvious reason why the more stringent recommendation of a physician’s diagnosis is required for the oral preparation	

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	In many European countries, oral horse chestnut preparations have been marketed as over-the-counter or behind-the-counter drugs for decades and no specific risk has arisen from this regulatory practice. Requesting a physician's diagnosis in any case for oral preparations would markedly change and limit patient access to these drugs and increase healthcare costs.	
4.6. Pregnancy and lactation	**Well-established medicinal use** We would like to mention that the German "Rote Liste 1971" mentions varicosis during pregnancy as an indication. Despite that fact, we do not suggest to change the draft.	No change in the monograph.
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~~. **No adverse effects have been reported in clinical studies involving pregnant women. Due to general safety considerations the herbal medicinal product should not be used without medical advice.** Horse chestnut seed extracts have been applied in clinical trials involving pregnant women. No adverse effects have been reported [Alter 1973, Steiner and Hillemanns 1990]. Additionally in Germany "Rote Liste 1975" the indication of gestational varicosis is given for an orally taken horse chestnut seed extract in a daily dosage of 100 mg triterpene glycosides calculated as aescin. Nevertheless, based on general safety considerations, herbal preparations containing horse chestnut seed extracts should not be administered during pregnancy and lactation without medical advice.	No change in the monograph.
4.6. Pregnancy and lactation	**Traditional use** From our point of view, the topical use should not be excluded in pregnancy and lactation, because a negative influence is not to be expected	No data available. No change of the monograph.

Superseded

4.6. Pregnancy and lactation	Traditional 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~~. **No adverse effects have been reported in clinical studies involving pregnant women. Due to general safety considerations the herbal medicinal product should not be used without medical advice.** Horse chestnut seed extracts have been applied in clinical trials involving pregnant women. No adverse effects have been reported [Alter 1973, Steiner and Hillemanns 1990]. Additionally in Germany "Rote Liste 1975" the indication of gestational varicosis is given for an orally taken horse chestnut seed extract in a daily dosage of 100 mg triterpene glycosides calculated as aescin. Nevertheless, based on general safety considerations, herbal preparations containing horse chestnut seed extracts should not be administered during pregnancy and lactation without medical advice.	No change in the monograph.
4.7. Effects on ability to drive and use machines	**Well-established medicinal use and traditional use** We suggest adding as a first sentence ***"There is no evidence of a potential influence on the ability to drive and use machines"*** because this is general knowledge and might explain the absence of studies	Standard text in monograph. No change.
4.7. Effects on ability to drive and use machines	**Well-established medicinal use and traditional use** We suggest to substitute the following sentences: Well-established use ~~No studies on the effect on the ability to drive and use machines have been performed.~~ **There is no evidence for a potential effect on the ability to drive and use machines.**	Standard text in monograph. No change.

Superseded

4.8. Undesirable effects	**<u>Well-established medicinal use</u>** According to experiences in some countries, e.g. Germany, and to pharmacovigilance data, we propose that the first paragraph be completed with frequencies: *"**Occasionally** gastrointestinal complaints, headache, vertigo**. In rare cases** pruritus and allergic reactions have been reported."* With regard to the preparation Venostasin retard (prolonged-release dosage form) we propose the wording ***"In rare cases gastrointestinal complaints, headache, vertigo, pruritus and allergic reactions have been reported."*** This is in line with the expert information of this preparation (Fachinformation Venostasin retard).	Standard text in monograph. No change.
4.8. Undesirable effects	**<u>Well-established use</u>** We propose the following gradation of the undesirable effects : <u>Well-established use</u> ~~Gastrointestinal complaints, headache, vertigo, pruritus and allergic reactions have been reported.~~ ~~The frequency is not known.~~ **Occasionally gastrointestinal complaints, headache, vertigo haven been reported.** **In rare cases pruritus and allergic reactions can occur**. A gradation of the frequencies of undesirable effects is given in the summary of product characteristics of products registered by regulatory agencies, e.g. the German BfArM.	Standard text in monograph. No change.

Superseded

4.8. Undesirable effects	**<u>Traditional use</u>** For oral use we suggest adding the following paragraph for the same reason: ***"Occasionally gastrointestinal complaints, headache, vertigo. In rare cases pruritus and allergic reactions have been reported."***	Standard text in monograph. No change.
4.8. Undesirable effects	**<u>Traditional use</u>** We propose the following gradation of the undesirable effects : **Occasionally gastrointestinal complaints, headache, vertigo haven been reported.** **In rare cases pruritus and allergic reactions can occur** A gradation of the frequencies of undesirable effects is given in the summary of product characteristics of products registered by regulatory agencies, e.g. the German BfArM.	Standard text in monograph. No change.
5.1. Pharmacody-namic properties	We have no co comments on this section except the need to replace *"quantified"* by *"standardised"*.	Proposal accepted.
5.1. Pharmacody-namic properties	**<u>Well-established use</u>** In accordance with the rationale of paragraph 2, we propose: Based on a systematic review (meta analysis) of 17 clinical trials it can be concluded that horse chestnut seed extract (~~quantified~~ **standardised on triterpene glycosides calculated as** aescin) significantly reduces symptoms of chronic venous insufficiency, such as edema, pain and pruritus compared to placebo.	Proposal accepted.

Superseded

5.2. Pharmacokinetic properties	We propose modifying this paragraph as follows (see table 1 for details): *"Available data on pharmacokinetic parameters for* ***~~the marker substance~~*** *aescin are* ***in accordance with the present dosage regimen.***" (deletion "marker substance" since aescin is the known pharmacologically active compound). The maximum serum concentration of aescin is achieved 1.9 ± 0.8 hours until 2.8 ± 0.8 hours after oral drug intake independent from release dosage form and maximum concentrations are reached of 12.2 ± 1.4 to 18.5 ± 6.5 ng/ml	In view that the extract now is considered standardised, the word "marker" should be deleted. No further changes are accepted (c.f. assessment report).
5.2. Pharmacokinetic properties	**<u>Well-established use</u>** We proposes to change: Available data on pharmacokinetic parameters for the ~~marker substance~~ **major active ingredient triterpene glycosides, calculated as** aescin, **in preparations for oral use** are of limited validity, **but** ~~and not considered relevant for~~ **in accordance with** the dosing regimen of the herbal preparation. The resulting text would be: **Available data on pharmacokinetic parameters for the major active ingredient triterpene glycosides, calculated as aescin, in preparations for oral use are of limited validity but in accordance with the dosing regimen of the herbal preparation.** Equal oral dosages of triterpene glycosides calculated as aescin resulted in similar maximum serum concentrations of 12,2±1,4 ng/ml [Bässler et al. 2003] to 18,5±6,5 ng/ml [Kunz et al. 1998] between 1,9±0,8 hours and 2,8±0,8 hours after intake of the preparation [Bässler et al. 2003]. This effect was independent from the galenic form. A study showing the absorption of aescin after topical has been published by Montenegro et al. [2007].	See above.

Superseded