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Committee on Herbal Medicinal Products (HMPC)

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# monograph on *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix (EMA/HMPC/560962/2010)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Pelargonium sidoides* DC and/or *Pelargonium reniforme* Curt., radix as released for public consultation on 15 April 2011 until 15 August 2011.

| | **Organisations and/or individuals** |
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| 1 | The Association of the European Self-medication Industry (AESGP) |
| 2 | Diapharm Regulatory Services GmbH, Germany |
| 3 | European Scientific Cooperative on Phytotherapy (ESCOP) |
| 4 | Frutarom Switzerland Ltd (FRCH) |
| 5 | Interest group Pelargonium:<br>Finzelberg GmbH & Co.KG, Agon GmbH and PhytoCon GmbH, Germany |
| 6 | Laboratoires Pierre Fabre, France |
| 7 | Dr. Willmar Schwabe GmbH & Co.KG, Germany |



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## General comments to draft document

Table 2: Discussion of comments

| Interested party | Comment and Rationale | Outcome |
|---|---|---|
| Diapharm | Diapharm welcomes the preparation of this Community herbal monograph which may provide harmonised assessment criteria for Pelargonium products and thus facilitate mutual recognition in Europe. In particular, we welcome that traditional use has been clarified in this monograph. | |
| ESCOP | ESCOP welcomes the draft Community herbal monograph on Pelargonium sidoides DC and/or Pelargonium reniforme Curt., radix accompanied with companion documents (draft assessment report and draft reference list), prepared by the Committee on Herbal Medicinal Products (HMPC).<br><br>The herbal preparation listed in the draft Community herbal monograph has been used through many decades in Germany and was first described in the Rote Liste as the active substance of the drug product "Umckaloabo-Stevenskur®" in 1939. Up to 2005, the product "Umckaloabo®" had a Traditional Use Registration.<br><br>The draft monograph and the draft Assessment Report do not reflect properly the long standing use conditions and recommendations of the drug substance, mainly regarding the therapeutic indication, recommended single and daily doses and the paediatric use in children below 6 years of age. Justifications and proposals for changes are given below. | For outcomes of comments on the therapeutic indication, posology and paediatric use see section *Specific comments on text.* |
| Interest group Pelargonium | On page 6/38 of the Assessment report on Pelargonium sidoides DC and/or Pelargonium reniforme Curt., radix (Draft) the extract of P. sidoides. EPs® 7630 is stated as "quantified". From our point of view the extract shall be classified as an "other extract", as constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity are not known. | Endorsed. |

| Interested party | Comment and Rationale | Outcome |
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| Interest group Pelargonium | On page 14/38, section 2.3, of the Assessment report on Pelargonium sidoides DC and/or Pelargonium reniforme Curt., radix (Draft) it is stated that according to the market overview, one extract (DER 1:8-10, extraction solvent: ethanol 11% m/m) of Pelargonii radix has been on the market for more than 30 years with the indication acute bronchitis (see product no. 4 in the German market overview, section 1.2).<br>However, on the same page, section 2.1, the information is given that Umckaloabo received a full market authorization by the German drug regulatory agency in 2005. Until this time, a tincture 1+10 from P. sidoides/reniforme was used. From 2005 the ingredients changed to a solution of P. sidoides (Brendler and van Wyk, 2008). Thus, the changes in the ingredients have not been assessed to be significant, as the procedure of re-registration ("Nachzulassung") was accepted by the BfArM. Otherwise this would have caused a new application.<br>It should be clarified, that the traditional extract (before 2005)<br>- was a tincture 1+10 from P. sidoides/reniforme;<br>- had the following indication: Acute and chronic infections, particularly infections involving the respiratory organs and ear-nose-throat areas, e.g. bronchitis (inflammation of the bronchi), sinusitis (inflammation of the paranasal sinuses), angina tonsillaris (infection of the tonsils) and anginopharyngitis (inflammation of the nose and throat),<br>- had the following dosage:<br>With acute infections, adults and children over 12 years take 20-30 drops 3 times/day.<br>Follow-up treatment, particularly with chronic illness or frequent relapses: 10-12 drops 3 times/day.<br>With acute infections, adults and children over 6-12 years take 10-20 drops 3 times/day.<br><br>Children under 6 years take 5-10 drops 3 times/day depending on age. | Indications and posology of the mentioned extract have been changed several times. The monograph on Pelargonii radix is based on the assessment of all these data, beyond those cited here. |

| Interested party | Comment and Rationale | Outcome |
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| FRCH | It was noted that an existing THR-certificate for DioCold and DioPelargo tablets was not considered in the draft monograph (THR 33518/0017-0018) During the evaluation of the application above, Traditional use was sufficiently demonstrated for pelargonium preparations. | All the data provided by national authorities were considered in the monograph. The list of preparations was updated according to the data received from the MHRA. However, the most important prerequisite to the preparation of a traditional use monograph is the proof of traditional use, complying with the Directive 2004/24/EC. Single decisions of national authorities on traditional use registrations are not assessed. |
| FRCH | In our view "traditional use" cannot be applied to extracts with substantial published clinical data. Those data should serve as proof for "established use" | The criterion for the preparation of a traditional use monograph is the proof of traditional use. Available clinical data are not disqualifying reasons for the preparation of a traditional use monograph. |
| Laboratoires Pierre Fabre | The Laboratoires Pierre Fabre appreciate the draft for a community herbal monograph on *Pelargonium sidoides DC* and/or *Pelargonium reniforme* prepared by the Committee on Herbal Medicinal Products (HMPC).<br><br>*However we have comments to § 2 Qualitative and quantitative composition and § 4.2 Posology and method of administration.* | |
| Schwabe | We and one of our affiliates are MAH of herbal medicinal products (liquid and solid pharmaceutical forms) containing *Pelargonium sidoides* extract (EPs® 7630) with the indication "acute bronchitis" in 7 EU member states. As our marketing authorizations in Romania, Bulgaria, Lithuania and Latvia are missing in the draft assessment report section 1.2 , we would request you to amend the corresponding table accordingly. In addition to that, we are registration holder of several traditional herbal medicinal products referred to in the draft assessment report section 1.2.<br><br>The active substance of all products is the same, namely *Liquid extract of Pelargonium sidoides roots (1 : 8-10), extraction agent: ethanol 11 % (m/m).* | All the data provided by national authorities were considered in the monograph. The assessment report can be amended only in case the Company provides all the necessary data (Preparations, Pharmaceutical form, Posology, Indication, Legal status, Since when is on the market). However, the inclusion of further, recently authorized products does not influence the preparation of a traditional use monograph. |

| Interested party | Comment and Rationale | Outcome |
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| | In manufacturing of solid or of alcohol-free liquid formulations the active substance is dried by adsorption onto an inert solid substance.<br>We welcome the majority assessment that the above active substance has a long tradition, but we strongly disagree with the negative assessment regarding the well-established use of the indication acute bronchitis. In contrast to the assessment (page 35 of the draft assessment report) we are convinced that the efficacy of *Pelargonium sidoides* extract (EPs® 7630) in patients with acute bronchitis has been clearly proven by randomised, double-blind, placebo-controlled clinical trials. Thus and also in the light of the efficacy assessments of other herbal substances/preparations in the respiratory area for which a well-established use was granted in a Community monograph (e.g. Hedera helix or Echinacea purpurea), the well-established use of *Pelargonium sidoides* extract (EPs® 7630) for treatment of acute bronchitis should also be granted in the Community monograph.<br><br>In accordance with Directive 2001/83/EC for EPs® 7630 a clinical drug development program has been set up and carried out which involved all required and necessary steps like studies in healthy volunteers and in patients with acute bronchitis to determine dosage, efficacy, safety and tolerability of EPs® 7630 compared to placebo and also to comparators. Broad study programs have been performed in adults on one hand and – in addition to that anticipating the spirit of the new European paediatric legislation as laid down in Directive 2006/1901/EC - specifically in children and adolescents on the other hand. In children and adolescents for several studies conducted three additional subgroup analyses confirmed the positive results for the total study population in the respective trials for subgroups of patients less than 7 years, between 7 and 12 years and above 12 years old.<br><br>The total drug development program for EPs® 7630 included a clinical part conducted in adults and an additional part conducted in children and adolescents as well as studies of the different required phases. In a phase-I-study healthy | Taking into account all the available clinical data, it was concluded that although there is remarkable evidence on the beneficial effects of the cited product, no indications can be accepted at well-established level in the course of the preparation of a Community Monograph.<br><br>We acknowledge the vast amount of clinical trials carried out products containing liquid extract of Pelargonium sidoides roots (1 : 8-10), extraction agent: ethanol 11 % (m/m) ) (or the dried liquid extract). These studies are included in the updated assessment report.<br><br>We acknowledge the importance of the BSS as appropriate tool for evaluation of clinically relevant symptom changes in patients with acute bronchitis. However, since this is a non-validated score, it was decided that as primary outcome measure is not sufficient to support the well-established use of the cited product.<br><br>All the studies focussing on acute bronchitis had changes in this non-validated symptom score as a primary endpoint. Studies based on symptom improvement are difficult to assess because of the lack of valid, responsive outcome measures. None of the trials were designed to examine more objective primary endpoints, such as time to complete symptom recovery based on a predefined clinically relevant difference. |

| Interested party | Comment and Rationale | Outcome |
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| | volunteers were included, one phase-II-dose-finding-study was conducted in children and one in adults with both of them serving as additional phase-III-trials due to their robust and clear results already at the time of the interim analyses, and more than the minimally required number of pivotal phase-III-studies were carried out as double-blind and placebo-controlled studies in both adults and children and additional reference-controlled phase-III-trials are also available. Phase IV of the development program included a couple of open outcomes and post-marketing surveillance studies again in adults and children. Both in the liquid as well as in the solid form EPs® 7630 was the extract studied in adults and in children with the latter starting from the age of 1 in patients with acute bronchitis for the liquid form.<br><br>The phase-I-study included a total of 72 healthy volunteers in a double-blind placebo-controlled trial with a high and a low dose EPs®-7630-group *[Matthys H and Köhler S (2010), Zind et al. (2011)]*.<br><br>Two phase-II-dose-finding-studies were conducted with EPs□ 7630: One study enrolled a total of 400 children and adolescents between 6 and 18 years of age *[Malek et al. (2007b), Kamin et al. (2010a)]* and the other enrolled a total of 406 adults *[Malek et al. (2007c), Matthys et al. (2010, 2010a)]*. Both studies did not only provide an informative basis for the dosage of EPs® 7630 but beyond that showed a dose-depending significant superiority of all EPs® 7630 doses (except for the 30 mg daily dosage in the study with children and adolescents *[Malek et al. (2007b), Kamin et al. (2010a)]* compared to placebo for the treatment of acute bronchitis. It is to emphasise that the confirmatory objective of both dose-finding-studies was reached already at the interim analysis as the studies were planned and performed with an adaptive interim analysis with both trials thereby serving as pivotal trial, too.<br><br>In addition to these studies another four pivotal double-blind, placebo-controlled studies have been performed to date: Two pivotal double-blind, placebo- | None of the studies examined reduction in the use of antibiotics. Shorter duration of symptoms or of illness due to acute respiratory infection could be translated into fewer lost days of work and less inappropriate antibiotic use.<br><br>Hence, the data in the overview on clinical data in appendix 1 are not sufficient to be the basis of a well-established use monograph of Pelargonii radix. |

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| | controlled studies were performed with EPs® 7630 including a total of 341 adult patients suffering from acute bronchitis *[Neidig (2002 a), Chuchalin et al. (2005), Golovatiouk and Chuchalin (2002), Schulz (2006) Romberg (2004 a), Matthys and Heger (2007a), Matthys and Funk (2008)]* and two other pivotal double-blind, placebo-controlled studies were performed in children with a total of 420 patients (aged 1 to 18 years) also suffering from acute bronchitis *[Malek et al. (2007 a), Kamin et al. (2010), Malek et al. (2007 d), Kamin et al. (2011) in preparation]*.<br><br>Furthermore, two comparative studies with acetylcysteine were performed, both in children *[Romberg (2004 b), Vornbäumen and Eisebitt (1998), Blochin et al. (1999),* one open outcomes study in adults *[Hövelmann (2004 d), Matthys and Heger (2007b)],* and two post-marketing surveillance studies *[Hövelmann (2004 g), Matthys et al. (2007), Dietl and Müller (2002 a), Haidvogl et al. (1996), Haidvogl and Heger (2007), Dome and Schuster (1996)],* the latter included children as well. In addition, two supportive placebo-controlled clinical trials of phase III are available: [*Romberg (2004c), Hövelmann (2004e), Friede and Handerson (2004d), Heger (2002), Matthys et al. (2003)*] and [*Hövelmann (2004f), Romberg (2004d)], Friede and Henderson 2004 e*].<br><br>Besides the good efficacy results, the investigations mentioned above also revealed a very good safety profile for EPs® 7630. The excellent safety profile was confirmed in an interaction study *[Arold and Wollny (2003), Roots (2004)]* where EPs® 7630 did not reveal an interaction potential with penicillin V.<br><br>In summary it can be stated that the proof of the efficacy of EPs® 7630 is based on an exhaustive and comprehensive clinical development program which covers a multitude of clinical studies with EPs® 7630 in acute bronchitis in children from the age of 1 year on, adolescents and adults. All studies revealed an excellent efficacy and safety profile for this drug in liquid as well as solid in accordance with directive 2001/83/EC. Furthermore, the clinical development | |

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| | program for minors of age reflects the spirit of modern European paediatric trials legislation as laid down in directive 2006/1901/EC due to an outstandingly exhaustive development program in children and adolescents.<br><br>Enclosed, please find the overview on clinical data and evaluation, on which the proof of efficacy for treatment of acute bronchitis is based **(Annex 5)**. The detailed study reports are available at the Competent Authorities who granted marketing authorizations and can be easily supplied to the HMPC by us if needed.<br>Furthermore information as to the BSS score is provided, confirming the importance of the BSS as appropriate tool for evaluation of clinically relevant symptom changes in patients with acute bronchitis.<br><br>The BSS used in the acute bronchitis studies carried out by Schwabe with the Pelargonium sidoides extract contained in Umckaloabo® comprises 5 items (i.e. coughing, pulmonary rales at auscultation, sputum, chest pain while coughing, and dyspnoea). The presence and the severity of each of these symptoms are rated on a scale from 0 (not present) to 4 (very severe). In accordance with the clinical diagnosis these symptoms are considered to be of prominent clinical relevance. The European Lung Foundation (Verheij, 2011) in its actual lung factsheet also uses three of the symptoms included in the BSS (coughing, sputum and dyspnoea) for the diagnosis of acute bronchitis. Since the definition of acute bronchitis is still under discussion (Alberta Clinical Practice Guideline Working Group, 2008; Wong et al., 2006; Hueston and Mainous, 1998) the diagnosis of this disease is particularly based on clinical findings.<br><br>The use of rating scales for gaining information from patients on their health conditions in a structured way is a well-known and widely used technique, examples are the Menopause rating scale (Heinemann, 2003), the Glasgow coma scale (Teasdale, 1974) or the Rivermead Mobility Index (Collen, 1991). In contrast to open questions such rating scales allow a standardized statistical | |

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| | analysis and the information obtained is at least comparable to visual analogue scales (Loos, 2008). Calculating the sum of single ratings is a simple and very commonly used method to create an aggregated measure of the disease status, which can easily be observed over time. Well established examples are the APACHE score (Knaus, 1981), the Glasgow coma scale (Teasdale, 1974) or the Short Form (36) Health Survey (Hays, 1995).<br><br>Rating scales and aggregated scores are also commonly used in clinical trials investigating the efficacy of different drugs in the indication acute bronchitis like in studies with Bronchicum Tropfen® (Gruenwald et al. 2005), Bronchipret Saft® (Kemmerich et al. 2006, Marzian 2007), Hedelix® (Cwientzek 2011) as well as ambroxol (Michnar 1996), fenoterol (Melbye et al. 1991), amoxicillin (Nduba et al. 2008) and azithromycine (Evans et al. 2002). The number of bronchitis trials listed above for a multitude of drugs corresponds to a longstanding common practice.<br><br>The BSS as an aggregated rating scale is in line with similar well known scores and is a useful tool for the clinician to operationalize the assessment of the clinical disease status within a clinical trial. We refer to **Annex 5**.<br><br>Based on the above stated arguments and data, we strongly plead for revision of the assessment report and for including the well-established use for treatment acute bronchitis into the Community monograph. The wording proposed for related assessment report sections and for the **well-established use** part in the Community monograph, please, find in the enclosed table "SPECIFIC COMMENTS ON TEXT" (no. 1, 2 and no. 3 - 8 , 10, 11, 13 – 16, 19 – 23 , resp.). | |
| Schwabe | Beside the above issues, please find in the enclosed table "SPECIFIC COMMENTS ON TEXT" furthermore<br><br>- 4 comments (no. 9, 10, 12, 16) on text in the Community monograph | For answers, see section Specific comments on text. |

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| | intended for traditional use products and the corresponding text proposals,<br>- 2 comments (no. 17 and 18) on text in another section in the assessment report and the corresponding text proposals. | |
| Schwabe | We ask the HMPC to refrain from using the term “Umckaloabo” in the assessment report, as this is a registered trademark [“Umckaloabo®”]. The term does neither have botanical nor pharmaceutical relevance, i.e. is not included in the European pharmacopoeia monograph. Official monographs (like HMPC monographs) principally do not refer to specific brands and/or manufacturers.<br><br>Based on the fact that Umckaloabo® is a registered trademark we also ask the HMPC to delete the speculations about the origin of the above tradename [(draft) assessment report page 13/38]. Vague assumptions should not be matter of official documents. | Endorsed. |

## SPECIFIC COMMENTS ON TEXT

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | AESGP | In Austria, 8 products are registered as traditional herbal medicinal products. There are no Marketing Authorisations. | Endorsed and Regulatory status overview amended. However, Section 1.2 can be completed with further products only in case all the necessary data (preparations, pharmaceutical form, posology, indication, legal status, since when on the market) for specific products are provided. |
| Draft Assess-ment report (page 35/38) concerning overall conclusion on efficacy | Schwabe (No. 1) | **Proposed change:**<br><br>**"4.3. Overall conclusion on clinical pharmacology and efficacy**<br>On the other hand, the definition of 'acute bronchitis' is still under discussion and the diagnosis is solely based on clinical findings without standardized diagnostic signs and sensitive or specific confirmatory laboratory tests. As a result of the current lack of standardized criteria, all outcomes applied in trials are subjective. The BSS score is not validated, but appears to be associated with a clinical benefit (Kamin et al., 2010). The Cochrane review on Pelargonium sidoides also drew attention that the studies used non-validated symptom scores as a primary outpoint and none of the trials were designed to examine time to complete symptom recovery based on a predefined clinically relevant difference. In spite of the shortcomings, the Cochrane review concluded that the herbal preparation may be effective in relieving symptoms in acute bronchitis in adults and children (Timmer et al., 2009). ~~However, it was decided that because the non-validated~~ | Not accepted. This sentence is the result of the assessment of the available scientific data. It is acknowledged that the BSS is a useful tool in the assessment of the clinical disease status, however, since this score is invalidated and provides no objective evidence for the effectiveness, it was decided that this score in itself is not sufficient to prove the efficacy of Pelargonii radix. Studies based on symptom improvement are difficult to assess because of the lack of valid, responsive outcome measures. None of the trials were designed to examine more objective endpoints. |

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| | | ~~BSS score was used in the trials, this indication can not be accepted at well-established use level.~~"<br><br>_____<br>*Comment:*<br>As justified before (see table "GENERAL COMMENTS") the BSS as an aggregated rating scale is in line with similar well known scores and is a useful tool for the clinician to operationalize the assessment of the clinical disease status within a clinical trial. So the clause "However, it was decided that because the non-validated BSS score was used in the trials, this indication can not be accepted at well-established use level." *should be deleted.* | |
| Draft Assessment report (page 14/38 and page 38/38) concerning fundamental differentiation between well-established and traditional use of *Pelargonium* extract | Schwabe (No. 2) | **Proposed change:**<br>"According to the market overview, one extract (DER 1:8-10, extraction solvent: ethanol 11% m/m) of Pelargonii radix has been on the market for more than 30 years ~~with the indication .... of common cold~~ <u>for treatment of bronchitis and symptoms of common cold (see product no. 4 in the German market overview, section 1.2). Meanwhile efficacy of this extract in treatment of acute bronchitis has been proved by an exhaustive and comprehensive clinical development program and fulfils the criteria for marketing authorization. So this indication should not be matter of traditional registration but is recognized for well-established use. With regard to traditional use, the following indication for traditional herbal medicinal products fulfils all criteria to be met according to Directive 2004/24/EC and, thus, is accepted: symptomatic treatment of common cold."</u> | Not accepted. Though this product is on the market in several European countries, this does not mean automatically that a community monograph on the well-established use would be prepared.<br>We agree on the proposed indication for traditional use. Contrary to the opinion of Prof. Matthys, in case of traditional herbal medicinal products acute bronchitis cannot be considered as an acceptable indication since a medical consultation is necessary for the reliable diagnosis of acute bronchitis. Therefore, this therapeutic indication does not comply with the Directive 2004/24/EC (Article 16a 1. A simplified registration procedure (hereinafter 'traditional-use registration') is hereby established for herbal medicinal products which fulfil all of the following criteria: (a) |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | _____<br>*Comment:*<br>*As justified before (see table "GENERAL COMMENTS") the efficacy of* Pelargonium sidoides *extract (EPs® 7630) in patients with acute bronchitis has been clearly proven. So fundamental differentiation between well-established and traditional use of* Pelargonium extract *[intended to be summarized equally in section 2.3 (page 14/38) and in section 6 (page 38/38) of the assessment report] should be established as proposed above. In this context, it is important to note that acute bronchitis is a typical OTC indication that does not require medical diagnosis and supervision. We refer to Annex 5.* | they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment. Acute bronchitis is not a typical OTC indication that does not require medical diagnosis. |
| 2. Qualitative and quantitative composition | Diapharm | Under ii) Herbal preparations we suggest to add:<br>"Dry extract (DER 4-7 : 1), extraction solvent ethanol 11 % m/m (= 14 % v/v)"<br>This native dry extract is equivalent to the native liquid extract described in the HMPC draft monograph. When drying a liquid extract DER 1:8-10 made with ethanol 11 % (m/m), the resulting dry extract is in the range of native DER 4-7:1.<br>In principle, a dry extract is already covered by the actual wording of the draft HMPC monograph, because a dry extract is nothing but the native dry residue of the liquid extract DER 1: 8-10, after removing the extraction solvent and drying.<br>But, just to make it more clear and precise, we suggest to mention the dry extract explicitly in section 2. | Partly endorsed. The proposal is in accordance with the Directive 2004/24/EC. The dry extract equivalent to the liquid extract (liquid extract (DER 1:8-10), extraction solvent ethanol 11% m/m) will be included in the monograph. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | Proof of traditional use of the liquid extract also covers proof of traditional use for the corresponding dry extract, as the native extract (which is regarded as the active principle according to current EU quality guidelines for Herbal medicinal products) is identical in both dry and liquid extract. In the case of pelargonium dry extract there is sufficient evidence for this because of a meanwhile huge number of Traditional Herbal Registrations granted according to Directive 2004/24 EU in several member states for Pelargonium film-coated tablets containing a Pelargonium dry extract, e.g. in AT, UK, NL, SE, ES, BE, IT, etc.<br><br>In some of these granted THR, the active principle is declared as “dried liquid extract of Pelargonium roots (DER 1:8-1)”, which is not clearly understandable for consumers, and also is not in line with the “Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products /traditional herbal medicinal products” EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1 where it is clearly stated on page 11, that for dry extracts the native DER of the dry extract should be given, not the DER of the preceding liquid extract. Therefore we suggest to include the correct declaration of the Pelargonium root dry extract as given in the MHRA Public Assessment Report for DiaCold /DiaPelargo Tablets THR 33518/0017 and THR 33518/0018 (see Annex 1):<br><br>“Dry extract (DER 4-7 : 1), extraction solvent ethanol 11 % m/m (= 14 % v/v)”<br><br>The same declaration for the dry extract is used in the SPC of | |

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| | | the recently granted THR DiaPelargo and DiaTussal Tablets by AGES PharmMed in Austria:<br><br>„Trockenextrakt aus *Pelargonium reniforme/sidoides*-Wurzeln (Droge-Extrakt-Verhältnis 4-7:1, Auszugsmittel Ethanol 14%,V/V)“ (see Annex 2)<br><br>The extraction solvent for the dry extract is identical to the liquid extract already mentioned in the draft HMPC monograph: ethanol 11 % (m/m) = 14 % (v/v). | |
| 2. Qualitative and quantitative composition | Interest group Pelargonium | In the monograph the following herbal preparation is described:<br><br>Liquid extract (DER 1:8-10), extraction solvent ethanol 11% m/m<br><br>From our point of view the extraction solvent should be given in a slightly broader range.<br><br>Please note that the concrete extraction solvent was labelled in 2005 for the first time, when marketing authorisation of Umckaloabo was granted in Germany.<br><br>As now declared [9], the extraction solvent used for the herbal drug is ethanol 11% m/m, the given ethanol-concentration is 12% V/V (= 9.2 % m/m). Taking account of the amount of glycerol (20%) contained in Umckaloabo® an ethanol-concentration of 11.5 % m/m is calculated for the Liquid extract (without glycerol).<br><br>Measurement of the ethanol concentrations of 10 batches of Umckaloabo® (mainly before 2005) showed a content of 9.2 to | Not endorsed. The extraction solvent contained in the monograph is that of the herbal preparation that serves as the basis of the community monograph, since this is the only preparation for which the duration of traditional application could be confirmed. We acknowledge the argumentation supported with measurement data, however, in line with the document EMA/HMPC/345132/2010 Rev.1 of HMPC, it is expected that if the extract solvent and/or concentration is/are different from those given in the monograph, comparability has to be demonstrated by using appropriate analytical data, for example chromatographic profile(s) and marker(s) content.<br><br>The measurements cited here concern quality issues, but do not have influence on the fact that the basis of the monograph should be a herbal preparation with confirmed traditional use. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | 10.8 % m/m with a mean of 10.1% m/m. [1, annex 1] This value is slightly higher than the value of 9.2% m/m (equivalent to 12% V/V) that was declared after 2005.<br><br>Calculation for the Liquid extract (without glycerol) results in an ethanol concentration of 11.5 to 13.5% m/m with a mean of 12.6% m/m. This means that the concentration of the extraction solvent must be a little bit higher than the concentration of the extraction solvent of 11% m/m declared later, particularly if the inevitable, slight ethanol losses which are regularly occurring during the maceration process are taken into account.<br><br>From these results also 12% m/m or (even better) 15% V/V should be covered as extraction solvent in the monograph. Beside that a concentration of the extraction solvent of 15% V/V is commonly used in Europe:<br><br>Austria: Peloide Tropfen (Pharmaselect) [4],<br>Phytocon Pelargonium Flüssigkeit zum Einnehmen (Faromed) [5]<br><br>Hungaria: PELOID belsőleges cseppek (Repharma EC) [6]<br>Croatia: Alfakut (Belupo) [7]<br>Norway: Fort Frisk (Pharbio/Cederroth) [8]<br><br>Furthermore, it should be taken into consideration to cover also the concentration of the extraction solvent of the mother tincture 15% m/m. Also the mother tincture was marketed in Latavia, Ukraine and Russia under the name Umkalor for many years. (Brendler and van Wyk, 2008). | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| 2. Qualitative and quantitative composition | Interest group Pelargonium | Also for a dry extracts several registrations had been granted. We would suggest to mention also the dry extract as this extract is based on the liquid extract. Both extracts can be regarded as equivalent.<br><br>Dry extract (DER 4-25* : 1), extraction solvent ethanol 11-12 % m/m (14-15% v/v)<br><br>*A narrow range may also be specified as extracts with a DER of 4-7: 1 are also registered. | Endorsed. The dry extract equivalent to the liquid extract (liquid extract (DER 1:8-10), extraction solvent ethanol 11% m/m) is included in the monograph. |
| 2. Qualitative and quantitative composition | FRCH | Well-established use:<br><br>Based on the vast amount of clinical data on the liquid extract mentioned under traditional use, this preparation, and its properties in further sections, should be listed as well-established use.<br><br>Traditional use:<br><br>Powdered herbal substance<br><br>Rationale: Include herbal substance as this is the basis for several preparations, made by pharmacies as so-called house specialties<br><br>Include following herbal preparation:<br><br>Dry extract (DER 4-7:1), extraction solvent ethanol 10 -50 % (m/m)<br><br>Rationale:<br><br>1. Recently approved MHRA THMP application of a product | As the result of the discussion in the MLWP, for reasons detailed in sections 4.3 and 6 of the assessment report, it was decided that the efficacy of Pelargonii radix is not proven properly to prepare a well-established use monograph.<br><br>The inclusion of a herbal preparation in a monograph should be supported with the confirmation of the traditional application complying with the Directive 24/2004/EC. Such data was not found in the literature and was not provided for the powdered herbal substance in the course of the preparation of the draft monograph or during the public consultation.<br><br>Partly endorsed. The dry extract equivalent to the liquid extract (liquid extract (DER 1:8-10), extraction solvent ethanol 11% m/m) will be included in the monograph.<br><br>However, ethanol in concentrations ranging from 10% to 50% m/m is not acceptable as extraction solvent. The provided internal data confirms only that the |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | containing a dry extract (DER 4-7:1), extraction solvent ethanol 14 % (v/v).<br><br>2. Based on internal data of FRCH, enclosed, in was shown that extraction solvents of 11, 15, 30, 40, 50 % EtOH result in products with comparable DER and constituent levels. | coumarin profiles and DERs of the extracts prepared with different solvents in this range is similar, but provides no information on other compounds. Since the components of Pelargonium responsible for the therapeutic effect are not known, the verification of the similarity of coumarin profiles is not sufficient to include EtOH 10-50% m/m as extraction solvent. |
| 2. Qualitative and quantitative composition Traditional use | Laboratoires Pierre Fabre | Comment:<br><br>We found that only the herbal preparation called "Liquid extract (DER 1:8-10), extraction solvent ethanol 11% m/m" is accepted in traditional use.<br><br>When reading the Assessment report EMA/HMPC/560962/2010, we noted that countries such as Belgium, Spain, Italy and Sweden marketed herbal medicine based on dry extract (DER 1:8-10), extraction solvent ethanol 11% m/m.<br><br>Moreover, we found that the first herbal medicine tablet form appear on the market in 1950 in Germany and in 1961 in Netherlands.<br><br>Proposed change:<br><br>We proposed to add a new section iii):<br><br>Herbal preparation<br><br>Dried extract (DER 1:8-10), extraction solvent ethanol 11 % m/m | Partly endorsed. The dry extract equivalent to the liquid extract (liquid extract (DER 1:8-10), extraction solvent ethanol 11% m/m) will be included in the monograph. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| 2.Qualitative and quantitative composition Well-established use | Schwabe (No. 3) | **Proposed wording:**<br>With regard to the marketing authorization application of Article 10(a) of directive 2001/83/EC as amended<br>*Pelargonium sidoides* DC, radix (pelargonium root)<br>i) Herbal substance<br>Not applicable.<br>ii) Herbal preparations<br>Liquid extract from the roots of Pelargonium sidoides (1 : 8 - 10), extraction agent ethanol 11% m/m [EPs® 7630] | Well-established use not endorsed, see above. |
| 3. Pharmaceutical form *Well-established use* | Schwabe (No. 4) | **Proposed wording:**<br>Herbal preparation in solid or liquid dosage form for oral use.<br>The pharmaceutical form should be described by the European Pharmacopoeia full standard term. | Well-established use not endorsed, see above. |
| 3. Pharmaceutical form | FRCH | Well-established use:<br>Herbal preparation in liquid dosage forms for oral use.<br>Traditional use:<br>Herbal substance<br>Herbal preparation in solid or liquid dosage forms for oral use. | Well established use not endorsed, see above.<br>Endorsed. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| 3. Pharmaceutical form | Interest group Pelargonium | We suggest including also solid dosage forms for oral use, as registrations for such products also had been granted in several European countries.<br><br>Additionally solid dosage forms should be included as stability may be better and it may be useful to have an ethanol-free dosage form.<br><br>The pharmaceutical form should be described by the European Pharmacopoeia full standard term. | Endorsed, see above. |
| 4.1 Therapeutic indications | Diapharm | In addition to the proposed indication:<br>*"Traditional herbal medicinal product for the symptomatic treatment of common cold."*<br><br>we suggest to add the symptoms of common cold, in order to make it easier for the consumer/patient to identify whether he should use this product in self medication or not. A suitable wording would be:<br>*"Traditional herbal medicinal product used to relieve the symptoms of upper respiratory tract infections including the common cold, such as sore throat, cough and blocked or runny nose, exclusively based upon long-standing use."*<br><br>This is exactly the wording of the indication of several Pelargonium products registered as THMP under Directive 2004/24 EU in the UK. E.g. DiaPelargo Tablets, THR 33518/0018, see Public Assessment Report of MHRA in **Annex 1.**<br>http://www.mhra.gov.uk/Publications/PublicAssessmentReports/PublicAssessmentReportsforherbalmedicines/index.htm | Not endorsed. HMPC monographs primarily refer to specific indication, however, the specification of symptoms could be added in the SPCs and PILs of registered products. Single decisions of national authorities are not assessed in the course of the preparation of the monograph. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| 4.1 Therapeutic indication | ESCOP | **<u>Comment</u>**<br><br>In Germany, up to 1988 (see attached Table 1), the finished product was therapeutically used as an *"adjuvant of chronic tuberculosis, scrofula and bronchitis"*. Then, the therapeutic indication was focused on acute and chronic infections of upper respiratory tract of viral and bacterial origin (bronchitis, sinusitis, tonsillitis, angina and rhinopharyngitis).<br><br>Consequently, it may be considered that the proposed therapeutic indication *"traditional herbal medicinal product for the symptomatic treatment of common cold"* does not reflect properly the long standing use of the medicinal product. The therapeutic indication, based on the traditional use of the product, should take into account the spectrum of infections of the airways more correctly and describe in a more detailed way symptoms of acute and chronic infections due to upper respiratory tract infections, as has been done in the granted UK registration.<br><br>**<u>Proposal</u>:**<br><br>**Change to "Traditional herbal medicinal product used to relieve the symptoms of upper respiratory tract infections including common cold, such as blocked or runny nose, sore throat and cough".** | The changes in the indications of the finished product were considered in the course of assessment. However, in view of the current indication and scientific data (the plausibility should also be taken into consideration), symptomatic treatment of common cold was adopted as traditional use indication. The present wording does not exclude the more detailed description of symptoms of common cold in the SPCs and PILs. |
| 4.1 Therapeutic indications | *Interest group Pelargonium* | In the monograph the following indication is described: "Traditional herbal medicinal product for the symptomatic treatment of common cold"<br><br>From our point of view, on the basis of the available clinical | Since this is a traditional use monograph, evidences deriving from clinical studies are not the primary sources when defining therapeutic indications. As the result of the discussion on the indication of the product |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | data, the indication should be given in a broader range described as: “Traditional herbal medicinal product for the symptomatic treatment of diseases of the respiratory tract such as common cold, acute bronchitis, tonsillopharyngitis and sinusitis”<br><br>In a large number of controlled clinical trials performed with patients suffering from infections of the respiratory tract such as bronchitis, tonsillopharyngitis, sinusitis and common cold, Pelargonium formulations were shown to be efficacious and tolerated well. In these studies Pelargonium root formulations were found to possess an efficacy superior to placebo in treatment of infections of the respiratory tract. Pelargonium solution was superior to placebo in the treatment patients with acute bronchitis in terms of a reduction of the Bronchitis Severity score (BSS) and an improvement of individual symptoms, health-related quality of life, working inability and duration of illness (Chuchalin 2005) (Golovatiouk 2002) (Schulz 2007a) (Matthys 2003) (Kamin 2010) (Matthys 2004) (Matthys 2007b) (Schulz 2007b) (Matthys 2008) (Anonymous 2008) (Kolodziej 2003) (Kamin 2009). Moreover, the Pelargonium solution showed an efficacy comparable to that of N-acetylcysteine in reference-controlled studies with children suffering from acute bronchitis (Blochin 1999) (Kolodziej 2003). Furthermore, the Pelargonium solution was proven effective in treatment of children with acute bronchitis in four non-controlled studies (Dome 1996) (Haidvogel 2007) (Haidvogel 1996) (Matthys 2007) and in one non-controlled study in adults with bronchitis (Matthys 2007a) in terms of an | with at least 30 years of tradition, it was decided that the indication common cold should be granted. This indication is in line with the traditional application of Pelargonium, and in contrast to the majority of the mentioned indications, does not need medical diagnosis and supervision. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | improvement of both symptoms of bronchitis and subjective complaints. In placebo-controlled studies with children suffering from acute tonsillopharyngitis the Pelargonium solution was superior compared to placebo in terms of the change of the Tonsillopharyngitis Severity Score (TSS), reduction of the severity of symptoms and shortening of the duration of illness (Bereznoy 2003) (Heger 2002) (Kolodziej 2003). In a reference-controlled study with children suffering from acute tonsillopharyngitis, treatment with the Pelargonium solution showed an efficacy better than symptomatic therapy in regard to the decrease of TSS (Kolodziej 2003). In addition, children and adults suffering from acute tonsillopharyngitis were treated successfully with the Pelargonium solution in a non-controlled study in terms of a reduction of TSS (Bereznoj 2009) (Kolodziej 2003). In three placebo-controlled trials the Pelargonium solution was superior to placebo in treatment of acute maxillary sinusitis in regard to reduction of the sinusitis severity score, change of symptoms and patient's health status (Bachert 2005) (Morck 2004) (Bachert 2009). In a non-controlled study the Pelargonium solution was effective in treatment of patients suffering from maxillary sinusitis in terms of a change of symptoms (Schapowal 2007) (Kolodziej 2003). Furthermore, the Pelargonium solution was effective in two non-controlled studies with patients with ear, nose and throat (ENT) and/or respiratory tract infections in regard to change in the subjective and objective symptoms (König 1995) (Heil 1994). In a placebo-controlled, trial with adult patients with cold symptoms, treatment with the Pelargonium solution was | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | proven effective in terms of a significant reduction of the severity of symptoms and shortening of the duration of the common cold compared with placebo (Lizogub 2007).<br><br>Overall, the clinical data on the efficacy of Pelargonium root formulations make the therapeutic indication: "Traditional herbal medicinal product for the symptomatic treatment of diseases of the respiratory tract such as common cold, acute bronchitis, tonsillopharyngitis and sinusitis" plausible. | |
| 4.1 Therapeutic indications | FRCH | Well-established use:<br><br>Herbal medicinal product for the treatment of upper respiratory tract infections.<br><br>Traditional use:<br><br>Traditional herbal medicinal product to relieve the symptoms of common cold. | Well-established use not endorsed, see above.<br><br>Not endorsed. The proposal for modification is not justified, moreover this wording is not substantially different from the actual wording of the monograph. |
| 4.1. Therapeutic indications<br><br>Well-established use | Schwabe<br><br>(No. 5) | Proposed wording:<br><br>Herbal medicinal product for the treatment of acute bronchitis. | Well-established use not endorsed, see above.<br><br>For proposal on indication see comments below. |
| 4.1. Therapeutic indications | Schwabe | **Comparison of the quality of clinical data on *Pelargonium s/r.* with those of other plants with WEU monographs**<br>We are convinced that the pivotal clinical trials on *Pelargonium* are by no means of lower quality than the ones on which the well-established use (WEU) statuses of *Hedera helix* and | The decision on the indication and the type of the monograph (WEU/traditional) was decided solely based on the available data on *Pelargonium*.<br>We acknowledge the vast amount of clinical trials carried out with Pelargonium products. However, after assessing all the available data, it was decided that as |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | *Echinacea purpurea* are based (which are used by patients in similar conditions as *Pelargonium* products in the respiratory area).<br>Approved WEU indications:<br><br>*Hedera*<br>Herbal medicinal product used as an expectorant in case of productive cough.<br><br>*Echinacea purpurea:*<br>Herbal medicinal product for the short-term prevention and treatment of common cold.<br><br>Comparison of clinical data:<br>The positive HMPC assessment regarding the VVEU status of Hedera helix and Echinacea purpurea is based on the studies listed in attachments 1 and 2. The tables in these attachments are taken from the relevant assessment report.<br><br>Comparing the placebo-controlled and reference-controlled studies of Hedera he/ix, *Echinacea purpurea* and *Pelargonium s/r*, we are convinced that the six pivotal placebo-controlled studies in the indication "acute bronchitis" conducted on *Pelargonium s/r* (attachment 3, tables taken from the draft assessment report) are of a quality comparable to the studies available on Hedera helix and Echinacea purpurea. In all six studies, Pelargonium sir. was superior to placebo.<br><br>One of the major criticisms In the *Pelargonium* draft AR is the non-validation of the BSS. We believe, however, that the BSS | primary outcome measure BSS is not sufficient to support the well-established use of the studied product. This score is not validated and provides no objective evidence for efficacy. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | is by no means inferior to the rating scores used in the studies on *Hedera helix* and *Echinacea purpurea*. In this context we also refer to the expert statement that was sent as appendix 2 of our comment of August 15, 2011 (attached pdf document).<br><br>When comparing the clinical evidence on *Hedera helix, Echinacea purpurea* and *Pelargonium s/r*, we are therefore convinced that a WEU status is appropriate for *Pelargonium sidoides/reniforme*, possibly with a modified indication as presented above.<br><br>We therefore kindly request the HMPC to reconsider and revise the draft assessment report and agree to the well-established use status of *Pelargonium sidoides/reniforme*. | |
| 4.1. Therapeutic indications | Schwabe | A review of marketing authorisations in the European Union has shown that only few marketing authorisations have been granted with the indication "acute bronchitis". Although we still believe that "acute bronchitis" is the appropriate indication for *Pelargonium s/r*., we would like to request the HMPC to take "productive cough" into consideration as alternative wording for the indication. "Productive cough" is used as a synonym for "acute bronchitis" in many EU countries and is the approved well-established use indication in the HMPC monograph on *Hedera helix* (well-established use).<br><br>Our proposal for the alternative wording of the indication would be:<br><br>"Herbal medicinal product for the symptomatic treatment of productive cough." | Well-established use not endorsed, see above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| 4.2 Posology and method of administration | FRCH | Well-established use:<br><br>*Adolescents, adults and elderly*<br>Single dose: 1.14 g, 3 times daily.<br><br>*Children between 6-12 years*<br>Single dose: 0.76 g, 3 times daily.<br>The use in children under 6 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').<br><br>Traditional use:<br><br>*Adolescents, adults and elderly*<br>Dosage of single preparations corresponding to the daily dose of 0.3-0.4 g powdered herbal substance<br><br>*Children between 6-12 years*<br>Dosage of single preparations corresponding to the daily dose of 0.25 g powdered herbal substance<br>The use in children under 6 years of age is not recommended (see section 4.4 'Special warnings and precautions for use').<br><br>**Duration of use**<br><br>If the symptoms persist longer than ~~1 week~~ 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.<br><br>Rationale: Taken from MHRA approved THMP product DiaCold, „After relief of symptoms, it is recommended to continue treatment for a further 2-3 days in order to prevent a relapse. However, treatment duration should not exceed two weeks. If | Well-established use not endorsed, see above.<br><br>Not endorsed, since powdered herbal substance is not covered by the monograph (see above).<br><br>There is no rational, scientifically established reason to reword the original sentence. The wording of the monograph is in line with the wordings of monographs with similar therapeutic indications. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. “ | |
| 4.2 Posology liquid extract | Diapharm | The given single dose for the liquid extract = 1.14 g is not comprehensible for us.<br><br>The traditionally used dosage of the German Pelargonium product Umckaloabo (ISO Arzneimittel GmbH) from 1974 – 2005 has been 20 – 30 drops 3 x daily (see PIL of Umckaloabo from 2005 in **Annex 3**). From 2006 on it has been 3 x 30 drops daily for adolescents and adults.<br><br>One single dose of 30 drops corresponds to 1.25 g of finished product Umckaloabo which can easily be checked by simple weighing of 30 drops. According to the official declaration of registered liquid Pelargonium products (= Kaloba oral drops in UK, NL, SE, DE, AT, etc.) 10 g = 9.75 ml of finished product Kaloba contain 8.0 g of Pelargonium root liquid extract 1:8-10. Therefore 1,25 g = **30 drops contain exactly 1.0 g of pelargonium root liquid extract**, not 1.14 g as stated in the draft monograph.<br><br>Correspondingly 20 drops are equivalent to 0.67 g of pelargonium root liquid extract.<br><br>(Maybe that the error results from misleading information with view to drops/volume relation. E.g. in the MHRA Public Assessment Report of Kaloba oral drops THR 05332/003 page 14: “30 drops is equivalent to approx. 1.5 ml” which would correspond to 1.54 g of finished product. But weighing of 30 | The posology was recalculated based on the official data of the reference product.<br><br>10 g of the preparation contains 8 g Pelargonii radix extract (DER: 1:8-10), extraction solvent: ethanol 11% (m/m).<br><br>Taking into account the density of the finished product (1.018 – 1.038, mean 1.028 g/ml), the density of the liquid extract (0.975 – 1.000, mean 0.9875 g/ml) and the drop count (20-21 drops/ml finished product):<br><br>30 drops finished product = 1.4286-1.5 ml = 1.4686-1.542 g = 1.1749-1.2336 g native extract= 1.1897-1.2492 ml native extract<br><br>20 drops finished product = 0.9524-1 ml = 0.9790-1.028 g = 0.7832-0.8224 g native extract= 0.7932-0.8328 ml native extract<br><br>Based on this, and taking into account safety aspects as well, the posology of Pelargonii radix containing products is as follows:<br><br>*Adolescents, adults and elderly:*1.19-1.25 ml liquid extract or equivalent amount of dried liquid extract, 3 times daily.<br><br>*Children between 6-12 years:* 0.79-0.83 ml liquid |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | drops results in 1.25 g of finished product, see above.)<br><br>Therefore we suggest to reword Posology of the liquid extract:<br><br>*Adolescents, adults and elderly*<br>Single dose: 1.0 g, 3 times daily.<br>*Children between 6-12 years*<br>Single dose: 0.67 g, 3 times daily. | extract or equivalent amount of dried liquid extract , 3 times daily |
| 4.2 Posology dry extract | Diapharm | We suggest to include:<br><br>"Dry extract (DER 4-7 : 1), extraction solvent ethanol 11 % m/m (= 14 % v/v)"<br><br>*Adolescents, adults and elderly*<br><br>Single dose: 20 mg dry extract, 3 times daily.<br><br>*Children between 6-12 years*<br><br>Single dose: 20 mg dry extract, 2 times daily.<br><br>This is reasonable because 1 tablet = 1 single dose of dry extract 20 mg corresponds exactly to 1 single dose = 30 drops of liquid extract. Reference is made to the Public Assessment Report for DiaCold /DiaPelargo Tablets THR 33518/0017 and THR 33518/0018 (see Annex 1), and to the SPC of the recently granted THR DiaPelargo and DiaTussal Tablets by AGES PharmMed in Austria THR-No. HERB-00048 and HERB-00047 (see Annex 2):<br><br>*„-Bei Erwachsenen und Jugendlichen über 12 Jahren: 3-mal täglich 1 Filmtablette (morgens, mittags, abends)* | Partially endorsed. The posology for the dry extract is expressed as the dry extract equal to the posology of the liquid extract in the reference product.<br><br>In case of children, the dry extract has to be administered 3 times daily, similarly to the liquid extract, since according to the Directive 2004/24/EC, Article 16c, 2. "A corresponding product, as referred to in paragraph 1(c), is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, ***equivalent*** strength and ***posology*** and the same or similar route of administration as the medicinal product applied for." |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | *- Bei Kindern im Alter von 6-12 Jahren: 2-mal täglich 1 Filmtablette (morgens, abends)“*<br><br>To achieve a comparable dosage of liquid and dry extract, it has to be considered that 10 g = 9.75 ml of liquid preparation Kaloba contain 0.8 – 1.0 g herbal Pelargonium drug, calculated from the given DER of the liquid extract = 1: 8-10. Experimental data show that 30 drops correspond to 1.25 g. This amount of liquid extract therefore corresponds to 100 – 125 mg (112.5 mg on average) herbal drug.<br><br>As one single dose of Pelargonium root dry extract is 20 mg (DER 4 - 7 : 1) equivalent to 80 – 140 mg of dried herb (110 mg on average), this dosage exactly relates to the dosage of the liquid preparation.<br><br>For a more detailed calculation, please refer to **Annex 4**, if necessary. | |
| 4.2 Duration of use | Diapharm | We suggest to reword:<br><br>“After relief of symptoms, it is recommended to continue treatment for a further 2-3 days in order to prevent a relapse. However, treatment duration should not exceed two weeks.”<br><br>This is quite reasonable to avoid a too early cessation of treatment, and this is exactly the wording to be found in several liquid and solid Pelargonium products registered as Traditional Herbal Medicinal Products under Directive 2004/24 EC in the UK. E.g. reference is made to the Public Assessment Report for DiaCold /DiaPelargo Tablets THR 33518/0017 and | There is no rational, scientifically established reason to reword the original sentence. The wording of the monograph is in line with the wording of the monographs with similar therapeutic indications. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | THR 33518/0018 (see **Annex 1**). | |
| 4.2 Posology | ESCOP | **Comment**<br><br>Firstly, it is to be noticed that single and daily dosages established for the medicinal product Umckaloabo®, supporting a traditional use of the herbal preparation, have not been consistent through years, being in a global range of 30 to 100 drops per day for adults (see **Annex 2** Table 1). Secondly, from 1990, a single dose has been clearly defined as a range and not as a fix number of drops.<br><br>Additionally, it may be noticed that according to the dropper used for a given product, the drop size may vary significantly which means that the number of drops, corresponding to a clearly defined weight per single dose could result in a figure which is not round or not standard.<br><br>**In consequence, posology should reflect all these variations and should be given as ranges.**<br><br>Remark: the single dose of medicinal products delivered as drops is usually defined as a range. This is the case of herbal preparations consisting of essential oils (e.g. following HMPC Community monographs: Anise oil, Juniper oil, Peppermint oil, Thyme oil, Cinnamon bark oil and Lavender oil).<br><br>**Proposal:**<br><br>On the assumption that the proposed single dose of 1.14 g corresponds to 30 drops (amount not justified in the draft | Partially endorsed. It is impossible to display the fluctuation of posology in the monograph, hence it was decided to include the most recent posology. Due to the variation of drop size depending on the dropper used for a given product, the posology is determined in grams and millilitres. Thus, the dose can be defined as a single value and not as a range.<br><br>The posology was recalculated (see above) based on the official data of the reference product. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Assessment Report), following single dosages look more appropriate for the different groups of population (see "4.4 Special warnings and precautions for use" regarding dosage justification for children aged 2 to 6 years):<br><br>Adolescents, adults and elderly: 0.76-1.14 g, 3 times daily (corresponding to 20-30 drops);<br><br>Children aged 6-12 years: 0.38-0.76 g, 3 times daily (corresponding to 10-20 drops);<br><br>Children aged 2 to 6 years: 0.19-0.38 g, 3 times daily (corresponding to 5-10 drops).<br><br>The use in children under 2 years of age is not recommended. | |
| 4.2 Posology and method of administration | Interest group Pelargonium | In the monograph the following dosage is given:<br><br>*Adolescents, adults and elderly*: Single dose: 1.14 g, 3 times daily.<br><br>*Children between 6-12 years*: Single dose: 0.76 g, 3 times daily.<br><br>The traditional dosage (before 2005) was 20-30 drops, three times daily for adults and juveniles from 12 years. For children, in the age of 6-12, the dosage was given as 10-20 drops, three times daily. After marketing authorisation of Umckaloabo was granted in Germany the dosage was stated more precisely:<br><br>30 drops for adults and adolescents, 3 times daily.<br><br>20 drops for children, in the age of 6-12, 3 times daily. | The dosage of the product has changed several times during the last decades. It is impossible to display the fluctuation of posology in the monograph, hence it was decided to include the most recent posology.<br><br>The posology was recalculated (see above) based on the official data of the reference product. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | 10 drops for children in the age of 1-5, 3 times daily.<br><br>As the traditional dosage for adults and adolescents is from 20-30 drops, 3 times daily a corresponding range should be covered by the monograph. This range is also covered by pharmacological and clinical studies of Umckaloabo. This is also valid for the traditional dosage for children between 6-12 years: Here the traditional dosage is 10-20 drops, 3 times daily.<br><br>Beside that it is not clear how the single dose of 1.14 g (resp. 0.76 g for children between 6-12 years) was derived.<br><br>Please find attached results of drop weight of Umckaloabo [2, Annex 2]:<br><br>A nominal mass of 1.16 g per dose (30 drops) was derived from the results of 9 batches Umckaloabo.<br><br>Taking into consideration the amount of 20% glycerol in Umckaloabo, an amount of 0.928g results for the liquid extract, in the case that the single dose is 30 drops.<br><br>As the traditional dosage (before 2005 [9]) was 20-30 drops the corresponding mass of the liquid extract should also be given as a range (0.62 to 0.93 g).<br><br>However, based on the information given for most of the products (Umckaloabo, Kaloba, Umckalor) based on EPs® 7630, an amount of 1.23g results for the liquid extract, in the case that the single dose is 30 drops. | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | This difference is caused by a divergent drop weight:<br><br>Information given for Kaloba & Umckalor: 1 ml is approximately 20 drops (in the case of Kaloba in Austria: 21 drops)<br><br>Analytical results on Umckaloabo acc. to the testing of "dose and uniformity of dose of oral drops" in Ph. Eur.-monograph "Liquid preparations for oral use":<br>1 mL corresponds to 26-27 drops. [2, Annex 2]<br><br>As the information given for Kaloba & Umckalor is not comprehensible (slightly different details, no reference to the used method), from our point of view the dosage should be derived from the analytical results.<br><br>At least this dosage:<br><br>(0.62 to*) 0.93 g for adolescents, adults and elderly, 3 times daily<br><br>0.62 (to 0.31*) g for children, between 6-12 years, 3 times daily<br><br>should also be covered by the monograph.<br><br>*in case the range will be accepted. | |
| 4.2 Posology and method of | Laboratoires Pierre Fabre | Comment:<br><br>Doses quoted for these herbal medicine based on dry extract | Partially endorsed. The posology for the dry extract is expressed as the dry extract equal to the posology of |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| administration<br><br>Traditional use | | (DER 1:8-10), extraction solvent ethanol 11% m/m, marketed in Belgium, Spain, Italy and Sweden, are as follows:<br><br>- Adolescents, adults and elderly:<br>20 mg of dry extract, 3 times a day;<br><br>- Children 6-12 years:<br>20 mg of dry extract, 2 times a day.<br><br>Proposed change:<br><br>We proposed to add a new section iii):<br><br>iii) Herbal preparations<br><br>Dried extract (DER 1:8-10), extraction solvent ethanol 11 % m/m<br><br>*Adolescents, adults and elderly*<br><br>Single dose:<br>20 mg, 3 times daily.<br><br>*Children between 6-12 years*<br><br>Single dose:<br>20 g, 2 times daily. | the liquid extract in the reference product.<br><br>In case of children, the dry extract has to be administered 3 times daily, similarly to the liquid extract, since according to the Directive 2004/24/EC, Article 16c, 2. "A corresponding product, as referred to in paragraph 1(c), is characterised by having the same active ingredients, irrespective of the excipients used, the same or similar intended purpose, ***equivalent*** strength and ***posology*** and the same or similar route of administration as the medicinal product applied for." |
| 4.2. Posology and method of | Schwabe (No. 6) | **Proposed wording:**<br><br><u>Posology</u> | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| administration<br>Well-established use | | Adolescents > 12 years, adults and elderly<br>a) 3 times daily 30 drops liquid dosage form containing 80 % (m/m) herbal preparation [30 drops = approx. 1.43 ml = approx. 1.47 g liquid dosage form]<br>b) 3 times daily 7.5 ml liquid dosage form containing 0.2506 % (m/m) dried herbal preparation [7.5 ml = approx. 8.0 g liquid dosage form]<br>c) 3 times daily 20 mg of dried herbal preparation in solid dosage form<br><br>Children between > 6 and 12 years<br>a) 3 times daily 20 drops liquid dosage form containing 80 % (m/m) herbal preparation [20 drops = approx. 0.95 ml = approx. 0.97 g liquid dosage form]<br>b) 3 times daily 5 ml liquid dosage form containing 0.2506 % (m/m) dried herbal preparation [5 ml = approx. 5.3 g liquid dosage form]<br><br>Children between 1 and 6 years<br>a) 3 times daily 10 drops liquid dosage form containing 80 % (m/m) herbal preparation [10 drops = approx. 0.48 ml = approx. 0.49 g liquid dosage form]<br>b) 3 times daily 2.5 ml liquid dosage form containing 0.2506 % (m/m) dried herbal preparation [2.5 ml = approx. 2.7 g liquid dosage form]<br>For liquid dosage forms, alternative volumes or dosage aids which result in above dosage related to the herbal preparation are accepted. | Well-established use not endorsed, see above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | _____<br>*Comment:*<br>*Corresponding to clinical data and referring to other Community monographs valid for liquid extract as herbal preparation, the dose is expressed as volume. Consequently, all additional information is given necessary to calculate the dosage related to the herbal preparation. So the posology may easily be transferred to other volumes or dosage aids.* | |
| 4.2. Posology and method of administration Well-established use | Schwabe (No. 7) | **Proposed wording:**<br><br>Duration of use<br>After relief of symptoms, continuation of treatment is recommended for several days in order to prevent a relapse.<br><br>Treatment duration should not exceed 3 weeks.<br>_____<br>*Comment:*<br><br>*The proposed wording corresponds with the duration of acute bronchitis and with the practise in treatment of infective diseases to prevent a relapse.* | Well-established use not endorsed, see above. |
| 4.2.<br><br>Posology and method of | Schwabe<br><br>(No. 8) | **Proposed wording:**<br><br>Method of administration | Well-established use not endorsed, see above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| administration<br><br>Well-established use | | Oral use. | |
| 4.2.<br><br>Posology and method of administration<br><br>Traditional use | Schwabe<br><br>(No. 9) | **Proposed wording:**<br><br>Adolescents > 12 years, adults and elderly<br><br>3 times daily 30 drops liquid dosage form containing 80 % (m/m) herbal preparation [30 drops = approx. 1.43 ml = approx. 1.47 g liquid dosage form]<br><br>Children between 6 and 12 years<br><br>3 times daily 20 drops liquid dosage form containing 80 % (m/m) herbal preparation [20 drops = approx. 0.95 ml = approx. 0.97 g liquid dosage form]<br><br>Alternative volumes or dosage aids which result in above dosage related to the herbal preparation are accepted.<br><br>_____<br><br>*Comment:*<br><br>*Corresponding to traditional use and referring to other Community monographs valid for liquid extract as herbal preparation, we propose to express the dose as volume. Consequently, we propose to add all additional information necessary to calculate the dosage related to the herbal preparation*. So the posology may easily be transferred to other volumes or dosage aids.* | The posology was recalculated (see above) based on the official data of the reference product. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | *… as to be taken from our registration file available at several national authorities [and being the basis of our product on the market in the corresponding Member States / see draft Assessment Report (section 1.2.)]. | |
| 4.3. Contraindica-tions<br>Well-established use<br>as well as<br>Traditional use | Schwabe<br>(No. 10) | **Proposed wording:**<br>Severe hepatic and renal diseases (as no sufficient experience is available in these fields).<br>Increased tendency to bleeding and application of coagulation-inhibiting drugs.<br>Hypersensitivity to the active substance.<br>_____<br>*Comment:*<br>*As there is no justification for any difference between well-established and traditional use products in this issue, the proposed wording is a harmonized one corresponding both to granted traditional registration and to granted marketing authorizations.* | Well-established use not endorsed, see above.<br>As for the wording proposed for the traditional use monograph, the suggested two additional sentences are not accepted. In case of hepatic and renal disorders there is no scientific evidence or warning sign on the potential harmful effect of Pelargonium in patients suffering in the above mentioned diseases.<br>Similarly, there is no scientific basis or evidence on the dangers of Pelargonium in patients who are taking anticoagulants. |
| 4.4 Special warnings and precautions for use | ESCOP | **Comment**<br>According to the draft monograph, "The use in children under 6 years of age has not been established due to lack of adequate data". This comment does not reflect the long standing use of the herbal preparation in children below the age of 6 years and data issued from observational studies in age groups below 6 years.<br>Through the different editions of the Rote Liste (see attached | Although there exist several clinical studies involving children under the age of 6 years, there is no stratification for age when assessing the safety (exact number of adverse events in this age group is not known) of the treatment. Hence, the confirmation of safety under 6 years was considered insufficient to allow the application in this age group in the |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | Table), a clear distinction was introduced regarding a specific dosage in children from the 1990 edition. It has been progressively detailed up to the 1998 edition which stated:<br><br>Children aged 6-12 years: 3 times daily 10-20 drops<br><br>Children below 6 years: according on age, 3 times daily 5-10 drops.<br><br>These children dosages should be taken into account in the Community herbal monograph on pelargonium root (see 4.2 Posology ).<br>Additionally, different observational studies [Heil, 1994; König, 1995; Dome and Schuster, 1996; Haidvogl, 1996; Haidvogl and Heger, 1996; Haidvogl, 2007; Matthys, 2007; Schapowal, 2007] included children population below the age of 6 years old (see attached Table 2). Efficacy and safety of the product were also investigated in a prospective, open multi-centre study in 1042 children up to 12 years old suffering from acute bronchitis [Kolodziej H, Schulz V, 2003]. The overall rate of children with adverse events was 1.2% (13 out of 1042). Adverse events with possible or probable relation with the medication were: diarrhoea or vomiting (3), rash (2), fever (1), dyspnoea (1) and psychomotor agitation (1).<br><br>The product having a well-established use in the paediatric population under 6 years of age as a traditional herbal medicinal product (including infants less than 2 years), it is justified to consider the use in children from 2 years (instead of from 6 years). This age limit is much more restricted than existing benefit-risk assessment based on observational studies | monograph. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | corresponding to more than 1100 children less than 6 years of age.<br><br>**<u>Proposal</u>:**<br>It should be read: "**The use in children under 2 years of age has not been established due to lack of adequate data"**. | |
| 4.4 Special warnings and precautions for use | Interest group Pelargonium | In the section 4.4 "Special warnings and precaution for use" of the monograph, the use in children is restricted to children between 6-12 years: "The use in children under 6 years of age has not been established due to lack of adequate data".<br><br>Consequently, in the section 4.2 "Posology and method of administration" of the monograph it is stated that "the use in children under 6 years of age is not recommended".<br><br>From our point of view, on the basis of the available clinical data, the use in children should be given in a broader age range also including children between 2-6 years of age.<br><br>Efficacy and safety data obtained from five clinical trials with a total of almost 1,300 children aged 0-6 years demonstrate that Pelargonium preparations are well tolerated and safe for short-term treatment of respiratory diseases such as acute bronchitis, tonsillopharyngitis and acute maxillary sinusitis in children of this age group.<br><br>In these clinical studies the age-dependent dosage of Pelargonium solution was as follows: children aged 0 to 2 years: 3 x 5 drops/day; children aged >2 to 6 years: 3 x 10 drops/day; children aged >6-12 years: 3 x 20 drops/day; | See above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | children > 12 years: 3 x 30 drops/day. These dosages were proven effective and tolerated well in the clinical trials with children aged 0 to >12 years.<br><br>A Pelargonium solution (Umckaloabo®) was effective in treatment of acute bronchitis in a non-controlled study with 742 children (237 aged 0-2 years; 312 aged 2-6 years) who suffered from acute bronchitis or acute exacerbation of a chronic bronchitis (Haidvogel 2007). A complete or partial remission of symptoms was noted in 90.2% of patients. In children aged 0-2 years, success rates were especially high. The symptoms headache, limb pain and sore throat completely resolved within three days of treatment and cough attacks resolved within eight days of treatment. The incidence of adverse drug reactions (ADRs) was 1.8% (1.1% with possible causal relationship). The ADRs were mild or moderate. There were no serious ADRs. ADRs resolved within two days. There were five drop outs.<br><br>In a non-controlled study a total of 2009 children (241 children aged 0-6 years) and adults with acute bronchitis or acute exacerbation of a chronic bronchitis were treated successfully with a Pelargonium solution in terms of an improvement of the BSS (Matthys 2007). The responder rate was 68.0%. Complete recovery was reported in 69% of patients and major improvement for 25% of patients. In the subgroup of infants, which included all children with less than 3 years of age the mean BSS decreased from 5.2 points at baseline to 1.2 points at the third follow-up. Total incidence of ADRs was 1.2%. The ADRs were mild or moderate. Most frequent ADRs were | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | gastrointestinal complaints.<br><br>In a non-controlled study 259 children (83 aged 0-2 years; 112 aged 0-6 years) with acute bronchitis or acute exacerbation of a chronic bronchitis were treated successfully with a Pelargonium solution in terms of an improvement of the BSS (Dome 1996). The percentage of patients who experienced recovery and/or improvement of individual symptoms were about 80%. High recovery rates for Pelargonium were observed for the symptoms chest pain, rattling in the throat, dyspnoea and expectoration. The incidence of ADRs was 2.3%. The ADRs were mild or moderate. There were no drop outs.<br><br>In a non-controlled study 166 children (112 aged 0-6 years) with acute or chronic viral or bacterial infections of the respiratory tract or ear, nose and throat were treated successfully with a Pelargonium solution in terms of an improvement of symptoms (Heil 1994). After one week of treatment of treatment, a total of 70% to 90% of the patients were without symptoms (cough, fever, expectoration, rhinitis, headache, sore throat, dysphagia, feeling of exhaustion, inappetence, limb pain and otalgia) or showed a major improvement. No adverse events or drop outs were reported.<br><br>In a placebo-controlled study 200 children and adolescents (1-17 years) with acute bronchitis were treated successfully with a Pelargonium solution in terms of an improvement of the BSS (Kamin 2010). The mean decrease in the three individual symptoms of the BSS total score from day 0 to day 7 was more pronounced in the Pelargonium group compared to placebo | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | with significant advantages of Pelargonium for the individual symptoms “coughing” and “pulmonary rales at auscultation”. The general symptoms “absence of appetite” and “headache” significantly more improved in the Pelargonium group as compared with placebo. The health status and quality of life showed significantly better results for the Pelargonium group compared with placebo. The incidence of adverse drug reactions (ADRs) was 30% (8 ADRs with possible causal relationship). The ADRs were mild or moderate. There were no serious ADRs.<br><br>Overall the efficacy and safety data obtained from these clinical trials with children aged 0-6 years demonstrate that Pelargonium preparations are well tolerated and safe for short-term treatment of respiratory diseases such as acute bronchitis, tonsillopharyngitis and acute maxillary sinusitis in children of this age group.<br><br>Thus the use of Pelargonium preparations for the treatment of respiratory diseases in children aged 2-6 years appears to be justified.<br><br>In accordance with the statement on page 14 of the HMPC assessment report on Pelargonium sidoides (“the clinical studies including children suggested 3 x 5 drops of liquid preparation for children under 2 years of age, 3 x 10 drops for children between 2-6 years of age and 3 x 20 drops for children between 6-12 years of age”) the following age-dependent dosage of Pelargonium solution should be additionally included in the section 4.2 “Posology and method of administration” of | |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | the monograph:<br><br>Children aged >2 to 6 years: 3 x 10 drops | |
| 4.4.<br><br>Special warnings and precautions for use<br><br>Well-established use | Schwabe<br><br>(No. 11) | **Proposed wording:**<br><br>If the symptoms do not improve within one week, in case of fever lasting for several days or in case of shortness of breath or bloody sputum, a doctor should be consulted.<br><br><The appropriate labelling for excipients taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use" must be included.> | Well-established use not endorsed, see above. |
| 4.4.<br><br>Special warnings and precautions for use<br><br>Traditional use | Schwabe<br><br>(No. 12) | **Proposed change:**<br><br>The use in children ….lack of adequate data.<br><br>If the symptoms worsen during the use of the medicinal product, <u>in case of fever lasting for several days or in case of shortness of breath or bloody sputum a doctor</u> should be consulted.<br><br><The appropriate labelling for excipients taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use" must be included.><br>_____<br><br>*Comment:*<br><br>*Precautions related to severe symptoms should be the same as recommended in well-established use and should be clarified* | Not endorsed. These conditions are covered by the current wording of the monograph, therefore it is not justified to deviate from the standard wording of the template.<br><br>The current wording is the standard wording of the template, therefore the proposal is not endorsed. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | *by a doctor anyway. As regards the reference to the excipients guideline, we propose to replace "ethanol" by "excipients".* | |
| 4.5.<br>Interactions with other medicinal products and other forms of interaction<br>Well-established use | Schwabe<br>(No. 13) | **Proposed wording:**<br>None reported.<br>_____<br>*Comment:*<br>*We propose the same wording as given for traditional use, because there is no justification for any difference in this issue.* | Well-established use not endorsed, see above. |
| 4.6.<br>Pregnancy and lactation<br>Well-established use | Schwabe<br>(No. 14) | **Proposed wording:**<br>Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.<br>_____<br>*Comment:*<br>*We propose the same wording as given for traditional use, because there is no justification for any difference in this issue.* | Well-established use not endorsed, see above. |
| 4.7.<br>Effects on ability to drive and use | Schwabe<br>(No. 15) | **Proposed wording:**<br>No studies on the effect on the ability to drive and use machines have been performed. | Well-established use not endorsed, see above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| machines<br><br>Well-established use | | _____<br><br>*Comment:*<br><br>*We propose the same wording as given for traditional use, because there is no justification for any difference in this issue.* | |
| 4.8. Undesirable effects<br><br>Well-established use<br><br>as well as<br><br>Traditional use | Schwabe<br><br>(No. 16) | **Proposed wording:**<br><br>Mild gastrointestinal complaints (diarrhoea, epigastric discomfort, nausea or vomiting, dysphagia), mild nasal and gingival bleeding, allergic reactions have been reported. The frequency is not known.<br><br>If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.<br><br>_____<br><br>*Comment:*<br><br>*We propose to add mild nasal and gingival bleeding and to use here the same wording for well-established and traditional use, because there is no justification for any difference in this issue.* | Well-established use not endorsed, see above.<br><br>For the traditional use monograph, the proposed changes are endorsed. |
| Draft Assess-ment report (page 36/38) concerning<br><br>4.8.<br><br>Undesirable effects | Schwabe<br><br>(No. 17) | **Proposed change:**<br><br>Coumarins belong to the typical compounds of *Pelargonium* extract. …. To date, no case has been recorded in all the clinical trials that definitely proved any increased bleeding tendency that could be attributed to the treatment with *Pelargonium* extract (Kolodziej, 2008) (see below). One *in vivo* experiment affirmed this hypothesis. None of the coumarin compounds so far identified in the *Pelargonium* preparation | Endorsed. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | used in this *in vivo* experiment meets the criteria of minimal structural requirements for anticoagulant characteristics in coumarins, which would correspond to a hydroxy group in position 4 and a non-polar rest in position 3. Indeed, no anticoagulant effects were observed in this study. In addition, it could be demonstrated that comedication has no effect on the pharmacokinetics of warfarin (Koch and Biber, 2007).<br>_____<br>*Comment:*<br>*The information about the* in vivo *experiment with* Pelargonium *coumarins could be specified according to the data given in the publication by Koch and Biber 2007.* | |
| Draft Assess-ment report (page 36/38) concerning<br>4.8.<br>Undesirable effects | Schwabe<br>(No. 18) | **Proposed change:**<br>According to a pharmacovigilance report from Italy, a patient suffering from congenital cardiac malformation, bronchial pneumonia, epilepsy, hypothyroidism, oligophrenia was taking a number of medicines, among them a Pelargonium product, and was diagnosed with acute hepatopathy. ~~Although there was a positive rechallenge, t~~ Taking into account ...., preparations containing no alcohol should be preferred.<br>_____<br>*Comment:*<br>*Concerning the pharmacovigilance report from Italy referred to* | According to the information provided by the Italian authorities, the word rechallenge was changed to dechallenge. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | *in the Assessment report, following item should be considered: According to the data which was provided to us via a regional pharmacovigilance centre in Italy by a pharmacist there has been no positive rechallenge in this 46 years old patient. The Pelargonium sidoides drops were given from 26.02.11 – 01.03.11, there has been no rechallenge at all in this case. (see **appendix 4)*** <br><br> *So the clause* „Although there was a positive rechallenge…“ *should be deleted.* | |
| 4.9. <br> Overdose <br> Well-established use | Schwabe <br> (No. 19) | **Proposed wording:** <br> No case of overdose has been reported. <br> _____ <br> *Comment:* <br> *We propose the same wording as given for traditional use, because this wording meets the use by patients with acute bronchitis, too.* | Well-established use not endorsed, see above. |
| 5.1. <br> Pharmaco-dynamic properties <br> Well-established use | Schwabe <br> (No. 20) | **Proposed wording:** <br> Pharmacotherapeutic group: <br> Cough and cold preparations <br> ATC code: R 05 <br> In animal experiments, inhibition of sickness behavior (unspecific illness symptoms occurring in the context of an infection) and antioxidative properties could be demonstrated after oral application of *Pelargonium sidoides* extract in mice. | Well-established use not endorsed, see above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| | | In vitro, the following effects are verified for *Pelargonium sidoides* extract:<br>Stimulation of unspecific defense mechanisms:<br>- stimulation of ciliary beat frequency of epithelial cells,<br>- modulation of interferon synthesis and proinflammatory cytokines,<br>- stimulation of activity of NK-cells<br>- stimulation of phagocytes, expression of adhesion molecules, chemotaxis.<br>Antimicrobial effects:<br>- moderate direct antibacterial and antiviral properties<br>- increase/inhibition of adhesion of A-streptococci to desquamated/living epithelial cells<br>- inhibition of ß-lactamase.<br>Cytoprotective properties:<br>- inhibition of human leukocyte elastase<br>- antioxidative properties.<br>_____<br>*Comment:*<br>*The wording is part of the SPC of our products authorized for treatment of acute bronchitis, as assessed by national authorities. Detailed data are available at national authorities and could be supplied to the HMPC at request.* | |
| 5.2. Pharmaco-kinetic | Schwabe<br>(No. 21) | **Proposed wording:**<br>No data available. | Well-established use not endorsed, see above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| properties<br>Well-established use | | _____<br>*Comment:*<br>*The whole extract is to be considered as the active substance. Pharmacokinetic data on the individual substances are not available.* | |
| 5.3.<br>Preclinical safety data<br>Well-established use | Schwabe<br>(No. 22) | **Proposed wording**:<br>According to state of knowledge the recommended doses are safe in terms of toxicological effects.<br>In tests on reproductive toxicity in rats (combined segment I and segment II study) and in rabbits (segment II study) no effect on fertility and embryo-fetal development was observed. Postnatal development after prenatal and postnatal exposition was not examined.<br>_____<br>*Comment:*<br>*The wording is part of the SPC of our products authorized for treatment of acute bronchitis, e.g. in Germany. Detailed data were provided in the marketing authorization procedure and could be supplied to the HMPC by us at request.* | Well-established use not endorsed, see above. |
| 6. Pharmaceutical particulars<br>Well-established use | Schwabe<br>(No. 23) | **Proposed wording:**<br>Not applicable. | Well-established use not endorsed, see above. |

**ANNEXES**

**Annex 1** ESCOP list of references

**Annex 2** ESCOP Table 1.

**Annex 3** ESCOP Table 2.

**Annex 4** Finzelberg list of references

**Annex 5** Schwabe list of references

**Annex 1** ESCOP list of references

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**Annex 2** ESCOP Table 1.

**Table 1.** Umckaloabo-Stevenskur® and Umckaloabo® in Rote Liste

| **Rote liste edition** | **Therapeutic indication** | **Active substance**<br>**Posology** |
|---|---|---|
| **1939** | Prevention and cure of organic and surgical tuberculosis | Tincture 10%<br>2-3 x daily 5 drops to 1 teaspoon in water half an hour before meals. |
| **1974** | Supportive in case of tuberculosis, scrofulosis and chronic bronchitis | Percolate 1:10<br>Start with 3 times daily to increase to 4 times daily with 20 drops. |
| **1989** | Acute and chronic infections of viral and bacterial origin with purulent processes | Percolate 1:8 (10.8% ethanol V/V)<br>Start with 3 times daily to increase to 4 times daily with 20 drops. |
| **1990** | Acute and chronic infections of viral and bacterial origin with purulent processes | Percolate 1:8 (10.8% ethanol V/V in oral drops, i.e. 10.75% m/m in percolate)<br>3-5 times daily 10-20 drops;<br>**Children**: 3-5 times daily, a number of drops according to age; in chronic disease 3 times daily. |
| **1992** | Acute and chronic infections of viral and bacterial origin with purulent processes, especially of upper airways | Percolate 1:8 (12% ethanol V/V in oral drops, i.e. 12.1% m/m in percolate)<br>3-5 times daily 10-20 drops;<br>**Children**: 3-5 times daily x drops according to age; in chronic disease 3 times daily. |
| **1995** | Acute and chronic bronchitis, sinusitis and tonsillitis | Alcoholic extract 1 + 10 (12% ethanol V/V in oral drops, i.e. 12.1% m/m in alcoholic extract)<br>**Adults**: acute illness 3-5 times daily 10-20 drops, chronic disease 3 times daily 10-20 drops;<br>**Children (depending on age**): with acute conditions 3-5 times daily 5-10 drops, 3 times daily 5-10 drops for chronic diseases. |
| **From 1998 to 2005** | Acute and chronic infections, especially infection of the respiratory tract and of the throat-nose-ear area, such as bronchitis, sinusitis, | Alcoholic extract 1 + 10 (12% ethanol V/V in oral drops, i.e. 12.1% m/m in alcoholic extract)<br>**Adults and children over 12 years**: acute infections 3 times daily 20-30 drops. For subsequent treatment, especially in chronic disease or frequent relapses, 3 times daily 10-20 drops.<br>**Children aged 6-12 years**: acute infections 3 times daily 10-20 drops. |

| Rote liste edition | Therapeutic indication | Active substance<br>Posology |
|---|---|---|
| | angina, tonsillitis, rhinopharyngitis | **Children below 6 years**: according on age, 3 times daily 5-10 drops. |

**Annex 3** ESCOP Table 2.

**Table 2.** Clinical studies with EPs® 7630 solution in children below 6 years

| Study | Study design | Study population | Treatment | Safety results |
|---|---|---|---|---|
| **Haidvogl, 1996 Haidvogl and Heger, 2007** | MC, O, UC | Acute bronchitis or acute exacerbations of chronic bronchitis<br>n = 742<br>**< 2 years: 237**<br>**2-6 years: 321**<br>6-12 years: 168<br>Mean age: 4 ± 3 | EPs® 7630 solution<br>**< 2 years: 3x5 drops**<br>**2-6 years: 3x10 drops**<br>6-12 years: 3x20 drops<br><br>Duration: max 14 days | Tolerability rated as good or very good in 94.9% (no data in 3.2%)<br>13 patients (1.8%) showed mild to moderate adverse events which usually disappeared within 2 days (in 8 patients, a causal relationship to the test medication was not excluded; 2 of them got exanthema and one got diarrhoea)<br>**Authors' conclusion: "due to the extremely low rate of side effects", the product "proves to be a safe measure for the treatment of acute bronchitis especially in pediatric practice" the test medication "is a safe treatment of acute bronchitis in children"** |
| **Matthys et al, 2007** | MC, P, OO | Acute bronchitis<br>n = 2099 including 498 patients aged up to 18 years with<br>**< 2 years: 78**<br>**2-6 years: 163**<br>6-12 years: 127<br>12-18 years: 130 | EPs® 7630 solution<br>**< 6 years: 3x10 drops**<br>6-12 years: 3x20 drops<br>12-18 years: 3x30 drops<br><br>Duration: 14 days | Mild and moderate adverse events occurred in 13/420 (3.1%) children (3-18 years) and 3/78 (3.8%) infants (2 years or less). Most of adverse events corresponded to gastrointestinal disorders. In only one child the relation to study medication of an hypersensitivity reaction was assessed as "possible".<br>**Authors' conclusion: the "study medication is a safe and well-tolerated treatment for acute bronchitis in adults, children and infants"** |

| Study | Study design | Study population | Treatment | Safety results |
|---|---|---|---|---|
| **Dome and Schuster, 1996** | MC, O, P | Acute bronchitis or acute exacerbations of chronic bronchitis<br>n = 259<br>**< 2 years: 83**<br>**2-6 years: 112**<br>6-12 years: 64 | EPs® 7630 solution<br>**< 2 years: 3x5 drops**<br>**2-6 years: 3x10 drops**<br>6-12 years: 3x20 drops<br>Duration: max 13 ± 6 days | Tolerability rated as good or very good in 96.5%. The severity of reported adverse events was classified as mild to moderate and short-term.<br>**Authors' conclusion: the product is "a valuable therapeutic alternative in treatment of pediatric bronchitis"** |
| **Heil , 1994** | MC, O, P | Respiratory tract infections<br>n = 166<br>**< 6 years: 56**<br>6-12 years: 52<br>12-19 years: 58 | EPs® 7630 solution<br>**< 6 years: 15-30 drops**<br>6-12 years: 30-60 drops<br>12-19 years: 60-90 drops<br>Duration: 11 ± 13 days | Tolerability was assessed as good or very good by nearly 100% of patients and children. Only one patient evaluated the tolerability as moderate.<br>**Authors' conclusion: the product "especially in children and adolescents represents a valuable therapeutic alternative to conventional anti-infectives"** |

MC = multicentre, O = open, O = observational, P = prospective, UC = uncontrolled

EPs® 7630 solution corresponds to the medicinal product Umckaloabo®

**Annex 4.** Finzelberg list of references


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