EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 July 2016
EMA/HMPC/436680/2015
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Althaea officinalis* L., radix

Final

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Althaea officinalis* L., radix
Herbal preparation(s)	Comminuted herbal substance Liquid extract (DER 1:19.5–23.5), extraction solvent water Macerate for preparation of syrup Dry extract (DER 3–9:1), extraction solvent water Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Comminuted herbal substance for macerate preparation for oromucosal use. Herbal preparations in liquid or solid dosage forms for oral or oromucosal use.
Rapporteur(s)	M. Heroutová
Peer-reviewer	G. Laekeman

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

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

- Herbal substance(s)

In accordance with the European Pharmacopoeia (8th ed., 01/2012:1126) marshmallow root (Althaeae radix) consists of peeled or unpeeled, whole or cut, dried root of *Althaea officinalis* L. It has a swelling index of minimum 10, determined on the powdered herbal substance.

The unpeeled, non-fragmented drug consists of cylindrical, slightly twisted roots, up to 2 cm thick, with deep longitudinal furrows. The outer surface is greyish-brown and bears numerous rootlet scars. The fracture is fibrous externally, rugged and granular internally. The section shows a more or less thick, whitish bark with brownish periderm, separated by the well-marked, brownish cambium from a white xylem. The stratified structure of the bark and the radiate structure of xylem become more distinct when moistened.

The peeled drug has a greyish-white, finely fibrous outer surface. Cork and external cortical parenchyma are absent (European Pharmacopoeia 8th ed., 01/2012:1126).

The roots are collected in the autumn from plants not less than two years old (British Pharmaceutical Codex 1949; Hänsel *et al.*, 1993; Bradley, 1992).

- Herbal preparation(s)

Comminuted herbal substance (for macerate preparation)

Liquid extract (DER 1:19.5-23.5), extraction solvent water

Dry extract (DER 3-9:1), extraction solvent water

Macerate for preparation of syrup

Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)

Rapporteur´s comment

The macerate is prepared in accordance with the pharmacopoeial monographs for Sirupus althaeae in Österreichisches Arzneibuch 1981, Československý lékopis 1954, Farmakopea Polska 1970 and 2002 or with the monograph Eibischsirup in Deutscher Arzneimittel-Codex 1979.

Differences in procedures for the preparation of marshmallow syrup in the pharmacopoeias/handbooks of the EU member states are summarised below:

Československý lékopis, 1954; Český lékopis, 2005

Sirupus althaeae is prepared from cold macerate (25 g Althaeae radix in the mixture of 10 g of ethanol 96% and 400 g of purified water, time of maceration 2 hours); to 360 g of the cold macerate 640 g of sucrose is added. The product is stabilised with methylparaben.

Österreichishes Arzneibuch, 1981, 2013

Sirupus althaeae is prepared by maceration of 5 parts of root with 110 parts of purified water for 2 hours. After filtering 100 parts of the filtrate are boiled with 160 parts of sucrose. Finally, the ethanolic solution of the preservatives is added.

Deutscher Arzneimittel Codex, 1979, 2004

Sirupus althaeae is prepared by maceration of 20 parts of root with 450 parts of purified water under stirring for 2 hours. The macerate is weighed; to 1 part of macerate 1.78 parts of sucrose are added and dissolved at 50°C under stirring. Short boiling follows. Finally, the ethanolic solution of the preservatives is added.

Farmakopea Polska, 2002

Sirupus althaeae is prepared by maceration of 5 parts of root with 1 part of ethanol (760 g/l) and 40 parts of purified water for 3 hours without stirring. In macerate obtained 64 parts of sucrose and 0.1 part of benzoic acid are solved. Short boiling follows.

Farmakopea Polska, 1954, 1970

Sirupus althaeae is prepared by maceration of 2 parts of root with 1 part of ethanol (95°) and 40 parts of purified water for 3 hours without stirring. In macerate obtained 64 parts of sucrose and 0.1 part of benzoic acid are solved. Short boiling follows.

Table 1: Differences in marshmallow syrup preparation described in MS pharmacopoeias/handbooks

Source	**Macerate preparation** **Althaeae radix/water**	**Sucrose added amount**	**Other components**	**Density/ Relative density**	**Amount of drug substance corresponding to 10 ml of syrup***
BPC 1949	40 g /560 ml maceration for 12 hours	900 g	Chloroform 2.5 ml	1.26-1.30 g/ml	ca 0.35 g
ÖAB 1981/2013	5 p/110 p, maceration for 2 hours under frequent stirring	160 p/100 p of macerate	Preservatives 0.18 p MPB + 0.09 p PPB /1.5 p ethanol	1.29-1.32	ca 0.27 g
DAC 1979/2004	20 p/450 p maceration for 2 hours under frequent stirring	1.78 x macerate amount	Preservatives 0.25 p PPB + 0.75 p MPB/ethanol ad 10 p	1.295-1.326	ca 0.21 g
ČL/ČSL 2005/1954	25 g/mixture of 400 g water + 10 g ethanol, maceration for 2 hours	640 g /360 g of macerate	Preservative MPB 1.5 g/10 g ethanol	1.30-1.32 g/cm^3	ca 0.29 g
Farmakopea Polska VI. ed., 2002	5 p/ethanol 760 g/l -1 p/40 p water maceration for 3 hours	64 p/100 p of the product	Preservative benzoic acid 0.1 p/100 p of the product	1.300-1.320 g/cm^3	ca 0.58 g
Farmakopea Polska III. ed., 1954/1970	2 p/ethanol 95° 1p/40 p water for maceration for 3 hours	64 p/100 p of the product	Preservative benzoic acid 0.1 p/100 p of the product	1.300-1.320 g/cm^3	ca 0.23 g

p – parts; MPB – methylparaben; PPB – propylparaben; BPC – British Pharmaceutical Codex ; ÖAB – Österreichisches Arzneibuch ; DAC – Deutscher Arzneimittel Codex ;ČL – Český lékopis (Czech Pharmacopoeia; ČSL - Československý lékopis (Czechoslovak Pharmacopoeia), * water absorbed by the herbal drug was not taken in consideration

Althaea syrup as defined in the British Pharmaceutical Codex 1949 is considered obsolete due to chloroform content and its potentially carcinogenic effect. Chloroform content in this product is ca 2500 ppm.

Cold macerates in syrups correspond to 0.21–0.58 g of marshmallow root in 10 ml of syrup.

Traditional use registration based on the pharmacopoeia monograph published in Farmakopea Polska VI. Edition (2002) was already granted in Poland.

Principal constituents of the herbal substance

Mucilage polysaccharides

5-11.6% mucilage (depending on vegetative period) – consisting of the mixture of colloidally soluble polysaccharides (Franz, 1966), particularly of acid arabinanogalactans, galacturonic rhamnans, arabans and glucans acidic heteropolysaccharide (with a MW ca 30 000) containing D-galactose, L-rhamnose, D-glucuronic acid and D-galacturonic acid in the molar ratios of 1.2:1.0:1.0:1.0 (Capek *et al.*, 1987) or in molar ratios 2:3:3:3 (Tomoda *et al.*, 1977), L-arabinans (Capek *et al.*, 1983); D-glucans (Capek *et al.*, 1984). Dominant neutral mucilage component is (1→6)-α-D-glucan (Nosáľova *et al.*, 1992, 1993).

By partial acid hydrolysis of Althaea mucilage O (representative mucous polysaccharide isolated from the roots of *Althaea officinalis* L.) the following oligosaccharides were obtained: *O*-α-(D-galactopyranosyluronic acid)-(1→2)-L-rhamnopyranose, *O*-β-(D-glucopyranosyluronic acid)-(1→3)-*O*-α-(D-galactopyranosyluronic acid)-(1→2)-L-rhamnopyranose and hexasaccharide, nonasaccharide, dodecasaccharide composed of a repeating unit having the structure of the trisaccharide through position 4 of the D-galacturonic acid residue (Tomoda *et al.*, 1980).

Partial acid hydrolysis of heteropolysaccharide isolated from the mucilage of the marshmallow indicated that the polymer backbone is composed of (1→4)-linked D-galactopyranuronic acid and (1→2)-linked L-rhamnopyranose units in the ratio of 1:1. Each D-galacturonic unit carries a single β-D-glucopyranuronic residue linked to C-3, and each L-rhamnopyranose unit carries D-galactopyranose residues, mainly as non-reducing terminals linked to C-4 (Capek *et al.*, 1987). In addition to reducing oligosaccharides, two other non-reducing oligosaccharides: α-D-galactopyranuronic acid, β-L-rhamnopyranose 1,2′:2,1′-dianhydride and 3-O-(β-D-glucopyranosyluronic acid)-α-D-galactopyranuronic acid β-L-rhamnopyranose 1,2′:2,1′-dianhydride have been identified (Capek *et al.*, 1988).

In hydrolysates of mucilages isolated from roots, leaves and flowers of *Althaea officinalis* L. and *Malva silvestris* L. ssp. *mauritiana* (L.) Thell., D-galactose, D- glucose, D-mannose, L-rhamnose, D-xylose, L-arabinose, D-galacturonic acid, and D-glucuronic acid were identified (Rosík *et al.*, 1984).

Pectins

11% (Blumenthal *et al.*, 2000)

Starch

25-35% (Blumenthal *et al.*, 2000)

Mono-, Di-saccharides

saccharose 10% (Gudej, 1991); crude mucilages contained 5% glucose in spring and 20% glucose in winter (Franz, 1966)

Flavonoids

0.14 – 0.28% (Gudej, 1990)

hypolaetin-8-glucoside, isoscutellarein-4´-methyl ether 8-*O*-β-D-glucoside-2´´-SO_3K (Gudej, 1991), kaempferol, quercetin, isoquercetin, astragalin (Ionkova, 1992), naringenin (Ninov *et al.*, 1992), hypolaetin-8-*O*-β-D-glucuronopyranosyl-1‴,4‴-β-*O*-D-glucopyranosid, hypolaetin-4‵-methylether-8-*O*-β-D-glucopyranosid-2‵‵-*O*-sulphate, hypolaetin-8-*O*-β-D-glucopyranosid-2‵‵-*O*-sulphate, isoscutellarein-4‵-methylether-8-*O*-β-D-glucuronopyranosid-3‵‵-*O*-sulphate, hypolaetin-4‵-methylether-8-*O*-β-D-glucuronopyranosid-3‵‵-*O*-sulphate, hypolaetin-4‵-methylether-8-*O*-β-D-glucuronopyranosid-3‵‵-*O*-sulphate, hypolaetin-8-*O*-β-D-glucuronopyranosid-3‵‵-*O*-sulphate (Theograndin II) (Böker, 2013)

Phenolic acids

caffeic, *p*-coumaric, ferulic, *p*-hydroxybenzoic, salicylic, syringic, p-hydroxyphenylacetic, vanillic acid (Gudej, 1991)

Coumarins

scopoletin (Gudej, 1991; Ionkova, 1992) scopoletin-*O*-β-D-glucopyranosyl-L-rhamnopyranosid (Böker, 2013)

Other compounds

phytosterols (Wichtl, 1994), calcium oxalate (Blumenthal *et al.*, 2000), fat, tannins (Bradley, 1992), amino acids (Rosík *et al.*, 1984; Böker *et al*., 2012), 2% asparagine (Bradley, 1992), glycine betain (Böker *et al*., 2012)

- 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

1.2. Search and assessment methodology

Databases and other sources used to research available pharmaceutical, non-clinical and clinical data on *Althaea officinalis* L, root or its relevant constituents.

Relevant articles and references retrieved from databases: PubMed, MEDLINE, TOXLINE. Search term: Althaea, *Althaea officinalis*, marshmallow, Eibisch.

Literature was provided by Kooperation Phytopharmaka in response to the call for scientific data in December 2014.

Libraries: EMA library, library of the State Institute of Drug Control, Prague.

Textbooks, pharmacopoeias and monographs.

A literature search was performed in April 2015.

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 2: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form	Regulatory Status
Comminuted herbal substance for macerate or infusion preparation	Sore throat and upper respiratory complaints	Herbal tea: 10 g of the comminuted herbal substance in 200 ml of water as a macerate Single dose 60 ml 2–3 times daily	Poland, at least since 1975
	Irritation of the oral and pharyngeal mucosa and associated dry cough	Herbal tea prepared from up to 6 g/daily (6 g divided in two or three portions)	Spain, before 1973
	An adjuvant in treatment of bronchitis; traditionally used in occasional mild cough; traditionally used to alleviate abdominal aches of digestive origin	1 cup of infusion prepared from 1 teaspoon (approximately 2 g) and 200 ml of boiling water 2 to 3 times daily	Romania, since 2001
Liquid extract of Althaeae radix (DER 1:19.5-23.5), extraction solvent water	Irritations of the mucosa in the oropharynx and therewith associated hacking dry cough	Syrup, 100 g (=76.44ml) syrup contains 35.610 g liquid extract Adolescents and adults >12 single dose: 10 ml syrup corresponds to 4.6 g liquid extract, 3-6 times daily Children between 6 and 12 years of age single dose: 5 ml syrup corresponds to 2.3 g liquid extract, 5 times daily Children between 3 and 5 years of age single dose :4 ml corresponds to 1.9 g liquid extract, 4 times daily Children between 1 and 2 years of age single dose: 3 ml corresponds to 1.4 g liquid extract, 4 times daily	Germany, WEU, at least since 1976, switched to TU 2005 Netherlands, TU 2013
Dry extract of Althaeae	Traditional herbal medicinal product for use	Lozenge, 160 mg	Germany, TU 2013

Active substance	Indication	Pharmaceutical form	Regulatory Status
radix (DER 3-9:1), extraction solvent water	as a demulcent preparation for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough	Children between 6 and 12 years of age single dose: 1 lozenge, 3 times daily. Adolescents and adults >12: single dose: 1 lozenge, several times daily if needed up to a maximum daily dose of 10 lozenges	
Macerate for syrup preparation	A demulcent for symptomatic treatment of dry irritable cough	Syrup prepared from the macerate (34.9 g) of 2 g Althaeae radix. The dosage is 2-8 ml. No information on frequency of use is available.	Lithuania, more than 100 years
	Traditional herbal medicinal product used for relieve of symptoms of upper respiratory tract irritations with accompanying cough	100 g of product contains macerate of 5 parts of *Althaea officinalis*, radix, with 40 parts of water + 1 part of ethanol 96% (V/V) Dosage: children 6-12 years of age 5 ml 3 times a day, adolescents and adults 15 ml 3 times a day	Poland, traditional registration, 2014
	Traditional medicinal product used as a means of soothing the symptoms of irritation of oral and throat mucosa and accompanying cough.	100 g of syrup contains macerate of 2 parts of *Althaea officinalis*, radix, with 40 parts of water + 1 part of ethanol 96% Dosage: children 3-6 years of age 5 ml up to 4 times daily, children 6-12 years of age 5 ml up to 5 times daily, adolescents and adults 10 ml 3–5 daily. No restriction of therapy duration.	National authorisation, 05.07.1996, based on Farmakopea Polska 1954 TU, 2015, Poland
	Traditional medicinal product possessing coating abilities. It is used for relieve of symptoms of irritation of oral cavity and throat mucosa and accompanying dry cough.	Syrup. 100 g of product contains macerate of 5 parts of *Althaea officinalis*, radix, with 40 parts of water + 1 part of ethanol 96% Dosage: children 3-6 years of age 2.5-5 ml 3 times daily, children 6-12 years of age 5-10 ml 3 times daily, adolescents and adults 10-15 ml 3 times	Poland, national authorisation, since 17.03.2010

Active substance	Indication	Pharmaceutical form	Regulatory Status
		daily Duration not restricted	
	Traditional medicinal product possessing coating abilities. It is used for relieve of symptoms of irritation of oral cavity and throat mucosa and accompanying cough.	Syrup. 100 g of product contains macerate of 5 parts of *Althaea officinalis*, radix, with 40 parts of water + 1 part of ethanol 96% (V/V) Dosage: children 3-6 years of age 2.5-5 ml (1/2-1 teaspoon) 3–4 times daily, children 6-12 of age 5 ml (1 teaspoon) 3–4 times daily adolescents and adults 15 ml 3–4 times daily Duration of use not limited	Poland, National authorisation, since 10.02.2000
	Dry cough, irritation of oral cavity and throat mucosa	Syrup. 100 g of product contains macerate of 5 parts of *Althaea officinalis*, radix, with 40 parts of water + 1 part of ethanol 96% (V/V) Dosage: children 6-12 years of age 2.5 ml (1/2 teaspoon) 2 times daily, adolescents and adults 2.5–10ml 3 times daily Duration of use not limited	Poland, National authorisation since 2006, based on Farmakopea Polska 2002
Althaea polysaccharides	An expectorant	1 tablet containing 50 mg of Althaea polysaccharides twice daily	Estonia, food supplement since 2004

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

The following relevant combination product is registered in in the EU/EEA.

An oral solution containing 0.83 g of liquid extract (DER 1:12-14) of the root of Althea *officinalis* L., extraction solvent water and 0.12 g of dry extract (DER 7-13:1) of *Thymus vulgaris* L. / *Thymus zygis* L. (leaves and flowers) extraction solvent water in 15 ml is registered in several member states (Croatia, Spain, Ireland, Austria, Bulgaria, Italy, Hungary, Portugal, Sweden, Slovenia and UK) and in Norway.

Indication: Traditional herbal medicinal product used in productive cough associated with cold, and to relief pharyngeal irritation and associated dry cough.

Posology: Adults and adolescents: 15 ml every 4 hours (4 times per day). If needed the maximum daily dose is 90 ml (6 doses per day).

Children 6-12 years of age: 7.5 ml every 3-4 hours (4 times per day). If needed the maximum daily dose is 45 ml (6 doses per day).

Additional relevant combination products marketed in the EU/EEA are the following

Croatia

Syrup containing 0.77 g liquid extract from *Thymus vulgaris* L./*Thymus zygis* L., herba (DER 1:2–2.5); extraction solvent: ammonia solution 10% m/m:glycerol 85% m/m:ethanol 90% V/V:water (1:20:70:109) and 0.66 g liquid extract from *Althaeae officinalis* L., radix (DER 1:20), extraction solvent water in 5 ml.

Indication: irritation of the throat; productive cough associated with cold

Posology: Adults and adolescents older than 12 years: 10 ml every 3 hours to 6 times daily

Latvia

Syrup containing 0.12 g Thymi herbae extractum siccum (DER 7-13:1, extraction solvent water) and 3.33 g Althaeae radicis sirupus in 15 ml.

Indication: Herbal cough suppressant with an expectorant, antispasmodic and anti-irritant effect.

Posology: adults and adolescents (from 12 years) 15 ml each 3-4 hours (4-6 times per day, maximum daily dose 90 ml), children (3-12 years) 7.5 ml each 3-4 hours (4-6 times per day, maximum daily dose 45 ml).

On the market since 2012 (TU).

Syrup containing 0.77 g Thymi herbae extractum fluidum (DER 1:2-2.5), extraction solvent ammonia solution 10% (m/m):glycerol 85% (m/m):ethanol 90% (V/V):water (1:20:70:109) and 1.710 g Althaeae radicis sirupus in 5 ml.

Indication: For relief of throat irritation and cough, expectorant.

Posology: adults and adolescents (from 12 years): 10 ml each 3 hours up to 6 times per day (4-6 times per day, maximum daily dose 60 ml), children (4-12 years) 5 ml each 3 hours up to 6 times per day (maximum daily dose 30 ml)

On the market since 2012 (TU).

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

Not applicable

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

Not applicable

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

Marshmallow has been used in traditional European medicine since ancient times. *Althaea* is often mentioned by ancient authors; however, it is not clear whether information is related really to *Althaea officinalis* as Theophrast describes his Althaea with yellow and Dioskurides with rose rot flowers. Hippocrates recommends decoction from the root as a wound remedy while Dioskurides in anuria, diarrhoea, lithiasis, internal injuries, nerve pain, bee sting, tooth-ache etc. In the Middle Ages Althaea was prescribed by Paracelsus as abscess emollient and cleanser, by Lonicerus and Matthiolus as an expectorant and diuretic, in internal injuries, externally as ulcers emollient, for burns treatment etc. (Madaus, 1938).

The medicinal use has been documented continuously in many pharmacopoeias, pharmacognostical texts and handbooks dating *e.g.* from 1926, 1938, 1949, 1969, 1977, 1998, 2002, 2003 and 2008 – Deutsches Arzneibuch 1926; Madaus, 1938; British Pharmaceutical Codex 1949, Hagers Handbuch (Kern *et al*., 1969); Martindale, The Extra Pharmacopoeia, 1977; British Herbal Pharmacopoeia 1983; The Complete German Commission E Monographs (Blumenthal *et al.*, 1998); WHO monographs on selected medicinal plants, 2002; ESCOP Monographs, 2003; European Pharmacopoeia 8.0, 2012. Marshmallow root is traditionally used as a demulcent and emollient in irritation of oral and pharyngeal mucosa and associated dry cough, in mild gastric complaints and for the treatment of minor skin inflammations.

The following traditional uses and posologies have been recorded for marshmallow root

- *Lehrbuch der Biologischen Heilmittel (Madaus, 1938)*

Indications: supportive treatment of respiratory catarrhs associated with irritation of respiratory organs, cough, and hoarseness; inflammations of urogenital and gastrointestinal tracts (cystitis, nephrolithiasis, enteritis, diarrhoea, gastric and duodenal ulcers), topically – as a gurgle in mouth inflammations; eye and skin inflammations; burns; furunculosis and carbunculosis

Dosage: daily dose – macerate prepared from 4 spoons of marshmallow root (17.2 g); 1 spoon of the "teep" preparation (50% of marshmallow root) 3 times daily

Duration of use: no information.

- *British Herbal Pharmacopoeia 1983*

Demulcent, diuretic, emollient, vulnerary

Indications: gastritis, gastric and peptic ulceration, enteritis; inflammation of the mouth and pharynx, respiratory catarrh with irritating cough; cystitis; locally – varicose and thrombotic ulcers

Dosage: three times daily dried root 2-5 g or by cold extraction; liquid extract 1:1 in ethanol 25% 2-5 ml three times daily, syrup (BPC 1949) 2-10 ml 3 times daily; ointment 5% powdered Althaea root in usual ointment base

Duration of use: no information.

- *The Complete German Commission E Monographs (Blumenthal et al., 1998)*

Indications: Irritation of the oral and pharyngeal mucosa and associated dry cough. Mild inflammation of the gastric mucosa.

Daily oral dose: 6 g of root or equivalent amount of preparations. "Marshmallow syrup" single dose: 10 g.

Duration of use: no information.

- *The Expanded Commission E Monographs (Blumenthal et al., 2000)*

Dosage: unless otherwise prescribed: 6 g per day of cut or ground root. Cold maceration: 2-5 g to 150 ml cold water for 30 minutes stirring frequently; strain and warm before drinking, up to three times a day. Dried root: 2-5 g, up to three times a day. Fluid extract 1:1 (g/ml): 2-5 ml, up to 3 times a day. Tincture 1:5 (g/ml), up to three times a day. Native dry extract 3.5-5.0:1 (w/w): 0.4-0.6 g, up to three times a day. Native soft extract 2.3-3.2:1 (w/w): 0.6-0.9 g, up to three times a day. Sirupus Althaeae: single dose: 10 ml, to be used only in treating throat irritation.

Duration of use: no information.

- *WHO Monographs on Selected Medicinal Plants (Volume 2, 2002).*

Indications: As a demulcent for symptomatic treatment of dry irritable coughs and irritations of oral and pharyngeal mucosa and as an emollient for wounds and dry skin.

Dosage: for dry cough, oral and pharyngeal irritation 0.5–3.0 g of the crude drug as an macerate up to daily dose of 15 g of crude drug, syrup 2–8 ml; for gastric irritation 3–5 g of crude drug as a macerate up to three times daily

Duration of use: no information.

- *ESCOP Monographs (2003)*

Indications: Dry cough; irritation of the oral, pharyngeal or gastric mucosa.

Adult single dose: For dry cough and oral or pharyngeal irritation, 0.5-3 g of the drug as an aqueous cold macerate, or 2-8 ml of syrup, repeated if required up to daily dose equivalent to 15 g of the drug. For gastrointestinal irritation, 3-5 g as an aqueous cold macerate up to 3 times daily.

Duration of use: no restriction.

- *British Herbal Compendium (Bradley, 1992)*

Indications: a) Internally: for gastroenteritis, peptic or duodenal ulceration, common and ulcerative colitis and enteritis. b) Topically as mouthwash or gargle for inflammation of the pharynx and as a poultice or ointment/cream in furunculosis, eczema and dermatitis.

Dosage: 3 times daily dried root, 2-5 g or as a cold infusion; tincture (1:5), 25% ethanol, 5-15 ml; syrup (BPC 1949), 2-10 ml, 5-10% preparations in an ointment or cream base

Duration of use: no information.

- *The British Pharmaceutical Codex (1949)*

Indications: Althaea is demulcent and emollient and is given by mouth in the treatment of bronchitis. It may be given in the form of syrup. Althaea has been applied to inflamed tissues as fomentation (1 part of powdered root to 5 parts of water).

Dosage: no information.

Duration of use: no information.

Althaeae sirupus: 40 g of Althaeae radix are macerated with 560 ml of water for 12 hours and filtered. In the filtrate 900 g of sucrose is dissolved, heated to boiling and cooled. Any water lost by evaporating is replaced. At the end 2.5 ml of chloroform is added.

Dosage: 2-8 ml.

- *Herbal Medicines. A guide for healthcare professionals (Barnes et al., 2002; Newal et al., 1996)*

Indications: Traditionally used internally for the treatment of respiratory catarrh and cough, peptic ulceration, inflammation of the mouth and pharynx, enteritis, cystitis, urethritis, and urinary calculus and topically: for abscesses, boils and varicose and thrombotic ulcers.

Dosage: Dried root 2-5 g or by cold extraction three times daily; 6 g; Root liquid extract (1:1 in 25% alcohol) 2-5 ml three times daily; Syrup of Althaea (BPC 1949) 2-10 ml three times daily.

Duration of use: no information.

- *Martindale Extra Pharmacopoeia (1977)*

Indications: Althaea is a demulcent and emollient, for irritation and inflammation of the mucous membranes of the mouth and pharynx. The boiled and bruised root has been used as a poultice.

Dosage: syrup (BPC 1949) 2-8 ml.

Duration of use: no information.

- *VIth Hungarian Pharmacopoeia Volumes 3 and 4 (1970)*

Dosage: dried root, average single dose: 0.50-1.00; average daily dose: 1.5-5.0 g

Dosage for children

Children age	**Single dose (g)**	**Daily dose (g)**
1 year	0.12	0.6
3 years	0.20	1.0
6 years	0.30	1.5
9 years	0.50	2.5
12 years	0.60	3.0
15 years	0.80	4.0

- *Gyógyszerrendelés (Issekutz and Issekutz, 1979)*

Indications: to relieve the irritation to cough, bowel catarrh

Dosage: adults 0.50–1.00 g 5 times daily; children 3 months of age 0.10 g, 1 year 0.12 g, 3 years 0.20 g, 6 years 0.30 g, 9 years 0.50 g and 12 years 0.60 g 5 times daily.

- *Český lékopis, 2005*

Dosage: Althaeae radix: for the treatment of upper respiratory tract inflammations – single dose: 0.5-3.0 g, daily dose: 15.0 g and for the treatment of gastrointestinal inflammations – single dose: 3.0-5.0 g, daily dose: 6.0-15.0 g.

- *Československý/Český lékopis, 1954, 2005*

Althaeae sirupus is prepared from cold macerate (25 g Althaeae radix in the mixture of 10 g of ethanol 96% and 400 g of purified water, time of maceration 2 hours); to 360 g of the cold macerate 640 g of sucrose is added. The product is stabilised with methylparaben. No information on syrup dosage.

Duration of use: no information.

- *Österreichishes Arzneibuch, 1981, 1990, 2013*

Dosage: Althaeae radix: Single dose as a macerate: 1.5 g for 1 cup.

Althaeae sirupus is prepared by maceration of 5 parts of root with 110 parts of purified water for 2 hours. After filtering 100 parts of the filtrate are boiled with 160 parts of sucrose. Finally, the ethanolic solution of the preservatives is added. No information on syrup dosage.

Duration of use: no information.

- *Deutscher Arzneimittel Codex, 1979, 2004*

Althaeae sirupus is prepared by maceration of 20 parts of root with 450 parts of purified water under stirring for 2 hours. The macerate is weighed; to 1 part of macerate 1.78 parts of sucrose are added and dissolved at 50°C under stirring. Short boiling follows. Finally, the ethanolic solution of the preservatives is added.

Use: against cough or for addition to cough mixtures.

Dosage: 5-10 ml several times daily.

- *Standard Zulassungen für Fertigarzneimittel, 1996*

Indication: Irritation of oral and pharyngeal mucosa and associated dry cough, mild irritation of gastric mucosa.

Dosage: macerate prepared from 2 g/150 ml of water 3 times daily.

Duration of use: 1 week.

- *Farmakopea Polska, 2002*

Althaeae sirupus is prepared by maceration of 5 parts of root with 1 part of ethanol (760 g/l) and 40 parts of purified water for 3 hours without stirring. In macerate obtained 64 parts of sucrose and 0.1 part of benzoic acid are solved. Short boiling follows.

Dosage: single dose: 10-30 g

- *Farmakopea Polska, 1954, 1970*

Althaeae sirupus is prepared by maceration of 2 parts of root with 1 part of ethanol (95°) and 40 parts of purified water for 3 hours without stirring. In macerate obtained 64 parts of sucrose and 0.1 part of benzoic acid are solved. Short boiling follows.

- *Heilpflanzen Praxis Heute (Bäumler, 2007)*

Indications: As a gargle for inflammation of the oral and pharyngeal mucosa; as a demulcent in case of dry cough; for the treatment of mild inflammation of the gastric mucosa and peptic ulcerations; for treatment of small wounds and burns; as a poultice in furunculosis and carbunculosis.

Dosage: Daily dose: 6 g of dried root or 10 g of syrup.

Dosage for children

Children age	Dried root	Syrup
0-1 year	-	-
1-4 years	1.5-3 g	2-4 g
4-10 years	3-4 g	4-6 g
10-16 years	4-6 g	6-10 g

Duration of use: no information.

- *Kinderdosierungen von Phytopharmaka (Dorsch et al., 2002)*

Indications: Irritation of oral and pharyngeal mucosa and associated dry cough, mild irritation of gastric mucosa.

Dosage in adults: 6 g of herbal drug in a form of macerate in 150 ml of cold water several times daily.

Corresponding dosage in children

0-1 year	1-4 years	4-10 years	10-16 years
	1.5-3 g	3-4 g	4-6 g

Syrup

Dosage in adults: single dose: 3-5 g.

Corresponding dosage in children

0-1 year	1-4 years	4-10 years	10-16 years
	2-4 g	4-6 g	6-10 g

Table 3: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
Comminuted herbal substance/comminuted herbal substance for macerate preparation	Supportive treatment of respiratory catarrhs associated with irritation of respiratory organs, cough, and hoarseness; inflammations of gastrointestinal tracts (enteritis, diarrhoea, gastric and duodenal ulcers), topically – as a gurgle in mouth inflammations	Daily dose: macerate prepared from 4 spoons of marshmallow root (17.2 g)), 1 spoon of the "teep" preparation (50% of marshmallow root) 3 times daily	Madaus, 1938
	To relieve the irritation to cough, bowel catarrh	Adults: average single dose: 0.50-1.00; average daily dose: 1.5-5.0 g	VIth Hungarian Pharmacopoeia 1970, Issekutz and Issekutz, 1979
	Gastritis, gastric and peptic ulceration, enteritis; inflammation of the mouth and pharynx, respiratory catarrh with irritating cough	2-5 g or by cold extraction 3 times daily	British Herbal Pharmacopoeia 1983 Barnes *et al.*, 2002, Newal *et al*., 1996
	Irritation of oral and pharyngeal mucosa and associated dry cough, mild irritation of gastric mucosa	Macerate prepared from 2 g/150 ml of water 3 times daily Duration of use: 1 week Daily dose: 6 g of root or equivalent amount of preparations Cold macerate: 2-5 g to 150 ml cold water up to three times a day Dried root: 2-5 g, up to three times a day Adults daily dose 6 g; children 1-4 years 1.5–3.0 g; children 4–10 years 3–4 g; children 10–16 years 4–6 g	Standard Zulassungen für Fertigarzneimittel, 1996 Blumenthal *et al.*, 1998 Blumenthal *et al.*, 2000 Dorsch *et al.*, 2002
	As a demulcent for symptomatic treatment of dry irritable coughs and irritations of oral and	For dry cough, oral and pharyngeal irritation 0.5–3.0 g of the crude drug as an macerate up to daily dose of	WHO monographs, 2002

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
	pharyngeal mucosa and as an emollient for wounds and dry skin	15 g of crude drug; for gastric irritation 3–5 g of crude drug as a macerate up to three times daily	
	Dry cough; irritation of the oral, pharyngeal or gastric mucosa	For dry cough and oral or pharyngeal irritation, 0.5-3 g of the drug as an aqueous cold macerate, repeated if required up to daily dose equivalent to 15 g of the drug. For gastrointestinal irritation, 3-5 g as an aqueous cold macerate up to 3 times daily	ESCOP Monographs, 2003
	For the treatment of upper respiratory tract and gastrointestinal inflammations	For the treatment of upper respiratory tract inflammations single dose: 0.5-3.0 g, daily dose: 15.0 g and for the treatment of gastrointestinal inflammations single dose: 3.0-5.0 g, daily dose: 6.0-15.0 g	Český lékopis, 2005
	As a gargle for inflammation of the oral and pharyngeal mucosa; as a demulcent in case of dry cough; for the treatment of mild inflammation of the gastric mucosa and peptic ulcerations;	Adults daily dose: 6 g; children 1-4 years 1.5–3.0 g; children 4–10 years 3–4 g; children 10–16 years 4–6 g	Bäumler, 2007
Syrup	Irritation of the oral and pharyngeal mucosa and associated dry cough.	Single dose: 10 g	Blumenthal *et al.*, 1998
	Throat irritation	Single dose: 10 ml	Blumenthal *et al.*, 2000
	Irritation of oral or pharyngeal mucosa and associated dry cough	Adults single dose: 3–5 g; children 1-4 years 2–4 g, children 4–10 years 4–6 g, children 10–16 years 6-10 g	Dorsch *et al.*, 2002
	Against cough	5-10 ml several times daily	Deutscher Arzneimittel-Codex, 1979, 2004
Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)	Gastritis, gastric and peptic ulceration, enteritis; inflammation of the mouth and pharynx, respiratory catarrh with irritating	2-5 ml 3 times daily	British Herbal Pharmacopoeia 1983 Barnes *et al.*, 2002;

Herbal preparation	Documented use / Traditional use	Pharmaceutical form	Reference
	cough; cystitis		Newal *et al.*, 1996 Blumenthal *et al.*, 2000
Dry extract (DER 3.5-5:1), extraction solvent not specified	Reference to the Commission E Monograph, British Herbal Compendium, ESCOP monograph, German Standard Licence	0.4-0.6 g up to 3 times daily	Blumenthal *et al.*, 2000
Soft extract (DER 2.3–3.2:1), extraction solvent not specified	Reference to the Commission E Monograph, British Herbal Compendium, ESCOP monograph, German Standard Licence	0.6-0.9 g up to 3 times daily	Blumenthal *et al.*, 2000
Tincture 1:5, extraction solvent ethanol 25% (V/V)	Internally: for gastroenteritis, peptic or duodenal ulceration, common and ulcerative colitis and enteritis. Topically: as mouthwash or gargle for inflammation of the pharynx	5–15 ml 3 times daily 10–25 ml up to 3 times daily	Bradley, 1992 Blumenthal *et al.*, 2000

2.3. Overall conclusions on medicinal use

Traditional use of *Althaea officinalis* (L.), root in the form of macerate 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 4: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Comminuted herbal substance for macerate preparation	Sore throat and upper respiratory complaints	Herbal tea: 10 g of the comminuted herbal substance in 200 ml of water as a macerate. Single dose 60 ml (corresponding to 3 g of the herbal substance) 2–3 times daily	Poland at least since 1975

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	Irritation of the oral and pharyngeal mucosa and associated dry cough	Herbal tea prepared from up to 6 g/daily (6 g divided in two or three portions)	Spain before 1973
		Adults daily dose: 6 g; children 1-4 years 1.5–3.0 g; children 4–10 years 3–4 g; children 10–16 years 4–6 g	Dorsch, 2002
	Gastritis, gastric and peptic ulceration, enteritis; inflammation of the mouth and pharynx, respiratory catarrh with irritating cough	2-5 g or by cold extraction 3 times daily	British Herbal Pharmacopoeia, 1983
	To relieve the irritation to cough, bowel catarrh	Adults: average single dose: 0.50-1.00 g; average daily dose: 1.5-5.0 g	VIth Hungarian Pharmacopoeia, 1970; Issekutz and Issekutz, 1979
Macerate for preparation of syrup	Traditional medicinal product used as a means of soothing the symptoms of irritation of oral and throat mucosa and accompanying cough	100 g of syrup contains macerate of 2 parts of *Althaea officinalis*, radix, with 40 parts of water + 1 part of ethanol 96% Children 3-6 years: 5 ml up to 4 times daily, Children 6-12 years: 5 ml up to 5 times daily, Adolescents and adults: 10 ml 3–5 daily	National authorisation, 05.07.1996, based on Farmakopea Polska 1954 TU, 2015, Poland
	Traditional herbal medicinal product used for relieve of symptoms of upper respiratory tract irritations with accompanying cough	100 g of product contains macerate of 5 parts of *Althaea officinalis*, radix, with 40 parts of water + 1 part of ethanol 96% (V/V). Children 6-12 years: 5 ml 3 times a day, Adolescents and adults: 15 ml 3 times a day	Poland, traditional registration, 2014, based on Farmakopea Polska 2002
Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)	Gastritis, gastric and peptic ulceration, enteritis; inflammation of the mouth and pharynx, respiratory catarrh with irritating cough	2-5 ml 3 times daily	British Herbal Pharmacopoeia, 1983
Liquid extract of	Irritations of the mucosa in the oropharynx and	Syrup, 100 g (=76.44 ml) syrup contains 35.610 g	Germany, WEU, at

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Althaeae radix (DER 1:19.5-23.5), extraction solvent water	therewith associated hacking dry cough	liquid extract Adolescents and adults: single dose: 10 ml syrup corresponds to 4.6 g liquid extract, 3-6 times daily, Children 6-12 years: single dose: 5 ml syrup corresponds to 2.3 g liquid extract, 5 times daily, Children 3-5 years: single dose: 4 ml corresponds to 1.9 g liquid extract, 4 times daily, Children 1-2 years: single dose: 3 ml corresponds to 1.4 g liquid extract, 4 times daily	least since 1976 Netherlands, TU 2013
Dry extract of Althaeae radix (DER 3-9:1), extraction solvent water	Traditional herbal medicinal product for use as a demulcent preparation for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough	Lozenge containing 160 mg of the extract Adolescents and adults: single dose: 1 lozenge, several times up to a maximum daily dose of 10 lozenges Children 6-12 years of age: single dose: 1 lozenge, 3 times daily	Germany TU 2013

The following indications are proposed for the European Union Monograph

Indication 1)

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

Indication 2)

Traditional herbal medicinal product used as a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort.

The topical use is mentioned in many references (WHO monograph, 2002; Barnes *et al*., 2002; Newal *et al*., 1996; Bäumler, 2007; Hänsel *et al*., 1993; Gruenwald *et al*., 1998; Martindale, 1977; BPC 1949, Bradley, 1992) for treatment of skin inflammations, ulcers, abscesses, burns, furuncles, carbuncles. Althaeae radix is described to be used in the form of ointments, poultices, cataplasms or fomentations; however, no sufficient information on the preparations has been found.

Although historically lower posologies for comminuted herbal substance and syrup have been documented, the proposed posology reflects currently applied dosages for these type of preparations.

Based on the literature data and information received from the Member States, the following posologies are suggested:

For indication 1)

Oral and oromucosal use

Comminuted herbal substance

Children 3-5 years of age: 0.5–1.0 g of the comminuted herbal substance in 150 ml of water as a macerate 3 times daily; daily dose: 1.5–3.0 g.

Children 6-11 years of age: 0.5–1.5 g of the comminuted herbal substance in 150 ml of water as a macerate 3 times daily; daily dose: 1.5–4.5 g.

Adolescents, adults and elderly: 0.5-3 g of the comminuted herbal substance in 150 ml of water as a macerate several times daily; maximum daily dose: 15 g.

Liquid extract (DER 1:19.5-23.5), extraction solvent water

Children 3-5 years of age: single dose: 1.9 g 4 times daily; daily dose: 7.6 g.

Children 6-11 years of age: single dose: 2.3 g 5 times daily; daily dose: 11.5 g.

Adolescents, adults and elderly: single dose: 4.6 g 3–6 times daily; daily dose: 13.8–27.6 g.

Macerate for preparation of syrup

Children 3-6 years of age: single dose: macerate amount corresponding to 0.1 to 0.29 g of the herbal substance (5 ml of syrup) up to 4 times daily; daily dose: macerate amount corresponding to 0.21 to 1.16 g of herbal substance (10–20 ml of syrup).

Children 6-11 years of age: single dose: macerate amount corresponding to 0.1 to 0.29 g of the herbal substance (5 ml of syrup) 3-5 times daily; daily dose: macerate amount corresponding to 0.32 to 1.45 g of the herbal substance (15–25 ml of syrup).

Adolescents, adults and elderly: single dose: macerate amount corresponding to 0.21 to 0.87 g of the herbal substance (10–15 ml of syrup) 3–5 times daily; daily dose: macerate amount corresponding to 0.63 to 2.9 g of the herbal substance (30–50 ml of syrup).

Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)

Adults and elderly: single dose: 2–5 ml 3 times daily; daily dose: 6–15 ml.

Dry extract (3-9:1), extraction solvent water

Children 3-5 years of age: single dose: extract amount corresponding to 0.5–1 g of herbal substance, 3 times daily; daily dose: extract amount corresponding to 1.5–3 g of herbal substance.

Children 6-11 years of age: single dose: extract amount corresponding to 0.5–1.5 g of herbal substance, 3 times daily; daily dose: extract amount corresponding to 1.5–4.5 g of herbal substance.

Adolescents, adults and elderly: single dose: extract amount corresponding to 0.5–3 g of herbal substance, several times daily; daily dose: extract amount corresponding to 15 g of herbal substance.

The oromucosal use in children under 6 years of age is not recommended because of dosage form (solid dosage form).

For indication 2)

Oral use

Comminuted herbal substance

Adolescents, adults and elderly: Herbal tea: 3-5 g of the comminuted herbal substance in 150 ml of water as a macerate 3 times daily; maximum daily dose: 15 g.

Liquid extract (DER 1:1), extraction solvent ethanol 25% (V/V)

Adults and elderly: single dose: 2–5 ml 3 times daily; daily dose: 6–15 ml.

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 Franz, 1989 information that the mucilage covers the mucosa with a kind of protecting layer which protects it from local irritation has been found. The only non-clinical study supporting this statement is an *in vitro* study of bio adhesive effects of polysaccharides isolated from Althaeae radix on isolated porcine buccal membrane by Schmidgall (see information below).

Bioadhesive effects

In vitro

Polysaccharides

Purified polysaccharides (carbohydrates content >95%) from *Althaea officinalis* root were investigated for bioadhesive effect on isolated porcine buccal membranes. Polysaccharides from marshmallow root showed a moderate adhesion to epithelial tissue. The adhesive effect was 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).

Antitussive effect

In vitro

Water extract

Weak inhibition (17.1%) of mucociliar transport in ciliated epithelium isolated from frog oesophagus has been observed after addition of 200 µl of marshmallow root macerate (6.4 g/140 ml) (Müller-Limmroth and Fröhlich, 1980).

In vivo

Extract/polysaccharides

An extract from marshmallow root (type of extract was not specified) and isolated mucilage polysaccharide were tested for antitussive activity in un-anaesthetised cats of both sexes at doses of 50 to 100 mg/kg body weight administrated orally. The cough was induced by mechanical stimulation. The antitussive effect of marshmallow root extract and isolated mucilage polysaccharide was compared with the cough-suppressing effects of Althaea syrup (1000 mg/kg), prenoxdiazine (30 mg/kg), dropropizine (100 mg/kg) and codeine (10 mg/kg). Both the extract and isolated polysaccharide significantly reduced the intensity and the number of cough efforts from laryngopharyngeal and tracheobronchial areas. The root extract was less effective than the isolated polysaccharide. The antitussive activity was found to be lower than that of codeine, but higher than those of the comparative non-narcotic drugs (prenoxdiazine, dropropizine) (Nosáľová *et al.*, 1992, 1992a and 1993).

Antitussive effect of the polysaccharide rhamnogalacturonan isolated from roots of *Althaea officinalis* (25 and 50 mg/kg bw administered orally) has been studied in an *in vivo* study with sensitised (ovalbumin) and unsensitised male guinea pigs. The cough of guinea pigs was induced by 0.3 M citric acid aerosol. The polysaccharide dose dependently inhibited cough reflex in unsensitised animals. The authors concluded that polysaccharide isolated from *Althaea officinalis* root possess dose dependent cough suppressive effect in unsensitised animals. The antitussive activity of the higher dose of rhamnogalacturonan was comparable to the antitussive activity of codeine (10 mg/kg bw administered orally) in unsensitised animals. Bronchodilatation is not involved in mechanism of antitussive action. Allergic airways inflammation shortens the duration of rhamnogalacturonan antitussive effect which was confirmed by histopathological evaluation (Šutovska *et al*., 2011).

Possible mechanism of dose-dependent cough suppressive effect described above has been studied in an additional *in vitro* and *in vivo* study with guinea pigs and with guinea pigs tracheal smooth muscle strips and lung tissue strips. Reactivity of the airways smooth muscle was not significantly affected by rhamnogalacturonan and thus bronchodilatatory activity did not participate in the cough suppression effect of the polysaccharide. Moreover, the cough suppression effect of the polysaccharide was not significantly modified by pre-treatment of K^+_{ATP} ion channels with selective antagonist (glibenclamide in the dose 3 mg/kg bw. intraperitoneally 20 minutes before per orally applied rhamnogalacturonan in the dose 50 mg/kg bw.) and therefore activation of this type of ion channels is not involved in the mechanism of rhamnogalacturonan cough suppression ability. On the contrary, pre-treatment of animals with selective 5-HT_2 receptors antagonist (ketanserin in the dose 1 mg/kg bw. administered intraperitoneally or directly into the nasopharynx in the dose 20 µl of 200 µM solution) significantly decreased rhamnogalacturonan antitussive efficacy. From this point of view it seems that the cough suppression effect of the polysaccharide is associated with the serotonergic 5-HT_2 receptor´s function (Šutovská *et al*., 2009).

Anti-inflammatory activity

In vivo

Water extract

An ointment containing an aqueous marshmallow root extract (20%) applied topically to the external ear of rabbits reduced irritation induced by UV irradiation or by tetrahydrofurfuryl alcohol. The ointment has been compared to pure dexamethasone 0.05% ointment and a combined marshmallow and dexamethasone product. The anti-inflammatory effect of marshmallow ointment was lower than that of a dexamethasone ointment. The combined product had higher anti-inflammatory effect than the ointments with the individual ingredients (Beaune and Balea 1966).

Ethanol extract

However, with a dry extract prepared from 100 g of the plant material and 300 ml of 80% ethanol administered orally to male Wistar rats (100 mg/kg bw), no inhibition of carrageenan induced rat paw oedema has been proved (Mascolo *et al.*, 1987).

Isolated compounds

Hypolaetin 8-glucoside has been tested for its anti-inflammatory, analgesic and anti-ulcer activity in rats. The flavonoid (30, 60 and 90 mg/kg i.p.) was more potent than phenylbutazone (30, 60 and 90 mg/kg i.p.) in suppressing the acute phase of adjuvant carrageenan-induced inflammation but had less effect in the prolonged inflammatory phase. In contrast to phenylbutazone, it did not cause gastric erosions. Analgesic activity of hypolaetin 8-glucosid has been found to be lower than the one of phenylbutazone. Anti-ulcer activity has been compared to cimetidine (40, 70 and 100 mg/kg i.p.). Both substances prevented the formation of cold-restraint induced gastric lesions, but cimetidine was more potent. Hypolaetin 8-glucoside was also more potent than troxerutin (both at the doses of 100, 200, 300 and 400 mg/kg s.c.) in inhibiting histamine-induced capillary permeability in rats (Villar *et al.*, 1984, Villar *et al.*, 1987, Alcaraz *et al.*, 1989).

Tissue regeneration

In vitro

Water extract/polysaccharides

Lyophilised aqueous extract from marshmallow roots (DER 1:20) (AE) in concentrations 1 and 10 g/ml had a stimulating effect on cell viability and proliferation of epithelial KB cells. Raw polysaccharide mixture (RPS) isolated from the same extract by precipitation with ethanol stimulated (at concentrations 1 and 10 μg/ml) cell vitality of epithelial cells significantly without triggering the cells into higher proliferation status. Neither AE nor RPS had any effect on fibroblasts. FITC (fluoresceinisothiocyanate)-labelled RPS was shown to be internalised into epithelial cells, but not into fibroblasts. FITC-RPS was shown to form bio adhesive layers on the cell surface of dermal fibroblasts. Microarray analysis indicated an up-regulation of genes related to cell adhesion proteins, growth regulators, extracellular matrix, cytokine release and apoptosis. The authors concluded that extracts and polysaccharides from the roots of *A. officinalis* are effective stimulators of cell physiology of epithelial cells (Deters *et al*., 2010, Ziffel *et al*., 2009).

Table 5: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
Cold macerate 6.4 g/140 ml	200 µl applied on ciliated epithelium isolated from frog oesophagus	*In vitro*	Müller-Limmroth and Fröhlich, 1980	Weak inhibition of mucociliar transport
Water extract (DER 1:20)	1 and 10 mg/l	*In vitro*	Deters *et al*., 2010, Ziffel *et al*., 2009	Stimulating effect on cell viability and proliferation of epithelial KB cells, no effect on fibroblasts
Raw polysaccharide mixture	1 and 10 mg/l	*In vitro*	Deters *et al*., 2010; Ziffel *et al*., 2009	Stimulation of cell vitality of epithelial cells without triggering the cells into higher proliferation status, no effect on fibroblasts; up-regulation of genes related to cell adhesion proteins, growth regulators, extracellular matrix, cytokine release and apoptosis.
Extract (type of extract not specified) and polysaccharide	50–100 mg/kg bw Oral administration (cats)	*In vivo*	Nosáľová *et al.*, 1992, 1992a and 1993	Reduction of intensity and cough efforts from laryngopharyngeal and tracheobronchial areas; extract less effective than isolated polysaccharide; antitussive activity lower than codeine but higher than prenoxdiazine, dropropizine
Purified polysaccharides	1 ml of 1% solution/cm^2 of mucous membrane	*In vitro*	Schmidgall *et al.*, 2000	Moderate bioadhesive effect
Isolated rhamnogalacturonan	25 and 50 mg/kg bw; oral administration (guinea pigs)	*In vivo*	Šutovská *et al.*, 2011	Dose: dependent cough suppressive effect in unsensitised animals
Isolated rhamnogalacturonan	50 mg/kg bw; oral administration (guinea pigs)	*In vitro and in vivo*	Šutovská *et al.*, 2009	Dose: dependent cough suppressive effect not significantly modified by pre-treatment of K^+_{ATP} ion channels with selective antagonist but significantly decreased after pre-

Herbal preparation tested	Posology	Experimental model	Reference	Main non-clinical conclusions
				treatment with selective 5-HT_2 receptors antagonist
Aqueous marshmallow root extract (20%)	Applied topically to the external ears of rabbits	*In vivo*	Beaune and Balea, 1966	Rabbits reduced irritation induced by UV irradiation or by tetrahydrofurfuryl alcohol
Dry extract prepared from 100 g of the plant material and 300 ml of 80% ethanol	100 mg/kg bw, oral administration (rats)	*In vivo*	Mascolo *et al.*, 1987	No inhibition of carrageenan induced rat paw oedema has been proved
Hypolaetin 8-glucoside	30, 60 and 90 mg/kg, intraperitoneal administration (rats)	*In vivo*	Villar *et al.*, 1984; Villar *et al.*, 1987; Alcaraz *et al.*, 1989	More potent than phenylbutazone in suppressing the acute phase of adjuvant carrageenan-induced inflammation but had less effective in the prolonged inflammatory phase. It did not cause gastric erosions. Analgesic activity lower than phenylbutazone. Anti-ulcer activity prevented the formation of cold-restraint induced gastric lesions, less potent than cimetidine was more potent. More potent than troxerutin in inhibiting histamine-induced capillary permeability in rats

3.1.2. Secondary pharmacodynamics

Antimicrobial activity

In vitro

Water and other extracts

A 10% decoction and methanolic extract prepared by exhaustive extraction from marshmallow root has been shown to possess an inhibiting activity able to diminish significantly the periodontal pathogens resident in the oral cavity (*Porphyromonas gingivalis, Prevotella spp., Actinomyces odontolyticus, Veilonella parvula, Eikenella corrodens, Fusobacterium nucleatum, Peptostreptococcus spp., Capnocytophaga gingivalis*). The methanol extract was active against *P. gingivalis*, *Prevotella* spp. and *Actinomyces* spp. (9 of 12 strains had a minimum inhibitory activity (MIC) ≤ 3125 mg/l). The decoction had higher MIC values (4096–8192 mg/l). The strains of *C. gingivalis, V. parvula, E. corrodens* and *Peptostreptococcus* spp. were inhibited by a MIC = 8192 mg/l (methanol extract) resp. ≥1684 mg/l (decoction), those of *F. nucleatum* by a MIC ≥ 1684 mg/l (both methanol extract and decoction) (Iauk *et al*., 2003).

Immunomodulatory activity

In vivo

Polysaccharides

Marshmallow mucilage polysaccharides administered intraperitoneally to mice at a dose of 10 mg/kg produced a 2.2-fold increase in phagocytic activity of macrophages in the carbon-clearance test (Wagner and Proksch, 1985).

Hypoglycaemic activity

In vivo

Polysaccharides

Isolated marshmallow root polysaccharide (Althaea-mucilage-O) administered intraperitoneally to non-diabetic mice at doses of 10, 30 and 100 mg/kg of body weight has been demonstrated to significantly reduce blood glucose (74%, 81% and 65% respectively) of the control level after 7 hours; after 24 hours only weak activity has been observed (93, 90 and 89% respectively) (Tomoda *et al.*, 1987).

Hypoglycaemic activity of water-soluble mucilage obtained from Althaeae radix administrated to non-diabetic mice has also been reported (Perez *et al.*, 1998).

Other activities

In vitro

Water extract

Antioxidant activity (DPPH radical scavenging activity) of polysaccharides extracted from *A. officinalis* roots in various experimental operating conditions (extraction temperature 10–90°C; particle size 6-24 mm and water to solid (W/S) ratio 10–50) has been studied. The optimum conditions to maximize yield (10.80%) and antioxidant activity (84.09%) were at extraction temperature 60-90°C, extraction time 12.01 hours, particle size 12.0 mm and W/S ratio of 40 (Ghavi, 2015).

Other extract

An extract (extraction medium 45% 1,3-butylene glycol solution) of marshmallow root was found to inhibit intracellular calcium mobilisation in normal human melanocytes activated by endothelin-1, and to strongly inhibit endothelin-1-induced proliferation of melanocytes. The extract can diminish the physiological effect of endothelin-1 on normal human melanocytes following UVB irradiation (Kobayashi *et al.*, 2002).

Cytoprotective effects of methanol/aqueous (1:1, V/V) polysaccharide depleted extract from marshmallow roots (containing very polar, low-molecular, water soluble compounds) have been studied in an *in vitro* investigation on keratinocytes by MTT-assay demonstrated that neither the extract of marshmallow roots nor the single compounds had any negative influence. As result of these data cytoprotective effects of extracts of *Althaea officinalis* L. could be explainable besides the proven active mucilage polysaccharides (Böker *et al.*, 2012).

3.1.3. Safety pharmacology

No data available

3.1.4. Pharmacodynamic interactions

It is mentioned in some literature sources (Barnes *et al.,* 2002; Hänsel *et al.*, 1993) 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

Marshmallow root is traditionally used as a demulcent preparation:

- for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough
- for the symptomatic relief of mild gastrointestinal discomfort

Marshmallow root preparations and isolated polysaccharides 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 marshmallow root as a demulcent for the symptomatic treatment of irritations of oral and pharyngeal mucosa with associated dry cough and for the symptomatic relief of mild gastrointestinal discomfort.

A study with isolated hypolaetin 8-glucoside can be considered supporting the use of the herbal substance and preparation thereof for the symptomatic treatment of mild gastrointestinal discomfort; moreover, this indication is considered plausible for traditional use of the herbal substance and preparations thereof as the mucilage contained in the products makes a kind of protecting layer on the mucosa which protects it from local irritation.

In the literature there is a hypothesis that absorption of concomitantly administrated 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 concerning pharmacokinetics.

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

3.3.1. Single dose toxicity

Mice were treated orally with the polysaccharide extract prepared from roots od *Althaea officinalis* (extract from 200 g of roots and 1 litre of purified water, purified and dried) in doses 2000, 3000, 4000 and 5000 mg/kg bw. Animals were observed daily for clinical signs of mortality over a period of two week following the treatment. The acute toxicity LD_{50} of *Althaea officinalis* extract in albino mice was found to be above 5000 mg/kg (Benbassat *et al*., 2013).

3.3.2. Repeat dose toxicity

No data available

3.3.3. Genotoxicity

An aqueous extract from marshmallow liquid extract from Althaeae radix, DER 1:12) in concentrations 31.6, 100, 316, 1000, 25000 and 5000 mg/plate was proved non-mutagenic in the reverse mutation assay with the *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 100 with and without metabolic activation (BSL BIOSERVICE Study No.: 131997, 2013).

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

Single dose toxicity tests with the dry aqueous extract prepared from roots of *Althaea officinalis* (extract from 200 g of roots and 1 litre of purified water) indicated the following data: no lethality was observed at doses up to 5 g/kg body weight after oral administration in mice.

An aqueous extract from marshmallow was proved non-mutagenic in the reverse mutation assay with the *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 100 with and without metabolic activation. However the no phytochemical similarity of the extract tested to the preparations

included in the EU monograph has been either demonstrated or discussed and therefore results of the test cannot be taken into consideration.

Tests on reproductive toxicity and carcinogenicity have not been performed.

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 marshmallow root as a demulcent for the symptomatic treatment of irritations of oral and pharyngeal mucosa with associated dry cough and for the symptomatic relief of mild gastrointestinal discomfort. None of the reported pharmacological studies constitute any cause for safety concern.

Specific data on pharmacokinetics and interactions are not available.

A negative test on genotoxicity has been provided; however, no phytochemical similarity of the extract tested to the preparations included in the EU monograph has been either demonstrated or discussed and therefore results of the test cannot be taken into consideration.

Tests on reproductive toxicity 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

Due to lack of data, no conclusion can be drawn.

4.2. Clinical efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Clinical studies available regarding indication a) (a demulcent preparation for the symptomatic treatment of oral or pharyngeal mucosa irritation and associated dry cough) are the post marketing surveillance study and the retrospective observational study in children mentioned below in section 4.2.3.

Other clinical study available is a double-blind placebo-controlled clinical trial with 63 patients (18 men and 45 women) of Iranian origin studying the effect of *Althaea officinalis* on dry cough associated with ACE inhibitors. Thirty patients were treated with 40 mg of *Althaea officinalis* in a form of drops (20 drops three times daily) and 30 with placebo. No details on the composition of the Althaea preparation have been given. Duration of treatment was four weeks. Three patients were excluded from the study for non-compliance. The tested parameters were cough score (0-4) and spirometry before and after intervention.

The mean cough score in the Althaea group was 2.66±0.95 before the intervention and 1.23±1 after the treatment (statistically significant reduction, $P<0.05$). No significant change was found in the placebo group (2.7±0.79 before the treatment and 2.33±0.84 after the treatment) (Rouhi and Ganji 2007).

Table 6: Clinical studies on humans, in irritated mucosa and associated dry cough

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Treatment of ACE inhibitors induced dry cough Efficacy study Rouhi and Ganji, 2007	Double-blind placebo controlled study	40 mg of *Althaea officinalis* in a form of drops (20 drops three times daily); no further details on composition of *Althaea* preparation duration: 4 weeks	63 patients (18 men; 45 women, 3 patients excluded for non-compliance (Althaea group 30 patients, placebo 30 patients)	Dry cough associated with ACE inhibitors therapy	Significant cough score reduction, no significant differences in the spirometry parameters	Statistically significant reduction, P<0.05	Significant cough score reduction
Treatment of mucous membrane irritation in the mouth and pharynx and associated dry irritating cough Efficacy and tolerability study Fasse *et al.*, 2005	Post-marketing surveillance study	Syrup containing 35.61 g/100 g = 76.45 ml of water extract from marshmallow root DER 1:19.5–23.5 2.5-10 ml 4-6 times daily Duration: 3 days in average	313 children (52.4% girls, 47.6% boys) Age groups: 0-3 years n=100; 3-6 years n=115; 6-12 years n=98 3 patients excluded	Mucous membrane irritation in the mouth and pharynx and associated dry irritating cough	Symptoms assessed: cough symptoms (cough intensity, cough frequency, extent of coughing during periods of the day), cough related symptoms (disorders in falling asleep and sound sleeping, pain in the neck, pain in the chest) and accompanying symptoms (catarrh, temperature) Efficacy very good to good 84.3%,	None	Results judged by physicians and patients or their parents, no objective measures were made

Type	Study	Test Product(s)	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
					satisfactory 7.7%, sufficient to poor 8% Tolerability very good to good 97%, satisfactory 2.2% 2 cases of AE/SAE in age group 0-3 years		
Treatment of mucous membrane irritation in the mouth and pharynx and associated dry cough Efficacy and tolerability study Bässler, 2005	Retrospective observational study	Syrup containing 35.61 g/100 g = 76.45 ml of water extract from Marshmallow root DER 1:19.5–23.5 1-5 ml 1-6 times daily Duration: 3-14 days	599 children Age groups: 0-3 months n=61; 3 months-3 years n=128; 3-6 years n=188; 6-12 years n=222	Mucous membrane irritation in the mouth and pharynx and associated dry cough	Efficacy: very good to good ≥90%; satisfactory 4.2%; inadequate 0,3% (2 cases) No adverse effects reported	None	Results judged by physicians and patients or their parents, no objective measures were made

4.3. Clinical studies in special populations (e.g. elderly and children)

Post-marketing surveillance study

313 children (0-3 years n=100; 3-6 years n=115; 6-12 years n=98; the youngest child was 3 months old and the oldest one 12.4 years of age) suffering from mucous membrane irritation in the mouth and pharynx and associated dry irritating cough were investigated to document efficacy and tolerability of syrup from marshmallow roots (containing water extract from marshmallow root DER 1:19.5–23.5, 35.61 g/100 g = 76.45 ml). The following symptoms were evaluated by the physicians and patients or by their parents: cough symptoms (cough intensity, cough frequency, extent of coughing during periods of the day), cough related symptoms (disorders in falling asleep and sound sleeping, pain in the neck, pain in the chest) and accompanying symptoms (catarrh, temperature). The dosage of the medicine was 2.5-10 ml depending on age, four to six times daily. The duration of treatment was three days (73.2%), in 24.6% of patients the treatment was continued and 2.2% of the patients were treated for less than three days. Three children were excluded from the efficacy study due to concomitant medication that was also indicated for dry irritating cough. During the study an adverse event (AE), development of obstructive bronchitis and a serious adverse event (SAE), development of bronchopneumonia resulting in hospitalisation occurred in the age group 0 to 3 years. The causal relationship of the SAE was judged by the physician as "unlikely", the causal relationship of the AE as "unrelated". The coughing intensity and frequency as well as cough-dependent symptoms were strongly reduced after three days. The tolerability of marshmallow root was very good (Fasse *et al.*, 2005).

Retrospective observational study

Data from 599 patients were documented by 53 physicians in the present retrospective data analysis of the experience with the application of syrup from marshmallow root water extract from marshmallow root (containing water extract from marshmallow root DER 1:19.5–23.5, 35.61 g/100 g = 76.45 ml) for the indication "mucous membrane irritations in the mouth and pharynx with associated dry cough" in children up to 12 years of age. The children were classified according to four age groups: 61 children 0-3 months of age, 128 children between 3 months and 3 years of age, 188 children between 3 and 6 years of age and 222 children between 6 and 12 years of age. The syrup was given 1-6 times per day in all age groups. 1-5 ml was given per single dose, whereby, on average, both the frequency of administration and, above all, the administered ml per single dose increased with age. The documented duration of treatment was, on average, 7.5 days, but varied from 3 days to 2 weeks. The efficacy was assessed as "very good", or "good" in over 90% of the cases in all age groups. No adverse effects were reported (Bässler, 2005).

4.4. Overall conclusions on clinical pharmacology and efficacy

Efficacy and tolerability of marshmallow syrup has been demonstrated in a post-marketing surveillance study in 313 children aged 3 months to 12 years and in a retrospective observational study in 599 children aged 0 to 12 years. As these studies are not randomised and controlled, their results cannot sufficiently support the well-established use for marshmallow root. They are however considered sufficient to support the traditional use as a demulcent for the symptomatic treatment of oral or pharyngeal mucosa irritation and associated dry cough. Efficacy has been demonstrated also in a double-blind, placebo-controlled clinical trial with 63 patients studying the effect of *Althaea officinalis* on dry cough associated with ACE inhibitors. The study cannot support the well-established use of marshmallow root as the herbal preparation was not sufficiently described. This study can nevertheless support the traditional use in dry cough.

As there are no clinical data available for indication b) (a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort) no conclusions can be drawn.

5. Clinical Safety/Pharmacovigilance

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

It the post-marketing surveillance study with 313 children by Fasse *et al.* (2005) an adverse event (AE) development of obstructive bronchitis and a serious adverse event (SAE), development of bronchopneumonia resulting in hospitalisation has been reported in the age group 0 to 3 years. The causal relationship of the SAE was judged by the physician as "unlikely", the causal relationship of the AE as "unrelated". The tolerability was assessed as very good to good in 97%, and satisfactory in 2.2% of patients. No other adverse effects were described.

No adverse events were reported in the retrospective observational study with 599 children (Bässler, 2005).

Table 7: Clinical safety data from clinical trials

Type	Study	Test Product(s)	Number of Subjects	Type of Subjects	Adverse reactions	Comments
Treatment of mucous membrane irritation in the mouth and pharynx and associated dry irritating cough Efficacy and tolerability study Fasse *et al.*, 2005	Post-marketing surveillance study	Syrup containing 35.61 g/100 g = 76.45 ml of water extract from marshmallow root DER 1:19.5–23.5 2.5-10 ml 4-6 times daily Duration: 3 days in average	313 children (52.4% girls, 47.6% boys) Age groups: 0-3 years n=100; 3-6 years n=115; 6-12 years n=98 3 patients excluded	Mucous membrane irritation in the mouth and pharynx and associated dry irritating cough	2 cases of AE/SAE in age group 0-3 years (AE obstructive bronchitis and SAE bronchopneumonia)	The causal relationship of the SAE judged by the physician as "unlikely", the causal relationship of the AE as "unrelated"
Treatment of mucous membrane irritation in the mouth and pharynx and associated dry cough Efficacy and tolerability study Bässler, 2005	Retrospective observational study	Syrup containing 35.61 g/100 g = 76.45 ml of water extract from marshmallow root DER 1:19.5–23.5 1-5 ml 1-6 times daily Duration: 3-14 days	599 children Age groups: 0-3 months n=61; 3 months-3 years n=128; 3-6 years n=188; 6-12 years n=222	Mucous membrane irritation in the mouth and pharynx and associated dry cough	No adverse effects reported	No adverse effects reported

5.2. Patient exposure

Data obtained from a post-marketing surveillance study with 313 children (Fasse *et al.*, 2005) and from retrospective observational study with 599 children (Bässler, 2005) showed good tolerance of the water extracts of marshmallow root.

A considerable patient/consumer exposure should be taken into consideration as marshmallow root is used as a flavouring agent in the food area.

If patients with known intolerance to *Althaea officinalis* are excluded, a traditional use is possible if administration follows the instructions as specified in the monograph.

5.3. Adverse events, serious adverse events and deaths

It the post-marketing surveillance study with 313 children by Fasse *et al.*, 2005 an adverse event (AE) development of obstructive bronchitis and a serious adverse event (SAE), development of bronchopneumonia resulting in hospitalisation has been reported in the age group 0 to 3 years. No other details on the cases are available. The causal relationship of the SAE was judged by the physician as "unlikely", the causal relationship of the AE as "unrelated".

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

Efficacy and tolerability of the dry cough treatment with marshmallow root extract syrup have been demonstrated by a post-marketing surveillance study in a group of 313 children, aged from 3 months to 12.4 years (Fasse *et al.*, 2005) and by a retrospective observational study in a group of 599 children, aged from 0-12 years (Bässler, 2005). A case of one adverse event (development of obstructive bronchitis) and a serious adverse event (development of bronchopneumonia resulting in hospitalisation) have been reported in the age group 0 to 3 years (Fasse *et al.*, 2005).

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special warnings and precautions for use

Indication 1)

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.

Preparations a), b), c) and d)

The use in children under 3 years of age is not recommended because of concerns requiring medical advice.

The use of the solid dosage forms in children under 6 years of age is not recommended because of the pharmaceutical form.

Preparation e)

The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

Indication 2)

Preparation a)

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

Preparation e)

The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

Indication 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.

If the symptoms worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

For extracts 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

It is mentioned in some literature sources (Barnes *et al*., 2002, Hänsel *et al.*, 1993) 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. As no tests on humans or animals were performed to confirm delayed absorption, 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.

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 for marshmallow root.

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 marshmallow root products can be derived from the long-standing use and experience as well as from clinical studies. In the post-marketing surveillance study in children one adverse event (development of obstructive bronchitis) and a serious adverse event (development of bronchopneumonia resulting in hospitalisation) has been reported in age group 0 to 3 years of age. The causal relationship was judged "unlikely" and/or "unrelated".

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

The indication 1) is appropriate for use in elderly, adults, adolescents and children over 3 years of age and the indication 2) for adolescents, adults and elderly (herbal substance) or for adults and elderly (ethanolic extract) without the supervision of a medical practitioner. The duration of use without medical advice is limited to one week for indication 1) and two weeks for indication 2).

Marshmallow root 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 European Union herbal monograph is established on the traditional uses of several preparations of *Althaea officinalis* L., radix. The traditional uses of Althaeae radix preparations fulfil 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 fulfil the requirements to demonstrate a well-established medicinal use with recognised efficacy for Althaeae radix 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:

Traditional herbal medicinal product for use as a demulcent preparation

- for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough
- for the symptomatic relief of mild gastrointestinal discomfort

Benefit-Risk assessment

The licensing of herbal medicinal products is subject to compliance with the requirements of a 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 including together 912 children aged 0–12.4 years, one adverse event (development of obstructive bronchitis) and a serious adverse event (development of bronchopneumonia resulting in hospitalisation) occurred in age group 0 to 3 years.

The causal relationship was judged "unlikely" and/or "unrelated".

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 European Union 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 Althaeae radix, according to current state-of the-art standards are available.

The duration of use is limited to one week for indication 1) and two weeks for indication 2) 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. Herbal medicinal products in liquid dosage forms containing aqueous preparations from Althaeae radix (macerates, aqueous extract) used in indication 1) are recommended for elderly, adults, adolescents and children over 3 years of age. Use in children under 3 years of age is not recommended because medical advice should be sought. Use of the products in solid dosage forms in children below six years is not advisable. The use of the herbal substance in indication 2) 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. The use of ethanolic extract (DER 1:1, extraction solvent ethanol 25% V/V) in indications 1) and 2) is 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 Althaeae radix 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 symptomatic relief of mild gastrointestinal discomfort, 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 marker can be recognised by the HMPC.

Test on genotoxicity (AMES test) has been performed with aqueous extract from marshmallow root (DER 1:12) only; however, the data cannot be extrapolated to any preparation included in the European Union monograph. Therefore a European Union list entry is not proposed due to lack of adequate data.

Annex

List of references