05 June 2018
EMA/HMPC/230276/2016
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix (EMA/HMPC/560961/2010)

Final

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monograph on *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix as released for public consultation on 26 October 2015 until 31 January 2016.

	Organisations and/or individuals
1	Dr. Willmar Schwabe GmbH & Co. KG
2*	Dr. Peter Kardos, M.D., Prof. Heinrich Matthys, M.D., Ph.D. and Prof. Wolfgang Kamin, M.D., Ph.D.
3*	Prof. Dr. Walter Lehmacher and Dr. Siegfried Lehrl

**Note: Provided comments only concerning the draft revised assessment report*

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome
Dr. Willmar Schwabe GmbH & Co. KG	We refer to our comments to the draft assessment report. We are convinced that the statistically significant superiority of Pelargonium extract EPs® 7630 over placebo in the pivotal clinical trials is clinically relevant and that the WEU status for the indication "acute bronchitis" is justified, in particular when the same criteria are applied as for other monographs in the same therapeutic area.	WEU indication cannot be accepted because clinically relevant effects have not been demonstrated. The rationale is provided in the Assessment Report. All comments related to the draft revised Assessment report have been taken into consideration and addressed as appropriate in the version revised after public consultation.
	Additionally, we suggest maintaining the indication "common cold" on the THMP level. There is precedence for the parallel status of the same active ingredient as both traditional and well-established use with different indications (Draft European Union herbal monograph on *Thymus vulgaris* L. and *Thymus zygis* L., herba and *Primula veris* L. and *Primula elatior* (L.) Hill, radix.) Therefore we propose the following wording for chapters 2-4.1:	Not relevant. See above.
Dr. Willmar Schwabe GmbH & Co. KG	In the first version of the HMPC monograph Pelargonium root extract of 2012, the well-established use for the indication "acute bronchitis" was rejected with the following rationale: "In conclusion, this indication cannot be accepted at well-established use level because the studies did not use a reliable and very important endpoint such as the use of antibiotics instead a non-validated score which is not considered a reliable instrument to evaluate the efficacy of	The adaption of Bronchitis Severity Scale (BSS) as validated method for clinical evaluation of medicines used in patients in the therapeutic area 'cough and cold' has not meant automatic acceptance of all the studies which used this method. According to HMPC meeting report (7 June 2013,

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	Pelargonium." (Assessment report, page 39.) Dr. Willmar Schwabe submitted data on the validity of the Bronchitis Severity Scale (BSS) which were evaluated by the HMPC. In June 2013, the HMPC then announced that it considers the BSS to be an acceptable, valid measurement instrument (7 June 2013, EMA/HMPC/301544/2013). As a consequence, a fifth **ivy extract** (that was previously assigned THMP status) was subsequently assigned WEU status based on a comparative study with the medicinal product Prospan® using the BSS as rating scale. Moreover, the WEU status **for three thyme / primula** combinations has been proposed in the recently published draft monograph (Thymus vulgaris L. and Thymus zygis L., herba and Primula veris L. and Primula elatior (L.) Hill, radix EMA/HMPC/130038/2010), again based on the acceptance of the validation of the BSS. It is unclear why the BSS data relating to these products are considered sufficient to support the well-established use status of the products concerned but not that of Pelargonium root extract itself.	EMA/HMPC/301544/2013): "Starting from July 2013, the HMPC checked consequences for existing monographs in this therapeutic area, according to each respective data situation, in line with the 'Reflection paper on the reasons and timelines for revision of final Community herbal monographs and Community list entries. Comment not specific for the monograph on Pelargonii radix.
Dr. Willmar Schwabe GmbH & Co. KG	In support of the WEU Monograph of Pelargonium root extract, Dr. Willmar Schwabe submitted comprehensive data on our clinical studies. Based on the acceptance of the BSS as a validated scale, the statistical superiority of our extract EPs® 7630 over placebo has been clearly recognised by the assessor. Unexpectedly, as a new obstacle for granting the WEU status, the clinical relevance of the study results is now being questioned. In our opinion, *the criterion for the clinical relevance applied* by the Clinical Assessor (i.e. not less than 20% of the theoretically achievable maximum BSS score of 20 points) **is not appropriate**. **In any case, there is no uniform**	It is agreed that the definition of the clinical relevance should be determined for each therapeutic field, for every clinical study individually **already before the start of the study**, under consideration of the circumstances of the specific patient population. The suggestion of **comparison the BSS (day 0) total score at baseline with the BSS total score at study end** (day 7) under consideration of the proposed 20% difference **cannot be accepted** since the milder the

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	definition of clinical relevance. It has to be defined for each therapeutic field individually, **under consideration of the circumstances of the specific patient population. Even if a 20% difference were taken as being clinically relevant**, **the mean change from baseline would be appropriate**, **as this takes the patients' clinical condition in the trials into consideration**. In fact, the difference between the mean scores in the verum and the placebo groups on day 7 in our studies exceeds 20% of baseline. We believe that this difference clearly demonstrates clinical relevance (details presented below).	disease is the smaller difference is considered clinically relevant. Since acute bronchitis a self-limiting disease a strong effect is needed *(details presented in the revised assessment report).* It is a correct that several clinical study reports were provided. Indeed, there are more clinical studies for Pelargonii radix preparations than for other herbal substances of the same therapeutic area clinically tested using the BSS (e.g. Ivy or thyme-primula combinations). However, not the number of the performed studies determines the effectiveness.

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
2. Qualitative and quantitative composition	Schwabe	**Well-established use:** With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix (Pelargonium root) i) Herbal substance Not applicable ii) Herbal preparations	Not endorsed. See above.

Section number and heading	Interested party	Comment and Rationale	Outcome
		Liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m) Dry extract, (DER 4-25:1), extraction solvent ethanol 11% (m/m) **Traditional use** With regard to the registration application of Article 16d(1) of Directive 2001/83/EC *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix (Pelargonium root) i) Herbal substance Not applicable ii) Herbal preparations Herbal preparations in liquid or solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term. Liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m) Dry extract, (DER 4-25:1), extraction solvent ethanol 11% (m/m)	Endorsed.
3. Pharma-ceutical form	Schwabe	**Well-established use:** Herbal preparations in liquid or solid dosage forms for oral use.	Not endorsed. See above.

Section number and heading	Interested party	Comment and Rationale	Outcome
		The pharmaceutical form should be described by the European Pharmacopoeia full standard term. **Traditional use:** Herbal preparations in liquid or solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term. Herbal preparations in liquid or solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.	Endorsed.
4. Clinical particulars **4.1. Therapeutic indications**	Schwabe	**Well-established use:** Herbal medicinal product for the symptomatic treatment of acute bronchitis. Liquid extract (DER 1:8-10), extraction solvent ethanol 11% (m/m) Dry extract, (DER 4-25:1), extraction solvent ethanol 11% (m/m) **Traditional use:** Traditional herbal medicinal product for the symptomatic treatment of common cold.	Not endorsed. See above. Acute bronchitis' is considered to be an inappropriate terminology and if WEU could be accepted the wording in the monograph would be similar to other cough medicine on the WEU side: Herbal medicinal product for the relief of productive cough associated with mild to moderate acute respiratory tract infection". Not endorsed. See above. Endorsed.

Section number and heading	Interested party	Comment and Rationale	Outcome
		The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.	