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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Cetraria islandica* (L.) Acharius s.l., thallus

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

### Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Cetraria islandica</i> (L.) Acharius s.l., thallus
Herbal preparation(s)	Comminuted herbal substance Soft extract (DER 2-4:1), extraction solvent water Soft extract (DER 0.4-0.8:1), extraction solvent water Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 40% (V/V)
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use Herbal preparations in liquid or solid dosage forms for oral or oromucosal use
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# 1. Introduction

## 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

*Cetraria islandica* (L.) Acharius s.l., thallus

Island moss (Lichen islandicus) consists of whole or cut, dried thallus of *Cetraria islandica* (L.) Acharius s.l. from the Parmeliaceae family.

The thallus, up to 15 cm long, is irregularly dichotomous and consists of glabrous, groove-shaped or almost flat, stiff, brittle bands, 0.3-1.5 cm wide and about 0.5 mm thick, sometimes serrated with the margin appearing ciliated (pycnidia). The upper surface is greenish or greenish-brown, the lower surface is greyish-white or light brownish and shows whitish, depressed spots (so-called respiratory cavities). On the apices of the terminal lobes, very rarely, there are brown, discoid apothecia.

The swelling value is minimum 4.5 (determined on the powdered drug) (Ph.Eur.8.0, 07/2010:1439).

*Cetraria islandica* grows in arctic and subarctic areas, in northern and eastern Europe, Siberia and North America (Wichtl, 1994; WHO monograph, 2004) and in middle ranged and alpine mountains in Germany, North Italy, Czech Republic, Slovakia, Poland and Russia (Hoppe, 1977).

Material for pharmaceutical use is from northern-, central- and east-European countries, especially from Scandinavian countries, Bulgaria, former Yugoslavia countries, Romania and from Canada (Hänsel *et al.*, 1993)

- Herbal preparation(s)

According to the information provided by the National Competent Authorities in the overview of the marketed products, the following herbal preparations have been available on the European market:

- Comminuted herbal substance
- Soft extract (DER 16-18:1), extraction solvent: water
- Soft extract (DER 2-4:1), extraction solvent: water
- Soft extract (DER 0.4-0.8:1), extraction solvent: water

Usage of tincture 1:5, extraction solvent ethanol 40% (V/V) is described in the British Herbal Pharmacopoeia (1971, 1976, 1983).

### Principal constituents of the herbal substance

Polysaccharides – 25-50%

- lichenan (or lichenin) – a hot water soluble, linear  $\beta$ -D-glucan with 1→4 and 1→3 links at a ratio of 2-3 : 1 (Peat *et al.*, 1957; Perlin and Suzuki, 1962; Cunningham and Manners, 1964; Chanda *et al.*, 1957)
- isolichenan (or isolichenin) – a cold water soluble, linear  $\alpha$ -D-glucan with 1→3 and 1→4 links at a ratio of approximately 55:45 (Peat *et al.*, 1961; Krämer *et al.*, 1995) or 3:2 (Chanda *et al.*, 1957; Fleming and Manners, 1966; Gagnaire *et al.*, 1975) with a molecular weight of about 6-8 kD

- an  $\alpha$ -D-glucan (denoted as Ci-3) resembling isolichenan, consisting of 1→3 and 1→4 linked  $\alpha$ -D-glucose residues at a ratio of 2:1, but with a much higher degree of polymerization and a MW of ca. 2000 kD (Olafsdóttir *et al.*, 1999)
- a polysaccharide consisting of (1→6)-linked  $\alpha$ -D-mannopyranosyl residues highly branched with  $\alpha$ -D-Galp-(1→2)- and  $\beta$ -D-Galp-(1→4) side-chains (Gorin and Iacomini, 1984; Ingólfssdóttir *et al.*, 1994)
- an alkali-soluble polysaccharide containing (1→3)-linked glucopyranose and glucuronic acid residues branched with (1→4)- and/or (1→6)-linked glucopyranose residues (Hranisavljević *et al.*, 1980)
- an alkali-soluble polysaccharide KI-M-7, branched galactomannan with a backbone composed of two structural elements; (1→6)- linked  $\alpha$ -D-mannopyranosyl and  $\alpha$ -D-(1→6)-galactopyranosyl units (Ingólfssdóttir *et al.*, 1994); the neutral sugar components were identified as galactose, mannose and rhamnose in a molar ratio of 13:9:1; the molecular weight of the polysaccharide is approximately 18 kD (Ingólfssdóttir, 2000)

#### Lichen acids

- depsidones fumaroprotocetraric acid (2.6-11.5%) (Gudjónsdóttir and Ingólfssdóttir, 1997; Sticher, 1965) and protocetraric acid (0.2-0.3%) (Huovinen *et al.*, 1986) depending on the collection site
- protolichesterinic acid, an aliphatic  $\alpha$ -methylene- $\gamma$ -lactone (0.1-1.5%) depending on the collection site (Gudjónsdóttir and Ingólfssdóttir, 1997; Ingólfssdóttir *et al.*, 1994; Sticher, 1965)
- usnic acid, a dibenzofurane derivative, was found in *Cetraria islandica* only in traces (0.04%) (Laakso and Gustafsson 1952, Shibata 1958, Virtanen and Kärki 1956 in Airaksinen, 1986a), whereas usnic acid was not detected by Sticher (1965) and by Ingólfssdóttir (2002)

#### Minerals

- lead (30 mg/kg), cadmium (0.30 mg/kg), mercury (0.075 mg/kg), arsenic (0.76 mg/kg), calcium (48 mg/kg), magnesium (270 mg/kg), iron (530 mg/kg) and other trace elements have been found in samples collected in Southern Finland (Airaksinen *et al.*, 1986a)

#### Other constituents

- hydrocarbons (mainly 1,8-heptadecadiene) (Solberg Y, 1986 in Bradley, 2006)
  - other carbohydrates consisting of cellulose and three hemicelluloses which give on hydrolysis mannose, galactose and glucuronic acid (Buston and Chambers, 1933)
  - fatty acids (linoleic, oleic and linolenic) (Solberg Y, 1986 in Bradley, 2006)
  - phospholipids, sterols, carotenoids (Kartnig, 1987)
- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

#### Not applicable

This assessment report supports the Community herbal monograph, which refers exclusively to *Lichen islandicus* as a single active substance. With respect to the overall evaluation of the existing data on efficacy, the monograph addresses only the traditional use.

## 1.2. Search and assessment methodology

A literature search was performed in July 2013 in scientific medical and toxicological databases (e.g. PubMed, MEDLINE, Cochrane Library, TOXLINE). The keywords were „Cetraria islandica“, „Lichen islandicus“, „Iceland moss“, Isländisches moos“. Additional hand searches were performed in books on herbal medicines and plant monographs in the EMA and NCA library. The bibliographies of included trials and other relevant reviews were searched to identify further potential trials.

## 2. Data on medicinal use

### 2.1. Information about products on the market

#### 2.1.1. Information about products on the market in the EU/EEA Member States

##### Information on medicinal products marketed in the EU/EEA

According to the information provided by the National Competent Authorities in the overview of the marketed products, the following herbal substances/preparations have been marketed in the EU/EEA:

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
<i>Cetraria islandica</i> (L.) Acharius s.l., thallus soft extract;  DER 2-4:1; extraction solvent water	Demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough	Oral gum  adults and adolescents over 12 years 13-20 oral gums containing 100 mg of extract per day; children 4-12 years 4-6 oral gums per day	MA- at least since 1976  Germany
<i>Cetraria islandica</i> (L.) Acharius s.l., thallus soft extract;  DER 0.4-0.8:1; extraction solvent water	No information	Lozenges (80 or 160 mg/lozenge)  1-2 lozenges several times daily	Since 1976 until 31 <sup>st</sup> December 2010  Germany
<i>Cetraria islandica</i> (L.) Acharius s.l., thallus soft extract;  DER 16-18:1; extraction solvent water	For symptomatic treatment of oral or pharyngeal irritation/inflammation and associated dry cough and hoarseness	Syrup (1 ml contains 6 mg of the extract)  adults and adolescents over 16 years: 15 ml 4 times daily; children 10-16 years: 10 ml 4 times daily; children 4-10 years 5 ml 4 times daily; children 1-4 years: 2.5 ml 4 times daily	TUR – since 2012  Slovenia
<i>Cetraria islandica</i> (L.) Acharius s.l., thallus soft extract;  DER 16-18:1; extraction solvent water	The product is a traditionally used herbal medicine recommended for:  - dry, irritating cough;  - mild inflammations of the upper respiratory tract and irritation of the oral and pharyngeal mucosa,	Syrup (1 ml contains 6 mg of Iceland moss soft extract, equivalent to 96-108 mg of Iceland moss)  adults and adolescents over 16 years: 15 ml 4 times daily; children 10-16 years: 10 ml 4 times daily; children 4-10 years: 5 ml 4 times daily;	TUR – since 2013  Latvia

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	including hoarseness and sore throat.	children 1-4 years: 2.5 ml 4 times daily	
<i>Cetraria islandica</i> (L.) Acharius s.l., thallus soft extract;  DER 16-18:1; extraction solvent water	Dry, irritating cough; mild inflammations of the upper respiratory tract and irritation of the oral and pharyngeal mucosa, including sore throat	<u>Adults and adolescents over 16 years of age</u> 15 ml syrup four times daily (equivalent to 360 mg extract/day)  <u>Children between 10 and 16 years of age</u> 10 ml syrup 4 times daily (equivalent to 240 mg of extract/day) <u>Children between 6 and 10 years of age:</u> 5 ml syrup 4 times daily (equivalent to 120 mg of extract/day) <u>Children between 4 and 6 years of age:</u> 5 ml syrup 4 times daily (equivalent to 120 mg of extract/day)  The use in children under the age of 6 years is not recommended without medical diagnosis and supervision.	TUR – since 2013  Hungary
<i>Cetraria islandica</i> (L.) Acharius s.l., thallus soft extract;  DER 2-4:1; extraction solvent water	For symptomatic treatment of oral or pharyngeal irritation/inflammation and associated dry cough and hoarseness	Lozenge (1 lozenge contains 100 mg of the extract)  adults and children over 4 years 1-2 lozenges several times daily	Since 2000  Slovenia
<i>Cetraria islandica</i> (L.) Acharius s.l., thallus soft extract;  DER 0.4-0.8:1; extraction solvent water	For symptomatic treatment of oral or pharyngeal irritation/inflammation and associated dry cough and hoarseness	Lozenges (80 mg/lozenge)  adults and children over 4 years 1-2 lozenges several times daily	Since 2000  Slovenia
<i>Cetraria islandica</i> (L.) Acharius s.l., thallus	Adjunctively in cough caused by irritation of mucosal membrane of throat or oral cavity	Comminuted herbal substance for oral use  2.5-4.0 g in 300 ml of water as a decoction 2-3 times daily	Since 2000  Poland

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

### Information on relevant combination medicinal products marketed in the EU/EEA

#### Austria

Lichen islandicus is a part of many registered combination products (herbal teas as well as extract preparation), which are manufactured in pharmacies and which are only allowed to be sold in the manufacturing pharmacy. The substances present in the combination products are the usual herbs used in the same indication (mucilage containing, or expectorants).

#### Belgium

Several combination medicinal products containing the comminuted herbal substance in a form of coated tablets, hard capsules and herbal teas are available on the Belgian market. Based on information on composition of the products it was considered that they are not relevant for the establishment of the monograph.

#### **Latvia**

A combination medicinal product containing *Cetraria islandica* together with other approximately 20 active substances is authorised since 2004.

#### **Poland**

Concentrate for oral solution, 100 g contain 90 g of extractum liquidum (1:3) ex: Thymi herba, Lichene islandico, Hyssopi herba, Saponariae radice (18/7/3/2); extraction solvent: ethanol 70% (V/V).

Indication: Inflammatory state of upper respiratory tract; difficulties in expectoration of bronchial secretions.

Posology: Adults and adolescents over 12 years of age: 5 ml dissolved in 125 ml of water 3 times daily.

On the market since 1976.

#### **UK**

1. A traditional herbal medicinal product – capsules - containing 19 herbal substances including Iceland moss, derived from a formula of Tibetan medicine, is registered in the UK since February 2013. Based on information on the indication, the product is considered not relevant for the establishment of the monograph.

2. A traditional herbal medicinal product – oral solution – containing 4 g of the extract from Aniseed (equivalent to 81 mg Aniseed fruit), Elderflower (equivalent to 81 mg Elderflower), Iceland Moss thallus (equivalent to 81 mg Iceland Moss thallus), Thyme herb (equivalent to 81 mg Thyme herb) and White Horehound herb (equivalent to 81 mg White Horehound herb), extraction solvent water in 5 ml of the product.

Indication: a traditional herbal medicinal product used for the symptomatic relief of dry and irritating cough, based on traditional use only.

#### **Information on other products marketed in the EU/EEA (where relevant)**

##### **Italy**

*Cetraria islandica*, thallus is included in the list of herbal substances and herbal preparations allowed in food supplements, published on the website of the Italian Ministry of Health, with the following indications: emollient and demulcent actions (oropharyngeal mucosa) and voice tone, digestive function, natural body defence.

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.

### **2.1.2. Information on products on the market outside the EU/EEA**

Not available.



## 2.2. Information on documented medicinal use and historical data from literature

The medicinal use of *Lichen islandicus* has been documented continuously in many pharmacopoeias, pharmacognostical texts and handbooks.

Madaus (1938) summarised the historical use of the plant starting with the reference to the medieval botanist Valerius Cordus who mentioned the plant for the first time as “*Muscus crispae Lacticae similis*”. Madaus also mentioned that the first picture with notation “*Muscus Eryngii folio*” was done by Breyne (1672); the plant with the name “*Lichen islandicus*” was described for the first time by Bartholin (1672), who considered it to be spring purgative aid. The first chemical research, which was undertaken by Hjärne (1744), who together with Borchius recommended the plant as a remedy, was also mentioned by Madaus.

Crawford (<http://web.uvic.ca/~stucraw/TableContents.html>) cites the old references in Perez-Llano, 1944 and Saklani and Upreti, 1992 on medicinal use, starting by Linnaeus (1737), who considered *Cetraria islandica* to be an important medicine used as an emollient and tonic in chronic affections. In 1838, Lindley reported that in Europe, *Cetraria islandica* was popular amongst some practitioners for treating pulmonary and digestive organs - particularly in phthisis - chronic catarrh, dyspepsia and chronic dysentery.

The medicinal use has been documented in many pharmacopoeias starting from Pharmacopoea Austriaca 8<sup>th</sup> edition (1906), Pharmacopoea Helvetica V (1953), Deutsches Arzneibuch 6 (1956), Československý lékopis (Pharmacopoea Bohemoslovenica) III (1970), Pharmacopoea Helvetica VI (1971), British Herbal Pharmacopoeia (1971, 1976, 1983), Arzneibuch der DDR (1975), Pharmacopoea Helvetica VII (1987), Deutsches Arzneibuch 10 (1991), European Pharmacopoeia 3<sup>rd</sup> edition (2001) to the currently valid version of European Pharmacopoeia 8<sup>th</sup> edition (2014).

Iceland moss is included in many pharmacognostical texts, handbooks and compendia, e.g. Lehrbuch der Biologischen Heilmittel (Madaus, 1938), Gift- and Arzneipflanzen (Gessner and Orzechowski, 1974), Drogenkunde (Hoppe, 1977), PDR for Herbal medicines (Gruenwald *et al.*, 2004 and 2007), WHO Monographs on Selected Medicinal Plants (Volume 4, 2009), The Complete German Commission E Monographs (Blumenthal *et al.*, 1998), Standard Zulassungen für Arzneimittel (1996), Herbal drugs and Phytopharmaceuticals (Wichtl, 1994), Hagers Handbuch der Pharmazeutischen Praxis (Hänsel *et al.*, 1993), Herbal Medicine (Weiss, 1988; Weiss and Fintelmann, 2000), ESCOP Monographs (2003), The Extra Pharmacopoeia (Martindale, 1977).

In most of the literature sources (e.g. Blumenthal *et al.*, 1998; Hänsel *et al.*, 1993; Bradley, 2006, ESCOP, 2003; Standard Zulassungen, 1996; WHO monographs, 2009, Gehrman *et al.*, 2005; Wyk and Wink, 2005) the herbal substance is recommended in irritation or inflammation of the oral and pharyngeal mucosa and associated dry cough and in loss of appetite. Other sources refer additionally to the use in bronchitis and bronchial catarrhs (British Herbal Pharmacopoeia 1971, 1976 and 1983; Madaus, 1938; Gessner and Orzechowski, 1974; Bradley, 2006; Zeprennick *et al.*, 1984; Benedum *et al.*, 2006; Weiss and Fintelmann, 2000; Weiss, 1988; Wren, 1975) or in gastrointestinal problems such as gastritis, gastroenteritis, dyspepsia, vomiting (British Herbal Pharmacopoeia 1971, 1976 and 1983; Madaus, 1938; Gessner and Orzechowski, 1974, Bradley, 2006; Wichtl; 1994, Gruenwald, 2004 and 2007; Benedum *et al.*, 2006; Weiss and Fintelmann, 2000). Some authors stated that the herbal substance is used externally for wounds healing (Madaus, 1938; Hoppe, 1977; Deters, 2003).

Several authors (e.g. Madaus, 1938; Gessner and Orzechowski, 1974) refer to the old literature sources, where the use in even more serious illnesses such as bronchial asthma, tuberculosis, pertussis, diarrhoea, typhus, gastric and duodenal ulcers is described.

Table 2: Overview of historical data

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
Comminuted herbal substance  Tincture 1:5 in 40% alcohol	Action: demulcent, antiemetic, expectorant  Indication: gastritis, dyspepsia, vomiting, cachexia, respiratory catarrh, bronchitis  Specific indication: cachexia with vomiting	1-2 g of the herbal substance in decoction 3 times daily  Tincture 1:5 in 40% alcohol 1-1.5 ml 3 times daily	British Herbal Pharmacopoeia, 1971, 1976 and 1983
Comminuted herbal substance  Tincture 1:5 in 40% ethanol  Aqueous extract (DER not specified)	Uses based on experience and tradition:  In irritation or inflammation of the oral and pharyngeal mucosa and associated dry cough, hoarseness and sore throat, bronchitis; bronchial asthma, respiratory catarrh  Digestive complains, gastritis and loss of appetite  Treatment of gastric and duodenal ulcers, irritable bowel syndrome, cachexia and tumours	1-2 g of dried lichen 3-4 times daily as a decoction or infusion  Tincture: 1-1.5 ml  Aqueous extract in a form of pastilles equivalent to 0.5-3 g of dried lichen per day	Bradley, 2006
Comminuted herbal substance or equivalent preparations	Irritation of the oral and pharyngeal mucous membranes and accompanying dry cough  Loss of appetite	Average daily dosage: 4-6 g of herbal substance, equivalent preparations	Blumenthal <i>et al.</i> , 1998
Comminuted herbal substance	A demulcent and expectorant for alleviating irritation of the throat in coughs  Lack of appetite  Gastroenteritis	Tea prepared from 1.5-2.5 g of finely chopped herbal substance /10 minutes	Wichtl, 1994
Comminuted herbal substance	Irritation of the oral and pharyngeal mucous membranes and accompanying dry cough  Loss of appetite	Average daily dosage: 4-6 g of herb,  Single dose 1.5 g/cup of tea	Hänsel <i>et al.</i> , 1993
Comminuted herbal substance	Loss of appetite  Bronchitis and laryngitis, cough, pulmonary tuberculosis	No information	Zepernick <i>et al.</i> , 1984

<p>Comminuted herbal substance</p> <p>Water extracts</p>	<p>Dry cough, irritation and inflammation of the oral and pharyngeal mucosa</p> <p>A bitter remedy for lack of appetite</p>	<p><i>For upper respiratory tract ailments</i></p> <p>Adults daily dose: 3-8 g of the herbal substance as a decoction or equivalent liquid preparation, taken in small amounts as required. In the form of pastilles containing aqueous extract from 50-300 mg of the herbal substance, 10 or more daily</p> <p><i>As a bitter</i></p> <p>Adults and elderly single dose: 1-2 g of the herbal substance as a cold macerate, infusion, tincture or other bitter tasting preparations</p>	<p>ESCOP Monographs, 2003</p>
<p>Comminuted herbal substance</p>	<p>Irritation of the oral and pharyngeal mucous membranes and accompanying dry cough</p> <p>Loss of appetite</p>	<p><i>In mucous irritation</i> an infusion prepared from 1.3 g of the herbal substance/150 ml boiling water/10-15 minutes 3-4 times daily</p> <p><i>In loss of appetite</i> a macerate prepared from 1.3 g of the herbal substance/150 ml cold water/1-2 hours, than heat to boil 3-4 times daily ½ an hour before meal</p> <p><i>Duration of use:</i> if the acute symptoms persist longer than 1 week or are recurrent a doctor should be consulted</p>	<p>Standard Zulassungen für Fertigarzneimittel, 1996</p>
<p>Comminuted herbal substance as infusion or other galenic formulations for internal use</p> <p>Comminuted herbal substance as macerate and other bitter tasting preparations for internal use</p>	<p>Cough</p> <p>Dyspeptic complaints</p> <p>Inflammations of the mouth and pharynx</p> <p>Loss of appetite</p>	<p>An infusion prepared from 1.5-2.5 g of the comminuted herbal substance, the daily dose 4-6 g</p>	<p>Gruenwald <i>et al.</i>, 2004 and 2007</p>
<p>Comminuted herbal substance for infusion or macerate preparation</p>	<p>Expectorant for dry cough</p> <p>Irritation of mouth, throat and pharyngeal mucosa</p> <p>Loss of appetite</p> <p>Gargle and cleansing</p>	<p>Internal 1.5 g/150 ml/10-15 minutes 3-4 times daily</p> <p>As appetite enhancer before meals: cold macerate prepared from 1.5 g /150 ml of cold water(1-2 hours, then heat to boiling point</p> <p><i>Duration of use:</i> if the acute symptoms persist longer than 1 week or are recurrent a medical practitioner should be consulted</p>	<p>Gehrman <i>et al.</i>, 2005</p>

In spite of the fact that lichen acids are poorly soluble in cold water (solubility of fumaroprotocetraric acid in water – 0.0325 mg/ml, Kristmundsdóttir *et al.*, 2005), in several literature sources a macerate of the herbal substance is recommended as appetite enhancer (Gehrmann *et al.*, 2005, Standard Zulassungen für Fertigarzneimittel, 1996, ESCOP Monographs, 2003). Taking into consideration solubility of the main constituents of *Lichen islandicus* the following preparation of the herbal tea is proposed:

- as a demulcent for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough:

Herbal tea: 1.5 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion or as a macerate 3 to 4 times daily

The macerate should be used immediately after preparation.

- in temporary loss of appetite:

Herbal tea: 1–2 g of the comminuted herbal substance in 150 ml of water as an infusion or decoction 3 times daily

### **2.3. Overall conclusions on medicinal use**

Traditional use of *Cetraria islandica* (L.) Acharius s.l., thallus in the form of infusion and decoction is well documented in a number of literature sources. Aqueous extracts of the herbal substances are used in the Member States for at least 30 years. Based on information provided by the National Competent Authorities in the overview of the marketed products and literature data the following herbal preparations fulfil the criteria set in Directive 2001/83/EC for at least 30 years of the medicinal use:

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Comminuted herbal substance, herbal tea	Action: demulcent, antiemetic, expectorant  Indication: gastritis, dyspepsia, vomiting, cachexia, respiratory catarrh, bronchitis  Specific indication: cachexia with vomiting	1-2 g of the herbal substance in decoction 3 times daily	British Herbal Pharmacopoeia, 1971, 1976 and 1983
Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 40% (V/V)	Action: demulcent, antiemetic, expectorant  Indication: gastritis, dyspepsia, vomiting, cachexia, respiratory catarrh, bronchitis  Specific indication: cachexia with vomiting	1-1.5 ml 3 times daily	British Herbal Pharmacopoeia, 1971, 1976 and 1983
Soft extract; DER 0.4-0.8:1; extraction solvent water	No information	Lozenges (80 or 160 mg/lozenge)  1-2 lozenges several times daily	Since 1976 until 31 <sup>st</sup> December 2010 Germany  Since 2000 Slovenia
Soft extract, DER 2-4:1, extraction solvent water	Demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough	Lozenges (100 mg/lozenge)  adults and adolescents over 12 years: 13-20 lozenges per day; children 4-12 years 4- 6 lozenges per day	At least since 1976  Germany

Although soft extract, DER 16-18:1; extraction solvent water, is registered as the active substance in traditional herbal medicinal products in Slovenia, Latvia and Hungary, this herbal preparation cannot be included in the Community Monograph as the data on traditional use are not available on public domain.

The following indications are proposed for the Community Monograph:

Traditional herbal medicinal product used

- 1) as a demulcent preparation for oral or pharyngeal irritation and associated dry cough
- 2) in temporary loss of appetite

## 3. Non-Clinical Data

### 3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

#### 3.1.1. Primary pharmacodynamics

In some literature sources (Franz, 1989; Kartnig, 1987) information has been found that the mucilage covers the mucosa with a kind of protecting layer which protects it from local irritation. The only non-clinical study supporting this statement is an *in vitro* study of bioadhesive effects of polysaccharides isolated from Lichen islandicus on isolated porcine buccal membrane by Schmidgall (2000) (see information below).

Nonclinical studies supporting the use of the herbal substance and preparation thereof in loss of appetite are not available.

#### **Bioadhesive effects**

*In vitro:*

#### Polysaccharides:

Purified polysaccharides (carbohydrates content >95%) from Lichen islandicus were investigated for bioadhesive effect on isolated porcine buccal membranes. Polysaccharides from Iceland moss showed a slight adhesion to epithelial tissue (10%). The adhesive effects were concentration dependent. This *ex vivo* system does not completely reflect the physiological status of the epithelia. Especially the naturally occurring mucus layer, originating from interaction of saliva or endogenously secreted glycoproteins with the epithelia can cause slightly different conditions (Schmidgall *et al.*, 2000)

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Strength Dosage Route of administration	<i>In vivo/ In vitro</i>	Reference Year of publication	Main non-clinical conclusions by the authors
other preparations				
Purified polysaccharides	1 ml of 1% solution/cm <sup>2</sup> of mucous membrane	<i>In vitro</i>	Schmidgall <i>et al.</i> , 2000	Bioadhesive effect

#### 3.1.2. Secondary pharmacodynamics

#### **Antimicrobial effects**

*In vitro:*

#### Aqueous or ethanolic extracts:

Antimicrobial activity against *Sarcina lutea* (now *Micrococcus luteus*) has been determined on five samples of the herbal substance from different origin, according to the method described in Pharmacopoea Helvetica. The inhibitions of 1 ml of the 10% aqueous extracts (5 g herbal substance boiled with 50 ml water for 30 min), corresponding to 100 mg herbal substance were comparable to that of 0.07 to 0.85 IU of penicillin (0.04-0.5 µg penicillin). It was assumed that the activity of the extracts depended on the quantity of fumaroprotocetraric acid present (Sticher, 1965a; Sticher, 1965).

Ethanolic extracts of *Cetraria islandica* (15 g/150 ml) were tested for their activity against *Escherichia coli*, *Enterobacter aerogenes*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis*, *Bacillus cereus var. mycoides*, *Bacillus sphaericus*, *Bacillus thurigiensis*, *Bacillus megaterium*,

*Mycobacterium smegmatis*, *Salmonella thyphimurium*, *Candida utilis*, *Candida albicans*, *Aspergillus flavus*, *Aspergillus oryzae*, *Aspergillus fumigatus*, *Trichophyton rubrum*, *Botrytis cineriae*, *Fusarium oxysporium*, *Streptomyces murinus* and *Nocardia corne*. It has been found that *Cetraria islandica* exhibited antimicrobial activity against some Gram (+) bacteria, but had no antimicrobial activity against Gram (-) bacteria, fungi and actinomycetes used in the study (Dülger and Gücin, 1998).

#### Other extracts:

Ethyl acetate, acetone and chloroform extracts of *Cetraria islandica* (15 g/150 ml of the solvent) were tested as described above (Dülger and Gücin, 1998). It has been found that *Cetraria islandica* exhibited antimicrobial activity against some Gram (+) bacteria, but had no antimicrobial activity against Gram (-) bacteria, fungi and actinomycetes used in the study.

#### Isolated substances:

Antimicrobial activity of protolichesterinic acid against *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Listeria monocytogenes* was investigated. Whereas the activity against *B. subtilis* and *L. monocytogenes* was bactericidal, activity against *E. coli* and *P. aeruginosa* was bacteriostatic. Minimum inhibitory concentrations (MIC) of 22.6 mM were found for *E. coli*, *B. subtilis* and *P. aeruginosa* and 11.3 mM for *L. monocytogenes* (Türk *et al.*, 2003).

Protolichesterinic acid from *Cetraria islandica* was screened for *in vitro* activity against *Mycobacterium aurum*, a non-pathogenic organism with similar sensitivity profile to *Mycobacterium tuberculosis*. The MIC of protolichesterinic acid was 250 µg/ml (Ingólfssdóttir *et al.*, 1998a).

Inhibitory activity of protolichesterinic acid (methanolic solution 1.0 mg/ml and sodium salt water solution 10 mg/ml) against 35 strains of *Helicobacter pylori* has been demonstrated, with MICs of 16-64 µg/ml. The MIC<sub>90</sub> (90% of the strains inhibited) was 32 µg/ml, considerably higher than that of ampicillin (0.125 µg/ml) and erythromycin (0.25 µg/ml) but only twice as high as that of metronidazole (16 µg/ml) (Ingólfssdóttir *et al.*, 1997).

### **Immunological effects**

*In vitro*:

#### Aqueous extract:

Traditionally prepared extract from *C. islandica* (prepared from 2 g of the herbal substance boiled in water for 15 minutes) was subjected to phagocytic testing. In the phagocytosis assay the lyophilized extract showed enhancement of granulocytic phagocytosis amounting to 92.6% at a concentration of 100 µg/ml. In order to establish whether the effects are solely due to the polysaccharide content, the extract was fractionated into low molecular weight- and polysaccharide fractions and these fractions were tested using the same test as the untreated extract. Results indicated that the phagocytic activity of the traditional extract was mainly due to the presence of polysaccharides (Ingólfssdóttir *et al.*, 1998; Ingólfssdóttir, 2000).

#### Polysaccharides:

Polysaccharides from a hot aqueous extract of Iceland moss fractionated by ethanol and ion-exchange chromatography were subjected to *in vitro* phagocytosis assay. Prior to aqueous extraction, low molecular weight compounds were removed from the plant material by organic extraction. Results showed that at a concentration of 100 µg/ml, stimulation of granulocytic phagocytosis amounting to 24-54% was exhibited by the four polysaccharide fractions (Ingólfssdóttir *et al.*, 1998).

Immunomodulating activity of an alkali-soluble polysaccharide KI-M-7 isolated from *Cetraria islandica* (branched galactomannan with a backbone composed of two structural elements; (1→6)- linked α-D-mannopyranosyl and α-D-(1→6)-galactopyranosyl units) have been demonstrated in an *in vitro*

phagocytosis test using human granulocytes. An enhancement of granulocytic phagocytosis amounting to 68% was found at a concentration of 100 µg/ml (Ingólfssdóttir *et al.*, 1994).

Immunomodulating activity of a polysaccharide Ci-3 isolated *Cetraria islandica* (composed of (1→3)- and (1→4)- α-D-glucopyranosyl units in the ratio 2:1) was tested in an *in vitro* phagocytosis assay. The results of the *in vitro* phagocytosis assay showed that at concentrations of 100 µg/ml, Ci-3 stimulated granulocytic phagocytosis by approximately 50% compared with control (Olafsdóttir *et al.*, 1999).

*In vivo:*

#### Aqueous extract:

Traditionally prepared extracts from *C. islandica* (prepared from 2 g of the herbal substance boiled in water for 15 minutes) untreated as well as fractionated were subjected to an *in vivo* carbon clearance test performed in mice. The test samples were administered intraperitoneally (1 mg/kg) and the rate of removal of injected colloidal carbon particles from the bloodstream was taken as a measure of reticuloendothelial phagocytic activity. The untreated lyophilized extract stimulated the rate of carbon elimination by a mean ratio of 1.9 compared with control. Results for polysaccharide- and low molecular weight-fractions of the traditional extract showed an increase in the rate of carbon elimination by mean ratios of 1.1 to 1.5, respectively. It can be concluded that the low molecular weight fraction of the traditional extract contributes significantly to the *in vivo* phagocytic results (Ingólfssdóttir *et al.*, 1998, Ingólfssdóttir, 2000).

#### Polysaccharides:

An alkali-soluble polysaccharide, KI-M-7, exhibited enhancement of phagocytosis in an *in vivo* carbon clearance test. When administered intraperitoneally to mice at a concentration of 10 mg/ml, the lichen polysaccharide gave rise to an increase in the rate of carbon elimination by a mean ratio of 1.9 compared with controls. This suggests a significant activation of the reticuloendothelial system (Ingólfssdóttir *et al.*, 1994).

### **Anti-inflammatory effects**

*In vitro:*

#### Aqueous extract:

Human monocyte-derived immature dendritic cells were cultivated with an aqueous extract from *Cetraria islandica* (prepared from 10 g of milled herbal substance boiled for 5 minutes in 500 ml of water, filtered and freeze dried) quantified with regard to the polysaccharides lichenan and isolichenan and secondary metabolites protolichesterinic acids and fumaroprotocetraric acids. The purified compounds were also tested individually. Their effects on the maturation of the dendritic cells were assessed by measuring secretion of IL-10 and IL-12p40 and expression of surface molecules. The aqueous extract (10 and 100 µg/ml) caused up regulated secretion of both IL-10 and IL-12p40, with IL-10 secretion being more prominent. Lichenan (10 and 100 µg/ml) had similar effects, whereas isolichenan (10 and 100 µg/ml) and the secondary metabolites (0.01, 0.1 and 1 µg/ml) were inactive, suggesting that the effect observed by the aqueous extract was mainly mediated by lichenan. The results suggest that the aqueous extract from *Cetraria islandica* has an anti-inflammatory effect, possibly by changing the cytokine secretion bias from IL-12p40 towards IL-10 (Freysdóttir *et al.*, 2008).

#### Isolated substances:

(+)-protolichesterinic acid inhibited the enzyme 5-lipoxygenase in porcine leucocytes with an IC<sub>50</sub> of 20 µM; 5-lipoxygenase is a catalyst in the biosynthesis of leukotrienes, which are potent bronchoconstrictors and are involved in inflammatory processes (Ingólfssdóttir *et al.*, 1994a).



Subsequently it was shown that (+)-protolichesterinic acid inhibited leukotriene B<sub>4</sub> biosynthesis in stimulated bovine polymorph nuclear leucocytes ( $p < 0.05$ ) with an IC<sub>50</sub> of 9  $\mu$ M (Kumar and Müller, 1999).

*In vivo:*

#### Aqueous extract:

The effect of the aqueous extract from *Cetraria islandica* (prepared from 10 g of milled herbal substance boiled for 5 minutes in 500 ml of water, filtered and freeze dried) quantified with regard to the polysaccharides lichenan and isolichenan and secondary metabolites protolichesterinic acids and fumaroprotocetraric acids on bovine serum albumin induced arthritis in rats was investigated. The purified compounds were also tested individually. During 2 weeks prior to arthritis induction and 5 subsequent weeks the rats were injected subcutaneously with 0.2 ml of aqueous extract from *C. islandica* at a concentration of 0.025, 0.25 and 2.5 mg/kg or saline only as a negative control. Significantly less arthritis was observed in rats treated with the highest concentration of aqueous extract compared with rats treated with saline alone, whereas the two lower concentrations has no effect. Further research is needed to confirm the anti-inflammatory effect of the extract, to prove its potential to exhibit the same effect after oral administration and explain mechanism of action. (Freysdóttir *et al.*, 2008).

### **Antiviral activity**

*In vitro:*

#### Polysaccharides:

Lichenan exhibited broad antiviral activity against mechanically transmitted viruses of different taxonomic groups in different *Nicotiana* ssp. In the *in vitro* test with tobacco mosaic virus it was demonstrated that lichenan at concentrations of 100 to 500  $\mu$ g/ml did not affect cell-free protein synthesis. Therefore, lichenan mediated virus inhibition cannot be explained by inhibitory effects towards structural components of the virus. Virus inhibition is more likely the result of suppressive effects on virus replication or cell-to-cell movement from initially occupied cells (Stübler and Buchenauer, 1996).

#### Isolated substances:

Protolichesterinic acid was found to be a potent inhibitor of the DNA polymerase activity of human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT), with 50% inhibitory dose of 24  $\mu$ M. It showed negligible cytotoxic activity with a variety of cultured mammalian cells (Pengsuparp *et al.*, 1995).

### **Antioxidative effects**

*In vitro:*

#### Aqueous or ethanolic extracts:

The antioxidant activity, reducing power, superoxide anion radical scavenging and free radical scavenging activities of the aqueous extract of *Cetraria islandica* (20 g/400 ml of water/stirred for 15 minutes) were studied. The antioxidant activity increased with the increasing amount of extracts (from 50 to 500  $\mu$ g) added to the linoleic acid emulsion. About 50, 100, 250 and 500  $\mu$ g of aqueous extract showed higher antioxidant activity than 500  $\mu$ g of  $\alpha$ -tocopherol. The samples showed 96, 99 and 100% inhibition on peroxidation of linoleic acid, while 500  $\mu$ g of  $\alpha$ -tocopherol showed only 77% inhibition. As well as antioxidant activity, the reducing power, superoxide anion radical scavenging and free radical scavenging activities depend on concentration and are increasing with increased amount of sample (Gülçin *et al.*, 2002).

#### Other extracts:

*Cetraria islandica* methanolic extract (20 g/250 ml/72 h in Soxhlet, lyophilised) was tested for effects on the activities of enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx) and malondialdehyde (MDA) in human blood cultures. Aflatoxin B1 (AFB<sub>1</sub>) was induced to the cell cultures to induce oxidative stress. The results showed that the MDA level decreased, while SOD and GPx activities increased when 5 µg/ml and 10 µg/ml of the extract were added to AFB<sub>1</sub>-treated cultures (Kotan *et al.*, 2011).

*In vivo:*

#### Aqueous extract:

To verify the hypothesis that antioxidant activity of lichens may decrease hyperglycaemia-induced oxidative stress and prevent the development of diabetic complications (including abnormality in haematological conditions effects of *Cetraria islandica* water extract on the haematological parameters of rats with type I diabetes mellitus) were investigated. Control Sprague-Dawley rats or streptozocin (STZ)-induced diabetic rats were either untreated or treated with an aqueous lichen extract (20 g/400 ml of water/stirred for 15 minutes) at the dose 5–500 mg/kg body weight/day administered intraperitoneally for two weeks, starting 72 h after STZ injection. On day 14 the animals were anaesthetized and haematological and metabolic parameters were determined. In addition, the total oxidative stress (TOS), a specific indicator of oxidative stress, and total antioxidant capacity (TAC) were measured by biochemical studies. The results suggested that the antioxidant activities of lichens might be the possible reason behind the observed antihematological status. However, the protective effect of lichen extract was inadequate on diabetes-induced microcytic hypochromic anaemia. In addition, the extract had no effect on metabolic complications. The experimental data showed that high doses of lichen extract had no detrimental effect on blood cells and TOC status of plasma (Çolak *et al.*, 2012).

#### Cognitive effects

*In vivo:*

#### Polysaccharides:

The effects of isolichenan isolated from *Cetraria islandica* on the hippocampal synaptic plasticity were investigated in rats. Isolichenan (1 mg/kg, administered intravenously) significantly enhanced short term potentiation evoked by a subthreshold tetanus, without any effect on the basal synaptic excitability (no tetanus stimulation). No effects on a supra-threshold tetanus evoked potentiation were found. Isolichenan did not influence learning behaviours of intact mice in passive-avoidance tests and intact rats in Morris water maze test. When learning ability of mice was impaired by 30% ethanol pre-treatment, isolichenan (>100 mg/kg, administered orally) significantly improved acquisition in passive-avoidance test. Similarly, isolichenan (100 mg/kg administered orally) repaired memory-impairment induced by  $\beta$ -amyloid peptide (fraction 25-35) in the Morris water maze test in rats. These results suggest positive effects of isolichenan on spatial memory formation in rodents (Smriga *et al.*, 1999, Smriga and Saito, 2000).

#### Anti-proliferative effects

*In vitro:*

#### Isolated substances:

Effects of protolichesterinic acid isolated from *Cetraria islandica* on cultured cells from man, including three malignant cell-lines (T-47D and ZR-75-1 from breast carcinomas and K-562 from erythro-leukaemia), as well as normal skin fibroblasts and peripheral blood lymphocytes were studied in an *in vitro* test. Protolichesterinic acid caused a significant reduction in DNA synthesis in all three malignant cell-lines. The dose inducing 50% of maximum inhibition (ED<sub>50</sub>) was between 1.1 and 24.6 µg/ml. The breast-cancer cell-lines were more sensitive than K-562. Significant cell death occurred in three

malignant cell-lines at concentration above 20 µg/ml. The proliferative response of mitogen-stimulated lymphocytes was inhibited with a mean ED<sub>50</sub> of 8.4 µg/ml. In contrast, the DNA synthesis, proliferation and survival of normal skin fibroblasts were not affected at doses up to 20 µg/ml (Ögmundsdóttir *et al.*, 1998).

Protolichesterinic acid was tested for anti-proliferative effects against 12 different human cancer cell lines from pancreas, breast, prostate, small cell lung, ovarian, stomach and colorectal cancers and acute pro-myelocytic, erythro- and T-cell leukaemia. Protolichesterinic acid showed an inhibitory effect against all cell lines with EC<sub>50</sub> ranging from 2.4–18.1 µg/ml (7.4–55.8 µM) (Haraldsdóttir *et al.*, 2004).

*In vivo:*

#### Polysaccharides:

Crude lichenin and isolichenin isolated from *Cetraria islandica* var. *orientalis* Asahina were tested for their activity on sarcoma-180, subcutaneously implanted to Swiss albino mice. A dose of 200 mg/kg/day was administered intraperitoneally for 10 day starting 24 h after tumour implantation. Significant inhibition in ratios 100 and 99.6% was shown (Fukuoka *et al.*, 1968).

#### Polysaccharide derivatives:

A semisynthetic derivative of lichenin,  $\gamma$ -propoxy-sulfo-lichenin (PSL) exhibited a strong antitumour effect against allogeneic sarcoma 180 in mice at concentrations 25 and 5 mg/kg (100% and 82% tumour inhibition). PSL also inhibited tumour growth by about 88% on syngeneic DBA/2-MC-SC-1-fibrosarcoma in mice at a concentration of 25 mg/kg. Three PSL fractions with different molecular masses (<25, 250, 1000 kD) were synthesized and tested against sarcoma 180. The highest activity was found for the polysaccharide with the highest molecular mass (100% inhibition at 5 mg/kg) (Hensel, 1995).

#### Other effects

*In vitro:*

#### Polysaccharides:

The inhibitory effects of polysaccharides isolated from the traditional extract were tested on the classical pathway of complement, using sensitised sheep erythrocytes and guinea pig complement. At a concentration of 100 µg/ml, all fractions showed considerable reduction of complementary-induced haemolysis, ranging from 49 to 85%. Although the degree of activity of the polysaccharide fraction was considerably greater, there was modest contribution from the low molecular weight fraction (Ingólfssdóttir, 1998).

The inhibitory effects of a polysaccharide (Ci-3), isolated from *Cetraria islandica* (composed of (1→3)- and (1→4)-  $\alpha$ -D-glucopyranosyl units in the ratio 2:1) were tested on the classical pathway of complement, using sensitised sheep erythrocytes and guinea pig complement. Ci-3 at a concentration of 100 µg/ml reduced the complementary-induced haemolysis about 80% (Ólafsdóttir *et al.*, 1999).

#### Isolated substances:

Several lichen compounds including protolichesterinic acid were investigated for their inhibitory activity on platelet-type 12(S)-lipoxygenase (12-LOX) using cell-based *in vitro* system in human platelets with respect to their known anti-proliferative and 5-lipoxygenase (5-LOX) inhibitory effects. Lobaric acid from *Stereocaulon alpinum* and (+)- protolichesterinic acid from *Cetraria islandica* Laur. were proved to be pronounced inhibitors of platelet-type 12(S)-lipoxygenase, both showing a clear dose-response relationship in the range of 3.33-100 µg/ml. According to the calculated IC<sub>50</sub> values the highest inhibitory activity was observed for lobaric acid (IC<sub>50</sub> = 28.5 µM) followed by protocetraric acid (IC<sub>50</sub> = 77.0 µM). The activity of lobaric acid was comparable to that of flavone baicalein, which is known as selective 12(S)-lipoxygenase inhibitor (Bucar *et al.*, 2004).

Protolichesterinic and lichesterinic acids were studied for their ability to mediate pigmentation in melanine and tyrosinase assays in B16 mouse melanoma cells with a non-toxic concentration of 5 µM. In both assays, B16 cells were cultured for 72 h in the presence or absence of the lichen compounds. Following treatment, cells were UVB radiated. Glycyrrhizic acid was included as a positive control for melanogenesis. The ability of protolichesterinic acid to increase melanin was confirmed to be the result of increased tyrosinase activity, with levels peaking at 4 h. Interestingly, lichesterinic acid was found to act synergistically with UVB irradiation to increase melanin (Abrahams *et al.*, 2013).

### 3.1.3. Safety pharmacology

No data available.

### 3.1.4. Pharmacodynamic interactions

It is mentioned in some literature sources (Herr, 2005) that absorption of concomitantly administered medicines can be delayed due to mucilage protecting layer. For this reason the product should not be taken ½ to 1 hour before or after intake of other medicinal products. However, no tests on humans or animals were performed to confirm delayed absorption.

### 3.1.5. Conclusions

Lichen islandicus is traditionally used

- as a demulcent for oral or pharyngeal irritation and associated dry cough
- in loss of appetite.

Iceland moss preparations and isolated polysaccharides and lichen acids have been investigated in several pharmacological *in vitro* and *in vivo* studies demonstrating several effects. A direct correlation of the test results (kind of extract, route of administration *in vitro* vs. *in vivo*) with the clinical situation is not possible. The reported pharmacological effects are not considered contradictory to the oral and oromucosal traditional use of herbal preparations of Lichen islandicus as a demulcent for the symptomatic treatment of irritations of oral and pharyngeal mucosa with associated dry cough.

Nonclinical studies supporting the use of the herbal substance and preparation thereof in loss of appetite are not available; however, due to bitter taste of lichen acids (protolichesterinic and fumaroprotocetraric acids) this indication seems plausible for traditional use of the herbal substance and bitter tasting preparations thereof.

In the literature there is a hypothesis that absorption of concomitantly administered medicinal products can be delayed due to mucilage protecting layer. As this hypothesis was not confirmed neither in non-clinical or clinical studies, this information has not been included in the section 4.5 'Interactions with other medicinal products and other forms of interaction', however, it has been introduced in the section 4.4 'Special warnings and precautions for use' as a precautionary measure.

## 3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No information available

### **3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof**

As well as other lichens, *Cetraria islandica* is extremely sensitive to atmospheric pollutants. *Cetraria islandica* was found to be able to absorb some toxic elements from the environment (Cercasov *et al.*, 2002). High levels of heavy metals, especially lead, but also cadmium and mercury (Pb 30 mg/kg, Cd 0.30 mg/kg, Hg 0.075 mg/kg) were found in samples originating from Finland (Airaksinen *et al.*, 1986). The natural radionuclides  $^{210}\text{Po}$ , and  $^{210}\text{Pb}$ , as well as  $^{137}\text{Cs}$  and  $^{90}\text{Sr}$  from nuclear test explosions, were also found to be accumulated in the lichen (Huovinen and Jaakola, 1991; Crawford, <http://web.uvic.ca/~stucraw/TableContents.html>; Sharma, 2004). Following the Chernobyl incident it has been difficult to obtain plant material with radioactivity less than 600 Bq from Scandinavian countries. The situation has improved since 1994 (Schilcher, 1997).

Untreated Iceland moss as 50% w/w mixture in food, was toxic to mice; they all died in 4-5 days. Boiling the lichen for 10 minutes only increased the survival time by 2 days. Ash-soaking (in 2% wood ash solution for 2 days) increased the survival time. With the ash soaked and boiled 50% Iceland lichen mixture, the mice lived 20-22 days, and with the corresponding 25% mixture the mice survived 6 weeks and were in good condition at the end (Airaksinen *et al.*, 1986a).

In a 3-months study with rats (8 young Wistar/Kuo rats, 4 of each sex in a test group and 16 in a control group) tolerability to ash-treated *C. islandica* was tested. The test group was fed with a flour containing 25% of ash-soaked Iceland moss boiled for 10 minutes and the control group received ground pellets. Rats tolerated ash-treated Iceland moss rather well, although the body weight did not increase as much as in controls. All blood tests at the end were normal; haemoglobin values were even higher than in controls. Urine tests were normal except increased value of protein. Several kidneys showed some focal tubular damage and an increase in glomerular cell contents. The histology of the other organs did not differ from controls. In urine of three animals (2 female and 1 male) some blood was found. Organ weights in the test group were similar to the control group. The proteinuria and the slight kidney changes after 3 months lichen diet are probably due to slight heavy metals poisoning, as the lichen used in the study contained high level of lead. Much higher content of lead was found in the kidneys of test group than in control. The increase of haemoglobin in the test group may be due to high iron content. The small increases of the body weight in test group correspond to the lower energy content of the food in comparison with the control food pellets (Airaksinen *et al.*, 1986, Airaksinen *et al.*, 1986a).

In May 2012, the European Food Safety Authority (EFSA) published a new version of the compendium of plants reported to contain toxic, addictive, psychotropic or other substances from 2009, "Compendium of botanicals reported to contain naturally occurring substances of possible concern for human health" (<http://www.efsa.europa.eu/en/efsajournal/pub/2663.htm>). *Cetraria islandica* (L.) Ach. has been listed there due to chemical concerns (content of dibenzofurane derivatives, e.g. usnic acid and reported ability of the plant to concentrate heavy metals).

#### **3.3.1. Single dose toxicity**

No data available

#### **3.3.2. Repeat dose toxicity**

No data available.

### 3.3.3. Genotoxicity

No published data available.

*Cetraria islandica* methanolic extract (20 g/250 ml/72 h in Soxhlet, lyophilised) was tested for antigenotoxic effect in sister chromatid exchange (SCE) and micronuclei (MN) assays in human lymphocyte cells, treated with Aflatoxin B<sub>1</sub> (AFB<sub>1</sub>). SCE and MN frequencies increased with increased AFB<sub>1</sub> concentration (5 and 10 µM), while the frequencies of SCE and MN decreased when 5 µg/ml and 10 µg/ml of the extract were added. Especially supplementation with the 10 mg/ml concentration of the extract restored the parameters to that of the negative control (Kotan *et al.*, 2011).

### 3.3.4. Carcinogenicity

No data available

### 3.3.5. Reproductive and developmental toxicity

No data available

### 3.3.6. Local tolerance

No data available

### 3.3.7. Other special studies

No data available

### 3.3.8. Conclusions

Although Iceland moss was demonstrated toxic in mice fed with a mixture of food containing 50% of lichen, it is well tolerated in humans at therapeutic dose levels without undesirable effects (Kempe *et al.*, 1997; Vorberg, 1981).

In spite of the fact that *Cetraria islandica* is on the EFSA list of naturally occurring substances of possible concern to human health, no safety concern should be raised for the herbal substance used for pharmaceutical purposes as usnic acid (dibenzofurane) has not been found in *Cetraria islandica* (Sticher, 1965, Ingólfssdóttir, 2002) or only in a traces (Airaksinen *et al.*, 1986a) and lead content is limited to 10.0 ppm in the Ph.Eur. monograph Iceland moss.

## 3.4. Overall conclusions on non-clinical data

Despite non-clinical data on several activities of the water extract and/or substances isolated thereof exist, a direct correlation of the test results (kind of extract, route of administration *in vitro* vs. *in vivo*) with the clinical situation is not possible. The reported pharmacological effects are not considered contradictory to the oral and oromucosal traditional use of herbal preparations of Lichen islandicus as a demulcent for the symptomatic treatment of irritations of oral and pharyngeal mucosa with associated dry cough.

Nonclinical studies supporting the use of the herbal substance and preparation thereof in loss of appetite are not available; however, due to bitter taste of lichen acids (protolichesterinic and fumaroprotocetraric acids) this indication seems plausible for traditional use of the herbal substance and bitter tasting preparations thereof.

No cytotoxic effect has been observed in normal skin fibroblasts at doses up to 20 µg/ml, even though protolichesterinic acid isolated from *C. islandica* showed negligible cytotoxic activity in an *in vitro* study with a variety of cultured cancer mammalian cells.

Specific data on pharmacokinetics and interactions are not available.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended.

## **4. Clinical Data**

### **4.1. Clinical pharmacology**

#### **4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

No data available

#### **4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

No data available

### **4.2. Clinical efficacy**

#### **4.2.1. Dose response studies**

In the Kempe study (see section 4.2.2) efficacy and tolerability of an aqueous extract from Iceland moss in three different doses corresponding to the daily dose of 0.48 g, 3 g or 5 g of the herbal substance were studied. No significant difference in the results was observed after 5 days of the treatment (Kempe *et al.*, 1997)

#### **4.2.2. Clinical studies (case studies and clinical trials)**

In a comparative double-blind study 63 patients (aged of 18 to 65 years) with inflammation and dryness of the oral cavity due to breathing only through the mouth after nasal surgery were divided in three random groups and treated daily with 10 pastilles, each containing an aqueous extract from Iceland moss equivalent to 0.048 g (n=23), or 0.3 g (n=18) or 0.5 g (n=22) of the herbal substance starting the first day after surgery. Placebo control was not included. The oral application was finished on the fifth day after operation. Coating, dryness and inflammation of mucosa, occurrence of lymph nodes, tongue coating and symptoms such as hoarseness and sore throat were assessed by physicians using biometric observations on a 0-3 scale. An improvement was observed without significant differences in all three test groups. Even the lowest dosage equivalent to 0.48 g of the herbal substance per day was sufficient. The therapy was well tolerated by all the patients. No adverse effects were reported (Kempe *et al.*, 1997).

In an open study, 100 patients aged 7 to 85 years with inflammations of oral or pharyngeal mucosa (laryngitis, pharyngitis) (63 patients), acute or chronic bronchial catarrhs (29 patients and more severe bronchial ailments such as asthma bronchiale, bronchial carcinoma or bronchoectasy (6 patients) were treated with 1-2 pastilles containing each 160 mg of an aqueous extract from Iceland moss and 5 mg of an extract from *Heracleum sphondylium* L (neither DER nor extraction solvent for extract from

*Heracleum sphondylium* was specified) applied every 2 to 3 hours for 4 days to 3 weeks. The results were assessed as significantly positive in 86%, whereas in case of adjuvant treatment in more severe bronchial ailments no significant effect was observed (Vorberg, 1981).



Table 5: Clinical studies on humans in irritated mucosa and associated dry cough

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score e.g. Jadad score	Comments of the investigator on clinical relevance of results
Treatment of inflammation and dryness of the oral cavity Efficacy and tolerability and dose response study Kempe <i>et al.</i> , 1997	Comparative double-blind study  duration: 5 days	Pastilles containing an aqueous extract from Iceland moss corresponding to 0.048, 0.3 or 0.5 g of the herbal substance, 10 pastilles per day	63 patients 18–65 years, no information on sex  0.048 g (n=23), or 0.3 g (n=18) or 0.5 g (n=22)	Dryness and inflammation of the oral cavity after nasal surgery	Significant improvement  Good tolerability, no adverse effects	None	Significant improvement of symptoms, no adverse reactions reported
Treatment of inflammations of oral or pharyngeal mucosa, acute or chronic bronchial catarrhs and more severe bronchial ailments  Efficacy study Vorberg, 1981	Open study  duration: 4 days to 3 weeks	Pastilles containing each 160 mg of an aqueous extract from Iceland moss and 5 mg of extract from <i>Heracleum sphondylium</i> L 1-2 pastilles every 2 to 3 hours	100 patients 7–85 years, no information on sex  inflammations of upper respiratory tract (63 patients), acute or chronic bronchial catarrhs (29 patients) and more severe bronchial ailments (6 patients)	Inflammations of oral or pharyngeal mucosa (laryngitis, pharyngitis) (63 patients), acute or chronic bronchial catarrhs (29 patients) and more severe bronchial ailments such as asthma bronchiale, bronchial carcinoma or bronchoectasy (6 patients)	Significantly positive in 86%, in case of adjuvant treatment in more severe bronchial ailments no significant effect observed  no adverse effects	None	Significant improvement of the symptoms

### **4.2.3. Clinical studies in special populations (e.g. elderly and children)**

Tolerability of Iceland moss lozenges (Lozenges A – Iceland moss soft extract, DER 0.4-0.8:1, extraction solvent water, 80 mg per lozenge and Lozenges B - Iceland moss soft extract, DER 2-4:1, extraction solvent water, 100 mg per lozenge) in upper respiratory tract diseases has been studied in a multi-centric post-marketing surveillance study with 3,143 children (1,648 girls, 1,483 boys, sex of 12 patients was not specified) aged 4 to 12 years, suffering from upper respiratory tract diseases (irritating cough, inflammation in mouth and pharynx, laryngitis, acute bronchitis). The patient received 4-6 lozenges for 1 to 2 weeks (lozenges A: n=1,848; lozenges B: n=1,295). The study was performed in 300 predominantly paediatric practices in Germany. Treatment access was assessed globally by investigators and the patients' parents. The parents were also asked to rate their children's symptoms before and after treatment. Tolerability was evaluated by assessing of adverse drug reactions (ADRs). During the observation period, 73 adverse events, most of which were related to the basic disease, were reported in 57 children (1.8%). In 6 children (0.2%) and 7 events a causal relationship with Iceland moss extract could not be excluded, therefore those events were evaluated as ADRs (for details see section 5.3.). All ADRs subsided spontaneously during the period of observation. The results confirmed good tolerability of Iceland moss dry extracts and support a favourable risk-benefit assessment (Hecker and Völp, 2004).

### **4.3. Overall conclusions on clinical pharmacology and efficacy**

There are no data available from controlled clinical studies. Available clinical data from a comparative, double blind study by Kempe (1997) and from an open study by Vorberg are considered not sufficient to support WEU due to the small number of subjects and due to the fact that the studies are not placebo controlled. However they sufficiently support traditional use of the herbal substance and preparations thereof as a demulcent for oral or pharyngeal irritation and associated dry cough.

## **5. Clinical Safety/Pharmacovigilance**

### **5.1. Overview of toxicological/safety data from clinical trials in humans**

In the clinical studies by Kempe (1997) and Vorberg (1981) (for details see section 4.2.2.) no adverse effects were reported.

In the post-marketing surveillance study in 3,143 children by Hecker and Völp (2004), several adverse events occurred. However, these ADRs were only mild and subsided spontaneously (for details see section 4.2.3. and 5.3.).

Forty-five patients with dermatitis primarily localised to light-exposed areas and with a history of photosensitivity were examined with a mixture of different lichen plants including *Cetraria* spp. in petrolatum. Furthermore, a series consisting of 14 different aromatic lichen substances including fumaroprotocetraric acid were isolated and purified and used for patch testing at concentrations of 1 and 0.1% in petrolatum. Sixteen patients (12 males and 4 females) showed positive reactions (erythema, oedema, vesicles) to the mixture of various lichen, but only in six of them were the reactions stronger after irradiation with UVA and UVB suggesting a possible photo allergy. Eleven patients revealed contact allergy to substances other than lichens as well. A patch test with isolated lichen acids showed sensitivity most frequently to atranorin (not isolated from *Cetraria islandica*) and also reacted to some other lichen substances. In patch tests with *Cetraria islandica* 8 positive reactions were observed, while reactions to fumaroprotocetraric acid were observed only in one case (Thune and Solberg, 1980).

Potential allergenic activity of sesquiterpene lactones derivatives including protolichesterinic acid was tested in a patch test with 35 patients with known allergic contact dermatitis caused by *Frullaria nisauallensis*. These patients showed a negative patch test to other compounds possessing an unsaturated methylene group including protolichesterinic acid (Mitchel *et al.*, 1972).

Table 6: Clinical safety data from clinical trials

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of Subjects (including age, sex, drop out)	Healthy Subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Adverse reactions	Comments of the investigator on clinical relevance of results
Treatment of inflammation and dryness of the oral cavity Efficacy and tolerability and dose response study Kempe <i>et al.</i> , 1997	Comparative double-blind study Duration: 5 days	Pastilles containing an aqueous extract from Iceland moss corresponding to 0.048, 0.3 or 0.5 g of the herbal substance, 10 pastilles per day	63 patients 18–65 years, no information on sex  0.048 g (n=23), or 0.3 g (n=18) or 0.5 g (n=22)	Dryness and inflammation of the oral cavity after nasal surgery	Significant improvement  Good tolerability	No adverse effects	Significant improvement of symptoms, no adverse reactions reported
Treatment of inflammations of oral or pharyngeal mucosa, acute or chronic bronchial catarrhs and more severe bronchial ailments  Efficacy study Vorberg, 1981	Open study Duration 4 days to 3 weeks	Pastilles containing each 160 mg of an aqueous extract from Iceland moss and 5 mg of extract from <i>Heracleum sphondylium</i> L 1-2 pastilles every 2 to 3 hours	100 patients 7–85 years, no information on sex  inflammations of upper respiratory tract (63 patients), acute or chronic bronchial catarrhs (29 patients) and more severe bronchial ailments (6 patients)	Inflammations of oral or pharyngeal mucosa (laryngitis, pharyngitis) (63 patients), acute or chronic bronchial catarrhs (29 patients) and more severe bronchial ailments such as asthma bronchiale, bronchial carcinoma or bronchoectasy (6 patients)	Significantly positive in 86%, in case of adjuvant treatment in more severe bronchial ailments no significant effect observed	No adverse effects	Significant improvement of the symptoms

Treatment of upper respiratory tract diseases  Tolerability study  Hecker and Völp, 2004	Multi-centric post-marketing surveillance study	Lozenges containing 80 mg of Iceland moss soft extract, DER 0.4 – 0.8:1 (lozenges A) or 100 mg of Iceland moss soft extract, DER 2-4:1, extraction solvent water (lozenges B)  lozenges A n=1,848; lozenges B n=1,295  4–6 lozenges for 1 to 2 weeks	3,143 children (1,648 girls, 1 483 boys, sex of 12 patients was not specified) age 4 to 12 years	upper respiratory tract diseases (irritating cough, inflammation in mouth and pharynx, laryngitis, acute bronchitis)	Good tolerability	73 adverse events related to the basic disease, were reported in 57 children (1.8 %). In 6 children (0.2 %) and 5 events a causal relationship with Iceland moss extract could not be excluded, so that were evaluated as ADRs  All ADRs subsided spontaneously	Good tolerability
Contact and photo allergy study  Thune and Solberg, 1980	No information on study design  Patch test	Lichens in petrolatum including <i>Cetraria islandica</i>  Isolated lichen acids including fumaroprotocetraric acid	45 patients	Patients with dermatitis primarily localised to light-exposed areas and with a history of photosensitivity	Positive reaction in 16 patients (12 males and 4 females), 6 of them stronger reaction after irradiation with UVA and UVB  In patch tests with <i>Cetraria islandica</i> 8 positive reactions but only 1 positive reaction to fumaroprotocetraric acid	Contact allergy proved in 16 patients, In 6 of them possible photo allergy, 8 patients with contact allergy to <i>Cetraria islandica</i> , 1 patient to fumaroprotocetraric acid	Contact allergy in sensitive patients
Potential allergenic activity study  Mitchel <i>et al.</i> , 1972	No information on study design  Patch test	Sesquiterpene lactones derivatives including protolichesterinic acid	35 patients	Patients with known allergic contact dermatitis caused by <i>Frullaria nisauaullensis</i> .	Negative patch test to compounds possessing an unsaturated methylene group including protolichesterinic acid	None reported	No contact allergy to protolichesterinic acid

## 5.2. Patient exposure

Lozenges containing an aqueous extract of Iceland moss are widely used either as registered medicinal products or as food supplements or medical devices.

Data obtained from clinical studies with 163 patients (Kempe *et al.*, 1997 and Vorberg, 1981) and from a post-marketing surveillance study with 3,143 children (Hecker and Völp, 2004) showed good tolerance of the water extracts of Iceland moss.

In older times lichens including *Cetraria islandica* were used in arctic and subarctic areas as an emergency food in famines but also in non-famines years for bread and dessert jelly preparation. The lichen was traditionally pre-treated with alkaline wood-ash and boiling water to remove bitter lichen acids (Airaksinen *et al.*, 1986).

## 5.3. Adverse events and serious adverse events and deaths

In the post-marketing surveillance study on tolerability of Iceland moss lozenges performed with 3,143 children aged 4 to 12 years the following adverse reactions were reported:

- In a 10 years old boy suffering from inflammation in mouth and pharynx itching on legs and back was observed after 3 days treatment with 4 lozenges/day containing 80 mg of the aqueous extract from Iceland moss DER 0.4-0.8: 1. The symptoms subsided spontaneously within 2 days.
- In a 11 years old girl suffering from pharyngitis itching on arms and legs was reported after 3 days treatment with 4 lozenges/day containing 80 mg of the aqueous extract from Iceland moss DER 0.4-0.8: 1. The symptoms subsided spontaneously within 2 days.
- In a 6 years old girl suffering from laryngitis, pharyngitis and acute bronchial catarrh nausea was reported after first receiving a lozenge containing 80 mg of the aqueous extract from Iceland moss DER 0.4-0.8: 1. Xylomethazon and Ambroxol were used as a co-medication. The child refused the next treatment with the Iceland moss lozenge.
- In a 11 years old girl suffering from irritating cough and laryngitis burning in the mouth was observed after first administration of a lozenge containing 80 mg of the aqueous extract from Iceland moss DER 0.4-0.8: 1. Ampicillin was used concomitantly. The child refused the next treatment with the Iceland moss lozenge.
- In a 10 years old girl suffering from irritating cough and pharyngitis abdominal pain and heartburn was reported after receiving the 5<sup>th</sup> dose of a lozenge containing 100 mg of the aqueous extract from Iceland moss DER 2-4: 1. Paracetamol 1500 mg/day was used concomitantly. The treatment with Iceland moss lozenges was stopped. The symptoms subsided spontaneously within 1 day.
- In a 9 years old girl suffering from inflammation in mouth, nausea was observed. Another herbal medicinal product containing extract from *Althaeae radix*, *Matricariae flos*, *Equiseti herba*, *Juglandis folium*, *Millefolii herba*, *Quercus cortex* and *Taraxaci herba* was used concomitantly. The problems occurred on the second day of treatment with lozenges containing 100 mg of the aqueous extract from Iceland moss, DER 2-4: 1. Due to the problems the treatment was stopped (Hecker and Völp, 2004).

## **5.4. Laboratory findings**

No data available

## **5.5. Safety in special populations and situations**

### **5.5.1. Use in children and adolescents**

In the post-marketing surveillance study with 3,143 children aged 4 to 12 years treated with two different products containing an aqueous extract from Iceland moss (for details see 4.2.3. and 5.3.) 73 adverse events, most of which were related to the basic disease, were reported in 57 children (1.8%). In 6 children (0.2%) and 7 events a causal relationship with Iceland moss extract could not be excluded, so that they were evaluated as ADRs. All ADRs subsided spontaneously during the period of observation. The incidence of ADRs was 1 event in 3,008 treatment days. As regard the symptoms, 39% of the children were fully recovered and another 55% were improved by the end of the period of the observation. The adverse events reported were generally mild and transient in the doses recommended for the therapeutic indications (Hecker and Völp, 2004).

### **5.5.2. Contraindications**

The herbal medicinal products are contraindicated in hypersensitivity to the active substance.

### **5.5.3. Special Warnings and precautions for use**

#### Indication 1

The use of comminuted herbal substance in children under 12 years of age has not been established due to lack of adequate data.

The use of aqueous extracts (soft extract (DER 2-4:1), extraction solvent water and soft extract (DER 0.4-0.8:1), extraction solvent water) in the form of lozenges in children under 6 years of age is not recommended because of the pharmaceutical form.

The use of tincture (ratio of herbal substance to extraction solvent 1:5, extraction solvent ethanol 40% V/V) in children and adolescents under 18 years of age has not been established due to lack of adequate data.

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.

#### Indication 2

The use of comminuted herbal substance and tincture (ratio of herbal substance to extraction solvent 1:5, extraction solvent ethanol 40% V/V) in children and adolescents under 18 years of age has not been established due to lack of adequate data.

#### Indications 1) and 2)

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.

For tinctures containing ethanol, the appropriate labelling for ethanol, taken from the 'Guideline on excipients in the label and package leaflet of medicinal products for human use', must be included.

#### **5.5.4. Drug interactions and other forms of interaction**

None reported.

#### **5.5.5. Fertility, pregnancy and lactation**

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 fertility data is available.

#### **5.5.6. Overdose**

No case of overdose has been reported.

#### **5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability**

No studies on the effect on the ability to drive and use machines have been performed.

#### **5.5.8. Safety in other special situations**

Not applicable

### **5.6. Overall conclusions on clinical safety**

The safety of use in defined conditions of Iceland moss products can be derived from the long-standing use and experience as well as from clinical studies. In the clinical studies with adult patients no adverse reactions were reported. In the post-marketing surveillance study in children adverse events occurred, however these ADRs were only mild and subsided spontaneously. No serious adverse events and deaths have been reported. There are no case reports on overdose, drug interactions, drug abuse, effects on ability to drive or operate machinery or impairment of mental ability.

On the basis of clinical studies and information on traditional use, *Lichen islandicus* containing medicinal products prove not to be harmful in the specified conditions of use.

The indication 1 is appropriate for use in adolescents and children over 6 years of age and the indication 2 for adults and elderly without the supervision of a medical practitioner. The duration of use without medical advice is limited to one week.

*C. islandica* preparations are contraindicated in patients with hypersensitivity to the active substance. Due to lack of data, the use is not recommended during pregnancy and lactation.

## **6. Overall conclusions (benefit-risk assessment)**

Based on the data documented in the assessment report, a Community herbal monograph is established on the traditional uses of several preparations of *Cetraria islandica* (L.) Acharius s.l., thallus. The traditional uses of *Cetraria islandica* preparations fulfill the requirement for at least 30 years of medicinal use at a specified strength and specified posology, according to Directive 2001/83/EC as amended. None of the data fulfill the requirements to demonstrate a well-established medicinal use with recognised efficacy for *Lichen islandicus* preparations, thus the monograph is restricted to traditional uses. The efficacy is plausible on the basis of long-standing use and experience for the following indications:

The following indications are proposed for the Community monograph:



Indication 1)

Traditional herbal medicinal product used as a demulcent for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough

Indication 2)

Traditional herbal medicinal product used in temporary loss of appetite.

### **Benefit-Risk assessment**

The licensing of herbal medicinal products is subject to compliance with the requirements of an European Pharmacopoeia monograph. As an unambiguous macroscopic, microscopic, chemical identification of the herbal material is possible, adulteration/contamination of the herbal substance therefore is not expected.

In the clinical studies no or only mild adverse effects which subsided spontaneously within several days were reported. No serious adverse events with a therapeutic posology of the herbal preparations are reported in the literature/reference sources with a well-documented history. Intoxications due to the herbal preparations are not reported in the literature/reference sources. No cases of overdose have been documented in the past 30 years.

Delayed absorption of concomitantly administered medicines is described in some literature sources, although this interaction is not confirmed by any results from tests on animals or humans. However, as a precautionary measure it is proposed to include this information in the Community Monograph section 4.4 'Special warnings and precautions for use'.

There are no reports on drug abuse, effects on ability to drive or operate machinery or impairment of mental ability.

No data on laboratory findings during treatment as well as data on single- and repeat-dose toxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance or other special studies of preparations from *Lichen islandicus*, according to current state-of-the-art standards are available.

*Lichen islandicus* was proved toxic in a study with mice fed with granules containing 50% of the herbal substance. However, no toxic effect can be expected with the therapeutic doses recommended for the Community Monograph. Allergic dermatitis is reported in patients with known hypersensitivity to other plants, including lichens.

The duration of use is limited to one week for both indications because the preparation is intended and designed for use without the supervision of a medical practitioner. Due to lack of data, the use is not recommended during pregnancy and lactation. Marketed preparations containing aqueous extracts from Iceland moss are used in indication 1 at specified dosages in adults, adolescents and children above 4 years of age. However, due to the dosage forms (lozenges) use in children below 6 years is not advisable. Due to the lack of adequate data, the use is not recommended in children under 4 years of age. Use of the herbal substance in indication 1 is recommended for adolescents, adults and elderly only. The use in children under 12 years of age is not recommended due to lack of adequate data. Use of the herbal substance in indication 2 and the tincture in indication 1 and 2 are recommended for adults and elderly only. The use in children and adolescents under 18 years of age is not recommended due to lack of adequate data.

It can be concluded that the benefit-risk assessment for *Cetraria islandica* preparations included in the monograph is positive for the use as a demulcent for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough and for the use in temporary loss of appetite, under the specified conditions of use and at the therapeutic dosages.

The therapeutic areas for browse search on the EMA website are "Cough and cold" and "Gastrointestinal disorders".

No constituents with known therapeutic activity or active markers can be recognised by the HMPC.

As the minimum required data on mutagenicity (AMES test) are not available for herbal preparations of *Lichen islandicus*, an inclusion to the Community list of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products is not recommended.

## **Annex**

### ***List of references***