15 January 2013
EMA/HMPC/697749/2012
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal monograph on *Solanum dulcamara* L., stipites (EMA/HMPC/734361/2011)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Solanum dulcamara* L, stipites, as released for public consultation on 10 May 2012 until 15 August 2012

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	AESGP welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for products containing Solanum dulcamara stipites, should facilitate mutual recognition in Europe. However, in our opinion Sections 2, 4.2 and 4.4 should be amended (cf. specific comments).	These general comments are discussed in detail in the section on specific comments on text below.

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
Comments on the draft assessment report	AESGP	In the draft assessment report, in section 1.2, information about the following products on the market is missing: Germany: Preparation: Extract (1:5), extraction solvent: ethanol 30% m/m, 70 g/100 g of the final product. Preparation on the market: Since 1990 (product still in registration process, name of the product: Cefabene). Pharmaceutical form: oral drops Therapeutic indication and posology: Adjuvant therapy of chronic eczemas, 30-40 drops 4-5 times daily.	Endorsed. The information is added in section 1.2 of the assessment report.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Preparation: Dry extract (5:1), extraction solvent: ethanol 30% m/m, 200 mg Preparation on the market: Since 1991 (product still in registration process, name of the product: Cefabene). Pharmaceutical form: film-coated tablets Therapeutic indication and posology: Adjuvant therapy of chronic eczemas, 1-3 times daily. Preparation: Extract (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product. Preparation on the market: Since 1993 (product still in registration process, name of the product: Cefabene). Pharmaceutical form: Ointment Therapeutic indication and posology: Adjuvant therapy of chronic eczemas, 3-5 times daily. The launch dates of the products marketed in Germany are supported by abstracts from the “Lauer-Taxe” and the “Rote Liste” (cf. annex 1 and 2, respectively). Bulgaria: Preparation: Extract (1:4-5), extraction solvent: ethanol 30% m/m, 9 g/100 g of the final product. Preparation on the market: Since 2006 (marketing authorisation, name of the product: Cefabene). Pharmaceutical form: Ointment Therapeutic indication and posology: For supporting treatment in case of chronic eczema, 3-5 times daily (cf. renewal certificate in annex 3).	

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		In the "regulatory status overview" these products should be amended accordingly. The preparations (ointment) authorised or registered in Bulgaria, Czech Republic, Germany, and Sweden are all identical.	
2. Qualitative and quantitative composition	AESGP	We propose to add the ointment to **well-established use**. ii) Herbal preparations Comminuted herbal substance *Ointment with extract of Solani dulcamarae stipites (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product.* From our point of view the available studies (listed in section 5.1 of the draft assessment report) which have a positive outcome are appropriate to prove the efficacy of the ointment with Dulcamara extract for the treatment of chronic eczema in the field of a well-established use. An additional study which has not yet been evaluated by the MLWP is attached (Tchaika M, Treatment of atopical eczema with Cefabene ointment - Results of a multicentre clinical trial, 1997, cf. annex 4). This study proves the efficacy and tolerance of Cefabene ointment compared with the reference product ointment. If well-established use should not be acknowledged by the MLWP, then alternatively the pharmaceutical form ointment should be added at least for traditional use (see next item).	Not endorsed. The studies included in the assessment report and the additional (unpublished) study submitted by AESGP do not fulfil the requirements for documenting efficacy for a herbal medicinal product with well-established medicinal use described 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 two clinical studies included in the draft assessment report section 5.1 (Eberhardt *et al*., 1995; Oestreich & Stoeter, 1995) are both open studies with no blinding and no control groups. Clearly they do not fulfill the criteria of "at least one controlled clinical study of good quality" that is required to substantiate efficacy for a herbal medicinal product with a well-established use, according to the mentioned guideline. The additionally submitted study by Tchaika is an unpublished study. According to the European Commission, references in support of a well-established

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			use application (Article 10a of Directive 2001/83/EC) must refer to 'published scientific literature' (see Notice to Applicants, Vol 2A, Chapter 1, section 5.4). The study by Tchaika can thus not be considered a valid basis for a well-established use application. Besides the fact that the clinical trial by Tchaika is unpublished, there are still some major scientific issues with the study : 1. The trial was performed in patients with either *acute* or chronic eczema. 2. The trial is small, with only 30 patients in the *Solanum dulcamara* extract-treated group. 3. No placebo group was used. The control group consisted of 30 patients that were treated with an ointment containing bufexamac (an NSAID). The authors concluded that after 4 weeks of treatment, the *Solanum dulcamara* extract and bufexamac had equivalent effects. The CHMP has recently (2010) assessed all clinical data available on bufexamac and concluded that no evidence of efficacy is available for this substance (see Q & A document on bufexamac on EMA website; EMA/CHMP/239923/2010 rev.1 EMEA/H/A-107/1260). From a scientific point of view, the study by Tchaika can thus not be used as evidence of efficacy of the *Solanum dulcamara* extract.

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			In conclusion, the unpublished study by Tchaika can neither for legal nor for scientific reasons be accepted as documentation of efficacy of the *Solanum dulcamara* extract in question.
2. Qualitative and quantitative composition	AESGP	We propose to add the ointment to **traditional use** in case a well-established use is not accepted: ii) Herbal preparations Comminuted herbal substance *Ointment with extract of Solani dulcamarae stipites (1:5), extraction solvent: ethanol 30% m/m, 10 g/100 g of the final product.* Traditional use is justified because of the existence of two registered traditional medicinal products in the EU and one well-established use marketing authorisation. The medicinal product in Germany is marketed with the trade name Cefabene ointment since April 1993 (See above). As stated in section 2.1 of the assessment report the herbal drug Solani dulcamarae stipites has been used for more than 30 years. According to the Commission E (Blumenthal et al., 1998) the herbal substance is used as an infusion or decoction for cutaneous use. The dosage form “ointment” is a further development based on exactly the same therapeutic principle compared with the infusion or decoction and should be included in the Community herbal monograph. Moreover, an ointment is easier to apply on the skin and is more suitable for storage. Enclosure 5 contains a detailed comparison of the dosage forms infusion, decoction and ointment.	Not endorsed. The preparations with extract of *Solanum dulcamara* L., stipites, (1:5), extraction solvent 30% ethanol m/m, have not been on the market for 30 years and should thus not be included in the Community monograph on traditional use. The question of ‘corresponding products’ must be solved within the framework of an individual application.

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4.2 Posology and method of administration 4.4 Special warnings and precautions for use	AESGP	The following sections should be changed: 4.1 "The use in children ~~and adolescents~~ under 6 ~~18~~ years of age is not recommended (see section 4.4 'Special warnings and precautions for use')." 4.2 Posology *Children over 6 years of age, adolescents, adults and elderly* 4.4 "The use in children ~~and adolescents~~ under 6 ~~18~~ years of age has not been established due to lack of adequate data." An additional analysis of the study published by Oestreich & Stoeter (1995) proves that the use in children and adolescents under 18 years is safe (additional evaluation of the study published by Oestreich & Stoeter, see annex 6). Therefore, it is not necessary to restrict the application of the product to adults. It is only deemed necessary to exclude children below 6 years from therapy with Dulcamarae stipites ointment. The study itself is already cited in the list of references of assessment report of the MLWP and was obviously only evaluated in respect of clinical safety of adults. The additional data are appropriate to prove the safety for the use in children and adolescents.	Not endorsed. The preparations with extract of *Solanum dulcamara* L., stipites, (1:5), extraction solvent 30% ethanol m/m, have not been on the market for 30 years and will not be included in the Community monograph. The question of safety and use in children of possible 'corresponding products' must be solved within the framework of an individual application.