12 July 2016
EMA/HMPC/339714/2016
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Althaea officinalis* L., radix (EMA/HMPC/436679/2015)

Final

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Althaea officinalis* L., radix as released for public consultation on 15 December 2015 until 15 March 2016.

	Organisations and/or individuals
1	Association of the European Self-Medication Industry (AESGP)
2	AGON Pharma GmbH
3	Diapharm GmbH & Co. KG
4	Pharmaceutical Manufacturing Company GEMI Nowakowski Grzegorz

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 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
AESGP	AESGP generally welcomes the update of the European Union herbal monograph on Althaea officinalis L., radix as we appreciate harmonised assessment criteria.	
Diapharm	Diapharm welcomes the update of this community herbal monograph which may provide further harmonised assessment criteria for Althaea officinalis L., radix. We thank for the opportunity to provide our input which you will find as follows:	
Diapharm	Diapharm would like to ask for a clarification regarding the classification of the age group “children 6-12 years of age” versus “children 6-11 years of age”. Recently the HMPC monograph on Hedera helix L., folium (EMA/HMPC/586888/2014) has been changed. The former age group of “children 6-12 years of age” has been revised to “children 6-11 years of age”. If this is a general change this should be taken into consideration of this HMPC monograph in question.	Endorsed Classification of the children age groups has been adapted according to EMEA/CHMP/PEG/194810/2005.

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
EU Monograph 2. Qualitative and quantitative	GEMI Poland	We propose Macerate for preparation of syrup[3]. **[3]Corresponding to 2–6g of herbal substance/100 g of syrup** and prepared in accordance with the pharmacopoeial	Not endorsed Reference to the Polish pharmacopoeias in the EU monograph is considered sufficient. Amount of the herbal substance and corresponding amount of syrup

Section number and heading	Interested party	Comment and Rationale	Outcome
composition; Traditional use ii) Herbal preparation c)		monographes for Sirupus althaeae in Osterreichisches Arzneibuch 1981, Ceskoslovensky lekopis 1954, Farmakopea Polska 1970 and 2002 or with the monograph Eibischsirup in Deutscher Arzneimittel-Codex 1979.	is included in section 4.2 Posology
EU Monograph 4.2 Posology and method of administration	AESGP	The draft of the HMPC monograph differentiates between oral and oromucosal use for the different preparations. Thus, preparations which contain Marshmallow root dry extract could not be used for oral use even if they are administered as a liquid dosage form or herbal instant teas. This is also true for solid dosage forms for oral or oromucosal use like tablets or lozenges. However, such dosage forms seem to be favourable for the proposed indication 1). Furthermore, the usage of dry extract can have many advantages regarding quality control and stability of corresponding products. Besides marshmallow root dry extracts have been used in oral drops (see HMPC assessment report EMEA/HMPC/98718/2008), in herbal instant teas (e.g. Heumann Bronchialtee Solubifix[1]) or in tablets[1] or capsules[1] for more than 30 years. The revised HMPC monograph of 2015 states: **Posology** Oral use Preparation a) Preparation b) Preparation c)	Endorsed Method of administration has been changed to oral and oromucosal use for all preparations in indication 1).

Section number and heading	Interested party	Comment and Rationale	Outcome
		Preparation e) Oromucosal use Preparation d) **Method of administration** Preparations a) b), c) and e) Oral use Preparation d) Oromucosal use The macerate should be used immediately after preparation. We suggest continuing the approach of the existing monograph. Thus, it should not be differentiated between oral and oromucosal use for preparations a), b), c), d) and e). <u>Proposed change</u> **Posology** Oral or oromucosal use Preparation a) Preparation b) Preparation c) Preparation d) Preparation e)	

Section number and heading	Interested party	Comment and Rationale	Outcome
		Method of administration Preparations a), b), c), d) and e) Oral or oromucosal use The macerate should be used immediately after preparation.	
4.2 Posology and method of administration	Diapharm	We suggest not to differentiate between oral and oromucosal use in consideration of the described preparations a), b), c), d) or e). The HMPC monograph of 2009 does not differentiate between oral and oromucosal use for the preparations a) to d). The revised HMPC monograph of 2015 states: **Method of administration** Preparations a) b), c) and e) Oral use Preparation d) Oromucosal use The macerate should be used immediately after preparation. Reason: As one consequence preparations which contain *Althaea radix* dry extracts could not be used for oral use even if they are administered as a liquid dosage form. With regard to scientific view syrups or other liquid or viscous dosage forms are optimal dosage forms for the proposed indication of symptomatic treatment of oral or pharyngeal irritation and associated dry cough. The compliance is enhanced and the	Endorsed Method of administration has been changed to oral and oromucosal use for all preparations in indication 1).

Section number and heading	Interested party	Comment and Rationale	Outcome
		administration is easier e.g. for elder people or for children under 6 years of age. Proposed change **Method of administration** ~~Preparations a) b), c) and e)~~ ~~Oral use.~~ ~~Preparation d)~~ ~~Oromucosal use.~~ **Oral or oromucosal use.** The macerate should be used immediately after preparation.	
EU Monograph 4.2 Posology and method of administration	AESGP	We suggest to reformulate the posology and method of administration for preparation d) dry extract (DER 3-9:1), extraction solvent water, in accordance with the posology provided in HMPC monograph of 2009. Aqueous dry extracts are extracted with cold water resp. water of room temperature. Thus, such extracts are very comparable to Herbal teas prepared as a macerate. Therefore, the posology of preparations a) and d) should be identical. In the draft monograph modified doses for children 6-12 years of age, adolescents, adults and elderly are given in terms of defined amount of native dry extract. Existing products on the market containing Marshmallow root dry extracts would be out	Partially endorsed. Posology has been changed in accordance with the current HMPC monograph of 2009; nevertheless, the use of solid dosage forms in children under 6 years of age cannot be recommended. According to the Reflection paper EMA/CHMP/194810/2005 (page 11) lozenges are only likely to be an acceptable dosage form for older children.

Section number and heading	Interested party	Comment and Rationale	Outcome
		of the scope of the monograph. Additionally, the current maximum daily dose proposed by the HMPC monograph of 2009 is supported by both the ESCOP[2] and WHO[3] monograph on Althaea radix. Also the ESCOP and WHO monograph on Althaea radix propose a maximum daily dose equivalent of up to 15g of the herbal substance for the relief of dry cough and oral or pharyngeal irritation. Therefore, we propose to state the posology in accordance with the current HMPC monograph of 2009 as given below: **d) Dry extract (DER 3-9:1)** Indication 1) Adolescents, adults and elderly 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 The use in children under 3 years of age is not recommended	

Section number and heading	Interested party	Comment and Rationale	Outcome
		(see section 4.4 'Special warnings and precautions for use').	
EU Draft Monograph 4.2 Posology and method of administration	AGON Pharma	In contrast to the previous Monograph the draft of the HMPC monograph differentiates between oromucosal and oral use for different herbal preparations. Due to this, preparations which contain Marshmallow root **dry extract** could, according to the draft Monograph not be applied orally even if they are administered as a liquid dosage form, a lozenge or as an oral gum. However, these types of dosage forms are to be considered very useful for the proposed indication. What is more, use of dry extracts has considerable advantages in terms of stability and quality control of the herbal preparation as well as corresponding dosage forms. We would like to stress that Marshmallow root dry extracts have been used in oral drops (see HMPC assessment report EMEA/HMPC/98718/2008), in herbal instant teas as well as in tablets or capsules for more than 30 years. However, comparable long-term usage cannot be shown for "oromucosal" use of such extracts, so it is difficult to understand, why oromucosal use should be considered traditional. What is more we would like to point out in reference to Ph.Eur. Sections 5.1.4 and 5.1.8 regarding microbiological quality, that for oromucosal preparations Ph.Eur. section 5.1.8 regarding "Microbiological quality of herbal medical products for oral use…" is not applicable (see Table 5.1.4-1. Acceptance criteria for microbiological quality of non-sterile dosage forms and	Partially endorsed Herbal medicinal products containing mucilage polysaccharides are traditionally used in a form of lozenges as a demulcent for the symptomatic treatment of oral or pharyngeal irritations and associated dry cough (see EU monograph for Cetraria islandica (L.) Acharius s.l., thallus). According to the definition of Ph.Eur. lozenges and pastilles are solid, single-dose preparations intended to be sucked to obtain, usually, a local effect in the oral cavity and the throat. As the mucilage contained in the products creates a kind of protective layer on the mucosa which protects it from local irritation, the dosage forms lozenges or pastilles are considered suitable for this purpose. Method of administration for all preparations in indication 1) has been changed to oral and oromucosal use. Microbiological quality of the finished product, as well as choice of the dosage form and excipients is in full responsibility of the registration holder. A traditional herbal medicinal product in a form of lozenges containing dry extract from Althaea officinalis L., radix

Section number and heading	Interested party	Comment and Rationale	Outcome
		Ph.Eur. Section 5.1.8). This means, that criteria for oromucosal use would apply for herbal medicinal products (TAMC 10^2, TYMC 10^1, absence of S. aureus and P. aeruginosa) which are impossible to fulfil for such preparations and at the same time no test for Salmonellae (as is required for oral forms containing herbal preparations) would be necessary. From our point of view this is not an appropriate categorization for dosage forms containing dry extract from herbal drugs like preparation d). Please note, that direct application of lozenges or oral gums to the affected area is not intended and not desirable, what makes these forms oral (and not oromucosal) dosage forms. Additionally the use of acacia-gum based dosage forms (oral gums), which are typical and especially well-suited for Althea dry extracts as for example preparation d) would be virtually impossible if such dosage forms were considered “oromucosal”. Due to the natural origin of acacia gum and the microbial limits defined by the corresponding Ph.Eur. Monograph 07/2015:0307 “Acacia”, especially regarding TYMC (10^4) use of this excipient in a dosage form considered “oromucosal” is not feasible. Please take into consideration that acacia gum has been and is being used for many years under the regulation given for oral dosage forms according to Ph.Eur. section 5.1.8. without any problems connected with potential microbiological contaminations. The Draft-revision HMPC monograph of 2015 states:	is already on the European market.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Posology Oral use a) Comminuted herbal substance b) Liquid extract (DER 1:19.5-23.5) c) Macerate for preparation of syrup e) Liquid extract (DER 1:1) Oromucosal use d) Dry extract (DER 3-9:1) **Method of administration** Preparations a) b), c) and e) Oral use Preparation d) Oromucosal use The macerate should be used immediately after preparation. Based on the above mentioned facts we strongly suggest to not differentiate between oral and “oromucosal” use for preparations a), b), c), d) and e) but to describe the application as “oral use” for all preparations including the dry extract (preparation d)). <u>Proposed change</u> **Posology** Oral use	

Section number and heading	Interested party	Comment and Rationale	Outcome
		a) Comminuted herbal substance b) Liquid extract (DER 1:19.5-23.5) c) Macerate for preparation of syrup d) Dry extract (DER 3-9:1) e) Liquid extract (DER 1:1) **Method of administration** Preparations a), b), c), d) and e) Oral use The macerate should be used immediately after preparation.	
4.2 Posology and method of administration	Diapharm	We suggest not to differentiate between oral and oromucosal use in consideration of the described preparations a), b), c), d) or e). The HMPC monograph of 2009 does not differentiate between oral and oromucosal use for the preparations a) to d). The revised HMPC monograph of 2015 states: **Method of administration** Preparations a) b), c) and e) Oral use Preparation d) Oromucosal use The macerate should be used immediately after preparation. Reason: As one consequence preparations which contain	Endorsed Method of administration has been changed to oral and oromucosal use for all preparations in indication 1).

Section number and heading	Interested party	Comment and Rationale	Outcome
		Althaea radix dry extracts could not be used for oral use even if they are administered as a liquid dosage form. With regard to scientific view syrups or other liquid or viscous dosage forms are optimal dosage forms for the proposed indication of symptomatic treatment of oral or pharyngeal irritation and associated dry cough. The compliance is enhanced and the administration is easier e.g. for elder people or for children under 6 years of age. Proposed change **Method of administration** ~~Preparations a) b), c) and e)~~ ~~Oral use.~~ ~~Preparation d)~~ ~~Oromucosal use.~~ **Oral or oromucosal use.** The macerate should be used immediately after preparation.	
EU Monograph 4.4 Special warnings and precautions for use	AESGP	As a consequence of the previous comments, the restriction of the use of preparation d) dry extracts in children under 6 years of age should be withdrawn, as dry extracts could also be used in liquid dosage forms or herbal instant tees. Furthermore, based on the EMA Reflection paper: formulations of choice for the paediatric population[4] (2006), page 22, tablets, i.e. lozenges and orodispersable dosage forms have	Not endorsed. See an explanation in section 4.2.

Section number and heading	Interested party	Comment and Rationale	Outcome
		favourable applicability for children from 2 to 5 years old and older. Therefore, we suggest to maintain the “a-posology” for children of age between 3 and 6 years as it is laid down in the current monograph as follow: Proposed change: withdrawal of the following advice Indication 1) ~~**Preparations a), b) and c)**~~ ~~The use in children under 3 years of age is not recommended because of concerns requiring medical advice.~~ ~~**Preparation d)**~~ ~~The use in children under 6 years of age is not recommended when administered as a solid dosage form.~~ **Preparations a), b), c) and d)** The use in children under 3 years of age is not recommended because of concerns requiring medical advice.	
4.4 Special warnings and precautions for use	Diapharm	We suggest to change the special warning for preparation d) (with reference to the above mentioned changes in part 4.2 Posology and method of administration): Proposed change	Endorsed However, slightly different wording is used: “The use of the solid dosage form in children under 6 years of age is not recommended because of the

Section number and heading	Interested party	Comment and Rationale	Outcome
		Preparation d) The use in children under 6 years of age is not recommended ~~because of the pharmaceutical form (solid dosage form)~~ **when administered in a solid dosage form.**	pharmaceutical form."
Assessment report 2.1.1. Information about products on the market in the EU/EEA Member States	AESGP	Please note that under herbal preparation d) Dry extract (DER 3-9:1) extraction solvent water, are also comprised herbal preparations with DER 3-7:1, 3-1:1 and 7-9:1. (see HMPC assessment report, Doc. Ref.: EMEA/HMPC/98718/2008, page 5/21 for more information). For this reason, we suggest to add in 2.1.1. Table 2 dry extracts with DER 3-7:1, 3:1 and 7-9:1. Hereby it gets clear, that DER 3-9:1 has to be seen as a possible range and extracts with a more narrow range of the DER are also covered by this monograph.	Partially endorsed A possibility to use a narrow range of the DER has been added to the EU monograph as a footnote 4.
Assessment Report 3.4 Overall conclusions on non-clinical data	AESGP	The 3rd paragraph of this section states the following: *"A negative test on genotoxicity has been provided; however the preparation of the test was not sufficiently described and therefore results of the test cannot be taken into consideration."* We would like to provide the following missing information about the preparation used in the AMES test: it is a **liquid extract (solvent water) of *Althaea officinalis* L. radix (Marshmallow root), DER 1:12.**	The DER of the extract tested in the Ames test does not correspond to any of the preparations included in the EU monograph. The phytochemical similarity of the extract tested in the Ames test to the preparations included in the monograph has been neither discussed nor demonstrated. Therefore the data cannot support the EU list entry.
Assessment	GEMI Poland	In Assessment Report on Althaea Officinalis L., Radix Doc. Ref.: EMEA/HMPC/98718/2008 London, 14 May 2009. In Information	Not endorsed. The products referred by the company cannot be included into the EU monograph as 30 years

Section number and heading	Interested party	Comment and Rationale	Outcome
Report Legal status		on legal status of products containing Althaea Officinalis L., Radix in member states, 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 10 ml 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 2-4 times daily.** In final community herbal monograph on *Althaea officinalis* L., Radix; Committee in herbal medicinal products (HMPC) Doc. Ref.: EMEA/HMPC/98717/2008, London, 14 May 2009, the qualitative and quantitative composition for traditional use in point 2.ii)C) Herbal preparations – syrup prepared from macerate, corresponding to 2–**6,5 g of herbal substance/100ml.** During the review on this monograph in draft version of 11 December 2015 for public consultation the point 2.ii) c) **has been changed** to Macerate for preparation of syrup[3]. [3]Prepared in accordance with the pharmacopoeial monographs	of traditional use has not been demonstrated for these two products.

Section number and heading	Interested party	Comment and Rationale	Outcome
		for Sirupus althaeae in Österreichisches Arzneibuch 1981, Ćeskoslovenský lékopis 1954, Farmakopea Polska 1970 and 2002 or with the monograph Eibischsirup in Deutscher Arzneimittel-Codex 1979. There is no mention in Draft – revision on Assessment report on *Althaea officinalis* L., radix about the version of Althaea syrup marketed in **Poland**. The syrup was prepared from macerate made **6 g Althaeae radix on 100 g of the product**. The draft of monograph and Assessment report deleted these information without justification. Pharmaceutical Manufacturing Company GEMI Nowakowski Grzegorz in Poland is the only one manufacturer and Marketing authorization holder in Europe that manufactures and markets this composition of 6 parts of marshmallow root for syrup. In 1998 Gemi applied to Registration Agency in Poland to marketing authorization of three syrup: RUBITAL FORTE, Althaeae radicis maceratio, 1.73 g/5ml syrup, DER 9:40, extraction solvent water with ethanol (46.7:1), **was registered on 15th of June 2000**, **Marketing authorisation No. 8147.** ALTE FORTE 6 PARTS OF MARSHMALLOW ROOT (previous name: ALTHAGEM), Althaeae radicis maceratio, 2.36 g/5ml syrup, DER 6:36, extraction solvent water with ethanol (47.9:1), **was registered on 15th of June 2000, Marketing**	

Section number and heading	Interested party	Comment and Rationale	Outcome
		authorisation No. 8148. In our opinion reception of the syrup containing 5 parts of marshmallow root was entered to Farmakopea Polska V 2002 bypassing procedures. While in Farmakopea Polska IV and in all pharmacopoeial monographs of marshmallow syrup in European countries only 2 parts of marshmallow root was use. After GEMI application of syrups containing 6 part of root, the reception of syrup in Farmakopea Polska V suddenly changed from 2 to 5 parts of root. **In this connection GEMI Pharmaceutical Manufacturing Company Nowakowski Grzegorz kindly requests to complete the revision of European Union herbal monograph on Althaea officinalis L., radix about information of syrups in Poland that are in traditional use on Polish market from the year 2000:** **RUBITAL FORTE** 100 g of syrup contains 26,6 g macerate from 9 g marshmallow root (Althaeae radicis maceratio 9:40). Extraction solvent – water and ethanol with sodium benzoate (46,7:1:0,3). ALTE FORTE 6 PARTS OF MARSHMALLOW ROOT 100 g of syrup contains 36 g macerate from 6 g marshmallow root (Althaeae radicis maceratio (6:36), extraction solvent water and ethanol (47,9:1), with benzoic acid.	