European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *THYMUS VULGARIS* L. AND *THYMUS ZYGIS* L., HERBA' EMEA/HMPC/234113/2006

Table 1: Organisations that commented on the document as released for consultation on 8 May 2007 until 15 August 2007

	Organisation
1.	Bundesinstitut für Arzneimittel und Medizinprodukte, Germany
2.	Laboratoire Monin-Chanteaud, France
3.	Europlant Phytopharm Sp, Poland
4.	Kooperation Phytopharmaka, Germany
5.	Bundesverband der Pharmazeutischen Industrie (BPI), Germany
6.	Association of the European Self-Medication Industry (AESGP)

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General comments	Comment and rationale	Rapporteur's comments
1	The Liquid extract DAB 2006 (herbal preparation type C) should be cancelled under "traditional use" and put under well-established use". Rationale: The AR contains a summary of observational studies with this type of extract. These articles are evaluated within the AR for the posology of children. They can also support the well-established use of this extract. For the recommended indication in the well-established use only a low level of evidence is necessary. In summary a lot of clinical evidence is based ion this extract, therefore it has to be assigned to well-established use. The available experimental and clinical data on thyme herb liquid extract according to DAB (1:2-2.5) justify the classification as well-established used herbal medicinal product. This is especially supported by its high importance as active substance of mono-preparations as well as of herbal combinations used for the treatment as an expectorant in cases of catarrhs of the upper respiratory tract and in cases of productive cough and acute bronchitis. A proven pharmacological and toxicological profile is available. Appropriate positive monographs substantiate the medicinal use of this thyme liquid extract for much more than 10 years. The therapeutic efficacy and tolerability for adults and children, already of less than one year of age are demonstrated by several clinical trials.	Well-established use has to be supported by at least one controlled clinical study of good quality of a certain herbal preparation. The clinical trial has to be performed with an equal or very similar herbal preparation. Thyme liquid extract according to the DAB is not yet tested in controlled clinical trials. No clinical data are available to support the well-established use of preparations of Thymi herba as the only active ingredient. The scientific evidence for combinations could be evaluated in a monograph for a fixed combination e.g. Thymi herba and Primulae radix. The well-established use for preparations containing Thymi herba as the only active ingredient cannot be supported.
	A list of 43 references is provided; the literature list should be amended and evaluated.	The list of references contains publications up from 1933, many of the references are citations from secondary sources. The interested party does not explain why a certain reference should be included in the AR and whether a reference would change the assessment of Thymi herba.

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2. Qualitative and quantitative composition	ii) Herbal preparations: Water extracts should be added to the list of herbal preparations. Rationale: Infusions of the herbal substance are traditionally used in Poland ("Receptariusz zielarski" 1963) and are described e.g. in: a) the draft in point no. 4.2 ("Posology and method of administration"), and b) monographs published e.g. by the Commission E, the ESCOP and the EMEA (Core data 2003).	The water extract is already considered under the point: comminuted herbal substance for tea preparation. A dry extract manufactured from a liquid extract prepared by water (equal to a tea preparation) can be considered as a 'corresponding product'.
2	Other ethanol extracts (e.g. dense extract (5-7:1, solvent ethanol 25% (V/V)) which is one of components of the Sinuforton Saft, a German product which is marketed for over 30 years) should be added to the list of herbal preparations. We propose to: a) define concentration of ethanol solvent as a range (e.g.: "Herbal preparations prepared with 24% (v/v) – 70% (v/v) ethanol"), and b) delete DERs from the monograph and recommend dosage of the herbal preparations on base of the dosage for the herbal substance Rationale: a) the draft proposes several extracts prepared with ethanol, among them are: liquid extract (24% (v/v) ethanol as solvent) and tincture (70 % (v/v) ethanol as solvent). Therefore the extract proposed by us fits very well in this line (it is produced with 25 % (v/v) as solvent). b) recommendation of dosage of herbal preparations on base of dosage for the herbal substance is clearer and is described e.g. in monographs of the ESCOP.	Inclusion of the dense extract endorsed. The DER provides essential information about the composition and manufacture of an herbal preparation. The dosage of some herbal preparations is a traditional one, which is not in accordance with calculations on equivalents of the herbal substance. The DER of the soft extract and the tincture is completely different, therefore a combination to a herbal preparation with a broad range for the strength of the extraction solvent cannot be supported.
2	Definition: Thymus vulgaris L. and/or Thymis zygis L., herba (thyme)	Wording in draft monograph complies with the monograph in the Ph. Eur.
2	i) Herbal substance -whole leaves and flowers separated from the previously dried stems **of Thyme**	According to the definition the monograph deals with thyme only. A repetition is not necessary.

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2	The DER (as a range) and the extraction solvent must be given for all mentioned preparations. For example, concerning the Thyme liquid extract describe in DAB 2006, this means: ii) Herbal preparation -liquid extract (1:2-2.5); extraction solvent: ammonia solution 10% (m/m): glycerol 85% (m/m) : ethanol 90% (v/v) : water (1 : 20 : 70 : 109) In addition, it is proposed to summarize mentioned preparations according to the following scheme, if possible: "liquid extracts [DER?] prepared with ethanol/water (ethanol x-y %)	The liquid extract DAB 2006 is presented in the draft monograph exactly in the proposed way. The extraction solvent for the tincture has to be mentioned in the monograph: D) Tincture (1:10); extraction solvent ethanol 70%, no details given whether v/v or m/m. The herbal preparations of thyme are too different that they could be summarized in the proposed manner.
2	It is proposed to include "expressed juice from fresh herb" in this chapter, because about 30 years of tradition were proven for the German market.	Inclusion of the expressed juice endorsed.
2	We suggest to add the following under "well-established medicinal use": **With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended: *Thymus vulgaris* L. or *Thymus zygis* L., or a mixture of both species, herba (thyme herb) as liquid extract (from DAB 7 onwards) (1:2-2.5); extraction solvent: ammonia solution 10 % (m/m) : glycerol 85 % (m/m) : ethanol 90 % (v/v) : water (1:20:70:109).** The German thyme liquid extract cannot be restricted to the thyme fluid extract according to DAB 2006, because this would exclude all other thyme fluid extracts from DAB 7 to 2006 from the definition of the monograph, although the quality has only been adapted to the current pharmacopoeial monograph. Thyme fluid extract DAB 2006 does neither have a well-established (10 years) nor a traditional (30 years) use. Therefore it is only useful to state "liquid extract DAB" (including DAB 7; 1969). The use of DAB liquid extract is widespread for more than 30 years. This definition is also in accordance with all other pharmacopoeia liquid extracts not declaring the year of the monograph, e.g. ÖAB (1:1).	Well-established use for the liquid extract DAB is not endorsed (see above). The liquid extract according to DAB 2006 does not have the tradition of 30 years. However, the current monograph is the endpoint of several improvements, since the quality of extracts prepared according to former monographs proved to be insufficient. Tradition must not be equal to the continuation of bad quality. Manufacturers of thyme liquid extract should use the current monograph in the DAB. However, herbal preparations manufactured according to monographs from DAB 7 onwards are tolerable. The liquid extract of the Austrian pharmacopoeia ÖAB remained unchanged at least since 1960.

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2	It has also to be taken into account that the pharmacopoeial procedures for thyme liquid extract have changed several times in the past, and are still being adapted (Gaedcke 2004). The aim of all changes or improvements since DAB 7 (1968) was to obtain a fluid extract which does not have a burning taste, is clearly soluble in water, is effective and allows economical production, with a content of *at least 0.03 % of phenols*. Therefore all thyme liquid extracts since DAB 7 to DAB 2006 have to be regarded as equivalent. The thyme liquid extract from DAB 7 onwards until today has in any case to be attached to the area of "well-established medicinal use". On the other hand, preparations, for which a long-term use is documented in reference books without clinical data (e.g. tea infusions, pressed juices, dry extracts) should be considered as traditional use preparations. The well-established medicinal use of thyme liquid extract from DAB 7 onwards can be justified by data from clinical studies conducted with thyme liquid extract DAB (1:2-2.5) as single active substance [Kaas 2003, Koch 2003, Knols et al. 1994; Internal study report cited as ref. 71 in ESCOP 2003], in combination products of thyme liquid extract DAB and primrose liquid extract (1:2) [Grünwald et al. 2005, 2006, Ernst et al. 1997, Fasse et al. 2006] as well as in combination products of thyme herb liquid extract DAB with primrose root liquid extract and ivy leaf liquid extract [Ismail 2003]. In Germany, herbal medicinal products containing thyme herb liquid extract DAB (1:2-2.5) preparations as single active substance or a combination of this extract with primrose root liquid extract as active substances are based on the German Commission E monographs "Thymi herba" and "Fixed combination of Primrose root and thyme herb" [1992]. In these positive monographs the efficacy was by definition accepted, provided the dosage of thyme herb preparations was within the range as defined by the Commission E monograph.	Kaas 2003: observational study Koch 2003: observational study Internal study report: open study None of the mentioned study is a controlled study, therefore not supporting well-established use. Knols 1994: thyme syrup: no details of the syrup given (According Austrian pharmacopoeia? Syrup containing liquid extract DAB?). Small population. No placebo-group. Reference insufficient for supporting well-established use. Studies dealing with combinations cannot support the well-established use of thyme liquid extract as the only active ingredient.

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2	For these reasons thyme liquid extract (1:2-2.5) prepared according to the DAB monograph is justified to be listed under **well-established medicinal use.** Its efficacy has been proven in clinical studies [Grünwald et al. 2005, 2006; Nauert 2003, Nauert et al. 2005, Kaas 2003, Koch 2003, Internal study report cited as ref. 71 in ESCOP 2003, Ernst et al. 1997, Fasse et al. 2006, Ismail 2003]. Well-established use **With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended** ***Thymus vulgaris* L. or *Thymus zygis* L. (alone or in mixture), herba (thyme herb) as liquid extract (from DAB 7 onwards) (1:2-2.5); extraction solvent: ammonia solution 10 % (m/m) : glycerol 85 % (m/m) : ethanol 90 % (v/v) : water (1:20:70:109)** Traditional use With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended *Thymus vulgaris* L. or *Thymus zygis* L., or a mixture of both species, herba (thyme herb) ~~i) Herbal substance~~ ~~Whole leaves and flowers separated from the previously dried stems~~ ii) Herbal preparations A) Liquid extract (ÖAB) (1:1), solvent ethanol 24% (v/v) B) Liquid extract (Czech Pharm.) (1:1.16); extraction solvent : glycerol 85% (m/m) : ethanol 25% (m/m) (0.1:2) C) ~~Liquid extract (DAB 2006) (1:2.2.5); extraction solvent: ammonia solution 10% (m/m) : glycerol 85% (m/m) : ethanol 90% (v/v) : water (1:20:80~~**70**~~:109)~~ D) Tincture (1:10 **and 1:5**) E) Essential oil F) Comminuted herbal substance for tea preparation G) Pressed juice from fresh leaves	Well-established use not endorsed. See above. The deletion of the herbal substance is not substantiated. No change. Tincture 1:5 endorsed, but no data on a traditional posology are provided. Pressed juice: endorsed. Liquid extract DAB 7 onwards: see comments above.

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	H) **Liquid extract (from DAB 7 onwards) (1:2-2.5); extraction solvent: ammonia solution 10% (m/m) : glycerol 85% (m/m) : ethanol 90% (v/v) : water (1:20:70:109)** **Dry extract (6-10:1); extraction solvent: ethanol (70%)** Background: The list of preparations from thyme appears too restrictive and do not reflect the broad spectrum of preparations used in practice. The intention of a Community monograph on traditional herbs is to facilitate the registration of herbal medicinal products. A restriction to the thyme fluid extract DAB 2006 would exclude all other thyme fluid extracts from DAB 7 to 2006 from the definition of the monograph, although they have only been adapted to the current DAB 2006 monograph. Thyme fluid extract DAB 2006 does not have either a well-established (10 years) nor a traditional (30 years) use. Therefore it is only useful to state "liquid extract DAB" (since DAB 7: 1969). DAB liquid extract has been in widespread use for more than 30 years. With regard to the exact nature of the extraction solvent, it should be noted that pharmacopoeial procedures for thyme liquid extract have changed several times in the past, and are still being adapted (Gaedcke 2004). In 1989, herbal medicinal products registered in Germany contained thyme liquid extracts according to DAB 7 to DAB 9. Today, the valid pharmacopoeial definition of thyme liquid extract is of 2006 (DER 1:2-2.5), and most products have adapted their composition accordingly. The HMPC draft monograph on thyme herb liquid extract includes the latest extract definition according to DAB 2006 which is a sensible approach. The following list shows entries on preparations containing thyme herb from the "Rote Liste 2007". The herbal drug is often combined with Primula root extract, a combination assessed positively by the German Commission E (Commission E 1992).	Dry extract (6-10:1), extraction solvent ethanol 70%: The evidence of a 30 year tradition is given, this type of herbal preparation will be included in the monograph.

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	Product	**Combination**	**Extract type**	
	Dr. Scheffler Bergischer Kräutertee Husten und Bronchialtee	Primula root	Dry extract (4.5-7.1:1), methanol 25%	
	Bronchipret Thymian Pastillen	–	Dry extract (6-10:1)	
	Bronchipret TP	Primula root	Dry extract (6-10:1), ethanol 70%	
	Bronchicum Kapseln	Primula root	Dry extract (6-10:1), 70% ethanol	
	Sinuforton Kapseln mit Anis bei Erkältung	Anise oil, Primula root	Dry extract (8-12:1), water	
	Equisil Saft	Horse chestnut, Horsetail, Ribwort, Primula root	Extract (25:1), 45% ethanol	
	Bronchicum Elixir/Tropfen	**Primula root**	**Fluid extract DAB**	
	Thymipin N Hustensaft/Tropfen	**–**	**Fluid extract**	
	Makatussin Tropfen	**Star anise, Eucalyptus oil**	**Fluid extract DAB**	
	Aspecton	**–**	**Fluid extract DAB**	
	Biotuss	**–**	**Fluid extract DAB**	
	Bronchipret Saft	**Ivy**	**Fluid extract DAB**	
	Bronchipret Tropfen	**Ivy**	**Fluid extract DAB**	
	Drosithym N Bürger Lösung	**Drosera, Primula root**	**Fluid extract DAB**	
	Expectysat N Bürger	**Primula root**	**Fluid extract DAB**	

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	GeloBronchial Saft	**–**	**Fluid extract DAB**	
	Hustagil Thymian Hustensaft/-tropfen	**–**	**Fluid extract DAB**	
	Melrosum Hustensirup	**–**	**Fluid extract DAB**	
	Pertussin Sirup	**–**	**Fluid extract DAB**	
	Phytobronchin Saft	**Primula root**	**Fluid extract DAB**	
	Soledum Hustensaft/-tropfen	**–**	**Fluid extract DAB**	
	Thymian ratiopharm Hustensaft Sirup	**–**	**Fluid extract DAB**	
	Thymiverlan Lösung	**–**	**Fluid extract DAB**	
	Tussamag Hustenlösung/Saft	**–**	**Fluid extract DAB**	
	Tussiflorin	**–**	**Fluid extract DAB**	
	Nimopect Hustensaft	**–**	**Fluid extract**	
	Thymian Curarina	**–**	**Fluid extract**	
	Kneipp Husten- und Bronchialtee	Fennel, Primula flower, Ribwort	Powder	
	tetesept Erkältung-skapseln	–	Powder	
	Florabio naturreiner Heilpflanzensaft Thymian Presssaft	–	Pressed juice	
	Expectysat N Bürger Saft	Primula root	Soft extract (5.5:1), methanol 25%	

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	Drosithym N Bürger Saft	Primula root, Drosera herb	Soft extract (5.5:1), methanol 25% (v/v)	
	Ephepect Pastillen	Anise oil, Eucalyptus oil, Fennel oil, Peppermint oil, Ammonium chloride	Soft extract (8:1), methanol 25%	
	Heumann Bronchialtee Solubifix	Licorice, Althaea, Primula root	Thyme oil	
	Nasulind Nasensalbe	Peppermint oil	Thyme oil	
	Penaten Baby Erkältungsbad	–	Thyme oil	
	Pulmotin Salbe	Anise oil, Camphor, Eucalyptus oil, Pine oil	Thyme oil	
	Thymian Li-iL Erkältungsbad	–	Thyme oil	
	The German list of pharmaceuticals "Rote Liste" of 1989 also listed various kinds of thyme preparations, e.g.: • Aqueous-ethanolic extract (1:1) (Thymipin Tropfen, Equisil) • Aqueous-ethanolic extract (1:6) (Soledum Hustensaft/-tropfen) • Dry extract (6.5:1), 25% ethanol (Anastil Dragees) • Aqueous dry extract (Knufinke Broncholind Husten- und Brusttee) • Aqueous soft extract (6.5:1) (Dr. Klinger's Bergischer Kräutertee Husten und Bronchialtee) • **Fluid extract (30% ethanol) (Eupatal)** • **Fluid extract DAB 7 (Antitussan Hustentropfen)** • **Fluid extract DAB 8 (Original Schneckensaft, Praecipect, Tussipect, Sedotussin Expectorans Sirup)**			See comments above on assessment of references.

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	• **Fluid extract DAB 9 (Hustagil Thymian Hustensaft/ -tropfen, Tussiflorin forte, Kneipp Kräuter Hustensaft Tannol, Primotussan, Anastil Hustensaft, Tussinfantum)** • Pressed juice (Kneipp Thymian Pflanzensaft, Expectysat Bürger, Drosithym, Schoenenberger naturreiner Heilpflanzensaft Thymian) • Thyme herb (Dr. Boether Bronchitten, Kneipp Husten- und Bronchialtee, Salus Bronchialtee) • Thyme oil (Aspecton, Bronchi-Sanol, Bronchostad, Heumann Bronchialtee Solubifix, Bronchicum Medizinalbad mit Thymian, Hustagil Erkältungsbalsam, Kneipp Erkältungsbalsam, Pertussin Hustenbalsam) • Tincture (1:5) (Thymian Tropfen Curarina, Melrosum, Bronchicum Elixir/Tropfen, Thymitussin Tropfen) **From our point of view, the thyme liquid extract from DAB 7 onwards should figure under the "well-established medicinal use" part of the monograph, for the following reasons:** Data are available from clinical studies conducted with thyme liquid extract DAB as single active substance [Kaas 2003, Koch 2003, Knols et al. 1994; Internal study report cited as ref. 71 in ESCOP 2003] as well as with thyme liquid extract DAB together with primrose liquid extract (1:2) in combination products [Grünwald et al. 2005, 2006, Ernst et al. 1997, Fasse et al. 2006, Ismail 2003]. A documented long-term clinical experience of combination products of thyme herb liquid extract DAB (1:2-2.5) with primrose root liquid extract and ivy leaf liquid extract also supports the well-established medicinal use. Their efficacy was proven in several recent studies of high quality standard. In Germany, herbal medicinal products containing thyme herb liquid extract DAB (1:2-2.5) preparations alone or in combination with primrose root liquid extract are based on the German Commission E	

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	monographs "Thymi herba" and "Fixed combination of Primrose root and thyme herb" [1992]. The efficacy of the liquid extract prepared according to the DAB monograph has been proven in clinical studies [Grünwald et al. 2005, 2006; Nauert 2003, Nauert et al. 2005, Kaas 2003, Koch 2003, Internal study report cited as ref. 71 in ESCOP 2003, Ernst et al. 1997, Fasse et al. 2006, Ismail 2003]. The traditional use for liquid extracts according to DAB in a lower dosage than for the well-established medicinal use is justified because medicinal products with a lower dosage have been on the German market for more than 30 years. Preparations, for which a long-term use is documented in reference books without clinical data (e.g. tea infusions, pressed juices, dry extracts) should be considered as traditional use preparations.	
3. Pharmaceutical form	The following wording is proposed for this chapter: "Herbal substance or herbal preparations in liquid dosage forms for oral use." "Comminuted herbal substance for tea preparation" should be deleted in this paragraph, because it is already covered by "herbal substance".	The proposed wording in the draft monograph is in line with already published monographs. Therefore no changes.
3	We propose to add the following under "well-established medicinal use": **Liquid extract (from DAB 7 onwards) (1:2-2.5); extraction solvent: ammonia solution 10% (m/m) : glycerol 85% : ethanol 90% (v/v) : water (1:20:70:109) in liquid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.** This definition corresponds to the products for which there is long-standing experience (more than 30 years) and to the definition of DAB and the German Commission E monograph (Commission E 1990, 1992). The definition is also in accordance with the recommendations in the ESCOP monograph (ESCOP 2003).	Comments on well-established use see above.

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	Well-established use **Liquid extract (from DAB 7 onwards) (1:2-2.5); extraction solvent: ammonia solution 10% (m/m) : glycerol 85% : ethanol 90% (v/v) : water (1:20:70:109) in liquid dosage forms for oral use.** **The pharmaceutical form should be described by the European Pharmacopoeia full standard term.** Traditional use ~~Herbal substance or~~ comminuted herbal substance for tea preparation or other herbal preparations in liquid, **semi-solid** and solid dosage forms for oral use. Essential oils for topical use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term. Background: This is in line with the pharmaceutical form of products with a long-standing experience (more than 30 years) on the market and with the definition of DAB and the German Commission E monograph (Commission E 1990, 1992). This is also in line with the recommendations in the ESCOP monograph (ESCOP 2003).	Comments on well-established use see above. See comment on pharmaceutical form above. Semi-solid dosage forms including the essential oil will be added to the monograph.
4.1 Therapeutic indication	Traditional herbal medicinal product used as **a spasmolytic and** an expectorant in cough associated with cold. **Dyspepsia**	No references are presented in order to substantiate the changes. Comment therefore not included.
4.1	Well-established use: Herbal medicinal product used as an expectorant in cough associated with cold and acute bronchitis.	Comments on well-established use see above.
4.1	We suggest to add the following text under "well-established medicinal use": **Catarrhs of the upper respiratory tract, productive cough and symptoms of acute bronchitis.** Thyme herb liquid extracts (1:2-2.5) fulfil all requirements of a well-established medicinal use having been used for more than 10 years in the Community. The indication suggested for well-established use corresponds to the one defined in the ESCOP monograph (ESCOP 2003),	Comments on well-established use see above.

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	the Hager monograph (Stahl-Biskup 2006), the WHO monograph (WHO 1999) and the German Commission E monograph (Commission E 1992). It was also investigated in published studies [Kaas 2003, Koch 2003, Knols et al. 1994; Internal study report cited as ref. 71 in ESCOP 2003]. The indication for the combination with Primulae radix is covered by recent controlled clinical trials [Grünwald et al. 2005, 2006] and supported by the data obtained from open studies [Nauert 2003, 2006; Ernst et al. 1997; Fasse 2006, Ismail 2003]. The monograph of Commission E listed the use of Thymi herba for symptoms of bronchitis and pertussis, and for catarrhs of the upper respiratory tract [Commission E 1984]; the monograph of the ESCOP [2003] recommended the use of Thymi herba for catarrh of the upper respiratory tract, bronchial catarrh and supportive treatment of pertussis; moreover, stomatitis and halitosis were listed.	
4.1	Well-established use **Catarrhs of the upper respiratory tract, productive cough and symptoms of acute bronchitis.** Traditional use Traditional herbal medicinal product used as an expectorant in cough associated with cold. **Traditional herbal medicinal product used to support the expectoration of mucus in the upper respiratory tract.** The product is a traditional herbal medicinal product for use in the specified indications exclusively based upon long-standing use. Background: 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 Thymi herba of at least ten years is well docu-	Comments on well-established use see above. The wording 'used as an expectorant' includes already the content of the proposed additional sentence.

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	mented in several monographs published e.g. by Commission E and ESCOP [2003], therefore the necessary time of medicinal use 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 [e.g. WHO 1999, Stahl-Biskup 2006, DAB, ESCOP]. The monograph of Commission E listed the use of Thymi herba for symptoms of bronchitis and pertussis, and for catarrhs of the upper respiratory tract [Commission E 1984]; the monograph of the ESCOP [2003] recommended the use of Thymi herba for catarrh of the upper respiratory tract, bronchial catarrh and supportive treatment of pertussis; moreover, stomatitis and halitosis were listed. It was also investigated in published studies [Kaas 2003, Koch 2003, Knols et al. 1994; Internal study report cited as ref. 71 in ESCOP 2003]. The indication for the combination with Primulae radix has been investigated in recent controlled clinical trials [Grünwald et al. 2005, 2006] and supported by the data obtained from open studies [Nauert 2003, 2006; Ernst et al. 1997; Fasse 2006, Ismail 2003].	
4.2 Posology and method of administration	Essential oil: Change single dose from 4-5 drops to 2-3 drops. Change daily dose from 12-25 drops to 6-12 drops	No references are presented in order to substantiate the changes. Comment therefore not included.
4.2	We propose to describe dosage of herbal preparations on base of dosage for the herbal substance, e.g.: "Dosage of a herbal preparation should be calculated in accordance with the dosage for the herbal substance (single dose: 1-2 g; daily dose: 3-8 g)." Rationale: Recommendation of dosage of herbal preparations on base of dosage for	The dosage of some herbal preparations of thyme herb is a traditional one which is not based on a calculation of equivalent amounts of herbal substance. Therefore the current presentation of the dosage is kept as it stands.

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	the herbal substance is much clear and is commonly used (it is described e.g. in monographs of the ESCOP).	
4.2	Well-established use Oral use: Adolescents, adults and elderly: C) Liquid extract: single dose: 2,1-4 g (correspond to 1-2 g herbal substance) Daily dose: The single dose should be taken 3 times daily. Maximal dosage: single dose 4 times daily Children 6-12 years of age: Single dose: 1,5 g liquid extract (correspond to 0.75 g herbal substance) Daily dose: 5 g liquid extract (correspond to 2.25 g herbal substance, divided into 3 single doses). Children 1-5 years of age: Single dose: 1 g liquid extract (correspond to 0.5 g herbal substance) Daily dose: 5 g liquid extract (correspond to 1.5 g herbal substance, divided into 3 single doses). Reason: In connection with the application for marketing authorisation or variations the majority of the studies we received were conducted with children. We agree to the proposed posology for children in the AR based on observational studies. We propose to put the text in line with the text of posology of the valerian root monograph. The sentences "the daily dosage is equivalent to … g of the herbal substance" should be added also in the monograph. The texts of the different monographs should be consistent.	Well-established use not endorsed. See comments above. The dosage of some herbal preparations of thyme herb is a traditional one which is not based on a calculation of equivalent amounts of herbal substance. Therefore the current presentation of the dosage is kept as it stands.
4.2	It is not understandable that for thyme herb liquid extract DAB a rather high dosage recommendation is proposed, although this typical thyme liquid extract (1:2-2.5) has been in the German market for about 40 years with the dosage of 1 - 2 g (single dose) and 1 - 6 g (daily dose).	The proposal for the dosage of thyme liquid extract DAB is based on the products currently on the market in Germany. Most products which contain this type of liquid extract as the only active ingredient recommend a single dose of

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	This dosage corresponds to the recommendation of the Commission E monograph and represents a high level of scientific knowledge. It cannot be accepted that the dosage recommendation for this thyme liquid extract in the draft monograph should be much higher than the one used traditionally.	thyme liquid extract between 1.5 and 2.7 ml, the daily dose is in the range of 4.5 to 14 ml. These data document a shift from a traditionally low dosage to higher values. It is acceptable to expand the single dose to 1 – 4 g; this would be a compromise between the proposals of all interested parties. A daily dosage of down to 1 g seems to be very low and is in contrast to the current dosage recommendations of products in Germany. The higher values proposed in the draft monograph seem to give no reason for safety concerns. The liquid extract must contain at least 0.03% of phenolic compounds; analytical data of the liquid extract demonstrate a value of app. 0.05%. Therefore the phenolic compounds in the liquid extract are diluted at the ratio 1:10 compared to the herbal substance, the essential oil content is only 30% of the herbal substance. Since the proposed dosage frequency is 1-4 times daily a daily dose of the liquid extract DAB in the range of 1-14 g could be recommended.
4.2	**<u>Posology and use in children</u>** We propose to add the following wording under "well-established medicinal use": ***Adolescents over 12 years of age, adults and elderly:*** **Thyme liquid extract DAB (1:2-2.5):** **Single dose 1-2 g (several times per day)** **Daily dose 2 - 6 (9) g** ***Children between 4 and 12 years of age:*** **Daily dose 1-6 g** ***Children between 1 and 4 years of age:*** **Daily dose 0.5 - 4 g** ***Children up to 1 year:*** **Daily dose 0.025 - 2 g**	Well-established use not endorsed. See comments above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	DAB thyme fluid extracts are on the German market for more than 30 years with a single dosage of 1-2 g and a DER of 1:2-2.5. This corresponds also to the first draft of the EMEA HMPWP Core data [EMEA 2003] which, however, had been changed during the further discussion without a scientific explanation. **Dosage of the Thyme herb fluid extract (1:2-2.5)** The monograph of the Commission E (**1992**) stipulates for thyme liquid extract DAB 9 to DAB 2003 a dosage of **1-2 g, 1-3 times** per day, which is independent from the DER but which is based on a minimum phenol content of 0.03 %. "**In this dosage thyme fluids have been used by physicians and pharmacists since more than 20 years as cough drops or juices in mono and fixed combination products**." (Quotation from Frauke Gaedcke) As explained by Frauke Gaedcke, the thyme fluid extract DAB is an **exception**, due to the following **deviations from all other fluids and from the *„general definition of fluida in the pharmacopoeia“:*** • Only the amount of *herbal drug to extraction solvent* is fixed (1:3). • The *ratio of the herbal drug to the resulting fluid extract* **(DER)** is open. • Since the DAB 2003 the m*anufacturing procedure* is not fixed (= suitable procedure). • The decisive parameter, - independent from the „DER“ -, is a content of *at least 0.03 % of phenols.* • Re-calculation of the dosage of thyme fluids DAB 9 to DAB 2003 via the DER to a 1:1 fluid extract or amount of herbal drug is **not** appropriate. The consequence would be considerable overdosages.	Comments on dosage of liquid extract DAB see above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	Use in children A limitation of the use in children and warnings against the use of thyme preparations in children are neither backed by the quoted monographs nor by tradition. A contraindication for children under 4 years of age does not reflect the fact that thyme preparations count among the most important cough preparations for children worldwide. The combination of Primrose root and thyme herb liquid extracts has been applied to children in clinical examinations, and was found safe (Nauert and Eckert 2003, Fasse 2006). Furthermore, exclusion of therapy for children up to 4 years is neither supported by the available clinical data for the suggested well-established medicinal products nor by the mentioned monographs. In addition, a recent post-marketing study in children between 0.5 and 1 year shows good tolerability of a combination of thyme herb liquid extract DAB (1:2-2.5) and Primrose root liquid extract (1:2) in this age group [Nauert 2007]. In general, the well-documented efficacy and tolerability of thyme herb liquid extract DAB in children should be taken into consideration [see studies by Koch 2003, ESCOP 2003, Kaas 2003, Ernst et al. 1997, Nauert and Eckert 2003, Nauert et al. 2005, Fasse et al. 2006, Nauert 2007, Dethlefsen 1997]. In these studies children below 12 years of age and even below 1 years of age were successfully and safely treated with the thyme herb liquid extract, also in combination with primrose root liquid extract, without any concerns regarding the tolerance of the preparations used. **Due to these results the use of thyme herb liquid extract DAB should be accepted for children under 4 years of age.**	The contraindication for children below 4 years of age is not caused by safety concerns attributed to thyme herb preparations. The working party agreed that the treatment of cough in children below 4 years of age needs the supervision of a doctor. Since traditional herbal medicinal products are intended to be used without medical supervision this contraindication was included.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
4.2	Well-established use ***Adolescents over 12 years of age, adults and elderly:*** **Single dose** **Thyme liquid extract DAB (1:2-2.5):** **1-2 g (several times per day)*** **Daily dose*** **2 - 6 (9) g** ***Children between 4 and 12 years of age:*** **Daily dose** **1-6 g** ***Children between 1 and 4 years of age:*** **Daily dose** **0.5 - 4 g** ***Children up to 1 year:*** **Daily dose** **0.025 - 2 g**	Well-established use not endorsed. See comments above.
	Traditional use ***1. Traditional herbal medicinal product used as an expectorant in cough associated with cold.*** *Adolescents over 12 years of age, adults, elderly* Single dose ~~Herbal substance: 1-2 g of dried herb.~~ Essential oil: 4-5 drops A) Liquid extract (ÖAB): 1-2 ml B) Liquid extract (Czech Pharm.): 1.2-2.4 ml C) ~~Liquid extract (DAB 2006); 1.5-4 g~~ D) Tincture (1:10): 40 drops E) Essential oil: 4-5 drops F) Comminuted herbal substance for tea preparation: 1-2 g G) Pressed juice: 10 ml H) Thyme liquid extract DAB (1:2-2,5): 0,1-0,2g (for children over 6	Extension of the traditional indication not endorsed. See comments above. In line with other monographs the dosage is also expressed for the herbal substance. Dosage of the pressed juice will be included in the monograph. The proposed dosage for the liquid extract DAB is considerably lower than listed in references or actually recommended in HMPs. The dosage proposed in the monograph is a traditional one; therefore there is no need for a further reduction of the dosage for traditional use.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	years of age, adolescents, adults and elderly)** I) Dry extract 0,15 to 0,2g Dosage frequency: May be taken up to a maximum of 3-5 times daily. <u>Daily dose</u> ~~Herbal substance: 3-8 g~~ A) Liquid extract (ÖAB): 3-8 ml B) Liquid extract (Czech Pharm.): 3.5-9.3 ml ~~C) Liquid extract (DAB 2006); 4.5-14 g~~ D) Tincture (1:10): 120 drops E) F) Essential oil: 15-25 drops G) Comminuted herbal substance for tea preparation: 3-8 g H) Thyme liquid extract DAB (1:2-2,5): 0,3-1,0g (for children over 6 years of age, adolescents, adults and elderly)** I) Dry extract 0,45-0,6 g J) Pressed juice: Adults and children over years: 3 - 4x daily 10 ml *** *Children 4 - 12 years* 4 x daily 5 ml pressed juice*** *Children 1- 4 years* 3 x daily 5ml pressed juice*** ***2. Traditional herbal medicinal product used to support the expectoration of mucus in the upper respiratory tract*** *Adults and children over 3 years of age* <u>Single dose:</u> Liquid extract (DAB 2006): 0,1 g Dose frequency: 3-4 times daily *Children between 1 to 3 years of age* <u>Single dose:</u> Liquid extract (DAB 2006): 0,05 g	The dry extract will be included in the monograph. The change of the dosage frequency is not substantiated. There are no data presented that would document the safety use of the pressed juice in the paediatric population. Therefore a posology for children is not endorsed. Additional indication: see comments above. The dosage of the liquid extract DAB proposed in the monograph is in accordance with dosages given in clinical studies. A lower dosage is not substantiated by the interested party. Use in children below 4 years of age: see comments above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	Dose frequency: 3-4 times daily ***) Comment: DAB fluid extracts have been on the German market for more than 30 years with a single dosage of 1-2 g and a DER of 1:2-2.5. This corresponds to the first draft of the EMEA HMPWP Core data [EMEA 2003] which, however, had been further modified. No scientific rational was given to explain the changes.** ****) Comment: In traditional use, the dosage of this extract can be lower** ***) **The children's dosage of pressed juice corresponds to a German marketing authorisation**. <u>Dosage of the fluid extract</u> The monograph of the Commission E (**1992**) stipulates a dosage of **1-2 g, 1-3 times** per day for thyme fluid extract DAB 9 to DAB 2003, which is independent from the DER but based on a minimum phenol content of 0.03 %. **"In this dosage thyme fluids have been used by physicians and pharmacists since more than 20 years as cough drops or juices in mono and fixed combination** products." (Quotation from Frauke Gaedcke, presentation attached). As explained by Frauke Gaedcke, the thyme fluid extract DAB is an **exception**, due to the following **deviations from all other fluids and from the *"general definition of fluids in the pharmacopoeia":*** • Only the amount of *herbal drug to extraction solvent* is fixed (1:3). • The *ratio of the herbal drug to the resulting fluid extract* **(DER)** is open. • Since the DAB 2003 the m*anufacturing procedure* is not fixed (= suitable procedure).	Dosage of liquid extract DAB: see comments above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	• The decisive parameter, - independent from the „DER" -, is a content of *at least 0.03 % of phenols*. • Re-calculation of the dosage of thyme fluids DAB 9 to DAB 2003 via the DER to a 1:1 fluid extract or amount of herbal drug is **not** appropriate. The consequence would be considerable overdosages. Since DAB 7 (1968) the manufacture and the quality parameters of the thyme fluid extracts constitute a compromise, with the aim to obtain a fluid extract which does not have a burning taste, is clearly soluble in water, is effective and allows economical production, with a content of *at least 0.03 % of phenols*. **Use in children** The limitation of the dose for children and the warnings against the use of thyme preparations in children is neither supported by the monographs nor by tradition. A contraindication for children under 4 years of age does not reflect the fact that thyme preparations count among the most important cough preparations for children worldwide. The use in children of the combination of Primrose root and thyme herb liquid extracts has been investigated in clinical studies, and was found safe (Nauert and Eckert 2003; Ziesenіß and Heusinger 2005, Fasse 2006). The exclusion of use in children younger than 4 years old goes against available clinical data (and monographs) supporting the well-established used of the medicinal products. In addition, a recent post-marketing study conducted in children between 0.5 and 1 year showed the good tolerability of a combination of thyme herb liquid extract DAB (1:2-2.5) and Primrose root liquid extract (1:2) in this age group [Nauert 2007]. A number of studies (by Koch 2003, ESCOP 2003, Kaas 2003, Ernst et al. 1997, Nauert and Eckert 2003, Nauert et al. 2005, Fasse et al. 2006,	Use in children below 4 years of age: see comments above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	Nauert 2007, Dethlefsen 1997) have documented the well-documented efficacy and tolerability of thyme herb liquid extract DAB in children. In these studies, children below 12 years old and even below 1, were efficaciously and safely treated by thyme herb liquid extract alone or in combination with primrose root liquid extract. No concerns regarding the tolerance of the preparations used were reported. **Based on the conclusion of the studies described above, the safe use of thyme herb liquid extract DAB in children under 4 years of age has been attested and should be reflected accordingly in the HMPC monograph.** With regard to the second proposed traditional indication, low doses (approx. 10 % of the well-established use dose) have traditionally been used to aid the expectoration of mucus, especially in children. National registrations have already been granted in Germany, e.g. for "Abtei Bronchial Sirup mit Thymian" based on documented traditional use for more than 30 years.	
4.2	Traditional use: Posology for expressed juice: Oral use: Adolescents, adults and elderly: Single dose: 10 ml (correspond to 4.1 – 6.6 g of herbal substance) Daily dose: 30 ml (correspond to 12.3 – 19.8 g of herbal substance)	Dosage of the expressed juice will be included.
4.2	Duration of use: Infants and children under the age of 12: The duration of use is not limited: If the symptoms persists longer than … Reasoning: The new formulation makes clear, a longer use on the supervision of a doctor is allowed.	A similar proposal for Primulae radix has been discussed in the MLWP. The MLWP did not endorse the change. Therefore the wording will be kept as it stands.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
4.2	**<u>Duration of administration</u>** We suggest to add the following under "well-established medicinal use": ***Children up to 12 years of age, adolescents, adults and elderly*** **According to the therapeutic needs. Medical attention should be sought if after 1 week of treatment the symptoms do not improve.** A limitation of the duration of use to 5 days in children is not covered by the ESCOP monograph, which does not give any statement on a restricted duration of intake (ESCOP 2003). The WHO monograph does not indicate any restrictions at all (WHO 1999). A disclaimer regarding the lack of improvement of symptoms is doubtlessly sensible, and would not only apply to children, but also to adolescents and adults. However, on the one hand, it does not make sense when the use for more than 5 days by patients is formulated as a strict contraindication, and on the other hand patients are referred to health practitioners. In view of the diversity of educational systems for health practitioners within the EU and specifically within Germany there is no definition of a "qualified" health practitioner. It is suggested that the formulation avoids such confusion by generally referring to medical advice. There is no data available which recommend to separate between 5 days of duration in children and 1 week (= 7 days) in adults. This does not reflect the situation in the reported clinical studies in which the duration of therapy was in the range of 7 - 10 days for both children and adults, in some studies even up to 14 days. As shown in the mentioned studies thyme herb liquid extract DAB can be used without any safety problems for up to 14 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 paediatrics. In general a treatment duration for 10-14 days for children and	Following the discussions on Primulae radix the duration of use shall be 1 week for all age groups. Traditional herbal medicinal products are intended to be used without medical supervision. 1 week of treatment is justifiable without medical supervision. If the symptoms persist longer than 1 week medical advice should be sought. The documented treatment in clinical studies longer than 1 week has been performed under medical supervision.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	adults is necessary, since the severity of viral infections of the respiratory tract can differ individually. Due to these differences a successful therapy with thyme herb liquid extract DAB can be used for up to 14 days or even longer without being a hazard for the treated patient.	
4.2	**Duration of use** Well-established use: ***Children up to 12 years of age, adolescents, adults and elderly*** According to the therapeutic needs. **Medical advice should be sought if after 1 week of treatment the symptoms do not improve.** Traditional use: ***Children up to 12 years of age, adolescents, adults and elderly*** According to the therapeutic needs. ~~*Children between 4 and 12 years of age*~~ ~~No restriction.~~ ~~*Adolescents over 12 years of age, adults, elderly*~~ ~~Medical attention should be sought if after 1 week of treatment the symptoms do not improve.~~ ~~If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.~~ Background: Neither the ESCOP monograph (2003) nor the WHO one (1999) states any restriction on the duration of use. The strict time limitation and the recommendation to see a health care professionals if symptoms persist during the use of the medicine seem to be contradicting one another. In view of the diversity of educational systems for health care professionals within the EU, it is suggested that the formulation avoids confusion by generally referring to 'medical advice' (or consultation of a 'health care professional')	Well-established use not endorsed. See comments above. Duration of use, traditional use: see comments above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	There is no data available which justifies the difference of use duration between adults (1 week) and children (5 days). This does not reflect the situation in the reported clinical studies, in which the duration of therapy was in the range of 7 - 10 days for both children and adults, in some studies even up to 14 days. As shown in the referenced studies thyme herb liquid extract DAB can be used without posing any safety concerns for up to 14 days. The compliance of the physicians and parents was very high, which is an important success factor in paediatrics. The severity and length of viral infections of the respiratory tract can differ from a person to another. Due to these differences, treatment with thyme herb liquid extract DAB can be followed up to 14 days or even longer without any risks for the treated patient.	
4.2	Method of administration Well-established use: **Oral use.** **Traditional use:** Oral and topical use.	Well-established use not endorsed. See comments above. Topical use will be included.
4.3 Contraindications	Well established use: Hypersensitivity to the active substance or to other members of the Lamiaceae	Well-established use not endorsed. See comments above.
4.3	Well-established use **Hypersensitivity to thyme herb or to other plants of the Lamiaceae family.** Traditional use Hypersensitivity to **thyme herb** or to other **plants** of the Lamiaceae family. ~~Children with a history of acute stenosing laryngo-tracheitis.~~ ~~Asthma.~~	Well-established use not endorsed. See comments above. Traditional use: The argumentation of the interested party is justified, the change is endorsed.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	Background: The WHO and ESCOP-monographs do not state any contraindication (WHO 1999; ESCOP 2003), except for a general statement concerning pregnancy and lactation. Hypersensitivity reactions may occur in very rare cases. The contraindication "*children with a history of acute stenosing laryngo-tracheitis"* and "*asthma"* has not been documented in any controlled or open clinical studies nor has been reported as a side effect. It is a theoretical assumption which does not reflect the longstanding use of Thymi herba preparations.	
4.4 - Special warnings and precautions for use	For liquid extracts DAB, the following wording seems to be appropriate under "well-established medicinal use": **If dyspnoea, fever or purulent sputum occurs, a physician should be consulted. For liquid extracts DAB, 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.** Herbal medicinal products containing thyme herb liquid extract DAB (1:2-2.5) alone or in combination with primrose root liquid extract (1:2) have been tested in observational studies involving about 1000 children of up to 4 years of age without any adverse effects [Nauert and Eckert 2005, Nauert et al. 2005, Kaas 2003, Koch 2003, Internal study report cited as ref. 71 in ESCOP 2003, Fasse et al. 2006, Nauert 2007, Dethlefsen 1997].	Well-established use not endorsed. See comments above.
4.4	Well-established use **If dyspnoea, fever or purulent sputum occurs, a physician should be consulted.** **For liquid extracts DAB, 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	Well-established use not endorsed. See comments above. Comments on the use in children below 4 years of age see

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	~~The use in children under 4 years of age is not recommended because medical advice should be sought.~~ When dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted. For liquid 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. Background: The special warning against the use in children under the age of 4 years under "traditional use" is not justified (see comments above). In addition, products of thyme herb liquid extract DAB, alone or in combination with primrose root liquid extract (1:2) have been tested in observational studies involving about 1000 children of up to 4 years of age without any adverse effects [Nauert and Eckert 2005, Nauert et al. 2005, Kaas 2003, Koch 2003, Internal study report cited as ref. 71 in ESCOP 2003, Fasse et al. 2006, Nauert 2007, Dethlefsen 1997].	above.
4.5 Interactions	Well-established use and traditional use: No studies on interactions with other medication have been performed. Interactions are not reported	Well-established use not endorsed. See comments above.
4.5	Well-established use **None reported.** Background: This corresponds to the WHO, ESCOP and Hager-monograph (WHO 1999; ESCOP 2003; Stahl-Biskup 2006).	Well-established use not endorsed. See comments above.
4.6 Pregnancy and lactation	Well-established use: The formulation should be the same as in traditional use.	Well-established use not endorsed. See comments above.
4.6	Well-established use **No indications of risks in pregnancy and lactation have appeared from the widespread use of thyme liquid extract DAB as a medicinal product and of thyme herb in food. Results of sufficient studies are not available. Due to general safety considerations the herbal medicinal product should not be used without medical advice.** Traditional use	Well-established use not endorsed. See comments above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	~~Safety during pregnancy and lactation has not been established.~~ ~~In the absence of sufficient data, the use during pregnancy and lactation is not recommended.~~ **No indications of risks in pregnancy and lactation have appeared from the widespread use of thyme as a medicinal product and in food. Results of sufficient studies are not available. Due to general safety considerations the herbal medicinal product should not be used without medical advice.** Background: The absence of data does not justify a contra-indication. Since no adverse effects or risks of thyme herb and preparations thereof during pregnancy have been reported, the use should be allowed under the above mentioned conditions.	The proposed wording is in contradiction with the definition of traditional herbal medicinal products. They are intended to be used without medical advice. Therefore a recommendation for the use during pregnancy and lactation cannot be given.
4.7 Effects on ability to drive and use machines	Well-established use **None known.** Traditional use ~~No studies on the effect on the ability to drive and use machines have been performed.~~ **None known.** Background: Corresponds to ESCOP monograph (ESCOP 2003) and to published reviews on herbal safety (Mills and Bone 2005).	Well-established use not endorsed. See comments above. Traditional use: In order to keep the monographs in line the proposed wording in the monograph will be kept as it stands.
4.8 Undesirable effects	Well-established use and traditional use: Hypersensitivity reactions (e.g. dyspnoea, skin rash, urticaria as well as facial edema, edema of the mouth an dthroat (Quincke edema), anaphylactic shock) or **gastrointestinal complaints** (spasms, nausea, vomiting, **diarrhoea**) have been observed. The frequency is not known. Reason: The majority of data in the national database of Germany refer to allergic reactions and second to the gastrointestinal reactions.	Well-established use not endorsed. See comments above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
4.8	Well-established use **In very rare cases hypersensitivity reactions have been reported.** Traditional use ~~Hypersensitivity reactions (e.g. dyspnoea, skin rash, urticaria as well as facial edema, edema of the mouth and throat (Quincke edema), anaphylactic shock) or stomach disorders (spasms, nausea, vomiting) have been observed. The frequency is not known.~~ **In very rare cases hypersensitivity reactions have been reported.** Background: It corresponds to ESCOP and Hager monograph (ESCOP 2003; Stahl-Biskup 2006), and to published reviews on herbal safety (Mills and Bone 2005). There are only some very few single reports in hypersensitivity reactions related to the use of thyme or its ingredient thymol [Benito et al. 1996, Armisen et al. 2003, Lorenzi et al. 1995]. Another case report of skin reactions was related to occupational contact with thyme dust, and is therefore not relevant for the application of thyme preparations as herbal medicinal products (Spiewak et al. 2001). External application of 8% thyme oil in Vaseline did not cause skin irritation (Opdyke 1974). Furthermore, clinical studies do not suggest adding such a detailed description of hypersensitivity reactions.	Well-established use not endorsed. See comments above. Traditional use: The statement of the frequency ('very rare') is not substantiated by clinical studies which were designed to detect the frequency of undesirable effects. Therefore it must be stated, that the frequency is not known. The detailed descriptions of symptoms can be deleted.
4.9 Overdose	Well-established use **No case of overdose has been reported for the liquid extract DAB.** Background: It corresponds to ESCOP monograph (ESCOP 2003) and published reviews of herbal safety (Mills and Bone 2005).	Well-established use not endorsed. See comments above.
5. Pharmacological properties	Well-established use and traditional use: A short summary of results of in-vitro and in-vivo studies with preparations of thymii herba, oleum thymii or thymol should be added.	Well-established use not endorsed. See comments above. For traditional use this information is not required.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
5.1 Phyrmacodynamic properties	We would like to propose addition of the following text under well-established use: **In experimental studies thyme herb liquid extract DAB (1:2-2.5) and the essential oil were reported to exert spasmolytic, bronchospasmolytic, antimicrobial, anti-inflammatory and antiviral effects in vitro. In vivo studies showed antiphlogistic and hepatoprotective effects as well as a stimulatory effect on the mucociliary clearance. The therapeutic effectiveness of medicinal products containing thyme herb liquid extract DAB was shown by the reduction of typical symptoms of catarrhs and acute bronchitis in clinical studies. Thyme herb liquid extract DAB and its combinations with primrose root extract or ivy leaf extract also have been shown to be clinically efficacious.** Many publications report about the pharmacodynamic effects of thyme herb preparations, of thyme essential oil and of the constituent thymol. These studies and their main results are listed in the ESCOP monograph [2003] as well as in the WHO monograph [1999] and the original papers are listed in the reference list of the draft monograph of the HMPC. Thyme essential oil, thyme extracts and isolated flavonoids were shown to have spasmolytic effects on smooth muscles of the guinea-pig ileum and trachea, the rat trachea and uterus and and the rat vas deferens (Brandt 1988; Meister et al. 1999; Reiter and Brandt 1985; van den Broucke and Lemli 1981; van den Broucke and Lemli 1983, Wienkötter 2007). Antibacterial and antifungal effects have frequently been demonstrated, as well as anti-inflammatory effects (ESCOP 2003; Aktug and Karapinar 1986; Beuchat 1976; Hitokoto et al. 1980; Huhtanen 1980; Llewellyn et al. 1981; Salmeron et al. 1990; Stahl-Biskup 2006; Wagner et al. 1986; Wagner and Wierer 1988). Thyme herb extract was also shown to possess antiviral effects in vitro (Herrmann and Kucera 1967). According to most recent research thyme extract enhances mucociliary clearance in mice, possibly through an effect on beta-receptors (Wien-	Well-established use not endorsed. See comments above.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	kötter et al. 2007). Similar effects have been observed in earlier studies (Freytag 1933; Gordonoff and Merz 1931; Schilf 1932; Vollmer 1932). More importantly, thyme preparations have been shown to be efficacious in clinical trials (Knols et al. 1994; Vecozols 1955). The combination of thyme herb extract with primrose preparations as recommended by the German Commission E monograph (Commission E 1992) 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 (van den Hoven et al. 2003). The combination with primrose root has also been positively tested in randomised clinical trials (Ernst et al. 1997; Gruenwald et al. 2005; Gruenwald et al. 2006) as well as in observational studies involving children of not more than 4 years of age (Fasse et al. 2006; Nauert and Eckert 2003). The combination of thyme herb liquid extract DAB with ivy leaf, aniseed and marshmallow root extract was found an effective and highly tolerable treatment of cough in an observational study with 62 patients (Buechi et al. 2005). In addition, a combination of thyme herb liquid extract DAB with ivy leaf extract was positively tested in a clinical double-blind and placebo-controlled setting in 361 patients with acute bronchitis (Kemmerich et al. 2006).	
5.1	Well-established use **In experimental studies thyme herb liquid extract DAB and the essential oil were reported to exert spasmolytic, bronchospasmolytic, antimicrobial, anti-inflammatory and antiviral effects in vitro. In vivo studies showed antiphlogistic and hepatoprotective effects as well as a stimulatory effect on the mucociliary clearance.** **The therapeutic effectiveness of medicinal products containing thyme herb liquid extract DAB was shown by the reduction of typical symptoms of catarrhs and acute bronchitis in clinical studies.**	Well-established use not endorsed. See comments above. For traditional use this information is not required.

Line no or section and paragraph no	Comments and rationale	Rapporteur's comment
	Thyme herb liquid extract DAB and its combinations with primrose root extract or ivy leaf extract also have been shown to be clinically efficacious. Background: Many papers cites the pharmacodynamic effects of Thymi herba preparations, of thyme essential oil and of the constituent thymol. These studies and their main results are listed in the ESCOP monograph [2003] as well as in the WHO monograph [1999] and the original papers are listed in the reference list of the draft monograph of the HMPC. Thyme essential oil, thyme extracts and isolated flavonoids were shown to have spasmolytic effects on smooth muscles of the guinea-pig ileum and trachea, the rat trachea and uterus and and the rat vas deferens (Brandt 1988; Meister et al. 1999; Reiter and Brandt 1985; van den Broucke and Lemli 1981; van den Broucke and Lemli 1983, Wienkötter 2007). Antibacterial and antifungal effects have frequently been demonstrated, as well as anti-inflammatory effects (ESCOP 2003; Aktug and Karapinar 1986; Beuchat 1976; Hitokoto et al. 1980; Huhtanen 1980; Llewellyn et al. 1981; Salmeron et al. 1990; Stahl-Biskup 2006; Wagner et al. 1986; Wagner and Wierer 1988). Thyme herb extract was also shown to possess antiviral effects in vitro (Herrmann and Kucera 1967). According to most recent research, thyme extract enhances mucociliary clearance in mice, possibly through an effect on beta-receptors (Wienkötter et al. 2007). Similar effects have been observed in earlier studies (Freytag 1933; Gordonoff and Merz 1931; Schilf 1932; Vollmer 1932). More importantly, thyme preparations have been shown to be efficacious in clinical trials (Knols et al. 1994; Vecozols 1955). The combination of thyme herb with primrose root preparations as recommended by the German Commission E monograph (Commission E 1992) 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 (van den Hoven et al. 2003).	

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	The combination with primrose root has also been positively tested in randomised clinical trials (Ernst et al. 1997; Gruenwald et al. 2005; Gruenwald et al. 2006) as well as in observational studies involving children of 4 years old or less (Fasse et al. 2006; Nauert and Eckert 2003; Zieseniß and Heusinger 2005). The combination of thyme herb liquid extract DAB with ivy leaf, aniseed and marshmallow root extract was found effective and well tolerated for the treatment of cough in an observational study involving 62 patients (Buechi et al. 2005). In addition, a combination of thyme herb liquid extract DAB with ivy leaf extract was positively tested in a clinical double-blind and placebo-controlled study involving 361 patients with acute bronchitis (Kemmerich et al. 2006).	
5.2 Pharmacokinetic properties	Well-established use **Thymol is absorbed from the intestines and exhaled within 140 minutes after intake of a single dose of thyme herb liquid extract DAB.** Background: According to data cited in the ESCOP monograph, thymol was detected rapidly after oral intake in the exhaled air [Ref. 72, 73 in ESCOP 2003]. Kinetic data for thyme extract is available with thymol as a marker compound. Thymol was demonstrated to be intestinally absorbed and pulmonarilly exhaled (Bischoff et al. 1998; Schindler et al. 2000, Kohlert et al. 2000, Kohlert et al. 2002)	Well-established use not endorsed. See comments above. For traditional use this information is not required.
5.3 Preclinical safety data	For the well-established medicinal use, we suggest the following wording: **In studies on acute and chronic toxicity thyme herb liquid extract DAB and thyme essential oil showed a rather low toxicity. Thyme oil did not cause relevant toxicity in acute toxicity testing (LD_{50} 2.8-4.7 g/kg in rats (p.o.), and 1.25 g/kg in mice). Thyme essential oil**	Well-established use not endorsed. See comments above.

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	had no mutagenic or DNA-damaging activity in either the Ames or *Bacillus subtilis* rec-Assay. Thyme essential oil did not show an influence on the growth and development of mouse embryos *in vivo*. Thymol did not show mutagenicity in several *Salmonella typhimurium* strains. Some data exist which demonstrate the lack of genotoxic effects: Essential thyme oil was negatively tested on genotoxic effects in the *Bacillus subtilis* rec-Assay and the *Salmonella*-microsome reversion assay (Azizan and Blevins 1995; Zani et al. 1991). An aqueous thyme extract was even found to possess antimutagenic effects against the dietary carcinogen Trp-P-2 (Natake et al. 1989). In mice the acute toxicity of an extract from thyme herb (extraction solvent: 95% ethanol; DER roughly 9:1) was investigated. No mortality was reported. At the tested dosages of 0.5, 1 and 3g extract/kg b.w. p.o. (5 animals in each group) a slightly reduced motor activity and depressed respiration was observed (no details) [Qureshi et al. 1991]. The oral LD_{50} of essential thyme oil has been determined as 2.84 g/kg and 4.70 g/kg in rats, respectively (Opdyke 1974; von Skramlik 1959), and as 1.25 g/kg in mice (without indication of way of application) (Akacic and Petricic 1956). The dermal LD_{50} in rabbits was >5 g/kg (Opdyke 1974). The intraperitoneal LD_{50} of Thymus zygis oil was 600 mg/kg in female mice (Jiménez et al. 1993). In mice the chronic toxic effects of an extract (extraction solvent: 95 % ethanol; DER roughly 9:1) of thyme herb given orally were investigated [Qureshi et al. 1991]. The extract caused reduced locomotor activity and a slight respiratory depression in mice with oral doses of 0.5 to 3.0 g/kg, corresponding to 4.3-26 g of dried plant material During the 90 days of treatment with 100 mg extract/kg b.w. (10 males and 10 females) 3 male and 1 female mice died whereas one animal died in each control group (10 male and 10 females). In the surviving animals there were no changes of haematologic parameters and no spermatotoxic effects. The	

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	weights of liver and testes increased (liver: 6.30±0.26 vs. 5.19±0.24, $p<0.05$; testes: 0.76±0.01 vs. 0.66±0.02, $p<0.01$); furthermore in the male mice weight gain was reduced ($p<0.05$) (31.3±1.5 vs. 34.0±0.9 g). In summary, these data showed a rather low toxicity of Thymi herba extracts and thyme essential oil. The genotoxic properties of essential oils obtained from thyme and several other herbs were studied in the *Bacillus subtilis* rec-assay (thyme oil: 10 und 30 µl) and Salmonella/microsome reversion assay (Ames test with TA1535, TA1537, TA98 and TA100 with/without S9 mix; thyme oil: 0.25, 0.5 and 1.0 µl/plate). In both tests, the thyme essential oil did not exert genotoxic effects [Zani et al. 1991].	
5.3	Well-established use **In studies on acute and chronic toxicity thyme herb liquid extract DAB and thyme essential oil showed a rather low toxicity. Thyme oil did not cause relevant toxicity in acute toxicity testing (LD_{50} 2.8-4.7 g/kg in rats (p.o.), and 1.25 g/kg in mice).** **Thyme essential oil had no mutagenic or DNA-damaging activity in either the Ames or *Bacillus subtilis* rec-Assay.** **Thyme essential oil did not show an influence on the growth and development of mouse embryos *in vivo*.** **Thymol did not show mutagenicity in several *Salmonella typhimurium* strains.** 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~~. Thyme essential oil had no mutagenic or DNA-damaging activity in either the AMES or *Bacillus subtilis* rec-Assay. Thyme essential oil did not show an influence on the growth and development of mouse embryos *in vivo*.	Well-established use not endorsed. See comments above. Traditional use: According to the guidance on the procedure of the preparation of a community monograph both deleted sentences have to be kept. The relevant literature has been considered in the assessment report, details which are of interest for the public safety are already mentioned in the draft monograph.

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	Thymol did not show mutagenicity in several *Salmonella typhimurium* strains. ~~Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.~~ Background: Directive 2001/83/EC does not require testing for reproductive toxicity, genotoxicity or carcinogenicity. Since there is no recognisable genotoxic or carcinogenic risk related to the use of thyme preparations, the call for additional data would not be appropriate. There is, however, some data demonstrating the lack of genotoxic effects: Essential thyme oil was negatively tested on genotoxic effects in the *Bacillus subtilis* rec-Assay and the *Salmonella*-microsome reversion assay (Azizan and Blevins 1995; Zani et al. 1991). An aqueous thyme extract was even found to possess antimutagenic effects against the dietary carcinogen Trp-P-2 (Natake et al. 1989). The acute toxicity of a thyme extract (extraction solvent: 95% ethanol; DER roughly 9:1) was investigated in mice. No mortality was reported. At the tested dosages of 0.5, 1 and 3 g extract/kg b.w. p.o. (5 animals in each group) a slightly reduced motor activity and depressed respiration was observed (no details) [Qureshi et al. 1991]. The oral LD_{50} of essential thyme oil has been determined as 2.84 g/kg and 4.70 g/kg in rats, respectively (Opdyke 1974; von Skramlik 1959), and as 1.25 g/kg in mice (without indication of way of application) (Akacic and Petricic 1956). The dermal LD_{50} in rabbits was >5 g/kg (Opdyke 1974). The intraperitoneal LD_{50} of Thymus zygis oil was 600 mg/kg in female mice (Jiménez et al. 1993). The chronic toxic effects of a thyme extract (extraction solvent: 95 % ethanol; DER roughly 9:1) given orally were investigated in mice [Qureshi et al. 1991]. The extract caused reduced locomotor activity and a slight respiratory depression in mice with oral doses of 0.5 to 3.0 g/kg, corresponding to 4.3-26 g of dried plant material During the 90 days of treatment with 100 mg extract/kg b.w. (10 males and 10 females) 3 male and 1 female mice died whereas one animal died in each control	There is no safety data published on the different types of liquid extracts of thyme herb.

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	group (10 male and 10 females). In the surviving animals, there were no changes of haematological parameters and no spermatotoxic effects. The weights of liver and testes increased (liver: 6.30±0.26 vs. 5.19±0.24, $p<0.05$; testes: 0.76±0.01 vs. 0.66±0.02, $p<0.01$); furthermore in the male mice weight gain was reduced ($p<0.05$) (31.3±1.5 vs. 34.0±0.9 g). In summary, these data showed a rather low toxicity of Thymi herba extracts and thyme essential oil. The genotoxic properties of essential oils obtained from thyme and several other herbs were studied in the *Bacillus subtilis* rec-assay (thyme oil: 10 und 30 µl) and in a Salmonella/microsome reversion assay (Ames test with TA1535, TA1537, TA98 and TA100 with/without S9-mix; thyme oil: 0.25, 0.5 and 1.0 µl/plate). In both tests, the thyme essential oil did not provoke genotoxic effects [Zani et al. 1991].	