



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 November 2010
EMA/HMPC/573720/2010
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Public statement on *Centella asiatica* (L.) Urban, herba (EMA/HMPC/579663/2009)

Table 1: Organisations and/or individuals that commented on the draft Public Statement on *Centella asiatica* URBAN, herba as released for public consultation on 17 September 2009 until 15 January 2010

	Organisations and/or individuals
1	NATUREX ASA



Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
NATUREX ASA	<p>The HPMC/EMA issued a Public Statement indicating that:</p> <p>“Based on the information on manufacturing process, the HMPC is of the opinion that TECA extract cannot be classified as an herbal preparation due to the manufacturing steps and composition.</p> <p>Therefore, despite the existing data on the safety and efficacy and the historical use within the Community of products containing TECA extract, it is not possible to propose any monograph for <i>Centella asiatica</i> preparations at this stage, because all the data do not refer to a herbal preparation.</p> <p>No information about the type of preparations and extent of use of unlicensed products is available. Should such information be provided, a monograph could be prepared.”</p> <p>Naturex is hereby able to provide compositional information and further overviews of tradition use, clinical and non-clinical evidence to enable drafting of a suitable monograph.</p>	Information provided cannot substantiate the traditional use of the proposed preparation.

SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and Quantitative Composition	NATUREX ASA	<p>Comments:</p> <p>A herbal drug specification is possible for an ethanolic extract.</p> <p>The starting material complies with the Eur. Ph. monograph (01/2008:1498), we attach as Appendix 1 the specification, HPLC and HPTLC trace for the ethanolic preparation below clearly shows the principle active ingredients, as defined in the Eur. Ph. monograph:</p> <ul style="list-style-type: none"> • Asiaticoside • Madecassoside • Asiatic acid • Madecassic acid <p>Proposed change (if any):</p> <p>We propose to describe the herbal ingredient for the purposes of this monograph as:</p> <p>Herbal preparations dry extract (3-5:1), extraction solvent: ethanol 70% v/v</p> <p>There is no selective extraction or extensive purification that would prevent it from meeting the definition of a herbal preparation. More detail on production of the extracts is available upon request.</p>	The extract can be considered as a herbal preparation and it is properly declared, but no evidence has been provided that the proposed extract has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the Community.

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3. Pharmaceutical Form	NATUREX ASA	<p>Suggested entry</p> <p><u>Traditional use</u></p> <p>Herbal preparation in solid or liquid dosage forms for oral use.</p> <p><i>The starting material complies with the Eur. Ph. monograph (01/2008: 1498)</i></p>	No information on marketed products containing the proposed extract has been provided to justify the proposed pharmaceutical form and route of administration.
4. Clinical Particulars	NATUREX ASA	<p>4.1 Therapeutic Indications</p> <p>Gotu Kola tablet is proposed as a traditional medicinal product used for skin and wound healing, poor circulation and relief of rheumatic conditions. All these claims are based on traditional use only.</p> <p>Gotu Kola is recorded as a dermatological agent for skin conditions, including leprosy for more than 50 years in the EU (Williamson 2003, BHMA 1983). These evidence justify the use of Gotu Kola tablet in skin conditions and wound healing. The same records contain evidence for the use of this herb in inflammations and rheumatism. In addition, Grieve (1931) provides evidence of its use in rheumatism. Gotu Kola was used for more than 25 years in the EU as a peripheral vasodilator, indicating that the herb helps in improving poor circulation (BHMA, 1983). Elsewhere outside the EU, it has been used for the same purpose for 33 years.</p> <p>Available evidence demonstrate that Gotu Kola tablet satisfies the requirements for registration as a traditional herbal medicinal product used for skin and wound healing, poor circulation and relief of rheumatic pains based on traditional</p>	<p>The bibliography mentioned and provided (see annex 2) does not contain the evidence of the claimed 50 years of use in the EU and of which preparation has been in medicinal use.</p> <p>The statement that outside the EU, it has been used for the same purpose for 33 years is not supported by any documentation.</p> <p>Comments to the bibliographic references of the “clinical overview presented in Appendix 2”:</p> <p>Williamson 2003: the period of use of powdered leaf, dose: 0.5-1 g daily, or equivalent extract as a “Vulnerary, dermatic, anti-leprotic, anti-inflammatory” is not specified. The claimed EU-52 year’s period of use cannot be found in the paper.</p> <p>BHMA 1983: 0.6 g or by infusion thrice daily, or equivalent extract as a “Mild diuretic, anti-rheumatic dermatological agent, peripheral vasodilator”. Mention of Gotu kola in BHMA with no evidence of the corresponding product on the market cannot be considered as a proof of the actual medicinal use and it</p>

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		<p>use only.</p> <p>A clinical overview is presented in Appendix 2 to demonstrate that Gotu Kola has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the EU.</p>	<p>is not useful to identify the preparation used.</p> <p>Grieve M (1031): The paper does not report any preparation, posology and route of administration, but only the plant part used. A disclaimer on the bottom of the page states: "Bear in mind "A modern Herbal" was written with the conventional wisdom of the early 1900's. This should be taken into account as some of the information may now be considered inaccurate or not in accordance with modern medicine" The content of the paper is very poor and cannot be considered as a good source of information.</p> <p>Martindale 1967: It refers to the use in India of fresh and dried leaves in "Skin diseases; leprosy; syphilis and as a diuretic." The European use is only for Madecassol, corresponding to the TECA extract (asiaticoside in Martindale), that is not considered to be an herbal preparation. Therefore the claimed EU-41 year's period of use of Gotu kola cannot be found in the paper.</p> <p>Natarajan, S, Paily, PP (1973): It is a research article and it does not substantiate the factual traditional use in psoriasis. The preparation used in the paper does not correspond to the ethanolic extract proposed by the IP, because it is a complex double decoction in water and castor oil.</p>

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4.2 Posology and method of administration		<p>Posology</p> <p><i>Adults</i></p> <p>Daily dose:</p> <p>once daily 225 to 375 mg of herb of Gotu Kola Herb</p>	<p>The proposed posology is not supported by any documentation.</p>
4.3–6		<p>Further data available upon request including a full Non-clinical Overview</p>	<p>Further data may be useful provided that they refer to a specific preparation for which the medicinal use throughout a period of at least 30 years, including at least 15 years within the Community, is properly substantiated.</p>

Appendix 1: Specification and typical analysis for proposed herbal preparation

Removed because of confidential data.

Appendix 2: Traditional Use Evidence and interpretation of References

Ref	Traditional Use: EU/Other	Active Ingredient(s)	Strength & Posology	Route of Administration	Purpose
1	EU-52 years	Gotu Kola	<u>Powdered Leaves</u> 0.5-1 g daily, or equivalent extract	Oral and External	Vulnerary, dermatic, anti-leprotic, anti-inflammatory.
2	EU-26 years	Gotu Kola	<u>Dried Leaves</u> 0.6 g or by infusion thrice daily	Oral and External	Mild diuretic, anti-rheumatic dermatological agent, peripheral vasodilator.
3	Other-78 years	Hydrocotyle	N/A	Oral	It is a valuable medicine for its diuretic properties; and has long been used in India as an aperient or alterative tonic, useful in fever and bowel complaints and a noted remedy for leprosy, rheumatism and ichthyosis.
4	EU-41 years	Gotu Kola	N/A	Oral and External	Skin diseases; leprosy; syphilis
5	Other-33 years	Gotu Kola	N/A	Oral	Gotu Kola is used as a peripheral vasodilator, in physical exhaustion, and psoriasis.

Interpretation of References

Ref	Author	Title	Year	Publisher	Page	Evidence Type
1	Williamson EM	Potter's Cyclopaedia of Botanical Drugs and Preparations	2003	The C.W. Daniel Company Ltd, Essex, England	229-230	Textbook
2	Scientific Committee, British Herbal Medicine Association	British Herbal Pharmacopoeia	1983	British Herbal Medicine Association	56-57	Pharmacopoeia
3	Grieve M	A Modern Herbal	1931	http://www.botanical.com/botanical/mgmh/h/hydc046.html	-	Electronic Textbook
4	Martindale	Extra Pharmacopoeia, 25 th Edition	1967	Cited in: A Guide to Traditional Herbal Medicines, British Herbal Medicine Association	116	Pharmacopoeia
5	Natarajan, S, Paily, PP	Effect of topical Hydrocotyle Asiatica in psoriasis.	1973	Indian Journal of Dermatology 18:82-85. Cited in www.naturalstandard.com	-	Research article