



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

24 November 2014  
EMA/HMPC/572698/2014  
Committee on Herbal Medicinal Products (HMPC)

## Overview of comments on draft assessment report on *Cetraria islandica* (L.) Acharius s.l. thallus EMA/HMPC/678891/2013

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Cetraria islandica* (L.) Acharius s.l., thallus as released for public consultation on 19 May 2014 until 31 August 2014.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	KRKA, d.d., Novo mesto, Slovenia



Table 2: Discussion of comments

### General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	<p>AESGP welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for <i>Cetraria islandica</i>-containing products, should facilitate mutual recognition in Europe.</p> <p>We have the following specific comments on the draft assessment report.</p>	The welcome note by AESGP is appreciated.

### SPECIFIC COMMENTS ON TEXT

Section number and heading	Interested party	Comment and Rationale	Outcome
AR - 2. 1.1. Information about products on the market in the EU/EEA Member States	AESGP	<p>With regard to the use of Icelandic moss as medical device, only Latvia is mentioned:</p> <p>"Some products, e.g., lozenges containing extract of <i>Cetraria islandica</i> are marketed as medical devices."</p> <p>According to information from our members, medical devices containing Icelandic moss are marketed in the following countries:</p> <p>Baltics, Belgium, Bosnia-Herzegovina, Croatia, Austria, Romania, Switzerland, Serbia, Slovenia, Hungary, Bulgaria, Poland, Slovakia, Czech Republic and Germany.</p>	<p>Partly endorsed</p> <p>Reference on the medical devices available in Latvia has been replaced with the following sentences:</p> <p>Products containing Lichen islandicus are on the European market as food supplements and medical devices as well. However, detailed information (DER, extraction solvent) on these products is not available.</p>

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2. Qualitative and quantitative composition	KRKA, d. d., Novo mesto	<p>ii) Herbal preparations</p> <p>e) Soft extract, extraction solvent water</p> <p>Rationale:</p> <p>Dosages of the herbal preparation should be defined on the basis of the corresponding amount of the herbal substance regardless of DER. Recommended daily doses are defined in monographs: ESCOP (1), Commission E monograph (2) and Phytopharmaka monograph (3).</p> <p>We agree that DER provide essential information about the composition and manufacture of a herbal preparation. However water herbal preparations of <i>Cetraria islandica</i> are a specific type of group of "Other extracts"</p> <p>Herbal preparations are prepared with water as an extraction solvent. No additional extraction steps/solvents or purification steps are involved. Only concentration is involved, where the solvent, i.e. water is removed.</p> <p>Because of very specific constituents of herbal preparation (polysaccharides) it is not possible to remove all water and obtain a dry extract. Therefore the DER of presented soft extracts represents only how the soft extract is concentrated and consequently any extract can be concentrated or diluted to a preferred ratio.</p> <p>To show that any water extraction processes is comparable, we performed extraction trails, with different conditions (ratio drug/water, extraction time and temperature). The report is enclosed in the Appendix 1 (Report is confidential, not for public domain - industrial property).</p> <p>Conclusion of the trail:</p> <p>Since different parameters of extraction have only little influence on the efficacy of extraction, it can be concluded that the main difference between</p>	<p>Not endorsed</p> <p>It is not possible to include in the monograph a "general" extract without indicating a DER range.</p> <p>Soft extracts with a DER 3: 1 and 0.5: 1 are already covered by the monograph. For extracts with higher DERs, neither the period of traditional use of 30 years nor the comparability of chemical composition with extracts with proven 30 years of traditional use has been demonstrated.</p>

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		<p>soft extracts with very different DERs (drug-extract ratios) is the different content of water, i.e. the different level of evaporation applied. With respect to therapeutic efficacy, an extract with a DER of 17:1 is therefore as effective as, for example, an extract with a DER of 3:1 or 0.5:1 if they are administered at the same dose expressed as the amount of the herbal drug. As a liquid extract can be prepared by adding a solvent to a dry extract, a soft extract with a DER of 3:1 can also be prepared by adding an appropriate amount of water to a soft extract with a DER of 17:1.</p> <p>According to the results, it can be claimed that the water extraction always yields a comparable amount of herbal substance in the extract. And from a therapeutically point of view, it is important that the posology is defined with drug substance equivalent. This can be endorsed also with “Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products; EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1«, where it is stated that for “Other herbal preparations” the quantity of genuine herbal preparation herbal can be quoted either with corresponding amount of substance (given as a range) or the DER genuine.</p> <p>The recommended daily doses are based on the following monographs: ESCOP (1), Commission E monograph (2) and Phytopharmaka monograph (3).</p> <table><tr><th>Age group</th><th>Recommended daily dose of herbal drug</th></tr><tr><td>Children 1 to 4 years</td><td>1 - 2 g</td></tr><tr><td>Children 4 to 10 years</td><td>2 - 4 g</td></tr><tr><td>Children 10 to 16 years</td><td>4 - 6 g</td></tr><tr><td>Adults</td><td>3 - 8 g / 4 - 6 g</td></tr></table>	Age group	Recommended daily dose of herbal drug	Children 1 to 4 years	1 - 2 g	Children 4 to 10 years	2 - 4 g	Children 10 to 16 years	4 - 6 g	Adults	3 - 8 g / 4 - 6 g	
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		<p>(1) Lichen islandicus. Iceland moss. ESCOP Monographs. The Scientific Foundation for Herbal Medicinal Products. Exter: Thieme. 2003; 286-9.</p> <p>(2)X Lichen islandicus (Islandisches Moos). In: . Monographie BGA/BfArM (Kommission E). 43. c1989 [cited 2011 Jul 11]. Available from: <a href="http://buecher.heilpflanzen-welt.de/BGA-Kommission-E-Monographien/lichen-islandicus-isländisches-moos.htm">http://buecher.heilpflanzen-welt.de/BGA-Kommission-E-Monographien/lichen-islandicus-isländisches-moos.htm</a>. p. 1.</p> <p>(3) Lichen islandicus (Isländisch Moos). In: Dorsch W, Loew D, Meyer-Buchtela E, Schilcher H. Kinderdosierungen von Phytopharmaka. Bonn: Hrsg.: Kooperation Phytopharmaka GbR. 2002; 83.</p>	
4.2. Posology and method of administration	KRKA, d. d., Novo mesto	<p>Posology</p> <p>Oral use</p> <p>e) Soft extract</p> <p>Adolescents older than 16 years, adults and elderly</p> <p>Single dose: Amount of extract corresponding to 1440 – 1620 mg of herbal drug</p> <p>Daily dose: Corresponding to 5.76–6.48 g of herbal drug</p> <p>Adolescents and children 10 - 16 years of age</p> <p>Single dose: Corresponding to 960 – 1080 mg of herbal drug</p> <p>Daily dose: Corresponding to 3.84 – 4.32 g of herbal drug</p> <p>Children 4 – 10 years of age</p> <p>Single dose: Amount of extract corresponding to 480 – 540 mg of herbal drug</p> <p>Daily dose: Corresponding to 1.92 – 2.16 g of herbal drug</p> <p>Children 1 - 4 years of age</p> <p>Single dose: Amount of extract corresponding to 240 – 279 mg of herbal drug</p> <p>Daily dose: Corresponding to 960 – 1080 mg of herbal drug</p>	Not endorsed, see justification above.

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		<p>This preparation should not be given to children 1 to 4 years of age without consulting a doctor first (see section 4.4 'Special warnings and precautions for use').</p> <p>The use in children under 1 year of age is not recommended (see section 4.4 'Special warnings and precautions for use').</p> <p>Rationale:</p> <p>Traditional use justification</p> <p>Krka's medicinal product containing Lichen islandicus has been available on the market since 2012. Although the product itself has not a long history of use, its development was based on the traditional use of Lichen islandicus as a demulcent in oral or pharyngeal irritation/inflammation and associated dry cough. The traditional use has been adequately justified in several countries within the European Union. Please find the justification in Appendix 2 (Document is confidential, not for public domain - industrial property).</p> <p>Posology justification</p> <p>The dosage is based on several bibliographic references, namely herbal monographs.</p> <p>Daily dose</p> <p>According to the Expanded Commission E monograph a dose of 4 - 6 g of cut drug per day is recommended. As defined by the ESCOP monographs, adult dosage may range from 3 to 8 g of drug per day as a liquid preparation, taken in small amounts.</p> <p>Daily doses, as defined by Phytopharmaka, were based on various monographs and are as follows: children, aged 1 to 4 years 1 - 2 g of herbal drug daily; children, aged 4 to 10 years 2 - 4 g of herbal drug daily and children, aged 10 - 16 years 4 - 6 g of herbal drug daily</p>	

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		<p>The following table presents a comparison of the recommended and proposed daily doses for iceland moss.</p> <p>Table 1: Recommended vs. proposed daily doses.</p> <table><tr><th>Age group</th><th>Recommended daily dose* of herbal drug</th><th>Daily dose of herbal drug – Krka’s Iceland moss syrup</th></tr><tr><td>Children 1 to 4 years</td><td>1 - 2 g</td><td>0.96 – 1.08 g</td></tr><tr><td>Children 4 to 10 years</td><td>2 - 4 g</td><td>1.92 – 2.16 g</td></tr><tr><td>Children 10 to 16 years</td><td>4 - 6 g</td><td>3.84 – 4.32 g</td></tr><tr><td>Adults</td><td>3 - 8 g / 4 - 6 g</td><td>5.76 – 6.48 g</td></tr></table> <p>*Recommended daily doses are based on the following monographs: ESCOP, Commission E monograph and Phytopharmaka monograph.</p> <p>This comparison clearly shows the proposed daily dosage of Herbion iceland moss syrup by Krka is compliant with daily doses defined in the cited bibliographic references. None of the doses exceed the maximal recommended daily dose; therefore safe use of the product can be justified. Additionally, the daily doses also correspond with reference products (data supported and presented in previously submitted documents).</p> <p>Daily dose</p> <p>Most of the literature references available only provide numeric values for daily doses of iceland moss herbal drug. It is then stated, that this dose should be taken in small amounts. Additionally, the division of the recommended daily dose in several smaller doses is in accordance of the dosage of some marketed products, for example the Isla brand products by Engelhard ArzneimittelThe recommended single dose is set by Hagers Handbuch der Pharmazeutischen Praxis, and it amounts to 1.5 g of herbal drug in one tea cup.</p>	Age group	Recommended daily dose* of herbal drug	Daily dose of herbal drug – Krka’s Iceland moss syrup	Children 1 to 4 years	1 - 2 g	0.96 – 1.08 g	Children 4 to 10 years	2 - 4 g	1.92 – 2.16 g	Children 10 to 16 years	4 - 6 g	3.84 – 4.32 g	Adults	3 - 8 g / 4 - 6 g	5.76 – 6.48 g	
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		<p>The proposed single dose of Herbion iceland moss syrup for adults is 10 ml of syrup, which corresponds to 1.5 g of herbal drug. The dosage is therefore in accordance with the dosage stated above.</p> <p>The literature does not provide single doses for the pediatric population. However, single doses were extrapolated from adult single dose, taking into account the daily recommended doses for children. The single doses are therefore diminishing with age by the same proportion as the daily dose.</p> <p>Table 2: Single doses for children as compared to daily and adult dosage.</p> <table><tr><th>Children age group</th><th>Proposed daily dose</th><th>Percentage of daily adult dose</th><th>Single dose (extrapolation)</th><th>Percentage of single adult dose</th></tr><tr><td>1 to 4 years</td><td>0.96 – 1.08 g</td><td>16.7 %</td><td>0.25 g</td><td>16.7 %</td></tr><tr><td>4 to 10 years</td><td>1.92 – 2.16 g</td><td>33.3 %</td><td>0.5 g</td><td>33.3 %</td></tr><tr><td>10 to 16 years</td><td>3.84 – 4.32 g</td><td>66.7 %</td><td>1.5 g</td><td>66.7 %</td></tr></table> <p>Use in children, aged 1 to 4 years</p> <p>The use in children aged 1 to 4 years is supported by data from Phypopharmaka, which also supports the proposed dosage. Additionally, there are other iceland moss containing products available on the market which are used in the same age group and have a similar intended purpose, for example Klosterfrau Isländisch Moss MOBIL Hustensaft, Klosterfrau Isländisch Moss Kinderhustensaft and Iceland moss syrup by Trešnjevka Laboratories. The safety of iceland moss is supported also by the clinical study by Hecker and Völp (6): despite the set age range of 4 to 12 years, 143 children, younger than 4 years were included in this study</p>	Children age group	Proposed daily dose	Percentage of daily adult dose	Single dose (extrapolation)	Percentage of single adult dose	1 to 4 years	0.96 – 1.08 g	16.7 %	0.25 g	16.7 %	4 to 10 years	1.92 – 2.16 g	33.3 %	0.5 g	33.3 %	10 to 16 years	3.84 – 4.32 g	66.7 %	1.5 g	66.7 %	
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		<p>which reported very few adverse effects, mainly corresponding with the underlying illness. It can also be noted that the dosage form, i.e. syrup, a liquid dosage form, is the formulation of choice for children of this age group. It is believed that the inclusion of children, aged 1 to 4 years, is sufficiently justified.</p> <p>However, as a precautionary measure and to assure safe use of Herbion iceland moss syrup in young children, an additional warning is proposed in sections 4.2 and 4.4 of the Summary of the Product Characteristic and sections 2 and 3 of the Patient Information leaflet.</p> <p>References used</p> <ol style="list-style-type: none"> <li>1. Lichen islandicus. Iceland moss. ESCOP Monographs. The Scientific Foundation for Herbal Medicinal Products. Exter: Thieme. 2003; 286-9.</li> <li>2. Lichen islandicus (Islandisches Moos). In: . Monographie BGA/BfArM (Kommission E). 43. c1989 [cited 2011 Jul 11]. Available from: <a href="http://buecher.heilpflanzen-welt.de/BGA-Kommission-E-Monographien/lichen-islandicus-isolaendisches-moos.htm">http://buecher.heilpflanzen-welt.de/BGA-Kommission-E-Monographien/lichen-islandicus-isolaendisches-moos.htm</a>. p. 1.</li> <li>3. Lichen islandicus (Isländisch Moos). In: Dorsch W, Loew D, Meyer-Buchtela E, Schilcher H. Kinderdosierungen von Phytopharmaka. Bonn: Hrsg.: Kooperation Phytopharmaka GbR. 2002; 83.</li> <li>4. Overview of comments received on 'Community herbal monograph on THYMUS VULGARIS L. AND THYMUS ZYGIS L., HERBA' EMEA/HMPC/234113/2006.</li> <li>5. Lichen islandicus (Islandisches Moos). In: Bruchhausen F, Dannhardt G, Ebel S, Frahm AW, Hackenthal E, Hansel R, et al. Hagers Handbuch der pharmazeutischen Praxis. Vol 5. Berlin: Springer-Verlag; 1992. p. 791-4.</li> <li>6. Hecker M, Volp A. Tolerability of Icelandic moss lozenges in upper respiratory tract diseases - multicentric drug monitoring study with 3143 children. Forsch Komplementarmed Klass Naturheilkd. 2004;11(2):76-82.</li> </ol>	

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		<p>Posology</p> <p>Oromucosal use</p> <p>a) Soft extract</p> <p>Adolescents adults and elderly</p> <p>Single dose: Amount of extract corresponding to 200 – 800 mg of herbal substance</p> <p>Daily dose: Corresponding to 4 – 8 g of herbal substance</p> <p>Children 6 - 12 years of age</p> <p>Single dose: Corresponding to 200 – 400 mg of herbal substance 4 to 6 times daily</p> <p>Daily dose: Corresponding to 0.8 – 2.4 mg of herbal substance</p> <p>The use in children under 6 years of age is not recommended (see section 4.4 'Special warnings and precautions for use')</p> <p>Rationale:</p> <p>Please refer to the explanation in section 2. Qualitative and quantitative composition.</p>	
4.4 Special warnings and precautions for use	KRKA, d. d., Novo mesto	<p>Indication 1)</p> <p>Preparations b), c) and e)</p> <p>If dyspnoea, fever or purulent sputum occurs during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.</p> <p>Absorption of concomitantly administered medicines may be delayed. As a precautionary measure, the product should not be taken ½ to 1 hour before or after intake of other medicinal products.</p>	Not endorsed, see justification above.

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		<p>Preparations b) and c)</p> <p>The use in children under 6 years of age is not recommended because of the pharmaceutical form (solid dosage form).</p> <p>Preparation e)</p> <p>The use in children under 1 year of age has not been established due to lack of adequate data.</p> <p>Children 1 to 4 years of age should only be given this medicine on a doctor's advice. They can only be given the preparation by their parents/caregiver.</p> <p>Rationale:</p> <p>Please refer to the explanation for section 4.2.</p>	