European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT ON *ALTHAEA OFFICINALIS* L., RADIX

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I. REGULATORY STATUS OVERVIEW[1]

MA: Marketing Authorisation;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Old products single and combinations, currently not available on the market Combinations
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: Food supplement	Combinations
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	+ Combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	On the market as a non-pharmaceutical product
Poland	☐ MA	☒TRAD	☐ Other TRAD	☐ Other Specify:	+ Combinations
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

Romania	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combination only Althaeae sirupus in Pharmacies
Spain	☐ MA	☒ TRAD*	☐ Other TRAD	☐ Other Specify:	* The MA granted in the old legislative frame, not the 2004/24/EC directive.
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only

INFORMATION ON LEGAL STATUS OF PRODUCTS CONTAINING *ALTHAEA OFFICINALIS* L., RADIX IN MEMBER STATES

Preparations marketed in Europe

Marshmallow root preparations are marketed in different countries with different status - authorised, registered and non-pharmaceutical products and food supplements.

Herbal drug for tea/macerate preparation

One standard marketing authorisation for Althaeae radix – monoproduct - in the pharmaceutical form of herbal tea has been reported by **Germany**. No information on indication and posology is available.

In **Poland** comminuted herbal substance in a form of herbal tea for macerate preparation (10 g of comminuted herbal substance/ 200 ml of warm water) has been traditionally used for more than 30 years in sore throat and upper respiratory complaints. Posology: 60 ml (1/3 of glass) 2 to 3 times daily.

Comminuted herbal substance for tea preparation is authorised in **Romania** since 2001 with the following indications: adjuvant in treatment of bronchitis; traditionally used in occasional mild cough; traditionally used to alleviate abdominal aches of digestive origin. Posology: 1 cup of infusion prepared from 1 teaspoon (approximately 2 g) and 200 ml of boiling water 2 to 3 times daily.

Herbal tea was authorised in **Spain** before 1973. The marketing authorisation was granted under the old legal framework. The herbal tea is used in irritation of the oral and pharyngeal mucosa and associated dry cough. The daily dose is 6 g of comminuted herbal substance divided in 2 or 3 portions.

Althaea syrup

Syrup prepared from the macerate (34.9 g) of 2 g Althaeae radix has been on the **Lithuanian** market for more than 100 years as a demulcent for symptomatic treatment of dry irritable cough. The dosage is 2-8 ml. No information on frequency of use is available.

Two versions of Althaea syrup are marketed in **Poland** since 1999 and 2000. The syrups are prepared from macerate made from 5 or 6 g Althaeae radix on 100 g of the product. The products are indicated for sore throat and larynx, smoothing throat's mucosa, dry cough, upper respiratory inflammations, hoarseness and bronchitis. The posology for syrups prepared from 5 g of Althaeae radix is 1 spoon 3 or 4 times daily. For the syrup prepared from 6 g of Althaeae radix the following posology is recommended: adults 10ml 3-4 times daily; children up to 2 years after medical advice; children from 2 to 6 years 5 ml 2-3 times daily; children above 6 years 5 ml 2-3 times daily; children above 13 years 10 ml 3-4 times daily.

Liquid extract

A syrup containing 35.610 g of liquid extract 1:19.5-23.5, extraction solvent water in 100 ml (76.3 g) is authorised in **Germany** at least since 1976. The product is indicated in irritations of the mucosa in the oropharynx and therewith associated hacking dry cough. Posology: Adults and adolescents over 12 years: 3-6 times daily 10 ml syrup, children 6-12 years: 5 times daily 5 ml syrup. Based on additional documentation provided by the MAH Germany could accept in addition to the above mentioned the following dosage: Children 3-6 years: 4 times daily 4 ml syrup Children 1-3 years: 4 times daily 3 ml syrup. The use in children below 1 year cannot be accepted.

Dry extract

During the consultation period information on products marketed in **Germany** containing dry extract 3-7:1, 7-9:1 and 3:1, extraction solvent water in a form of pastilles and oral drops has been received.

Althaea polysaccharides

Tablets containing 50 mg of Althaea polysaccharides are marketed in **Estonia** as a food supplement since 2004. The tablets are used as an expectorant. The dosage is 1 tablet twice a day.

Combination products containing marshmallow root and marshmallow root preparations are authorised/registered in Austria, Czech Republic, Germany, Hungary, Latvia, Lithuania, Poland, Slovakia, Slovenia, Spain and the UK.

II. ASSESSMENT REPORT ON HERBAL SUBSTANCE WITH TRADITIONAL USE

ALTHAEA OFFICINALIS L., RADIX

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 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 (marshmallow root)
Herbal preparation(s)	Comminuted herbal substance for macerate preparation Liquid extract, extraction solvent water Syrup prepared from macerate Dry extract, extraction solvent water
Pharmaceutical forms	Comminuted herbal substance for macerate preparation or other mucilage containing herbal preparations in liquid or solid dosage forms for oral and oromucosal use
Rapporteur	Marie Heroutová

II.1 INTRODUCTION

II.1.1 Description of the herbal substance:

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

Information on period of medicinal use in the Community regarding the specified indication
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, The Complete German Commission E Monographs (Blumenthal et al. 1998), WHO monographs on selected medicinal plants 2002, ESCOP Monographs 2003, European Pharmacopoeia 6.0 2008. 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.

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Compounds:
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 1.2:1.0:1.0:1.0 (Tomoda 1977, Capek 1987), L-arabinans (Capek 1983); D-glucans (Capek 1984).
Dominant neutral mucilage component is (1→6)-α-D-glucan (Nosalova 1992, 1993).
By partial acid hydrolysis 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 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 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 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 1984).

Pectins	11 % (Blumenthal 2000)
Starch	25-35 % (Blumenthal 2000)
Mono-, Di-saccharide	saccharose 10 % (Gudej 1991); crude mucilages contained 5 % glucose in spring and 20 % glucose in winter (Franz 1966)
Flavonoids:	Hypolaetin-8-glucoside, isoscutellarein-4´-methyl ether 8-*O*-β-D-glucoside-2´´-SO_3K (Gudej 1991), isoquercitrin, kaempferol 3-*O*-glucoside (Gudej1989), kaempferol, quercetin (Ionkova 1992), naringenin (Ninov 1992)
Phenolic acids:	caffeic, *p*-coumaric, ferulic, *p*-hydroxybenzoic, salicylic, syringic, p-hydroxyphenylacetic, vanillic acid (Gudej 1991)
Coumarins:	scopoletin (Gudej 1991)
Other compounds:	phytosterols (Wichtl 1994), calcium oxalate (Blumenthal 2000), fat, tannins (Bradley 1992), amino acids (Rosík 1984), 2 % asparagine (Bradley 1992)

II.2.1.2 Pharmacodynamics

The mucilage from marshmallow root covers the mucosa with a kind of protecting layer which protects it from local irritation (Franz 1989, Müller-Limmroth 1980).

***In vitro* experiments:**

Antitussive activity

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

Antimicrobial activity

A methanolic extract prepared by exhaustive extraction from marshmallow root has been shown to posses 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.) (Iauk 2003).

Antimicrobial activity against *Pseudomonas aeruginosa*, *Proteus vulgaris* and *Staphylococcus aureus* has been documented for chloroform and methanolic extracts of marshmallow roots (Recio 1989).

Immunomodulatory effects

Althaea-mucilage O, an acidic polysaccharide isolated from marshmallow root, has been demonstrated to have an anti-complement activity on normal human serum in concentrations of 100 – 1000 μg/ml (Yamada 1985).

Other activities

Bioadhesive effects of purified polysaccharides (>95 %) from medicinal plants on porcine buccal membranes were studied; polysaccharides from marshmallow root showed moderate adhesion to epithelial tissue (Schmidgall 2000).
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 2002).

***In vivo* experiments:**

Antitussive activity

An extract from marshmallow root (type of extract was not specified) and isolated mucilage polysaccharide were tested for antitussive activity in unanaesthetised 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) (Nosalova 1992, 1992a and 1993).

Anti-inflammatory and immunomodulatory activity

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 1966).
However, with a dry 80% ethanolic extract administered orally (100 mg/kg b.w.), no inhibition of carrageenan induced rat paw oedema has been proved (Mascolo 1987).
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, ESCOP 2003).

Hypoglycaemic activity

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 reduce significantly 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 1987, ESCOP 2003, NMCD 2008).

Hypoglycemic activity of water-soluble mucilages obtained from Althaeae radix has also been reported (Perez 1998).

Pharmacological activities of constituents

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 1984, Villar 1987, Alcaraz 1989).

II.2.1.3 Assessor's overall conclusions on pharmacology

Marshmallow root and its isolated polysaccharides have been investigated in several pharmacological *in vitro* and animal studies. These studies are considered to be sufficient to support the use of marshmallow in the treatment of dry cough, irritation of the oral and pharyngeal mucosa as well as gastric inflammations.

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No data available.

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

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

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

There are no data on acute toxicity, genotoxicity, carcinogenicity and/or reproductive and developmental toxicity available on marshmallow root.

II.2.3.2 Assessor's overall conclusions on toxicology

Although no toxicity data are available, the main constituents (polysaccharides) of marshmallow root indicate that marshmallow root can be regarded as safe under normal conditions of use, this fact is confirmed by historical use within the food area.

Since minimum required data on mutagenicity (Ames test) are not available, inclusion in the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

II.3.1.1 Pharmacodynamics

II.3.1.1.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No data available.

II.3.1.1.2 Assessor's overall conclusions on pharmacodynamics

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

II.3.1.2 Pharmacokinetics

II.3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No data available.

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

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

II.3.2 Clinical Efficacy

The only available clinical study is a post-marketing surveillance study in children (see section II.3.2.4). As this study is non-controlled, non-randomised, it is considered not acceptable to support the well-established use of marshmallow root as a herbal medicinal product, but sufficient to support its traditional use.

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

The Complete German Commission E Monographs (Blumenthal 1998)
a) Irritation of the oral and pharyngeal mucosa and associated dry cough.
b) 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 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.
Syrupus 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).
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: no information.
Duration of use: no information.

ESCOP Monographs (2003)
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)
Internally: for gastroenteritis, peptic or duodenal ulceration, common and ulcerative colitis and enteritis.
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)
Althaeae radix – action and uses: 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)
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)
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 Volume III and IV (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

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.
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, 1990
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.

Deutsches Arzneimittel Codex, 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.

Farmakopea Polska, 2002
Althaeae syrupus 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

Heilpflanzen Praxis Heute (Bäumler, 2007)
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)
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

Assessor's comment on Marshmallow syrup use:
In several pharmacopoeias and handbooks the use of marshmallow syrup is described. However, preparation of the syrup, especially the ratio of marshmallow root and water used and times of maceration differ significantly (see table bellow):

Source	Cold 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	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	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	25g/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 0.20 g
Farmakopea Polska	5 p/ethanol 760 g/l -1 p/40 p water maceration for 3 hours	64 p/100p of the product	Preservative benzoic acid 0.1 p/100 p of the product	1.300-1.320 g/cm^3	ca 0.65 g
Product from Latvia	maceration ex 2 g Althaeae radicis	no information	no information	no information	ca 0.20 g
Products from Poland	5-6 g/100 g of product	no information	no information	no information	ca 0.5 – 0.6 g

Abbreviations:
p – parts; MPB – methylparaben; PPB – propylparaben; BPC – British Pharmaceutical Codex (1949);
ÖAB – Österreichisches Arzneibuch (2007); DAC – Deutsches Arzneimittel Codex (2004);
ČL – Český lékopis (Czech Pharmacopoeia 2005); Ph. – 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 from other sources correspond to 0.2-0.65 g of marshmallow root in 10 ml of the product.

Although syrup is generally not considered to be a herbal preparation but a pharmaceutical dosage form, in this case an exception should be made due to the fact that the exact content of marshmallow root cannot be calculated.

Information on use of other herbal preparations than cold macerate/tea, aqueous liquid extract (1:19.5-23.5), syrup and aqueous dry extract has not been confirmed for single drug by the Member States.

II.3.2.1 Assessor's overall conclusion on the traditional medicinal use

Traditional medicinal use of *Althaea officinalis* L., radix in the form of comminuted herbal substance for macerate preparation, aqueous extract or syrup is well documented in a number of bibliographic sources. The requirement of medicinal use for at least 30 years (including at least 15 years within the Community) according to Directive 2001/83/EC as amended is considered fulfilled.

Based on literature data and information received from Member States, the following traditional indications are proposed:

Traditional herbal medicinal product for use as a demulcent preparation
a) for the symptomatic treatment of oral or pharyngeal mucosa irritation and associated dry cough
b) 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. 1992, PDR 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 more information on the preparations has been found.
BPC 1949 recommends the use of fomentation (1 part of powdered root to 5 parts of water), application of such hot poultice could be acceptable only in case of furuncles maturation but not other skin inflammations. However, treatment of furunculosis is not considered to be a suitable indication for traditional use registration as this indication requires medical supervision.

There are however insufficient data that can clarify the main pharmacological properties. Therefore, the use as a poultice cannot be regarded as plausible.

II.3.2.2 Dose response studies

There are no dose response studies available.

Information on dosage described in the literature and that sent by the Member States differ significantly and so does the way of preparation of the macerate. The daily dose of comminuted herbal substance for cold macerate preparation varies between 1.5 g (Pharmacopoea Hungarica 1970) and 15 g (ESCOP 2003, Bradley 1992, Newal 1996, Blumenthal 2000, Český lékopis 2005) and the single dose from 0.5 g (ESCOP 2003, Pharmacopoea Hungarica 1970, Český lékopis 2005) to 5 g (Blumenthal 2000, ESCOP 2003, Bradley 1992, Newal 1996, Český lékopis 2005).
Herbal preparation (macerate) is prepared with cold water (Blumenthal 2000, ESCOP 2003, Bradley 1992, Newal, 1996), warm water (information from Poland) or as tea, i.e. with hot water (information from

Spain). However, the temperature during maceration should not exceed 40°C to avoid starch extraction and to prevent polysaccharides degradation, as polysaccharides have been demonstrated to be sensitive to high temperatures (Madaus et al. 1987; Franz, Madaus 1990). On the other hand, risk of microbial contamination when cold water is used should be taken into consideration. Schmidgall et al. (2000) recommends bringing cold macerate to a boil to reduce microbiological contamination. Recommendation to immediate use of the cold macerate has been included in sections 4.2 'Posology and method of administration' and 6 'Pharmaceutical particulars' of the Community herbal monograph.
Time of maceration recommended in the literature differs and it is reported from 30 minutes with stirring (Blumenthal 2000) to 1.5 hour with stirring (Hänsel et al. 1992) or 2-3 hours without stirring (Schmidgal et al. 2000).

Based on the literature data and information received from the Member States, the following posology is suggested:

For indication a)
Comminuted herbal substance for cold macerate preparation
Adolescents over 12 years of age, adults: 0.5-3g several times daily up to a maximum daily dose of 15 g
Children between 6 and 12 years of age: single dose 0.5-1.5 g, 3 times daily
Children between 3 and 6 years of age: single dose 0.5-1 g, 3 times daily

To make a macerate, pour 150 ml of cold water (maximum temperature 40°C) over 0.5-3 g of comminuted herbal substance. Steep for 30 minutes stirring frequently. The macerate should be used immediately after use.

Liquid extract (1:19.5-23.5), extraction solvent water
Adults and adolescents over 12 years: 5 ml, 3-6 times daily
Children between 6 and 12 years of age: 2.5 ml, 5 times daily
Children between 3 and 6 years of age: 2.5 ml, 4 times daily

Syrup
Adults and adolescents over 12 years: 2-10 ml, 3 times daily
Children between 6 and 12 years of age: single dose 1-1.5 ml, 4 times daily
Children between 3 and 6 years of age: single dose 0.5-1 ml, 4 times daily

Dry extract (3-9:1), extraction solvent water
Adults and adolescents over 12 years: single dose corresponding to 0.5-3 g of herbal substance several times daily up to a maximum daily dose of 15 g
Children between 6 and 12 years of age: single dose corresponding to 0.5-1.5 g of herbal substance, 3 times daily
Children between 3 and 6 years of age: single dose corresponding to 0.5-1 g of herbal substance, 3 times daily

Duration of use:

If the symptoms persist for more than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

The limitation of the duration of use and the exclusion of children below the age of 3 years is based on the clinical conditions in those groups and not on specific safety concerns related to the active substance.

For indication b)
Comminuted herbal substance for macerate preparation

Adolescents over 12 years of age and adults: 3-5 g, 3 times daily

Duration of use:
No information on restrictions has been found in the literature. Regarding this indication, the following information should be given:
If the symptoms persist for more than 2 weeks a doctor or a qualified health care practitioner should be consulted.

II.3.2.3 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 II.3.2.4.

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).
No significant differences in the spirometry parameters before and after the treatment were found either in the Althaea group or in the placebo group.
Althaea officinalis showed a beneficial effect in the treatment of ACE inhibitors induced dry cough. The study is not of a sufficient quality for a well-established use as the herbal preparation was not sufficiently defined. However, it can support the traditional indication in dry cough (Rouhi and Ganji 2007).

There are no clinical data available for indication b) (a demulcent preparation for the symptomatic relief of mild gastrointestinal discomfort).

II.3.2.4 Clinical studies in special populations (e.g. elderly and children)

Post-marketing surveillance study: 313 children (0-3y n= 100; 3-6y n= 115; 6-12y 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 (Phytohustil® irritating cough suppressant syrup). 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 (development of obstructive bronchitis) and a serious adverse event (development of bronchopneumonia resulting in hospitalisation) occurred in the age group 0 to 3 years. 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 Phytohustil® Syrup 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. Phytohustil® Syrup was given 1-6 times per day in all age groups. 1-5 ml were 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).

II.3.2.5 Assessor’s overall conclusions on clinical 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. With regard to this indication, the use is not recommended for children under 3 years of age.
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.

II.3.3 Clinical Safety/Pharmacovigilance

No other data are available than those mentioned in section II.3.2.4
No pharmacovigilance actions taken on medicinal products containing marshmallow root have been reported by Member States.

II.3.3.1 Patient exposure

Products containing *Althaea officinalis* L., root are widely available. The products have various regulatory statuses. A considerable patient/consumer exposure should be taken into consideration as marshmallow root is used as a flavouring agent in the food area.

II.3.3.2 Adverse events

No other data are available than those mentioned in section II.3.2.4.

II.3.3.3 Serious adverse events and deaths

No other data are available than those mentioned in section II.3.2.4.

II.3.3.4 Laboratory findings

None reported on marshmallow root.

II.3.3.5 Safety in special populations and situations

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).

II.3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

Safety and efficacy of marshmallow root products in patients with liver or kidney diseases have not been established.
Hypersensitivity or allergy to the active substance is a contraindication.
When dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted. This is in accordance with the monographs concerning common cold.

II.3.3.5.2 Drug interactions

It is mentioned in some literature sources (Barnes et al. 2002, Hänsel et al. 1992) 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.

II.3.3.5.3 Use in pregnancy and lactation

Safety in pregnant or breast-feeding women has not been established. There are no data on use of marshmallow root in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Due to lack of adequate data, the use of marshmallow root cannot be recommended during pregnancy or lactation.

II.3.3.5.4 Overdose

No case of overdose has been reported for marshmallow root.

II.3.3.5.5 Drug abuse

None reported.

II.3.3.5.6 Withdrawal and rebound

None reported.

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

No studies on effects on ability to drive and/or operate machinery and/or impairment of mental ability are available.

II.3.3.6 Assessor's overall conclusions on clinical safety

Marshmallow root is generally recognised as safe. However, the use of marshmallow root cannot be recommended during pregnancy or lactation due to lack of adequate data and in children under 3 years of age. For use in children under 3 years of age, a consultation with a doctor is recommended. The limitation of the duration of use and the exclusion of children below the age of 3 years is based on the clinical conditions in those groups and not on specific safety concerns related to the active substance.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

Traditional medicinal use of marshmallow root as a demulcent preparation for the symptomatic treatment of oral or pharyngeal mucosa irritation and associated dry cough and for the symptomatic relief of mild gastrointestinal discomfort fulfils the requirement of medicinal use for at least 30 years (including at least 15 years within the Community) according to Directive 2001/83/EC as amended.
Concerning the use for treatment of minor skin inflammations insufficient data are available that can explain the main pharmacological properties. Therefore, the topical use cannot be regarded as plausible.

Efficacy has been demonstrated 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.
Efficacy and tolerability of marshmallow syrup has been demonstrated in a post-marketing surveillance and retrospective observational studies in children aged 0 months to 12 years. As these studies are not randomised and controlled, their results cannot sufficiently support the well-established use for marshmallow root, however, they are considered sufficient to support the traditional use for the symptomatic treatment of oral or pharyngeal mucosa irritation and associated dry cough. With regard to this indication, the use is not recommended for children under 3 years of age.

Marshmallow root is generally recognised as safe. However, the use of marshmallow root cannot be recommended during pregnancy or lactation due to lack of adequate data and in children under 3 years. The limitation of the duration of use and the exclusion of children below the age of 3 years is based on the clinical conditions in those groups and not on specific safety concerns related to the active substance.

As minimum required data on mutagenicity (Ames test) are not available, an inclusion in the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

III. ANNEXES

III.1 COMMUNITY HERBAL MONOGRAPH ON *ALTHAEA OFFICINALIS* L., RADIX

III.2 LITERATURE REFERENCES