European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *PRIMULA VERIS L., PRIMULA ELATIOR (L.) HILL*, RADIX' (EMEA/HMPC/143370/2006)

Table 1: Organisations providing comments on the draft 'Community herbal monograph on *Primula veris* L., *Primula elatior* (L.) Hill, radix' as released for consultation in March 2007 until 15 June 2007.

	Organisation
1.	The Association of the European Self-Medication Industry (AESGP)
2.	Bundesinstitut für Arzneimittel und Medizinprodukte, Germany
3.	Kooperation Phytopharmaka, Germany
4.	Europlant Phytopharm Sp z o.o., Poland

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Table 2: Discussion of comments

General comments	Comment and rationale	Rapporteur's comments
1	Well-designed clinical trials have only been performed with Primulae radix in combination with Thymi herba (see Appendix 1). But since both herbal drugs possess different modes of action with respect to their pharmacological effects, efficacy and safety must be assumed for each single drug. Different kinds of clinical trials, such as a randomized controlled clinical study with high level of evidence (Gruenwald 2005, 2006) and other well-designed trials (Ernst 1997) and drug monitoring studies (Nauert 2003, 2005) confirm the scientific credibility. The results demonstrate the efficacy and safety of primrose root preparations for more than 10 years, justifying the assessment of Primulae radix as a well-established used herbal drug, according to the guidelines EMEA/HMPC/104613/2005. Additionally, the well-documented efficacy and tolerability of primrose root preparations in children should be taken into consideration (Ernst 1997, Nauert 2003, 2005).	The draft monograph on Primula root covers only aspects of herbal medicinal products containing Primula root as the only active ingredient. No controlled studies have been performed with the herbal substance alone. A well-established use will be reconsidered during the preparation of a monograph for fixed combinations with Primula root. The well-established use for Primula root alone is not endorsed.
2	Inclusion of well-established medicinal use in accordance with the monographs published by ESCOP and Commission E	see above
3	Inclusion of well-established medicinal use in accordance with the monographs published by ESCOP and Commission E	see above
4	The literature list should be amended and evaluated:	
	1) de Corres LF, Corrales JL, Munoz D, Leanizbarrutia I (1984): Dermatitis alergicas de contacto por plantas. Allergol et Immunopathol 12/4: 313-319	The authors investigated Primula obconica not P. veris or P. elatior. Reference therefore not included.
	2) Ernst E, Sieder C, März R (1995): Adverse drug reactions to herbal and synthetic expectorants. Internat J Risk safety Med 7/3: 219-225	The authors studied not Primula flower alone but the combination product "Sinupret". The contribution of P. flower to the adverse effects cannot be estimated. Reference therefore not included.
	3) Ernst E (1995): Nebenwirkungen pflanzlicher und synthetischer Expektorantien. Z Phytother Abstractband 6. Phytotherapiekongress 5.-7.10.1995, Berlin	The reference is an abstract of a congress contribution. The content is identical with the reference cited above. Reference therefore not included.
	4) Fregert S, Hjorth N (1977) The Primula allergen primin. Contact Dermatitis 3: 172-174	Primin occurs in the aerial parts of P. veris and P. elatior only. The authors did not specify the plant part investigated. The stated absence of primin for P. elatior cannot be strictly assigned to Primulae radix. Reference therefore not included.

	5) Gaisböck F (1924): Radix Primulae als Expektorans und Diuretikum. Klein. Wschr 3/19: 474-479	Anecdotal reports of the expectorant and diuretic effect of Primulae radix. Analytical methods out of date. Reference supports the traditional use. Included in list of references.
	6) Grecu L, Cucu V (1975): Saponine aus Primula officinalis und Primula elatior. Planta Med 27: 247-253	Analytical methods out of date. Reference therefore not included.
	7) Grujic-Vasic J, Kovac EE, Rimpapa Z (1983): Noxious effects of Primula veris, Cyclamen europaeum and Saponaria officinalis saponins on fish. Folia Med Fac Med Univ Saraviniensis 18: 127-32	Fish-toxicity is a general property of saponins, no connection to safety or efficacy of Primula flower. Reference therefore not included.
	8) Hjorth N (1966): Primula dermatitis Trans St. John's Hospital Dermatol Soc 52: 207-219	The authors investigated Primula obconica not P. veris or P. elatior. Reference therefore not included.
	9) Jentzsch K, Kubelka W, Kvarda B (1973): Untersuchungen über den Saponingehalt von Radix Primulae veris L. im Verlauf mehrjähriger Kultur. Sci Pharm 41/2: 162-165	Does not contain valuable information fort he assessment of Primulae radix. Reference therefore not included.
	10) Lepoittevin JP, Benezra C (1991): Allergic contact dermatitis caused by naturally occurring quinones. Pharm Weekblad Scient 13/3: 119-122	The authors investigated Primula obconica not P. veris or P. elatior. Reference therefore not included.
	11) Logan RA, White IR (1988): Primula dermatitis: prevalence, detection and outcome. Contact Dermatitis 9/1: 68-69	The authors investigated Primula obconica not P. veris or P. elatior. Reference therefore not included.
	12) Merfort I (2002) Heil- und Nutzpflanzen mit Haut-Tücken. Pharm. Ztg 147/3: 10-15	No additional information. Secondary literature. No relevance for Primulae radix. Reference therefore not included.
	13) Nakamura T. Primula dermatitis in Japan. Contact Dermatits 328-329	The authors investigated Primula obconica not P. veris or P. elatior. Reference therefore not included.
	14) Oberst R (1986) Akute Tracheobronchitis. Kassenarzt 26:45-46	The article describes an open study with Phytobronchin, a product containing several herbal ingredients as well as ephedrine hydrochloride and guaifenesin. The contribution of the extract of Primulae radix cannot be estimated. Reference therefore not included.
	15) Primorac M, Sekulovic D, Antonic S (1985): In vitro determination of the spermicidal activity of plant saponins. Pharmazie 40/8: 585	Spermicidal activity is a general property of saponins, no connection to safety or efficacy of Primula flower. Reference therefore not included.
	16) Schubert HJ, Prater E, Sell M: Patch testing with primin in white petrolatum. Contact dermatitis 286	No relevance for Primulae radix. Reference therefore not included.
	17) Sterner W, Chibanguza G, März R (1983): Experimentelle Überprüfung der sekretolytischen Eigenschaften eines Phytopharmakons (Sinupret) und seiner Einzelkomponenten. Postervortrag 54. Jahresversammlung Deutsche Gesellschaft HNO-Heilkunde, Kopf- und Hals-Chirurgie Travemünde 15.-19.1983 101	Only abstract of a congress contribution. Original data later published (see AR reference Chibanguza et al (1984).

	18) Wagner H (1993). Neues über die Therapie von Bronchitis und Sinusitis. Z. Phytother 14: 73-74	Evaluation of the activity of Sinupret, a combination of 5 herbal substances including Primulae flos. Reference therefore not included.
	19) Wilde W (1979): Kontrollierte offene Studie mit Phytobronchin in einer Lungenfachpraxis. Die Therapiewoche 29: 7306-09	The article describes an open study with Phytobronchin, a product containing several herbal ingredients as well as ephedrine hydrochloride and guaifenesin. The contribution of the extract of Primulae radix cannot be estimated. Reference therefore not included.
5	Additional references	
	Bässler D, Zieseniß E (2005): Behandlung akuter Erkältungskrankheiten bei Kindern – Ergebnisse einer Anwendungsbeobachtung mit einem Primel-Thymian Präparat. Kongressband Phytopharmaka Phytotherapie. p 23.	Already considered in the AR
	Boyd EM (1954): Expectorants and respiratory tract fluid. J Pharm Pharmacol 6: 521-542.	Already considered in the AR
	Büechi S (1996). Antivirale Saponine. Pharmakologische und klinische Untersuchungen. Deutsche Apothekerzeitung 136: 89-98.	Already considered in the AR
	Cebo B, Krupinska J, Sobanski H, Mazur J, Czarnecki R (1976): Pharmacologica properties of saponin fractions from Polish crude drugs: Saponaria officinalis, Primula officinalis, and Aesculus hippocastanum. Herba Polon 22: 154-162.	Already considered in the AR
	Commission E (1988): Monographie: Primula Radix. Bundesanzeiger Nr. 122 vom 06.07.1988	Already considered in the AR
	Commission E (1990): Monographie: Primula Radix. Berichtigung von Bekanntmachungen über die Zulassung und Registrierung von Arzneimitteln. Bundesanzeiger Nr. 50 vom 13.03.1990	Already considered in the AR
	Ernst E, Maerz R, Sieder CH (1997): A controlled multi-centre study of herbal versus synthetic secretolytic drugs for acute bronchitis. Phytomedicine 4 (4): 287-293.	Included in AR. No change in conclusions.
	ESCOP (1997): PRIMULA RADIX (Primula Root). ESCOP Monographs First Edition.	Already considered in the AR
	ESCOP (2003): PRIMULA RADIX (Primula Root). ESCOP Monographs Second Edition.	Already considered in the AR
	European Pharmacopoeia (2004), Council of Europe (ed.), 5th edition.	Already considered in the AR
	Gruenwald J, Graubaum HJ, Busch R (2005): Efficacy and tolerability of a fixed combination of thyme and primrose root in patients with acute bronchitis. Arzneim.-Forsch./Drug Res. 55 (11): 669-676.	Already considered in the AR

	Gruenwald J, Graubaum HJ, Busch R (2006a): Evaluation of the Non-inferiority of a fixed combination of thyme fluid- and primrose root extract in comparison to a fixed combination of thyme fluid extract and primrose root tincture in patients with acute bronchitis. Arzneim.-Forsch./Drug Res. 56 (8): 574-581.	Already considered in the AR
	Gruenwald J, Graubaum HJ, Busch R, Bentley C, Fiebich B (2006b): Thymian und Primelwurzel – ein starkes Doppel gegen akute Bronchitiden. Zeitschrift für Phytotherapie 27: 214-220.	Summary of results of several clinical trials, al of them are already considered in the AR. Reference therefore not included.
	Hänsel R, Keller K, Rimpler H, Schneider G, eds. (1994): Primula. In: Hagers Handbuch der Pharmazeutischen Praxis. 5th ed. Volume 6: Drogen P-Z. Berlin: Springer-Verlag, 269-287.	Already considered in the AR
	Hostettman K, Marston A (1995): Saponins. Cambridge: Cambridge University Press.	Already considered in the AR
	Ismail C, Willer G, Steindl H (2003): Bronchipret® bei akuter Bronchitis. Schweizerische Zeitschrift für GanzheitsMedizin 15: 171-175.	
	Joachimowitz R (1920): Die Radix primulae, ein neues Expektorans. Wiener Klinische Wochenschrift 28: 606-608.	No relevant information. Already considered in the AR
	Loew D, Schroedter A, Schilcher H (1997): Phytopharmaka bei katarrhalischen Erkrankungen der oberen und unteren Atemwege. In: Loew D, Rietbrock N (eds) - Phytopharmaka III. Forschung und klinische Anwendung. Steinkopff, Darmstadt, 179-190.	Standard secondary literature. Already considered in the AR
	Nauert C, Eckert C (2003): Fixe Kombination aus Thymian-Fluidextrakt und Primelwurzel-Fluidextrakt zur oralen Therapie von Kleinkindern und Kindern mit Husten und Bronchialkatarrh. Zeitschrift für Phytotherapie 24: 130.	Abstract in a congress-report. No details given to the study medication. Reference therefore not included.
	Nauert C, Bentley C, Fiebich B (2005): In-vitro-Untersuchungen zur mukolytischen Wirkung einer fixen Kombination von Thymian und Primula. Kongressband Phytopharmaka Phytotherapie, Berlin, p. 31	Already considered in the AR
	Rao GS, Sinsheimer JE, Cochran KW (1974): Antiviral activity of triterpenoid saponins containing acylated b-amyrin aglycones. J Pharm Sci 63: 471-473.	Already considered in the AR
	Steinegger E, Hänsel R (1992): Primulasaponine und Primelwurzel. In: Pharmakologie, 5th ed. Berlin: Springer-Verlag, 210-211.	Standard secondary literature. Already considered in the AR
	Tschesche R, Wulff G (1965): Über die antimikrobielle Wirksamkeit von Saponinen. Z Naturforsch 20b, 543-546.	Already considered in the AR
	Tschesche R, Wulff G (1973): Chemie der Biologie der Saponine. In Herz W, Grisebach H, Kirby GW, (eds). Fortschritte der Chemie organischer Naturstoffe / Progress in the Chemistry of Organic Natural Products. Vienna-New York, Springer Verlag. Volume 30, 461-606.	Already considered in the AR
	Vogel G. (1963): Zur Pharmakologie von Saponinen. Planta Med 11: 362-376.	Already considered in the AR

	Wagner H, Wiesenauer M (1995): Phytotherapie – Phytopharmaka und pflanzliche Homöopathika: Atemwegserkrankungen. Gustav Fischer Stuttgart, 93-124.	Standard secondary literature. Already considered in the AR
	Wichtl M (1997): Teedrogen und Phytopharmaka: Primulae radix, Primulawurzel, 3th edition, WVG Stuttgart, 457-459.	Standard secondary literature. Already considered in the AR
	Wichtl M (2002): Teedrogen und Phytopharmaka – Ein Handbuch für die Praxis auf wissenschaftlicher Grundlage. 4. Auflage, 472-474.	Standard secondary literature. Already considered in the AR
	Wichtl M, Neubeck M (1999): Primelwurzel – Primulae radix. In: Hartke K, Hartke H, Mutschler E, Rücker G & Wichtl M, eds. Kommentar zum Europäischen Arzneibuch. Stuttgart: Wissenschaftliche Verlagsgesellschaft, Eschborn: Govi-Verlag, 92.	Already considered in the AR

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
2. Qualitative and quantitative composition	The pragaraph is incomplete with regard to the list of herbal preparations, which are in traditional use in EU and should be amended: Dense extract (6-10:1, water, preservative potassium sorbate 0,2%), Bronchosol Syrup Dense extract (5,6-10:1, water), Sinuforton Saft	The comment is supported with a reference (Myszynski: Fitoterapie, 1954). Include in monograph: soft extract (5-10:1), extraction solvent water.
2	Concerning herbal preparations, the declaration of the mentioned preparations must be brought in line with the mentioned Procedure Paper (EMEA/HMPC/182320/2005 Rev. 2), already existing monographs and currently developing guidance (Draft "Guideline on Declaration…" EMEA/HMPC/CHMP/287539/2005). Therefore, the DER and the extraction solvent should be given according the following example: -liquid extract (1:1), extraction solvent: ethanol 25% (V/V). Notice that for liquid extracts the DER has to be (1:1) otherwise the DER must be given as a range of the yielded extract.	endorsed
2	According the assessment report from 15.02.2007 based the mentioned herbal preparation ii F) soft extract (1-4:1, 20-55% V/V ethanol on the medicinal product: "Ipalat Halspastillen" and "Ipalat Halspastillen zuckerfrei". From our point of view the DER and the extraction solvent is not correct. The German medicinal products "Ipalat Halspastillen" and "Ipalat Halspastillen zuckerfrei" contain a soft extract (6-10:1), methanol, water, ammonia solution 10% (50,0:49,5:0,5). It has to be corrected or otherwise the following herbal preparation should be added to point ii) herbal preparations: ii) Herbal preparation: - soft extract (6-10:1); extraction solvent: Methanol, water, ammonia solution 10% (50,0:49,5:0,5).	endorsed
2	Point D): "Syrup (containing 1,5% dry extract A) must be deleted in this paragraph, because Syrup is not a herbal preparation. It is according Ph. Eur. monograph 1/2007:0672 defined as a pharmaceutical form. The containing herbal preparation: "dry extract" is already mentioned in A).	endorsed

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
2	Notice that for tinctures (see ii E) the currently developing guidance (Draft "Guideline on Declaration…" (EMEA/HMPC/CHMP/CVMP/ 287539/2005) demands the declaration of the drug extract ratio and not the drug extraction solvent ratio as it has been practicable before.	
2	Section well-established use: i) Herbal preparations A) Dry extract (3-9:1; 40-50 % v/v ethanol) B) Soft extract (7.7:1, 50% methanol) C) Soft extract (1-4:1, 20-55% v/v ethanol) D) Liquid extract (1:1; 70 % v/v ethanol), E) Liquid extract (1: 2-2.5; 70% v/v ethanol) F) Tincture (1:5; 70 % v/v ethanol) Reasons: The German "Rote Liste 2007" lists all herbal preparations containing Primula radix; it should be noted that all preparations are combinations (usually with thyme extract). These preparations are based on the German Commission E monographs "Primulae radix" [2] and "Fixed combination of *Primula* root and thyme herb" [1]. The efficacy was by definition accepted, provided the quantity of Primulae radix was within the boundaries defined by the monograph. The German Commission E monographs specifically state the dose range of comminuted herb and tincture within corresponding preparations. The ESCOP monograph likewise does not define the qualitative and quantitative composition more precisely. Again, all preparations equivalent to 0.5-1.5 g of the herbal drug substance are accepted [3].	Soft extract B) included in monograph under traditional use. See general comments. Well-established use not endorsed
3. Pharmaceutical form	The term "liquid and solid dosage forms for oral use" in paragraph "pharmaceutical form" includes "syrup". Therefore it is not necessary to list the term "syrup" in this paragraph.	The published draft monograph does not list the term "syrup" in the paragraph "pharmaceutical form".
3	<u>Well-established use</u> Dry, soft and liquid extracts with ethanol or methanol as extraction solvent. Tinctures (1:5) with ethanol 70%.	See general comments. Well-established use not endorsed

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
	Reasons: This definition would correspond to the products for which there is long standing experience, and which correspond to the definition of the German Commission E monographs [1;2]. The definition is also in accordance with the recommendations in the ESCOP monograph [3].	
4.1 Therapeutic indications	Well-established use *Catarrhs of the respiratory tract with viscous mucus, treatment of symptoms of bronchitis, productive cough* Reasons: The indication suggested for the well-established medicinal use of Primula root corresponds to the one defined in the ESCOP-monograph [3], the Hager monograph [4], and the German Commission E monograph (1,2). In case of combination with thyme, the indication is also covered by clinical trials. Moreover, Primula root fulfils the requirements of a well-established medicinal use having been used for more than 10 years in the Community. According to EMEA/HMPC/104613/2005 "*the period of time required for establishing a well-established medicinal use of herbal substance/herbal preparation must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community*". The medicinal use of Primulae radix of at least ten years is well documented in several monographs published e.g. by Commission E (1988, revised 1990) (2) and ESCOP (3; first edition 1997), therefore the necessary time of medicinal use of primrose root has been passed to classify this herbal substance as "well-established". Also the provisions defined by EMEA/HMPWP/23/99: "*The inclusion of a herbal drug in official pharmacopoeias of different Member States or the inclusion in scientific reference textbooks may contribute to substantiate a well-established medicinal use*" are fulfilled (5). The draft monograph prepared by the HMPC indicates the traditional use of Primulae radix as an "expectorant in cough associated with cold". In contrast, both, Commission E and ESCOP have taken a further step and support the use of Primula radix in the treatment of (a) productive cough (6,7), (b) catarrh of the respiratory tract (6,8), and (c) chronic bronchitis (9). Several well-designed clinical trials have been performed within the	See general comments. Well-established use not endorsed Amendment of indication for traditional use: the treatment of bronchitis would need supervision of a doctor.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
	last ten years proving the efficacy and safety of preparations with primrose root in the treatment of acute bronchitis (see Appendix 1, Table). Therefore it is strongly recommended to include this indication within the well-established section.	
4.1	Well-established use "For the treatment of symptoms of acute bronchitis and infections of the respiratory tract with viscous mucus." The monograph draft prepared by HMPC indicates the traditional use of Primulae radix as an "expectorant in cough associated with cold". In contrast, both, Commission E and ESCOP have taken a further step and support the use of Primula radix in the treatment of (1) productive cough (Wichtl 2002, Steinegger 1992), (2) catarrh of the respiratory tract (Wichtl 2002, Hänsel 1994), and (3) chronic bronchitis (Wichtl 1999). Especially the indication bronchitis should be of major concern, since several well-designed clinical trials have been performed within the last ten years proving the efficacy and safety of preparations with primrose root in the treatment of acute bronchitis (see Appendix 1). Therefore it is strongly recommended to include this indication to the draft under discussion, but within the well-established section.	See general comments. Well-established use not endorsed
4.2 Posology and method of administration	Add: Adolescents over 12 years of age, adults, elderly: F) soft extract (6-10:1) extraction solvent: methanol, water, ammonia solution 10% (50,0:49,5:0,5): 22,5 mg (corresponding 135-225 mg herbal substance) Recommended mean daily dose: F) soft extract (6-10:1) extraction solvent: methanol, water, ammonia solution 10% (50,0:49,5:0,5): 22,5 mg (corresponding 405-675 mg herbal substance) We propose to put the text in line with the text of posology of the valerian root monograph. In the AR the dosage is calculated towards x g drug. The sentence "The daily dosage is equivalent/correspond to … g of the herbal substance." should be added also in the monograph. The texts of different monographs should be consistent.	The proposed daily dosage in milligrams is obviously wrong. From the calculation of the amount of corresponding herbal substance it is concluded that the mentioned soft extract is administered 3 times daily, therefore the daily dosage should be 67,5 mg Dosage for soft extract included in monograph. A dosage for children is given only for those herbal preparations, which were included in clinical trials. The data concerning the dosage are calculated on the basis of the dosage in the clinical trials and not on the basis of equivalents to the herbal substance.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
	Duration of use: Children between 4 and 12 years of age and adolescents: The duration of use is not limited. If the symptoms persist longer than one week, a doctor or a qualified health care practitioner should be consulted. Reasoning: The new formulation makes clear, a longer use on the supervision of a doctor is allowed. It is not necessary to distinguish the duration of use (without the supervision of a doctor) in 5 days and one week for the different classes of age.	Duration of use: Not endorsed. The indication is only cough associated with cold, a self limiting disorder. If cough lasts longer than 1 week it needs a different treatment.
4.2	<u>Well-established use</u> Posology *Recommended mean daily doses* *Adolescents between 10 and 18 years of age, adults and elderly* Herbal preparations corresponding to 0.5-1.5 g of herbal drug substance Tincture (1:5): 1.5-3 g *Children between 4 and 10 years of age* Herbal substance for tea preparation: 0.5 to 1.0 g Herbal preparations correspondingly Tincture (1:5): 1-2g *Children under 4 years of age* Herbal substance for tea preparation: 0.3-0.8 g Herbal preparations correspondingly Dosage frequency: May be taken every 2 to 3 hours (up to a maximum of 6 times daily) *Duration of use* Medical attention should be sought if after 10-14 days of treatment the symptoms do not improve. *Method of administration* Oral use	See general comments. Well-established use not endorsed

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
	Traditional use Posology *Recommended mean daily doses* *Adolescents between 10 and 18 years of age, adults and elderly* Herbal substance for tea preparation: 0.5 to 1.5 g Tincture (1:5): 1.5-3 g Herbal preparations correspondingly Dosage frequency: May be taken every 2 to 3 hours (up to a maximum 3 times daily) *Children between 4 and 10 years of age* Herbal substance for tea preparation: 0.5 to 1.0 g Herbal preparations correspondingly Tincture (1:5): 1-2 g *Children under 4 years of age* Herbal substance for tea preparation: 0.3-0.8 g Herbal preparations correspondingly *Duration of use* Medical attention should be sought if after 10-14 days of treatment the symptoms do not improve. *Method of administration* Oral use Tea preparation: 0.2 to 0.5 g of herbal substance or comminuted herbal substance for decoction, infusion or macerate. As an expectorant one cup of tea every 2 to 3 hours. Background: The very specific dose indications for traditional use do not appear appropriate in view of the very broad dose definition in the Primulae radix monographs [1-4]. The limitation of the dose for children is not supported by the monographs. Likewise, a contraindication for children under 4 years old does not reflect the fact that combination products from thyme herb and *Primula* root count among the most important cough preparations for children worldwide. The well-documented efficacy and tolerability of primrose root prepara-	Traditional use: it has been agreed that the treatment of cough in children below 4 years of age needs supervision of a doctor. Therefore this age group cannot be considered under traditional use. The very specific dosage for children is taken from the clinical trials. Only those herbal preparations are considered, where data are available. Duration of use: The number of days, after which a doctor should be consulted, has been discussed intensively. The working party discussed this issue once more after the consultation phase. The members agreed to propose 1 week for the duration of use for all patients.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
	tions in children should be taken into consideration (10,11,12,13,31). In these studies children younger than 1 year old were successfully treated with Primula root preparations, also in combination with thyme, without any concern regarding the tolerance of the preparations used. Due to these results it is justified to extend the use of primrose root preparations for children under 4 years of age. A strict limitation of the duration of use to 5 days in children and 7 days in adolescents and adults is not supported by the ESCOP monograph, which states a de facto unlimited duration of intake (3). As shown in the above mentioned studies primrose root preparations can also be used in this patient group without any safety problems for at least 7 to 10 days. Children benefited from this therapy and the compliance of the physicians and parents were very high, which is an important success factor in pediatrics. In general the limitation for the treatment to 1 week should be extended to 10-14 days, since the severity of viral infections of the respiratory tract can individually differ. Due to these differences a successful therapy with primrose root preparations can last 10 days or even longer without being a hazard for the treated patient.	
4.2	The well-documented efficacy and tolerability of primrose root preparations in children should be taken into consideration (Ernst 1997, Nauert 2003, 2005). In these studies children up to an age of 1 year were successfully treated without any concern regarding the tolerance of the preparations used. Due to these results it is justified to extend the use of primrose root preparations for children of an age of 1 year and older. In addition it makes no sense to limit the duration of use for children to 5 days. As shown in the above mentioned studies primrose root preparations can also be used in this patient group without any safety problems for at least 7 to 10 days. Especially children benefit from this therapy and the compliance of the physicians and parents was very high, which is an important success factor in pediatrics. In addition the first sentence under point 4.4 (Special warnings…) should be withdrawn. Furthermore the limitation for the treatment of adults to 1 week should be extended to 10-14 days, since the severity of viral infections of the respiratory tract can individually differ. Due to these differences a successful therapy with primrose root preparations can persist up to 10 days or even longer without being a hazard	See above

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
	for the treated patient. In summary the first sentence under the point *Duration of use* should be: "*Children over 1 year of age, adolescents over 12 years of age, adults, elderly: Medical attention should be sought if after 10-14 days of treatment the symptoms do not improve.*"	
4.3 Contraindications	Well-established use Hypersensitivity to the active substance or to other *Primula* species.	See general comments. Well-established use not endorsed
4.4 - Special warnings and precautions for use	Well-established use None required. If dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted. For tinctures and extracts, the appropriate labelling for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use", must be included. Traditional use ~~The use in children under 4 years of age is not recommended because medical advise should be sought.~~ Caution is recommended in patients with gastritis or gastric ulcer. If dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted. For tinctures and extracts, the appropriate labelling for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use", must be included. Reasons: The special warning not recommending the use in children under the age of 4 years in the "Traditional use" section is not appropriate since the use of thyme/*Primula* root combinations in children is frequently recommended by paediatrics. In addition, a combination product of *Primula* root and thyme has explicitly been tested in observational studies involving >300 children of 1 to 4 years of age each [11,13]. We believe that this statement should be deleted.	See general comments. Well-established use not endorsed Traditional use: See above. Changes not endorsed.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
4.5 Interactions	The following text should be introduced: No studies on interactions with other medications have been performed. Interactions are not reported.	Not endorsed. The proposed wording 'none reported' has been chosen for other monographs too.
4.5	Well-established use None reported.	See general comments. Well-established use not endorsed
4.6. Pregnancy and lactation	Well-established use Safety during pregnancy and lactation has not been established. No adverse effects have been reported from the use of Primula root as a medicinal product during pregnancy and lactation. Due to the missing data Primula root preparations should only be used after consultation of a qualified health care practitioner. Traditional use Safety during pregnancy and lactation has not been established. No adverse effects have been reported from the use of Primula root as a medicinal product during pregnancy and lactation. Due to the missing data Primula root should only be used after consultation of a qualified health care practitioner. Reasons: Missing data do not justify the original formulation. Since no adverse effects or risks of Primula root formulations during pregnancy have been reported, the use should be allowed under the above mentioned conditions.	See general comments. Well-established use not endorsed Traditional use: Since no data on safety during pregnancy and lactation are available, a qualified health care practitioner has no scientific basis for an advice. The long traditional use cannot guarantee safety during pregnancy and lactation. Therefore no recommendation for the use could be given.
4.7. Effects on ability to drive and use machines	Well-established use None known. Reasons: Corresponds to ESCOP monograph (3).	See general comments. Well-established use not endorsed
4.8. Undesirable effects	Well-established use Stomach upset, nausea and vomiting have been observed in very rare cases with overdosing. Allergic reactions may occur in very rare cases.	See general comments. Well-established use not endorsed

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	If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted. <u>Traditional use</u> Stomach upset, nausea and vomiting may occur on overdosing. ~~The frequency is not known.~~ Allergic reactions may occur in very rare cases. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted. <u>Reasons:</u> This corresponds to ESCOP and Hager monograph (3,4). These effects usually arise after intake of *Primula* roots at much higher level than those recommended. Their mechanism of action is reflex increase of mucosal activity through non-specific irritation of the gastric mucosa (4). As this adverse effect may occur in case of overdose of *Primula* root, the statement on the unknown frequency is misleading and should be deleted. Allergic reactions are not reported in the most recent Hager monograph (4), but can occur in very rare cases.	Traditional use: Such ADRs have been reported from the clinical trials, particularly from children. These adverse effects are reported when the study medication was given in the correct amount. A statement on the frequency has to be given. Since no detailed numbers are reported the sentence "The frequency is not known" has to taken.
4.9 Overdose	<u>Well-established use</u> Overdose may lead to stomach upset, vomiting or diarrhoea.	See general comments. Well-established use not endorsed
5. Pharmacological properties	A short summary of results of in-vitro and in-vivo studies with preparations of Primula flos should be added.	Since data on pharmacological properties are not required the MLWP agreed to present these details in the assessment report only.
5	Numerous studies reported the expectorant and secretolytic activity of primrose root, which is also depicted in the monographs of ESCOP (2003) and Commission E (1988, 1990). The following literature should be taken into consideration: Joachimowitz 1920, Boyd 1954, Steinegger 1992, Hänsel 1994, Hostettman 1995, Wagner 1995, Loew 1997, Wichtl 1997 among others. Additionally, a lot of studies investigating toxicological aspects were performed: Vogel 1963, Tschesche 1965 & 1973, Cebo 1976, Hostettman 1995 among others. Reports of antiviral effects are given by e.g. Rao 1974, Büechi 1996. The study models for the *in-vitro* and *in-vivo* studies, as well as the detection methods were adequate and appropriate to prove the pharmacological-toxicological profile of primrose root. In these preclinical studies the efficacy and safety profile was clearly confirmed. This should be added to	See general comments. Well-established use not endorsed Traditional use: Since data on pharmacological properties are not required the MLWP agreed to present these details in the assessment report only.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
	the corresponding section in the HMPC monograph draft. In addition these results support the assessment of primrose root being a well-established herbal drug for the use as an expectorant in the treatment of acute bronchitis.	
5.1 Pharmacodynamic properties	Well-established use For *Primula* root preparations as a single substance scientific data are available. These data document that Primula root acts through an irritation of the gastric mucosa by saponins, which provokes a reflex increase in bronchial secretion. This in turn dilutes the bronchial mucus and reduces its viscosity. Combinations of *Primula* root preparations with thyme extracts have been shown to be clinically efficacious. Background: An increase in the ciliary activity of throat epithelium of the curarized frog was observed under the influence of an undefined mixture or *Primula* root saponins [14]. *Primula* root preparations have not been tested in isolated form. However, the combination with thyme as recommended by the German Commission E monograph (1) was tested in horses suffering from respiratory tract symptoms. Pulmonary pressure and airway resistance of the horses' lungs were significantly improved after one month of treatment, although the severity of the clinical signs and the arterial oxygen partial pressure had not improved significantly (15). Numerous studies reported the expectorant and secretolytic activity of Primula root, which is also depicted in the monographs of ESCOP (3) and Commission E (1,2). The following literature should be taken into consideration: e.g., Joachimowitz 1920 (16), Boyd 1954 (17), Steinegger 1992 (7), Hänsel 1994 (8), Hostettman 1995 (18), Wagner 1995 (19), Loew 1997 (20), Wichtl 1997 (21). Additionally, many studies were performed to investigate the toxicological aspects, e.g. Tschesche 1965 & 1973 (22,23), Cebo 1976 (24), Hostettman 1995 (18). Reports on antiviral effects were published by Rao 1974 (25) and by Büechi 1996 (26). The *in-vitro* and *in-vivo* studies models as well as the detection methods were adequate and appropriate to provide reliable information on the	See general comments. Well-established use not endorsed Traditional use: Since data on pharmacodynamic properties are not required the MLWP agreed to present these details in the assessment report only.

Line no or section and paragraph no	Comment and rationale	Rapporteur's comments
	pharmacological-toxicological profile of primula radix. In these preclinical studies the efficacy and safety profile were clearly confirmed. This should be added to the corresponding section of the HMPC monograph draft. In addition these results support well-established use of Primula radix as an expectorant in the treatment of acute bronchitis. The results of two *in-vitro* studies investigating the mucolytic activity of primrose root and thyme (12,27) and their possible synergistic effects, were recently published. In those studies, a validated and standardized model was used to assess both the combined and individual impact of primrose root and thyme fluid extract on the synthesis of interleukin-8 (IL-8) in lipopolysaccharide (LPS)-pre-treated primary human monocytes. After a rhinoviral infection the production of IL-8 is considerably increased in the nasal mucosa and bronchia. This results in a mobilization of migratory immune cells leading to characteristic cold symptoms such as synthesis of mucus. It could be shown that primrose root fluid-extract inhibits LPS-induced release of IL-8 in a dose-dependent manner, with statistically significant inhibition at concentrations of 0.25%, 0.5% and 1%. In contrast, thyme fluid-extract only caused a slight dose-dependent inhibition of IL-8 at concentrations of 0.01% and 1%. This corroborates the important role of primrose root in the treatment of infections of the respiratory tract. The combination of thyme and primrose root fluid-extracts provoked a stronger inhibition of IL-8 than each individual extract. These results were also found in a second investigation (27). The molecular mode of action regarding this synergistic inhibition is not clearly understood so far, but it is possible that thyme extract influences another intracellular target than primrose root. Nevertheless, these *in-vitro* studies have proven that primrose root is the more effective component within the combined preparation and therefore appears to be mainly responsible for the therapeutic effect. Clinical data No clinical data are available on mono-preparations of *Primula* root. The combination with thyme has, however, been positively tested in randomized clinical trials (10,28,29) as well as in observational studies involving children under 4 years old (11,13,31) (see also information listed in Appendix 1). The pharmacological effects, efficacy and safety of both herbal	

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	drugs can be explained by their different modes of action. Different kinds of clinical trials, such as a randomized controlled clinical study with high level of evidence (28,29) and other well-designed trials (10) and drug monitoring studies (11,12,31) provides more credibility. The results demonstrate the efficacy and safety of primrose root preparations for more than 10 years, justifying the assessment of Primulae radix as a well-established used herbal drug, according to the guidelines EMEA/HMPC/104613/2005. Additionally, the well-documented efficacy and tolerability of primrose root preparations in children should be taken into consideration (10,11,12).	
5.2 Pharmacokinetic properties	Well-established use No specific data available. Saponins are generally poorly absorbed by the body. Background: *The* saponins in *Primula* root provoke an irritation of the gastric mucosa, which provoke in turn a reflex increase in bronchial secretion, leading to a dilution of the mucus and a decrease of its viscosity (3,4). Pharmacokinetic studies are not likely to yield meaningful data as the effect is mostly due to a local action of Primula saponins and not due to a systemic effect.	See general comments. Well-established use not endorsed Traditional use: Since data on pharmacokinetic properties are not required the MLWP agreed to present these details in the assessment report only.
5.3 Preclinical safety data	Well-established use No relevant toxicological effects are apparent from prolonged intake of saponin-containing food and medicinal plants. Traditional use Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended~~, unless necessary for the safe use of the product~~. ~~Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.~~ Background: Directive 2001/83/EC does not require pre-clinical safety data. Safety of traditionally applied products is sufficiently characterized by long-standing experience. Thus, the restriction "unless necessary for the safe use of the product" is misleading in the case of *Primula*, as there is no evidence of unsafe use.	See general comments. Well-established use not endorsed Traditional use: Since preclinical safety data are not required the MLWP agreed to present these details in the assessment report only. Since data on genotoxicity are required for a community list entry, the statement 'Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed' indicates that a list entry is not supported.

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	Toxicological examinations would have to be based on a relevant absorption of the saponins from *Primula* root. However, these compounds are only poorly absorbed and exert a local reflectory effect via the gastric mucosa (3,4). Toxicity studies with *Primula* root are therefore not likely to produce meaningful results. The oral LD_{50} of plant saponins ranged from 50 to 960 mg/kg in rodents (30). The saponin fraction from *Primula veris* had an LD_{50} of 24.5 mg/kg on testing in mice (4). No relevant toxicity is therefore to be expected from the oral intake of recommended doses of *Primula* root preparations (4).	