European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON
COMMUNITY HERBAL MONOGRAPH ON *ALTHAEA OFFICINALIS* L., RADIX

Table 1: Organisations that commented on the draft 'Community herbal monograph on *Althaea officinalis* L., radix' as released for consultation on 3 July 2008 until 15 November 2008.

	Organisation, country
1	Kooperation Phytopharmaka, Germany
2	PhytoLab, Germany
3	Association of the European Self-Mediacation Industry (AESGP)
4	Bundesverband der Pharmazeutischen Industrie (BPI), Germany
5	European Scientific Cooperative on Phytotherapy (ESCOP)

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Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT	OUTCOME
The Draft of the monograph Althaea is valuable in that respect, that it gives a frame within traditional use of this truly European herbal drug, which is, due to its excellent safety, especially important for the treatment of small children. There are three main points which should be better adapted to the traditional therapeutic reality. The one is the dosage, which should be adapted to that of registered products in the market, as far as possible. The second is the use also of a solid form, which should be also included into the monograph. The third and most important point is the fact, that the traditional use of the preparation also includes its use in toddlers and infants below 3 years. Regarding the safety of this use it has to be mentioned, that the mechanism of action of this medication is a merely physical one, and with short lasting, so that the use is well tolerated also in children below 3 years and does not mask possible severe causes of a cough. The use of this medicine in children below 3 years does not interfere with the fact, that medical advice should be sought for children of this age in any case of cough. But regarding this fact it would be sufficient to include the sentence "Medical advice should be sought for children under 3 years of age" into the package leaflet. It would be a great and unnecessary loss for the traditional use of Althea syrup, if this could not, as traditionally, be used also in children below 3 years. Here it is especially relevant, that the traditional use of this preparation at least in Germany is to a large part based on the recommendation of paediatrics and other physicians, as is documented e.g. by the leading German physicians reference manual on the use of pharmaceuticals from 1929 and a recent observational study. This traditional use would be questioned, if Althaea radix would not be recommended also for children below 3 years, without a concomitant improvement of the risk/benefit-ratio. Hopefully the HMPC will not, instead of supporting the traditional use of herbal preparations in Europe, restrict and discourage the use in toddlers, children and paediatrics in the case of such an important remedy as it is Althaea radix.	Partially endorsed. See the answer in relevant sections.
We appreciate the draft for a Community Herbal Monograph on "*Althaea officinalis* L. radix" prepared by the Committee on Herbal Medicinal Products (HMPC). However we consider the following addition to §3 necessary (see Section 3 Pharmaceutical form)	Endorsed

SPECIFIC COMMENTS ON TEXT		
2 QUALITATIVE AND QUANTITATIVE COMPOSITION		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	We suggest to add under ii) Herbal preparations: **D) Dry extract (3 – 7 :1), extraction solvent water** This corresponds to the preparation Eibisch-Hustenpastillen, marked in Germany by Kräuterhaus Sanct Bernhard KG, Helfensteinstraße 47, 73342 Bad Ditzenbach [1].	Endorsed. Although no 30 years of traditional use has not been demonstrated, this type of extract has been included taking into consideration the fact that water extract is similar to the macerate. DER has been adapted to 3 – 9 : 1
	Traditional use ii) Herbal preparations **D) dried extract 7-9:1, extraction solvent water (This extract has been used at least since 1991 in Germany)**	See answer above.
	D) Dry extract (3 – 7 :1), extraction solvent water Reason: A preparation for oral use (one pastille contains 170 mg marshmallow dry extract (3:1), extraction solvent water) is on the German market. It is manufactured by Kräuterhaus Sanct Bernhard KG, Helfensteinstr. 47, D-73342 Bad Ditzenbach, Germany.	See answer above.
	There are cough drops in the market (Kräuterhaus Sanct Berhard KG, Helfensteinerstraße 47, 73342 Bad Ditzenbach, Germany), which contain 170 mg marshmallow root dry extract (3:1, extracted with solvent water) as medicinally active ingredient. Proposed change: ii) **D) Dry extract (3-7:1), extraction solvent water**	See answer above.

3 PHARMACEUTICAL FORM		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
3 Pharmaceutical form	Addition to the text:"... or other mucilage containing herbal preparations in liquid dosage forms..." Substitute the above for: " ... or other herbal preparations in liquid dosage forms..." As other herbal preparations that do not contain the essential water-soluble mucilage could be prepared, it is advisable to add to the text, that "mucilage" must be present in the final pharmaceutical form.	Endorsed
4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.2. Posology and method of administration	We suggest to replace, adjust and add the following points: Traditional use: Indication a) *Adolescents and adults* B) single dose 5 **- 10** ml, 3-6 times daily C) single dose 2 **-** 10 ml, 3**-6** times daily **D) single dose corresponding to 0.5 - 3 g of herbal substance, several times daily up to maximum daily dose of 15 g** *Children between 6 and 12 years of age* B) single dose ~~2.5~~ **5** ml, 5 times daily C) single dose ~~1 – 1.5~~ **5** ml, ~~3~~ **5** times daily **D) single dose corresponding to 0.5 - 1 g of herbal substance, 3 times daily** *Children between 3 and 6 years of age* B) single dose ~~2.5~~ **5** ml, 4 times daily	Dosage of preparation B) Not endorsed as the recommended dosage for preparation B corresponds to the extract and not to the final product. Product referred by the interested party Phytohustil contains 35.61 g of liquid extract (1: 19.5 – 23.5)/ 100 g Dosage of preparation C) The dosage has been adapted in line with literature provided by the interested party (Kinderdosierungen von Phytopharmaka, 2002) as follows: *Adolescents and adults* Not endorsed *Children between 6 and 12 years of age* Partially endorsed 1 – 1.5 ml 4 times daily (corresponds to daily dose of ca 5.2 to 7.8 g) *Children between 3 and 6 years of age* Partially endorsed 0.5 – 1 ml 4 times daily (corresponds to daily dose of 2.6 – 5.2 g)

	C) single dose ~~0.5 – 1~~ **5** ml, ~~3~~ **4** times daily **D) single dose corresponding to 0.5 - 1 g of herbal substance, 3 times daily** ~~The use in children under 3 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').~~ ***Children between 3 months and 3 years of age*** **A) The use in children between 3 months and 3 years of age is not recommended.** **B) single dose 3 ml, 4 times daily** **C) single dose 3 ml, 4 times daily** ***Children under 3 months of age*** **A) The use in children under 3 months of age is not recommended.** **B) single dose 2.5 ml, 4 times daily** **C) single dose 2.5 ml, 4 times daily** The dose for adolescents and adults for indication a) are adjusted to the specifications of ESCOP Monograph (2003) for Althaeae radix [2]. Further changes are incorporated with respect to a better uniformity between the factual use of existing products, e.g. Althaea syrup Phytohustil (Steigerwald Arzneimittelwerk GmbH, Germany) and Eibisch-Hustenpastillen (Kräuterhaus Sanct Bernhard KG, Germany) [1, 3]. The dosage for children is adjusted to our recommendations for the dosage of herbal medicinal products in children [4] as well as to recommendations of physicians and paediatrics for children and infants, which were documented and analyzed in a retrospective observational study for Phytohustil [5]. We do not agree with the exclusion of children under 3 years of age for the indication a). Colds are especially in children the most frequently occurring diseases, which comprehend dry irritating cough during the first three days [6]. Dry irritating cough has no physiological benefit and causes	Density of the syrup is ca 1.3 g/ml Dosage of preparation D) Endorsed Indication a) Use in children below 3 years: Restriction of use for children below 3 years of age is not caused by safety concerns attributed to marshmallow preparations. The working party agreed that the treatment of cough in children below 3 years of age needs the supervision of a doctor. Since traditional herbal medicinal products are intended to be used without medical supervision, this restriction was included.

	pain in neck and chest [6]. A recent post-marketing surveillance tested explicitly the efficacy and tolerability of Althaea syrup in children from 3 months up to 12 years of age. 100 (of 313) of the included children were under 3 years of age, which attest the relevant application of this syrup in this age group. The observations of this study are quoted in the following: "A clear and statistically significant improvement of all investigated symptoms of the irritating cough was found mostly during the three-day treatment and surveillance period. A rapidly occurring and longer lasting alleviation of the coughing and cough-related symptoms was achieved in all age groups. […] Marshmallow syrup was found to be an effective herbal preparation for treatment of dry irritating cough in this PMS of 313 children aged up to 12 years. […] The acceptance of marshmallow syrup by the children was very high (99.7%)." [6]. The good tolerability and safety of Althaea syrup is also confirmed by pharmacoviligance data, obtained for Althaea preparations according to B), C) and D). These preparations have been regular pharmaceutical drugs registered by the German BfArM. There have never been any safety concerns due to side effects or misuse in children, including those under three years of age. A retrospective observational study about the use of Althaea syrup in 599 children up to 12 years documented independent from age group no adverse reactions and a good acceptance. Furthermore 98.3% of the 61 children under 3 months of age and 92.2% of the children between 3 months and 3 years (128 children) showed a good or very good efficacy [5]. The efficacy of Althaea syrup was described by over 90% of the patients in all age groups as very good or good [5]. These study reports clearly demonstrated the efficacy of Althaea syrup in all age groups. It reflected furthermore that Althaea syrup is a valuable and relevant drug for physicians and paediatrics in the therapy of dry cough in children. In addition to the demonstrated clinical use, the good tolerance, the post-marketing surveillance and the observational study, the application of *Althaea officinalis* in infants and children is also backed by tradition.	

4.2. Posology and method of administration	Traditional use **4.2 Posology and method of administration:** **D) Adolescents and adults: single dose 65 mg 3 – 6 times daily**	Partially endorsed. *Adolescents and adults* 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
4.2. Posology and method of administration	Traditional use **Posology** Indication a) *Adolescents and adults* A) single dose 0.5 – 3 g, several times daily up to maximum daily dose of 15 g B) single dose 5 **- 10** ml, 3-6 times daily C) single dose 2 **-** 10 ml, 3-**6** times daily **D) single dose corresponding to 0.5 - 3 g of herbal substance, several times daily up to maximum daily dose of 15 g** *Children between 6 and 12 years of age* A) single dose 0.5 – 1.5 g, 3 times daily B) single dose ~~2.5~~ **5** ml, 5 times daily C) single dose ~~1 – 1.5~~ **5** ml, ~~3~~ **5** times daily **D) single dose corresponding to 0.5 - 1 g of herbal substance, 3 times daily** *Children between 3 and 6 years of age* A) single dose 0.5 – 1 g, 3 times daily B) single dose ~~2.5~~ **5** ml, 4 times daily C) single dose ~~0.5 – 1~~ **5** ml, ~~3~~ **4** times daily **D) single dose corresponding to 0.5 - 1 g of herbal substance, 3 times daily**	Partially endorsed. See answer to 4.2. on page 4.

	~~The use in children under 3 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').~~ ***Children between 3 months and 3 years of age*** **A) The use in children between 3 months and 3 years of age is not recommended.** **B) single dose 3 ml, 4 times daily** **C) single dose 3 ml, 4 times daily** ***Children under 3 months of age*** **A) The use in children under 3 months of age is not recommended** **B) single dose 2.5 ml, 4 times daily** **C) single dose 2.5 ml, 4 times daily** Indication b) *Adolescents and adults* A) 3 – 5 g, 3 times daily **D) single dose corresponding to 3 - 5 g of herbal substance, 3 times daily** The use in children under 12 years of age is not recommended (see section 4.4 'Special warnings and precautions for use'). To make a macerate, pour 150 ml of water (maximum temperature of 40°C) over the comminuted herbal substance. Steep for 30 minutes stirring frequently. The macerate should be used immediately after preparation. Reason: *Modification of dosages* The doses for adults of preparations B), C) and D) are adjusted to correspond to dose of products on the market e. g. marshmallow syrup Phytohustil[1] and Eibisch-Hustenpastillen[2]. The same applies to the doses for children respectively between 6 and 12 years and 3 and 6 years.	

	Note: The use of Althaeae radix is also supported by a recent placebo-controlled double-blind study (Rouhi and Ganji 2007), showing a significant improvement of cough severity and spirometry results. The preparation used is close to B). It documents the efficacy and safety of Althaeae radix. <u>*Use in children under 3 years old*</u> The use of *Althaea officinalis* as prepared in B) and C) in children up to 3 years old is supported by a long-term and extensive paediatric use in some EU countries. The clinical and pharmacovigilance data available attest the safety of the product. A recent post-marketing surveillance study on the use of marshmallow syrup in children aged up to 12 years, divided into three age groups (< 3 years, ≥ 3 to ≤ 6 years and > 6 to ≤ 12 years) showed a good efficacy and tolerability [Fasse et al. 2005]. In this study, about one third of the children included were younger than 3 years of age and the youngest patient was 3 months old. A clear and statistically significant improvement of all investigated symptoms of the irritating cough was found during the three-day treatment and surveillance period. A rapidly occurring and longer lasting alleviation of the coughing and cough-related symptoms was achieved in all age groups. The tolerability was assessed as "very good" and "good" to 97 % both by the physicians as well as by the patients and their parents." [Fasse et al. 2005]. Also the acceptance of marshmallow syrup by the children, including those under 3 years of age, was very high (99.7%) [Fasse et al. 2005]. This study was performed with children from 0 up to 12 years of age and reflects the fact that physicians and paediatricians recommend traditional herbal drugs like *Althaea officinalis* especially for children under 3 years of age. Together with other available documents cited below, it also reflects the long-term use (at least several decades) of *Althaea officinalis* syrup by parents to treat their infants and children. The study demonstrates efficacy, tolerability and acceptance of *Althaea officinalis* also in children younger than 3.	

	Additionally, over the past 70 years or so, there have been numerous reports on the use of marshmallow syrup in infants and children as illustrated in the following excerpts. Especially the preparations mentioned in the first two excerpts are consistent with the herbal preparations B), C), and D), mentioned in section 2.ii. - "---Medicinal Action and Uses---The great demulcent and emollient properties of Marsh Mallow make it useful in inflammation and irritation of the alimentary canal, and of the urinary and respiratory organs. The dry roots boiled in water give out half their weight of a gummy matter like starch. Decoctions of the plant, especially of the root, are very useful where the natural mucus has been abraded from the coats of the intestines, The decoction can be made by adding 5 pints of water to 1/4 lb. of dried root, boiling down to 3 pints and straining: it should not be made too thick and viscid. It is excellent in painful complaints of the urinary organs, exerting a relaxing effect upon the passages, as well as acting curatively. This decoction is also effective in curing bruises, sprains or any ache in the muscles or sinews. In haemorrhage from the urinary organs and in dysentery, it has been recommended to use the powdered root boiled in milk. The action of Marsh Mallow root upon the bowels is unaccompanied by any astringency. Boiled in wine or milk, Marsh Mallow will relieve diseases of the chest, constituting a popular remedy for coughs, bronchitis, whooping-cough, etc., generally in combination with other remedies. It is frequently given in the form of a syrup, which is best adapted to infants and children." [Grieve 1931 and 1971]. - In the "Handbook of the general and special medical description for physicians by Klemperer and Rost, fifteenth edition, 1929", a leading textbook for physicians of that time, the following instructions are given: "Sirupus Althaeae. Germ.., Austr., Dan., Helv., Jap., Nederl., Norv., Ross., Succ. Sciroppo di Alttea. Ital. Marshmallow syrup. (…) Internally used unmixed teaspoonwise as expectorans, especially for children (…).". - "The marshmallow syrup is prepared of the decoction of the	

	radix with sugar, which is usually given to children with catarrh." [Auerswald, 1920] - "Marshmallow syrup was a very popular cough mixture in paediatrics in prior times." [Pahlow, 1979] - "*Althaea officinalis*, application: Mucilage of catarrhs of the air passages and urinary tract, kidney disease and colitis, especially in the therapy of infants/children" [Hoppe, 1975] - "Recipes: for bronchitis of infants/children (according to Rost-Klemperer, 1929): Syrup Althaea 50,0 […]" [Madaus 1938] - And also in current literature, Marshmallow syrup is still recommended to children with dry cough and bronchitis as a traditional drug [e.g. Zehenter, 2008]. These texts document the traditional use of preparations according to B), C) and D) for children and infants. The safe and successful traditional use of these preparations in the paediatric population is covered by European tradition. For example, in Germany, Althaea preparations according to B), C) and D) are medicinal products which have been authorised by the BfArM and which are covered by the pharmacovigilance system for medicinal products. There have never been any safety concerns due to side effects or misuse in children, including those under three years of age. The extensive and well-documented European tradition of the use in children should be reflected in the HMPC monograph on *Althaea officinalis*. The exclusion of children under 3 years of use would deprive children, parents and physicians of valuable herbal medicinal products containing this plant. **Due to these facts, the sentence "the use in children under 3 years of age is not recommended" should be deleted.**	

4.2. Posology and method of administration	Indication a) The dose for adolescents and adults were adjusted to recommendations of BfArM for Phytohustili and to specifications of ESCOP Monographsii for Althaea radix dosage. With respect to a better uniformity between the factual use of existing products, as e.g. marshmallow syrup Phytohustil1 and Eibisch-Hustenpastilleniii, changes were incorporated. The age group of children under 3 years of age should be included in this monograph for traditional use for several reasons: 1) The efficacy and tolerability of marshmallow syrup was documented in a post-marketing surveillance with 313 children up to 12 years of ageiv. 100 of these children were under 3 years of age, the youngest patient was 3 months of age. Children, treated with this syrup showed "a clear and statistically significant improvement of all investigated symptoms of the irritating cough", including those under 3 years of age4. 2) *Althaea officinalis* is a well established medicinal product for children. Its application is assured by recommendations of physicians and paediatrics, which is reflected by the above mentioned study, done by infants and children. 3) The wide-spread application of marshmallow under medical advice is also backed by tradition, according to preparations B), C) and D) in infants and children are reported since 1920. Some citations are quoted in the following: 1920: "The marshmallow syrup is prepared of the decoction of the radix with sugar, which is usually given to children with catarrh." 1929: "Sirupus Althaeae. Germ., Austr., Dan., Helv., Jap., Nederl., Norv., Ross., Succ. Sciroppo di Alttea. Ital. Marshmallow syrup. […] Internally used unmixed teaspoonwise as expectorans, especially for children […]." 1931: "The great demulcent and emollient properties of Marsh Mallow make it useful in inflammation and irritation of the alimentary canal, and of the urinary and respiratory organs […]. It is frequently given in the form of a syrup, which is best adapted to infants and children." 4) Althaea syrup is still recommended for cough in paediatrics in current literatureviii. It was and still is a valuable drug for children, parents, physicians and paediatrics.	Partially endorsed. See answer to 4.2. on page 4.

	5) The antitussive activity of *Althaea officinalis* is mainly based on a temporary local physical effect, with no influence on expectoration nor adverse effects. This effect is mediated by the acidic polysaccharides contained in *Althaea officinalis*, which reduce the number of cough efforts, the cough intensity and the pain in neck and chest. The generally accepted principle of the effect of plant polysaccharides is their ability to protect the mucous membranes, respectively the cough receptors, by a layer against irritation (by exogeneous and endogenous tussigens). The polysaccharides only adsorb to epithelia and no transport to basal tissues occurs xv. So, the formation of such a layer is also the principle of action of *Althaea officinalis*. Comparable traditionally used products based on such plant polysaccharides, e.g. products from *Certraria islandica*, have the regulatory status of medicinal products and are safely used without restrictions regarding to age. Therefore, preparations of Althaea radix, which are safe drugs with good efficacy and tolerability, should be also recommended for children under 3 years of age. Due to the fact that other diseases are not masked, there are -especially for children- no reasons not to take this medicine for getting alleviation of cough at first before consulting a physician or paediatrician. Medical advice can definitely never be substituted only by medicine, independent from drug or age group of patients. Therefore the application of this herbal drug to children under 3 years of age should be included into this monograph for traditional use. <u>Proposed change</u>: Traditional use Posology Indication a) *Adolescents and adults* B) single dose 5 **- 10** ml, 3-6 times daily C) single dose 2 - 10 ml, 3-**6** times daily **D) single dose corresponding to 0.5 - 3 g of herbal substance, several times daily up to maximum daily dose of 15 g**	

	Children between 6 and 12 years of age B) single dose ~~2.5~~ **5** ml, 5 times daily C) single dose ~~1 – 1.5~~ **5** ml, ~~3~~ **5** times daily **D) single dose corresponding to 0.5 - 1 g of herbal substance, 3 times daily** *Children between 3 and 6 years of age* B) single dose ~~2.5~~ **5** ml, 4 times daily C) single dose ~~0.5 – 1~~ **5** ml, ~~3~~ **4** times daily **D) single dose corresponding to 0.5 - 1 g of herbal substance, 3 times daily** ***Children between 3 months and 3 years of age*** **A) The use in children between 3 months and 3 years of age is not recommended.** **B) single dose 3 ml, 4 times daily** **C) single dose 3 ml, 4 times daily** ***Children under 3 months of age*** **A) The use in children under 3 months of age is not recommended** **B) single dose 2.5 ml, 4 times daily** **C) single dose 2.5 ml, 4 times daily** ~~The use in children under 3 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').~~ Indication b) *Adolescents and adults* A) 3 – 5 g, 3 times daily **D) single dose corresponding to 3 - 5 g of herbal substance, 3 times daily**	

4.4 Special warnings and precautions for use	We propose to replace the following sentence: Traditional use: ~~The use in children under 3 years of age is not recommended because medical advice should be sought.~~ **Medical advice should be sought for children under 3 years of age.** Colds are the most frequently occurring diseases of children [6]. The dry irritating cough often occurs during the first three days of a cold and has no physiological benefit [6]. It is discomforting, causes pain in neck and chest and especially in children it leads furthermore to a stressful time, associated with restless nights for children and their parents [6, 11]. Althaeae radix is highly effective and well tolerated, also by children under 3 years of age [5, 6]. Its antitussive activity is mainly based on local physical effects mediated by acidic polysaccharides [13-15].This is the mechanism resulting in alleviation of cough and is very helpful for patients and moreover does not mask other diseases. We agree that especially children under 3 years of age are in need of special care. Independent of age or drug, a medicine can never replace medical advice. Because Althaeae radix does not mask other diseases, there is no counter-argument for children under 3 years of age not to take this drug at first before consulting paediatricians or physicians. Therefore children under 3 years of age should not be excluded. If there are nevertheless reasons for precaution for children in this age group, we propose the above mentioned sentence.	Not endorsed. The working party agreed that the treatment of cough in children below 3 years of age needs the supervision of a doctor. Since traditional herbal medicinal products are intended to be used without medical supervision, this restriction was included. Restriction of use for children below 3 years of age is not caused by safety concerns attributed to marshmallow preparations.

	Indication a) ~~The use in children under 3 years of age is not recommended because medical advice should be sought.~~ **Medical advice should be sought for children under 3 years old.** <u>Reason:</u> Children under the age of 3 years deserve special care and for this reason we propose the above-referred wording. In countries where medicines based on Althaea radix preparations according to B), C) or D) were used, no adverse events were reported although no such warning was included. The proposed warning intends to take care of eventual concerns expressed by Member States not having a similar medical tradition. The tradition of use of these preparations in younger children, as documented in Germany, is to a large extent based on prescriptions from general practitioners or medical specialists. This has also been documented in studies e.g. in the study of Fasse et al. [2005], where Althaea radix was used upon recommendation of physicians, especially paediatricians. In case the sentence "Medical advice should be sought for children under 3 years of age.", as proposed, should seem to be too unspecific, a wording like "Use in children under 3 years only after consultation of a physician." would also be acceptable	See answer above.
	Medicines can never replace medical advice for patients, independent of age group. Nevertheless, patients under 3 years of age require our special care. Due to the fact, that Althaea radix is highly effective and excellently tolerated, also in children under 3 years of age, and finally does not mask other diseases, the use in children under 3 years of age should not be restricted (see rational of point 4.2). <u>Proposed change</u>: Indication a) ~~The use in children under 3 years of age is not recommended because medical advice should be sought.~~ **Medical advice should be sought for children under 3 years of age.**	See answer above.

4.5 Interactions with other medicinal products and other forms of interaction	We suggest to substitute the following sentence: Traditional use: ~~Absorption of concomitantly administered medicines may be delayed. For this reason the product should not be taken ½ to 1 hour before or after intake of other medicinal products.~~ **None reported.** In the following a citation is quoted about the polysaccharide preparations from Althaeae radix by Alban and Blaschek (2007) [17]. The authors are accepted experts in polysaccharide chemistry: "The anionic polysaccharide fraction reduced the level of blood sugar in animal experiment. The last one could theoretically indicate that the resorption of concomitantly administered medicines may be delayed. However, the required concentration of polysaccharides will hardly be reached in practice."	Partially endorsed. Due to lack of clinical data, this information has been included into section 4.4 'Special warnings and precautions for use' as a precautionary measure.
	~~Absorption of concomitantly administered medicines may be delayed. For this reason the product should not be taken ½ to 1 hour before or after intake of other medicinal products.~~ **None reported.** <u>Reason:</u> From our point of view this statement is not supported by any scientific evidence derived from therapeutic use. No delayed absorption of concomitantly administered medicines can be demonstrated in current literature. E.g., in patients treated with ACE inhibitors and concomitantly administered *Althaea officinalis* a significant reduction in cough scores was achieved (double blind, randomized study). Interactions were not observed [Rouhi and Ganji 2007]. The efficacy of *Althaea officinalis* is based on acidic heteropolysaccharides, which are part of the mucilage [e.g. Capek et al 1987]. Marshmallow root preparations of dried root of *Althaea officinalis* contain 6.2-11.6% mucilage polysaccharides as described	See answer above.

	in the monograph of *Althaea officinalis* [Basch et al. 2003]. A significant proportion (27.8 %) of these mucilage polysaccharides are galacturonic acids [Franz 1966]. α-1-4 glycosidic linked D-galacturonic acids are also major components of pectins [Mukhiddinov et al. 2000, Sriamornsak 2003]. Pectins are not only present in the root of *Althaea officinalis* but also in apples (1-1.5% of fresh weight), apricots (1% of fresh weight) and carrots (1.4% of fresh weight). They are also used in the food industry and cosmetics as gelling agents, thickening agents and stabilising agents. In the European Union, pectins are accepted as food additives (E 440, according to Directive 95/2/EC) and commonly used, for example, in jam and jelly without any quantitative restriction. Limitations are defined for fruit juice (3 g/l), for acidulated infant formula (5 g/l) and for foods intended for consumption by babies and infants with gastrointestinal disorders (10 g/l). In comparison to this, a single dose of Althaea preparation B) contains a maximum of 0.025 g of mucilage polysaccharides, respectively 0.007 g galacturonic acids. For example, even food like an apple of 180 g contains a minimum of 1.8 g galacturonic acids, 200 ml of fruit juice contain 0.6 g galacturonic acids and even 100 ml of acidulated infant formula still contain 0.5 g galacturonic acids. In comparison to the high contents of pectins contained in common aliments, the proportion of acidic polypeptides in *Althaea officinalis* extract is negligible.	
	A delayed absorption of concomitantly with mucilage administered medicines would be theoretically possible, but it is not plausible for the small amounts of the ingested Althaea radix preparations. In comparison to ingested acidic polypeptides with food like apple, fruit juice or jelly, the additional proportion of acidic polypeptides of Althaea radix based on preparation B) is negligible. Acidic polypeptides -like pectins - are accepted and popular food additives in the European Union: fruit juice can contain a maximum of 3 g/l and even acidulated infant formula may comprise a maximum of 5 g/l. A single dose (10 ml) of Althaea radix based on preparation B) contains 0.025 g of mucilage polysaccharides, of which 0.007 g are	See answer above.

	galacturonic acids. Additionally in a recent placebo-controlled double-blind study with a Althaea radix preparation resembled to B), no delayed absorption of concomitantly administered medicines occured. Furthermore, there is a drug for the therapeutic indication "mild diarrhoea" (3.2g/100g pectins) in the market, which is recommended with a starting single dose of 0.5 g pectins. For this drug no interactions with other medicinal products or other forms of interactions are declared in the package leaflet. Since no adverse effects of Althaea radix in preparations and dosages of this monograph are verified, the declaration that none interactions are reported is appropriate. Proposed change: ~~Absorption of concomitantly administered medicines may be delayed. For this reason the product should not be taken ½ to 1 hour before or after intake of other medicinal products.~~ **None reported.**	
4.6 Pregnancy and lactation	We suggest to allow the usage in pregnancy and lactation: Traditional use: ~~In the absence of sufficient data, the use during pregnancy and lactation is not recommended.~~ **Due to generate safety considerations the herbal medicinal product should not be used in pregnancy and lactation without medical advice.** The restriction is not based on scientific data. Neither current literature nor pharmacological nor clinical data give any hint for potential safety concerns during pregnancy and lactation. Thus the administration should not be restricted. If there are nevertheless reasons for precaution, we propose the usage with medical advice. This is also in accordance with the ESCOP Monograph (2003) for Althaeae radix [2].	Not endorsed Since traditional herbal medicinal products are intended to be used without medical supervision, this restriction should be kept.

	Safety during pregnancy and lactation has not been established. ~~In the absence of sufficient data, the use during pregnancy and lactation is not recommended.~~ **Due to general safety considerations the herbal medicinal product should not be used without medical advice.** Reason: In the absence of reported adverse effects for *Althaea officinalis* containing medicines during pregnancy, and given that the pharmacological and clinical data do not give any indication of any potential safety concerns, the use should be allowed under the above mentioned conditions.	See answer above.
	In accordance with the ESCOP Monographs2, the use should be allowed with medical advice. The efficacy of Althaea radix drugs is based on local adsorbing polysaccharides to epithelia15 (see rational point 4.2), so there are no adverse effects or risks during pregnancy and lactations. This is also supported by current literature and pharmacovigilance data, where no adverse effects or potential safety concerns during pregnancy and lactations are reported. Therefore, restrictions of use in pregnancy and lactation are not based on any data or suspicions pointing to a potential harm for these patient groups. Therefore it would be rational not to include warnings for these patient groups. If, for precautional reasons, such texts are nevertheless rated as necessary, then the texts proposed here would seem to be adequate. Proposed change: Safety during pregnancy and lactation has not been established. ~~In the absence of sufficient data, the use during pregnancy and lactation is not recommended.~~ **In accordance with general medicinal practice, the product should not be used during pregnancy and lactation without medical advice.**	See answer above.