9 July 2013
EMA/HMPC/897630/2011 *Corr.*[1]
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal monograph on *Thymus vulgaris* L. and *Thymus zygis* L., herba and *Primula veris* L. and *Primula elatior* (L.) Hill, radix (EMA/HMPC/130042/2010)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Thymus vulgaris* L. and *Thymus zygis* L., herba and *Primula veris* L. and *Primula elatior* (L.) Hill, radix as released for public consultation on 15 February 2011 until 15 August 2011

	Organisations and/or individuals
1	Krka, d.d., Slovenia
2	Kooperation Phytopharmaka, Germany
3	Association of the European Self-Medication Industry - AESGP

[1] Correction on page 18 concerning the dosage recommendation for preparation f) in adolescents, adults and elderly

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Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	**Comment and Rationale**	**Outcome**
KOOP PHYTO	Kooperation Phytopharmaka, a German scientific organisation, would like to comment on the HMPC draft monograph on *Thymus vulgaris* L. and *Thymus zygis* L., herba and *Primula veris* L. and *Primula elatior* (L.) Hill, radix The preparation of a draft combination monograph on this combination is welcomed by Kooperation Phytopharmaka, as it is used in some of the most widely used herbal medicinal products in Europe. Taking into account the available information on preparations in the market, their clinical use and the published literature, Kooperation Phytopharmaka would like to suggest some modifications of the monograph, with respect to the range of preparations covered (inclusion of a further preparation), the use in children of lower age, and the assignment of preparations to traditional use. On the other hand, data from clinical studies suggest that an assignment of some preparations to well established use is adequate. The combination of thyme and Primula roots has been described by the German Commission E in its monograph from 1992, as far as the component extracts were covered by the respective monographs of the same commission (Primulae radix 1988, thyme herb 1984). Recently, some publications and guidance documents, some of which are cited in the list of references of the HMPC have investigated whether acute bronchitis and cough associated with cold can be successfully treated by medicinal products at all. This includes the Cochrane review published by Smith et al. in 2008 covering a set of studies conducted with OTC medicines. However, it did not include herbal medicines. The studies planned and conducted specifically to show the efficacy	**General remark to the comments related to well-established use:** Although the controlled clinical trials which were performed with some of the herbal preparations suggest a certain activity the discussions on the monograph resulted in the decision that well-established use cannot be supported. Rationale: As pointed out in the comments of interested parties there is at the moment no 'gold standard' for end points used in clinical trials with the indication 'cough'. The BSS symptom score, which was used in some of the clinical trials, is a non-validated score. Even when positive signals were detected for the total score as well as for the single symptoms, the lack of validation remains as critical deficiency. Moreover the inclusion criterion 'acute bronchitis' remains unclear. Acute bronchitis is not well defined. In the comments of interested parties it is stated that 'acute bronchitis' is an inappropriate wording and should be read as 'common cold'. However, the total set of symptoms of common cold was not considered in the clinical trials. For the support of well-established use it is impossible to replace inclusion criteria from

GENERAL COMMENTS		
	of these medicines do not cover the preparations and studies mentioned in the current draft monograph. Also e.g. the ACCP practice guidelines, published by Irving et al. in 2006, question the validity of some of the parameters used for measuring the treatment outcome in clinical studies. This publication however has a scope that largely differs from the patient groups and medications mentioned in the present monograph draft, mainly focussing on different types of chronic cough and not including any herbal medicine. The same applies to the ERS guideline published by Morice et al. in 2007 and the DEGAM guideline from 2008. In the first of these both guidelines, it is even stated, that the testing methology "depends greatly upon the mode of action of the agent", which makes clear that herbal medicines are out of scope of these guidelines. With regard to the methodology of the clinical studies with combinations of thyme herb and Primula root, it can be stated that it has been successfully used to describe the course of acute bronchitis and cough associated with cold and the clinical usefulness of herbal medicines in these indications in a large number of studies. These studies therefore should cover the requirements of the guideline EMEA/HMPC/104613/2005 stating that at least one controlled clinical study (clinical trial, post-marketing study, epidemiological study) of good quality is required to substantiate efficacy. Even in the case of the absence of a controlled clinical trial for a specific preparation similar to those used in clinical studies, a case-by-case assessment taking into account possible benefits, risks and types of disease should allow to rate it as in well established use. There also might questions arise from the fact that the indication wording in the of the monograph is "cough associated with cold", while the wordings of the indications of the clinical studies are not identical with this wording. Indications in the clinical studies are e.g.: ▪ Acute bronchitis (Grünwald et al. 2005, 2006; Nauert et al. 2005; Ernst et al. 1997, Ismail et al. 2003) ▪ Acute bronchitis with productive cough (Kemmerich et al. 2007) ▪ Cough and bronchial catarrh (Nauert et al. 2006) ▪ acute upper respiratory tract infections (Fasse et al. 2006)	clinical trials with different wordings. Taking all facts of the clinical trials together, the HMPC was of the opinion that the criteria for well-established use as defined in the legislation and defined in the guideline EMEA/HMPC/104613/2005 are not fulfilled, because the quality of the studies was not of the required level.

GENERAL COMMENTS		
	In the monograph of Commission E, 'Fixed combination of Primula root and thyme herb' German Comission E 1992), the wording of the indication is: 'Common cold of the upper respiratory tract with secretion of mucus. In the more recent ESCOP monographs the indication is "Catarrh of the upper respiratory tract, bronchial catarrh and supportive treatment of pertussis" (ESCOP 2003 'Thymi herba') and "Productive cough, catarrh of the respiratory tract, chronic bronchitis" (ESCOP 2003 'Primulae radix') When referring to the use of the clinical terminology by general practitioners to diagnose cough associated with cold in Germany, where these studies have been conducted, it becomes obvious, that this condition is almost always diagnosed as "acute bronchitis". Therefore this indication, which has been used in some of the clinical studies conducted with the combination, can be respected as addressing the same indication as the wording used in the monograph draft (cough associated with cold). It can be stated that the combinations of thyme herb and primula root, which have been in the market in Germany since a long time, have been proven to be safe in self medication. From our point of view, not the fact, whether the wording of the indication is "cough associated with cold" or "acute bronchitis", is decisive for the safe use in self medication, but the texts recommending the consult ation of a doctor or qualified health practitioner if the symptoms worsen and/or persist longer than 1 week during the use of the product. By these precautions, a safe use in self medication also in children below 4 years of age is given, taking into account the published studies, especially the observational studies in children, and the pharmacovigilance data available e.g. in Germany for more than 30 years of widespread use. The observational studies in children, partly even below 1 year of age, which have been conducted with the preparations c, g, h and i, are impressively demonstrating the safe use in this age group. Taking into account all these considerations, from our point of view the following changes of the draft are well-founded and also are clearly rational from a scientific point of view: The preparations, for which good quality double blind placebo controlled studies	

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	exist, as are preparation g and i, clearly qualify for well established use. The same applies to pharmaceutically and pharmacologically very similar preparations c and h, for which open or observational studies clearly indicate safety and usefulness in therapy, qualifying them as being in well established use. Taking into account that also preparations a and f have been registered in the frame of well established use in Germany, as likewise being in accordance with the commission E monograph, also these both preparations qualify for well established use. From a scientific point of view, also the preparations b and e and other similar preparations qualify for well established use. In the following, detailed remarks are given.	
AESGP	AESGP in principle welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for products containing Thyme and Primula, should facilitate mutual recognition in Europe. We have the following specific comments.	

SPECIFIC COMMENTS ON TEXT			
Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	Krka, d.d., Novo mesto	**Traditional use** **ii) herbal substance** j) Liquid extract from the mixture of primula root (DER 1:2-4.6) and thyme (DER 1:3.3) Extraction solvent: water.	Endorsed
2. Qualitative and quantitative composition	KOOP PHYTO	**Comment:** Herbal preparations g and i qualify for well established use due to existing double-blind, placebo-controlled studies. Preparations c and h qualify likewise for well established use due to open or observational studies. Preparations a and f have been rated as being in well established use as they are similar to the preparations mentioned before. These preparations should be transferred from the right to the left column. **Rationale:** We refer to the reasons given on the general comments.	See above: general comments on well-established use.
2. Qualitative and quantitative composition	KOOP PHYTO	**Comment:** There is a further preparation in the market in Germany at least since 1978 (trade name Brust- und Hustentee tassenfertig, manufacturer Bad Heilbrunner Naturheilmittel GmbH & Co., Bad Heilbrunn, Germany). This should be added to the monograph:	Not endorsed. According to the information provided by the German Agency this medicinal product contains the combination of thyme and primula only since 1993. Before 1993 the medicinal product contained beside several other components thyme oil, but not thyme and primula root.

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		j. Dry extract (DER 4-6:1) of a combination of thyme herb and primula root (25:4.2), extraction medium: water **Rationale:** The monograph is supposed to include all relevant preparations in the market in the EU.	Therefore the criterion of 30 years of medicinal use is not fulfilled.
2. Qualitative and quantitative composition	AESGP	**<u>Well established use</u>** We propose to approve the following two fixed combinations of herbal preparations of thyme herb and primrose root as "well-established use" preparations: **Fixed combination g):** **Liquid extract from thyme (DER 1:2-2.5), extraction solvent ammonia solution 10% m/m : glycerol 85% m/m : ethanol 90% v/v : water (1:20:70:109) and tincture from primula root (ratio herbal substance to extraction solvent 1:5), extraction solvent ethanol 50% v/v** <u>Reasons:</u> The clinical efficacy and tolerability of this fixed combination of thyme fluid extract and primrose root tincture was tested in a double-blind, randomized, placebo-controlled, multicentre, prospective study [Phytopharm & research Study CAS/K/01203 2004; Gruenwald 2005]. A total of 150 outpatients suffering from acute, not previously treated bronchitis, lasting for less than 48 h, were randomized and treated with either verum or placebo over a time period of 7 to 9 days. The inter-group (verum/placebo) difference of 5.8 points in the Bronchitis Severity Score (BSS) at the end of the study was highly significant ($p \leq 0.01$) in favour of the verum medication. Fixed combination g) showed clinically relevant effects with a more pronounced decrease of bronchitis symptoms and a shorter duration of the acute bronchitis as compared to placebo. **Fixed combination h):**	See above: general comments on well-established use.

SPECIFIC COMMENTS ON TEXT			
		Liquid extract from thyme (DER 1:2-2.5), extraction solvent ammonia solution 10 % m / m : glycerol 85 % m / m : ethanol 90 % v / v : water (1:20:70:109) and liquid extract from primula root (DER 1:2-2.5), extraction solvent ethanol 70 % m / m Reasons: In a single-blind, randomized, bi-centric, prospective study, the non-inferiority of fixed extract combination h) was evaluated by comparison to fixed extract combination g). The patients took either 6 x 5 ml of fixed extract combination h) or 5 x 1 ml of fixed extract combination g) daily. A total of 189 outpatients suffering from acute, not previously treated bronchitis, lasting for less than 48 h, were randomized and treated with either fixed extract combination h) or fixed extract combination g) over a time period of 7-9 days [Phytopharm Research Study CAS/K/00304 2005, Gruenwald 2006]. The study demonstrated that both fixed combinations of extracts of the thyme herb and primrose root were well tolerated and showed comparable results regarding their efficacy, e.g. the decrease of the bronchitis symptoms and the relief of symptoms. With regard to the clinical study for the fixed extract combination g) whose efficacy is clearly proven in comparison to placebo, these results lead to the conclusion that fixed extract combination h) is as effective as fixed combination g). **Fixed combination i):** **Dry extract from thyme (DER 6-10:1), extraction solvent ethanol 70 % v / v and dry extract from primula root (DER 6-7:1), extraction solvent ethanol 47.4 % v / v** Reasons: In a randomised, double-blind, placebo-controlled, multicentre study (25 centers) with parallel groups the efficacy and tolerability of fixed extract combination i) was investigated in	

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		adults suffering from acute bronchitis with productive cough as the main symptom. Patients were treated with 3 tablets a day. Each film-coated tablet contained the actives as described in 2. Qualitative and Quantitative Composition. A total of 361 patients showing clinical symptoms of acute bronchitis, onset of bronchial mucus production with impaired ability to cough up mucus for a maximum of 2 days prior to recruitment were randomized and treated with verum or placebo over a period of 10 days [Kemmerich B.: Evaluation of Efficacy and Tolerability of a Fixed Combination of Dry Extracts of Thyme Herb and Primrose Root in Adults Suffering from Acute Bronchitis with Productive Cough. A prospective, double-blind, placebo-controlled multicenter clinical trial Arzneim.-Forsch./Drug Res. (2007); 57(9): 607-615] The superiority of fixed extract combination i) compared to placebo was shown by the clinically relevant rates of responders after visit 2 (Day 4) and 3 (Day 10/end of treatment) (at visit 2 77.5% vs. 60.1%, p = 0.0006; at visit 3 92.9% vs. 75.8%, p<0.0001). The study has shown that the fixed extract combination i) is superior to placebo in patients suffering from acute bronchitis with productive cough.	
2. Qualitative and quantitative composition	AESGP	**<u>Traditional use</u>** We propose to add the following combination which is in the German market as Brust– und Hustentee tassenfertig, a soluble tea preparation of the company Bad Heilbrunner Naturheilmittel GmbH & Co: **ii) Herbal preparations** **j) Dry extract (DER 4-6:1) from a mixture of thyme and primula root (25:4.2), extraction solvent water** The traditional use can be proven since 1978, according to the attached history of the product (see encl.1).	Not endorsed. According to the information provided by the German Agency this medicinal product contains the combination of thyme and primula only since 1993. Before 1993 the medicinal product contained beside several other components thyme oil, but not thyme and primula root. Therefore the criterion of 30 years of medicinal use is not fulfilled.

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Traditional use	AESGP	Herbal preparation i) This fixed extract combination has been firstly placed in the market on 23 September 1993, so less than 18 years ago. There are no other products containing actives in the amount and quality of fixed extract combination i). Therefore also for formal reasons a classification as 'traditionally used' is not in line with the legal basis. The Regulatory Status Overview is incomplete. Besides marketing authorizations in AT, CZ, DE, HU herbal preparation i) has also been approved in Lithuania (LT/1/10/2149) and Romania (Reg.No. 3362/2011/01-02-03). The assessment report should be corrected accordingly.	Not endorsed. According to the information provided by the Germany Agency this combination is in medicinal use at least since 1976. The variations regarding the composition are not considered to break the evidence of traditional use.
4.1. therapeutic indications	KOOP PHYTO	**Comment:** For the preparations in well established medicinal use (as given above), the indication might be adapted more closely to the indications investigated in the clinical trials. It could therefore be e.g.: "Herbal medicinal product for the treatment of symptoms of acute bronchitis and of catarrhs of the upper respiratory tract associated with viscous mucus" or "Herbal medicinal product for use as an expectorant in case of productive cough. **Rationale:** As stated above (in the general comments), the well established use is supported by clinical data in the relevant indication, which can be described by different wordings; however are essentially synonymous.	See above: general comments on well-established use.
4.1 Therapeutic indications	AESGP	**Well-established use** We propose the following therapeutic indication for the three fixed combinations of herbal preparations of thyme herb and primrose root that should be listed under well-established medicinal use:	See above: general comments on well-established use.

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		"Herbal medicinal product for the treatment of the symptoms of an acute bronchitis, and catarrhs of the upper respiratory tract associated with viscous mucus." <u>Reasons:</u> In three controlled clinical studies [Phytopharm & research Study CAS/K/01203 2004; Phytopharm Research Study CAS/K/00304 2005], [Kemmerich B.: Evaluation of Efficacy and Tolerability of a Fixed Combination of Dry Extracts of Thyme Herb and Primrose Root in Adults Suffering from Acute Bronchitis with Productive Cough. A prospective, double-blind, placebo-controlled multicenter clinical trial Arzneim.-Forsch./Drug Res. (2007); 57(9): 607-615] the primary respectively secondary (herbal preparation i))efficacy parameter was the Bronchitis Severity Score (BSS, range 0 – 20). This score covers the most important symptoms of acute bronchitis (cough, sputum, rales/ronchi, chest pain during coughing and dyspnoea). The diagnosis and criteria for inclusion were an acute bronchitis of a duration ≤ 48 hrs, no previous treatment with other drugs and a BSS ≥ 5 points. The above-mentioned well-established use indication is therefore completely covered by these inclusion criteria and the symptom evaluation of the three controlled clinical studies. In the Assessment report of this HMPC monograph [Assessment report EMA/HMPC/130038/2010] it is stated that the treatment for acute bronchitis needs medical supervision and should therefore not be suitable for traditional herbal medicinal products. For the "traditional use" status, it is partly comprehensible that the treatment of acute bronchitis should be excluded. For the "well-established use" status it is not comprehensible at all, because this disease was evaluated by the three controlled clinical studies mentioned above. By restricting the indication to **acute** bronchitis (not chronic bronchitis) and by limiting the duration of the self-medication to 1 week, enough safeguards are put in place and delay of (more) appropriate treatment in case of severe disease cannot be feared.	

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4.2. Posology and method of administration	Krka, d.d., Novo mesto	***Traditional use*** **Posology** *Adolescents, adults and elderly* j) Single dose: 3.08 g of an aqueous extract which is equivalent to 0.22–0.51 g of primula root and 0.62 g of thyme. Daily dose: 4 times daily *Children between 4 and 12 years of age* j) Single dose: 3.08 g of an aqueous extract which is equivalent to 0.22–0.51 g of primula root and 0.62 g of thyme. Daily dose: 3 times daily	Posology for adults and adolescents: accepted Posology for children 4-12 years of age: not accepted. No data on the safe use of this combination in this age group are available.
4.2. Posology	KOOP PHYTO	**Comments:** For preparation j (see above), the posology is proposed to be added: "Adolescents, adults and elderly j) Single dose: 164.5 mg dry extract (DER 4-6:1) from a combination of thyme and primula root (25:4.2) Daily dose: 3 times daily" Preparations as mentioned above (section 2) should be transferred from traditional to well established use. For preparations c, g and h, the sentence "The use in children under 4 years of age is not recommended." should be changed into "The use in children under 6 month of age is not recommended.". For the age group from 6 month to 4 years of age, the following posology should be added: c) Single dose:	Preparation j: Not endorsed, because the combination does not fulfil the criteria for traditional use. Use in children below 4 years of age: Not endorsed. The treatment of cough in children of this age group requires medical supervision.

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		Fixed combination of 460 mg liquid thyme extract and 70 mg of primula root extract Daily dose: 3 times daily g) Single dose: Fixed combination of 0.43 g liquid thyme extract and 0.21 g primula root tincture Daily dose: 5 times daily h) Single dose: Fixed combination of 0.5 g thyme liquid extract and 0.25 g liquid primula root extract Daily dose: 4 times daily For preparation i, the sentence “The use in children under 12 years of age is not recommended.” should be changed into “The use in children under 6 years of age is not recommended.”. For the age group from 6 years to 12 years of age, the adult dose should be given. **Rationale:** The usefulness of these preparations is supported by observational studies showing a safe use in these age groups, which is supported also by pharmacovigilance data demonstrating their suitability for the use in self medication as an expectorant in case of productive cough. For preparation c, this is shown by the study of Fasse et al., 2006. For preparations g and h, this is shown by the studies of Nauert and Eckert 2003 and Nauert and Grünwald 2005. In the latter, post-marketing surveillances in total 423 children between 1 and 4 years of age and 543 children between 5 and 12 years of age have been included. Safety and efficacy were	

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		documented. Only 3 cases of adverse events occurred in total (Nauert and Eckert 2003, Nauert and Grünwald 2005). Besides, the importance of these preparations for children younger than 4 years is taken into account, as almost half of the patients belonged to this age-set. These data of good tolerability are confirmed by another post-marketing surveillance with 300 children with age groups of 1-3 years (n=98), 3-6 years (n=112) and 6-12 years (n=90). Only 3 adverse events were documented (Fasse et al. 2006). Additionally, also a clinical study was conducted with 200 babies aged 6-12 months treated with combined thyme herb and primrose root preparations. Likewise this study showed good tolerability, only one adverse event (eczema) was detectable (Nauert et al. 2008). In total only 7 adverse events were detectable in all clinical studies comprising 1466 treated children younger 12 years of age, 721 of them being younger than 4 years. This is a statistical probability less than 1%. Therefore, the combined preparations of thyme herb and primrose root are qualified to classify as “safe”, and the use in children younger than 4 years of age is appropriate. The exclusion of these preparations in children below 4 years would withdraw physicians and parents a valuable and safe therapeutic option for the treatment of these children. A “wait, watch, review” strategy, which may be justified with respect to chemically defined cough medicines with a typically much less favourable safety profile in this age group, cannot reasonably be transferred to the herbal medicines in scope of this monograph, with their well established tolerability and safety in this age group. In the draft monograph preparation i is only proposed for adults and elder patients. However, at least one clinical study has been performed in children (Kemmerich 2007). In this controlled, multicentre (771 general physicians), post-	Kemmerich 2007: only adults! Ernst et al 1997: no posology for children published.

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		marketing surveillance study, 1490 children 5.7 ± 2.9 years of age were included who received the fixed combination of thyme and Primula root. The other patients received ambroxol (n=479 children), n-acetylcysteine (n=299 children) or herbal medicinal products (n=207 children, e.g. extracts of Hederae folium, thyme, combination of essential oils). The rate of adverse events was clearly below 1% (in 1490 children 0.60%). This study, despite not randomised or placebo-controlled, has sufficiently demonstrated the safe use of the herbal preparation i in children. Therefore we recommend to accept herbal preparation i as a herbal medicinal product used as an expectorant in cough associated with cold in children aged 6 years and older.	
4.2 Posology and method of administration	AESGP	**<u>Well-established use</u>** **Posology and use in *adolescents, adults and elderly* for preparations g), h) and i)** We propose to add the respective dosage recommendation for the above-mentioned preparations listed as 'well-established use' g), h) and i) **g) Single dose: Fixed combination of 0.43 g liquid thyme extract and 0.21 g primula root tincture Daily dose: 5 times daily** **h) Single dose: Fixed combination of 0.5 g thyme liquid extract and 0.25 g liquid primula root extract Daily dose: 4 times daily** **i) Single dose: Fixed combination of 160 mg dry thyme extract and 60 mg dry primula root extract Daily dose: 3 times daily** <u>Reasons:</u> As shown in the three controlled clinical trials with these three	See above: general comments on well-established use.

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		herbal preparations [Phytopharm & research Study CAS/K/01203 2004; Phytopharm Research Study CAS/K/00304 2005], [Kemmerich B.: Evaluation of Efficacy and Tolerability of a Fixed Combination of Dry Extracts of Thyme Herb and Primrose Root in Adults Suffering from Acute Bronchitis with Productive Cough. A prospective, double-blind, placebo-controlled multicenter clinical trial Arzneim.-Forsch./Drug Res. (2007); 57(9): 607-615] the above listed dosage recommendations were effective and well tolerated. Herbal preparation h): This herbal preparation is used in Germany as drug substance in an authorised drug product as mentioned in the Draft assessment report on this monograph (EMA/HMPC/130038/2010) page 5 character H. The frequency of the administration should be adapted to the authorised dosage recommendation of this drug product in Germany. As shown in the clinical trial [Phytopharm Research Study CAS/K/00304 2004] the total daily dose achieved by this dosage recommendation is effective. The authorised dosage recommendation of 7.5 ml 4 times daily differs from the dosage recommendation 5.0 ml 6 times daily in the clinical trial [Phytopharm Research Study CAS/K/00304 2004] that was the scientific basis for the authorisation in Germany. The posology was adapted to 7.5 ml 4 times daily due to a complaint of the German authorities. The rationale for this complaint was that an administration of 4 times daily will lead to a better compliance than an administration of 6 times daily. The requirement of a consistent administration of the drug product and the drug substance throughout the day is fulfilled in both cases. This change in the frequency of administration does not lead to differences in the evaluation of the safety and/or efficacy profile of this herbal preparation.	

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4.2 Posology and method of administration	AESGP	**<u>Well-established use</u>** **Posology and use in *children between 4 and 12 years of age* for preparations g) and h)** Due to the non-interventional studies [Nauert and Eckert 2003, Nauert 2005] and the long-standing post-marketing experience, the efficacy and safety of these herbal preparations in children of that age can be regarded as established. There is no reason, especially no safety reason, to refuse a well-established use status in children. We therefore propose to add the following posology for preparations g) and h): **g) Single dose: Fixed combination of 0.36 g liquid thyme extract and 0.18 g primula root tincture** **Daily dose: 3-5 times daily** **h) Single dose: Fixed combination of 0.5 g thyme liquid extract and 0.25 g liquid primula root extract** **Daily dose: 4 times daily**	See above: general comments on well-established use.
4.2 Posology and method of administration	AESGP	**<u>Traditional use</u>** **Posology for preparation j)** We propose to add the respective dosage recommendation for the above-mentioned preparation j): **Adolescents, adults and elderly** **j) Single dose: 164.5 mg dry extract (DER 4-6 : 1) from a mixture of thyme and primula root (25:4.2)** **Daily dose: 3 times daily**	Not endorsed, because the combination does not fulfil the criteria for traditional use.

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4.2 Posology and method of administration	AESGP	**<u>Traditional use</u>** **Posology and use in adolescents, adults and elderly for preparation f)** We propose to correct the respective dosage recommendation for preparation f): **f) Single dose: Fixed combination of 128 mg of soft thyme extract and 18 mg soft primula root extract. Daily dose: 3-5 times daily** <u>Reasons:</u> Herbal preparation f): This herbal preparation is used in Germany as drug substance in an authorised drug product with the dosage form oral liquid [Assessment report EMA/HMPC/130038/2010) page 5 character F]. The density of the drug product has to be taken into account because the amount of the drug substance in the drug product is declared as weight (m/m), while the posology is fixed as volume (ml). The data for the single dose should therefore be corrected as mentioned above.	Posology of the single dose: endorsed. Daily dose: according to the information provided by the national competent authority the frequency should remain 3-4 times daily.
4.2 Posology and method of administration	AESGP	**<u>General recommendation for the use of preparations c), f) and h) in children under 4 years of age</u>** We propose to delete preparations c, f and h from the exclusion of use in children under 4 years of age regardless of a well-established use or a traditional use status. The respective posology for children under 4 years of age should be: **c) Single dose: 464 mg liquid thyme extract and 70mg soft primula root extract** **Daily dose: 3 times daily** **f) Single dose: Fixed combination of 128 mg soft thyme extract and 18 mg soft primula root extract.**	Use in children below 4 years of age: Not endorsed. The treatment of cough in children of this age group requires medical supervision.

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		Daily dose: 2 times daily **h) Single dose: Fixed combination of 67 mg liquid thyme extract and 33 mg liquid primula root extract** **Daily dose: 6 times daily** <u>Reasons:</u> A contraindication for children under 4 years of age disregards the role of combined thyme herb and primrose root preparations as the most important cough preparations for children worldwide: For a fixed combination product consisting of 1.16 g thyme liquid extract and 0.17 g primula root soft extract, 222,869 packages were sold between 2004 and 2009. Fixed combination f) and fixed combination h) are used as drug substances for drug products that are both authorised in Germany for children under 4 years of age. Fixed combination f) is authorised in a product for children from the age of 1 year, the fixed combination h) is authorised in a product for children from the age of 6 months onwards. Between 2008 and 2010 an amount of 391,777 packages for a product with fixed combination f) and 697,380 packages for a product with fixed combination h) were sold for use in children [Nielsen Trend Report (Cassella-med) 2011]. Within these years, no side effects were spontaneously reported in children of this age for Germany. In addition no hints for any tolerance problems became obvious in the PSURs covering the period from March 2004 until December 2009 [PSUR 2007, PSUR 2010]. Combined thyme herb and primrose root preparations were administered to numerous children in several studies: in two post-marketing surveillance studies carried out with fixed combination h), 423 children between 1 and 4 years of age and 543 children between 5 and 12 years of age were included. The fact that almost half of the patients included in this surveillance were under 4 years of age demonstrates the importance of	

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		combined thyme herb and primrose root preparations in younger children. Safety and good tolerability of the preparation were documented, as only 3 cases of adverse events occurred (pruritus) [Nauert and Eckert 2003; Nauert 2005] The good tolerability for fixed combination c) was confirmed by another post-marketing surveillance study with 300 children in the following age ranges: between 1 and <3 (n=98), 3 and ≤6 (n=112) as well as >6 and 12 (n=90) [Fasse 2006]. Furthermore, a post-marketing study in toddlers between 6 and 12 months of age with 200 children included, carried out with fixed combination h), showed good tolerability in this group. Only one adverse event (eczema) was recorded [Nauert 2008]. In total, only 7 adverse advents occurred: pruritus, eczema (3), eczema with pruritus, aggravation of neurodermitis (2). The frequency was less than 1%. The severity of symptoms does not justify the exclusion of these patient groups. Furthermore, the exclusion of children younger than 4 years would withdraw a valuable medicinal product for children, patients and physicians without alternative. **For these reasons the use of the combination of thyme herb and primrose root preparations for children under 4 years of age should be accepted.**	
4.4. Special warnings and precautions for use	KOOP PHYTO	**Comments:** For herbal preparations c, g and h, the sentence "The use in children under 4 years of age has not been established due to lack of adequate data" should be omitted. **Rationale:** As described above, these preparations have been safely used	Partly endorsed. The treatment of cough in children below 4 years of age requires medical supervision. Therefore the sentence is changed to: The use in children under 4 years of age has not been established because treatment of cough in this age group requires medical supervision.

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		in this age group in clinical studies, but also in self medication, with wide-spread use at least in Germany. Therefore such a warning is not adequate. In case of the inevitability of some recommendation, a more appropriate wording for these preparations could be: "Data point to a safe use also in children below 4 years of age. Due to general precautional considerations the use in children below 4 years of age should be supervised by a physician or qualified health practitioner." Such a wording would not be introduced due to safety problems with the herbal preparation, but due to general precautional considerations, that in case of these diseases resp. symptoms in children below 4 years of age always a physician should be consulted.	
4.4 Special warnings and precautions for use	AESGP	As appropriate data on the use of a combination of thyme herb and primrose root preparations for children under 4 years of age do exist and show a good tolerability, preparations c), f) and h) should be deleted from the preparations excluded for children under 4 years of age. **Herbal preparations c), f), h)** **There is data available that the herbal preparation is safe in children under 4 years of age. Due to general precautions the use in children under 4 years should be performed under medical control.** <u>Reasons:</u> The wording of this special warning should be more precise in pointing out that it is a general precaution to consult a qualified health care practitioner before treating children below 4 years and that it is not a safety precaution due to the herbal preparation.	Partly endorsed. Traditional herbal medicinal products are intended to be used without medical control. Therefore children below 4 years of age cannot be included in the monograph. However, the reasoning in 4.4 is modified to: The use in children under 4 years of age has not been established because treatment of cough in this age group requires medical supervision.

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5.1. Pharmacodynamic properties	KOOP PHYTO	**Comment:** Data on this point need to be added for the preparations assigned to well established use. The wording could be e.g.: Well-established use: In vitro experiments report spasmolytic, antimicrobial, antiinflammatory, antioxidative and antiviral effects of thyme fluid extract. In vivo experiments showed antiphlogistic and hepatoprotective effects and enhancement of the mucociliary clearance by thyme fluid extract. Primula saponins act locally by irritating the gastric mucosa and therefore, provoking a reflexively increased bronchial secretion. In vitro experiments revealed growth inhibition of bacteria, fungi and viruses. In vivo experiments could show increased ciliary activity." **Rationale:** Numerous publications reported the pharmacodynamic effects of thyme. These studies are listed in the ESCOP monograph 'Thymi herba' (Ref. 28-29, 33-50, 51-52, 56-58, 65 in ESCOP 2003 'Thymi herba'). Furthermore, it was published that thyme also enhances mucociliary clearance in mice (Wienkötter et al. 2007). The expectorant and secretolytic activity of primrose root is also depicted in the monographs of ESCOP 'Primulae radix' (Ref. 24-30 in ESCOP 2003 'Primulae radix').	See above: general comments on well-established use.
5.2. Pharmacokinetic properties	KOOP PHYTO	**Comments:** Data on this point need to be added for the preparations assigned to well-established use. The wording could e.g. be: Well-established use: Thymol as a marker substance of thyme herb is absorbed from	See above: general comments on well-established use.

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		the intestines after intake of a single dose of thyme herb liquid extract DAB. Thymol is exhaled within 140 minutes after intake with maximal expiration after 30-60 minutes. **Rationale:** Several publications demonstrated intestinal absorbtion and pulmonary exhalation of thymol as marker substance for kinetic data of thyme extract (Ref. 72-73 ESCOP 2003 'Thymi herba', Kohlert 2000, 2002)	
5.3. Preclinical safety data	KOOP PHYTO	**Comments:** Data on this point need to be added for the preparations assigned to well-established use. The wording could e.g. be: For thyme essential oil, relevant toxicity was not detectable in acute toxicity testing (LD50 2.8-4.7 g/kg b.w. in rats (p.o.), and 1.25 g/kg b.w. in mice). Thyme essential oil had no mutagenic or DNA-damaging activity in either the Ames or Bacillus subtilis rec-Assay and did not show mutagenicity in several Salmonella typhimurium strains. Thyme essential oil did not influence growth and development of mouse embryos in vivo. For the saponin-fraction of *Primula veris*, the intraperitoneal LD50 was determined with 24.5 mg/kg b.w. in mice; the LD50 (i.v.) of primula acid was 1,2 mg/kg b.w. in rats. **Rationale:** Several aspects of the Preclinical safety of thyme oil are depicted in the monograph of ESCOP 'Thymi herba'. The oral LD_{50} of essential thyme oil has been determined as 2.84 g/kg (Ref. 75 ESCOP 2003 'Thymi herba') and 4.70 g/kg in rats (Opdyke 1974) and as 1.25 g/kg in mice (without	See above: general comments on well-established use.

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		indication of way of application) (Akacic and Petricic 1956). Mortality was not reported after testing the acute toxicity of a thyme herb extract in mice (extraction solvent: 95% ethanol; DER roughly 9:1). To test the chronic toxic effects of a thyme extract (extraction solvent: 95 % ethanol; DER roughly 9:1) 10 male and 10 female mice were treated with 100 mg extract/kg b.w. for 90 days. 3 male and 1 female mice died, in each control group (10 male and 10 female mice) one animal died. In the surviving animals changes of haematological parameters and spermatotoxic effects were not detected. Weights of liver and testes increased slightly (liver: 6.30±0.26 vs. 5.19±0.24, $p<0.05$; testes: 0.76±0.01 vs. 0.66±0.02, $p<0.01$); In summary, these data reveal a rather low toxicity of Thymi herba extracts and thyme essential oil (Ref. 74 from ESCOP 2003 'Thymi herba'). The genotoxic properties of the essential thyme oil were studied in the Bacillus subtilis rec-assay (thyme oil: 10 und 30 µl) and Ames test (with thyme oil: 0.25, 0.5 and 1.0 µl/plate). In both tests, the essential thyme oil did not reveal any genotoxic effects (Ref. 76 from ESCOP 2003 'Thymi herba'). The oral LD_{50} of plant saponins ranged from 50 to 960 mg/kg in rodents (Ref. 32 in ESCOP 2003 'Primulae radix'). The saponin fraction from Primula veris had an LD50 of 24.5 mg/kg on testing in mice (Schöpke). No relevant toxicity is to be expected from oral intake of Primula root preparations in recommended doses.	
Comment on Assessment Report 4.3 Overall conclusions	AESGP	**Cochrane Review** The cited Cochrane review on OTC medications for cough [Smith et al. 2008] assesses the efficacy of different types of oral OTC drugs: Antitussives, expectorants, mucolytics, antihistamine-decongestant combinations, other drug combinations and antihistamines. Out of these drugs only	

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on clinical pharmacology and efficacy		expectorants and mucolytic drugs are - from the view point of their pharmacological profile - comparable with the herbal drug combination under consideration for this HMPC monograph. In these two categories, only three controlled clinical studies (2 studies with guaifenisin und 1 study with bromhexine) were assessed. No other controlled clinical studies - neither with any herbal drug nor with the combination of thyme herb and primrose root – were considered in this review at all. Due to these missing data the validity of this Cochrane review seems to be very limited for the evaluation of the herbal drug combination under consideration. Since the controlled clinical studies with the herbal drug preparation under consideration were not assessed, they cannot be evaluated by this review. **Bronchitis Severity Score (BSS)** This score was used in several controlled [Matthys et al. 2000, Matthys et al. 2003, Matthys et al. 2007c, Matthys et al. 2008, Matthys et al. 2010a, Gruenwald 2005, Gruenwald 2006], [Kemmerich B.: Evaluation of Efficacy and Tolerability of a Fixed Combination of Dry Extracts of Thyme Herb and Primrose Root in Adults Suffering from Acute Bronchitis with Productive Cough. A prospective, double-blind, placebo-controlled multicenter clinical trial Arzneim.-Forsch./Drug Res. (2007); 57(9): 607-615] and uncontrolled clinical studies [Matthys et al. 2007a, Matthys et al. 2007b, Matthys et al. 2010b, Nauert et al. 2003, Nauert et al. 2005, Nauert et al. 2008] with different herbal drug preparations in the indication acute bronchitis. It scores the most important symptoms of acute bronchitis: cough, sputum, rales/rhonchi, chest pain during coughing and dyspnoea [Macfarlane et al. 2002, Williamson 1984]. These are clinical relevant outcome measures for the treatment of acute cough and acute bronchitis. The extensive use of this score proves its clinical relevance, validity, reliability and easy use in randomized controlled clinical studies. In addition the raw data of the three controlled clinical studies with the herbal preparations g), h) and i) show a consistent course and a higher improvement rate for all symptom scores under consideration for the verum group in comparison to	

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		placebo [Phytopharm & research, Study CAS/K/01203; pp. 49-53], [Kemmerich B.: Evaluation of Efficacy and Tolerability of a Fixed Combination of Dry Extracts of Thyme Herb and Primrose Root in Adults Suffering from Acute Bronchitis with Productive Cough. A prospective, double-blind, placebo-controlled multicenter clinical trial Arzneim.-Forsch./Drug Res. (2007); 57(9): 607-615]. This backs up the validity of the score and the effectiveness of the verum therapy. In addition, the distribution of complaint free and not complaint free patients at study end was significantly higher in the verum group compared with placebo in these studies [Phytopharm & research, Study CAS/K/01203; pp. 49-53], [Kemmerich B.: Evaluation of Efficacy and Tolerability of a Fixed Combination of Dry Extracts of Thyme Herb and Primrose Root in Adults Suffering from Acute Bronchitis with Productive Cough. A prospective, double-blind, placebo-controlled multicenter clinical trial Arzneim.-Forsch./Drug Res. (2007); 57(9): 607-615]. Considering all these aspects together, it is not justified to doubt the relevance of the clinical studies or to deny the validity of the Bronchitis Severity Score used in these RCT`S. **DEGAM Guideline No. 11: Cough, 2008** This guideline [DEGAM 2008] assesses different chemical (Acetylcystein, Bromhexin, Ambroxol) and herbal expectorants (Myrtol, Cineol) for the therapy of acute bronchitis. Again the existing studies with herbal preparations g), h), i) and other existing controlled clinical studies with herbal drugs are neither mentioned nor evaluated. This means that also from these data it cannot be concluded that there is no sufficient evidence for the use of these herbal preparations for the treatment of acute cough and acute bronchitis. In contrast to the cited DEGAM Guidelines the Cough Guidelines of the German Respiratory Society 2010 gives strong recommendation for the use of combination herbal drugs like extract combinations of thyme herb/primula root for acute cough with moderate evidence of efficacy.	

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		Conclusion **Due to the existing controlled clinical studies the "well-established use" status is justified for herbal preparations g), h) and i). This is in accordance with the requirements of the HMPC Guideline EMEA/HMPC/104613/2005 and the principles of Evidenced Based Medicine. Due to these facts the indication should be:** ***Herbal medicinal product for the treatment of the symptoms of an acute bronchitis, and catarrhs of the upper respiratory tract associated with viscous mucus.***	
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