5 April 2016
EMA/HMPC/85124/2015
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Thymus vulgaris* L. or *Thymus zygis* L., herba and *Primula veris* L. or *Primula elatior* (L.) Hill, radix

Final

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Thymus vulgaris* L. or *Thymus zygis* L., herba and *Primula veris* L. or *Primula elatior* (L.) Hill, radix
Herbal preparation(s)	WEU a) 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 of herbal substance to extraction solvent 1:5), extraction solvent ethanol 50% V/V b) 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 c) 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

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Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Thymus vulgaris* L. or *Thymus zygis* L., herba and *Primula veris* L. or *Primula elatior* (L.) Hill, radix
	TU a) Dry extract from Thyme (DER 6-10:1), extraction solvent ethanol 70% V/V and dry extract from Primula root (DER 3.5-4.5:1), extraction solvent water b) 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 soft extract from Primula root (DER 3-7:1), extraction solvent methanol: water: ammonia solution 26% (50:49.5:0.5) c) 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 soft extract from Primula root (DER 1-2:1), extraction solvent ethanol 55% V/V d) Dry extract from Thyme (DER 4.5-7:1), extraction solvent methanol 25% V/V and dry extract from Primula root (DER 4-6:1), extraction solvent water e) Liquid extract from Thyme (DER 1:2-3), extraction solvent ethanol 20% V/V and liquid extract from Primula root (DER 1:2-3), extraction solvent ethanol 15% V/V f) Soft extract from Thyme (DER 5-7:1), extraction solvent methanol 25% V/V and soft extract from Primula root (DER 6-10:1), extraction solvent water 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 h) 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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Thymus vulgaris* L. or *Thymus zygis* L., herba and *Primula veris* L. or *Primula elatior* (L.) Hill, radix
	Primula root (DER 1:2-2.5), extraction solvent ethanol 70% m/m i) Liquid extract from the mixture of Thyme (DER 1:3.3) and Primula root (DER 1:2-4.6), extraction solvent water
Pharmaceutical form(s)	Liquid or solid dosage forms for oral use
Rapporteur(s)	R. Länger
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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

The phytochemical composition of both Thyme and Primula root and their preparations have been discussed in the assessment reports on
Thyme (Doc. Ref. EMA/HMPC/342334/2013)
Thyme essential oil (Doc. Ref. EMA/HMPC/131903/2009)
Primula root (Doc. Ref. EMA/HMPC/113577/2012).

- Herbal preparation(s)

Tschiggerl & Bucar (2011) investigated the influence of saponins of Primula root on the concentration of compounds of the essential oil of Thyme in a herbal tea. Saponins dose-dependently lowered the content of total essential oil and the relative content of thymol in the herbal tea whereas the relative content of monoterpene hydrocarbons increased.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

The herbal preparations with marketing authorisations consist of fixed combinations of dry extracts (prepared with ethanol/water, methanol/water or water), soft extracts (prepared with ethanol/water, methanol/water or water) or liquid extracts (prepared with a mixture of ammonia solution 10% m/m: glycerol 85% m/m: ethanol 90% V/V: water (1:20:70:109) or ethanol/water) of Thyme and Primula root.

All of these products are marketed in Germany, some of them are authorised also in Austria, the Czech Republic and Slovakia.

1.2. Search and assessment methodology

Databases assessed (date, search terms) and other sources used:

- Search terms: *Thymus vulgaris*, Thyme, *Primula*, primrose, combination
- Databases: Pubmed, Medline and Toxnet

Libraries: University Vienna, centre of pharmacy; Medical University Vienna, central library

2. Data on medicinal use

The historical use of Thyme and Primula root has been discussed in the assessment reports on Thymi herba and Primulae radix (Doc. Ref. EMA/HMPC/342334/2013 and EMA/HMPC/113577/2012, respectively).

2.1. Information about products on the market in the EU Member States

According to the information provided by the National Competent Authorities[1]

Austria

Combination of 160 mg dry extract from Thyme (DER 6-10:1), extraction solvent ethanol 70% V/V and 60 mg dry extract from Primula root (DER 6-7:1), extraction solvent ethanol 47.4% V/V. Date of authorisation: 2000.

Czech Republic

Combination of 160 mg dry extract from Thyme (DER 6-10:1), extraction solvent ethanol 70% V/V and 60 mg dry extract from Primula root (DER 6-7:1), extraction solvent ethanol 47.4% V/V. Date of authorisation: 2001.

Germany

Code in AR and monograph	Composition	On the market	Posology
TU a	1 capsule contains: 75 mg dry extract from Thyme (DER 6-10:1), extraction solvent ethanol 70% V/V and 37.5 mg dry extract from Primula root (DER 3.5-4.5:1), extraction solvent water	at least since 1976	6-12 year: 2 times daily 1 capsule ≥ 12 year: 3 times daily 1 capsule
TU b	100 g (=98.23 ml) liquid contain: 75 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 3 g soft extract from Primula root (DER 3-7:1), extraction solvent methanol: water: ammonia solution 26% (50:49.5:0.5)	at least since 1976	≥ 12 year: 3 times daily 35 drops (=1.5 g)
TU c	100 g (=77.5 ml) liquid contain: 12 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)	at least since 1976	1-3 year: 3 times daily 3 ml

[1] Data are collected using the template entitled 'Document for information exchange for the preparation of the assessment report for the development of European Union monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the list' (EMEA/HMPC/137093/2006)

Code in AR and monograph	Composition	On the market	Posology
	and 1.8 g soft extract from Primula root (DER 1-2:1), extraction solvent ethanol 55% V/V		3-6 year: 3 times daily 5 ml 6-12 year: 3-4 times daily 5 ml ≥ 12 year: 4 times daily 7.5 ml
TU d	100 g granules contain: 3.36 g dry extract from Thyme (DER 4.5-7:1), extraction solvent methanol 25% V/V and 0.64 g dry extract from Primula root (DER 4-6:1), extraction solvent water	at least since 1976	≥ 12 year: 3 times daily 8 ml (=3.28 g) granules prepared as tea
TU e	10 ml liquid contain: 6.9090 g liquid extract from Thyme (DER 1:2-3), extraction solvent ethanol 20% V/V and 2.2504 g liquid extract from Primula root (DER 1:2-3), extraction solvent ethanol 15% V/V	at least since 1976	≥ 12 year: 3-5 times daily 36 drops (=1.8 ml)
TU f	100 g (=88.1 ml) contain: 2.25 g soft extract from Thyme (DER 5-7:1), extraction solvent methanol 25% V/V and 0.325 g soft extract from Primula root (DER 4-6:1), extraction solvent water	at least since 1976	1-6 year: 2 times daily 5 ml 7-12 year: 2-3 times daily 5 ml ≥ 12 year: 3-4 times daily 5 ml
WEU a, TU g	100 g (=92.081 ml) liquid contain 40 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 20 g tincture from Primula root (Ratio herbal substance to extraction solvent 1:5), extraction solvent ethanol 50% V/V	at least since 1976	6-12 year: 3-5 times daily 25 drops ≥ 12 year: 5 times daily 30 drops
WEU b, TU h	100 g (=75.36 ml) liquid contain 5 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)	at least since 1976	6-12 months: 6 times daily 1 ml 1-4 year: 6 times daily 2.5

Code in AR and monograph	Composition	On the market	Posology
	and 2.5 g liquid extract from Primula root (DER 1:2-2.5), extraction solvent ethanol 70% m/m		ml ≥ 5 year: 4 times daily 7.5 ml
WEU c	1 film-coated tablet contains: 160 mg dry extract from Thyme (DER 6-10:1), extraction solvent ethanol 70% V/V and 60 mg dry extract from Primula root (DER 6-7:1), extraction solvent ethanol 47.4% V/V According to Ernst *et al.* (1997) the dry Thyme extract contains essential oil.	since 1993	≥ 12 year: 3 times daily 1 tablet
not considered in monograph	10 g (=10.3 ml) liquid contain: 6 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 4 g tincture from Primula root (1:5), extraction solvent ethanol 70% V/V	since 2007	≥ 12 year: 5 times daily 75 drops (ca. 2.3 ml)

Poland

A combination of Extractum compositum spissum (3:1; aq.) ex: Thyme herb and Primula root with the isolated compound thymol is on the market since 2000. Due to the combination with an isolated compound and the short marketing period this combination is not considered in the monograph.

Slovakia

A combination product was authorised in 2005. Due to the short marketing period this combination is not considered in the monograph.

Slovenia

Code in AR and monograph	Composition	On the market	Posology
TU i	Liquid extract from the mixture of Thyme (DER 1:3.3) and Primula root (DER 1:2-4.6), extraction solvent water 5 ml (single dose) of the finished product contains 3.08 g of	Since 1981	*Adolescents, adults and elderly* Single dose: 3.08 g of an aqueous extract which is equivalent to 0.22–

Code in AR and monograph	Composition	On the market	Posology
	the liquid extract.		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* 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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Czech Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Poland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
Slovak Republic	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	no product

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national traditional systems of registration

This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

2.2. Information on documented medicinal use

The traditional indication as well as the current indication for Thyme, Primula and combinations thereof is use as an expectorant in cough associated with cold.

Indications

Both Thyme and Primula root are traditionally used as expectorants in cough associated with cold. This indication is also appropriate for traditional herbal medicinal products containing a fixed combination of these two herbal substances.

In clinical trials on combinations of Thyme and Primula root the inclusion criterion was stated as 'acute bronchitis'. 'Acute bronchitis' is considered inappropriate terminology and should be read as describing 'common cold with productive cough'.

Specified strength / posology / route of administration / duration of use for relevant preparations and indications

Posology

The posologies for all combinations in the monograph are based on the authorised posologies of the respective corresponding products.

Duration of use

No restriction on the duration of use has been reported for fixed combinations of Thyme herb and Primula root.

Results from clinical trials indicate an onset of the treatment effect on days 3 to 5. The use of combinations of Thyme and Primula should be restricted to 7 days as agreed for the European Union herbal monographs for the single active ingredients for the same indication.

Method of administration

Oral use

2.3. Overall conclusion on medicinal use

The fixed combination of Thyme and Primula root is a European tradition. All combinations of herbal preparations included in the monograph for traditional use are in medicinal use in the EU at least since 1976. Some of the combinations underwent variations regarding composition, posology or wording of the indication during their life cycle. All such modifications were regarded by the national competent authorities as variations within a dossier and not as of such importance that a new application was requested. The variations regarding the wording of the indication are in line with the legislation, as all the combinations were used throughout their lifecycle for the 'same or similar intended purpose' as indicated in Article 16c of Directive 2001/83/EC as amended.

The combinations proposed for well-established use have been in medicinal use in the EU for more than 10 years.

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

The phytochemical composition, pharmacology, pharmacokinetics and the toxicology of both Thyme and Primula root and their preparations have been discussed in the assessment reports on
Thyme (Doc. Ref. EMA/HMPC/342334/2013)
Thyme essential oil (Doc. Ref. EMA/HMPC/131903/2009)
Primula root (Doc. Ref. EMA/HMPC/113577/2012).

Main pharmacological effects

Thyme

Spasmolytic activity: *in vitro* experiments show spasmolytic activity of different types of extracts. Recent investigations suggest that thymol, which is considered by the European Pharmacopoeia as a relevant constituent for the quality of Thyme, does not contribute to the spasmolytic activity (Engelbertz *et al.* 2008).

Antimicrobial activity: the essential oil exhibits strong antimicrobial activity.

Further details see assessment report on Thyme (Doc. Ref. EMA/HMPC/342334/2013) and Thyme essential oil (Doc. Ref. EMA/HMPC/131903/2009).

Primula root

Saponins, which are considered as the most important constituents of Primula root, are considered to increase bronchial secretion by irritation of the gastric mucosa. Additionally, saponins exhibit antifungal, antibacterial and antiviral activities.

Further details see assessment report on Primula root (Doc. Ref. EMA/HMPC/113577/2012).

Non-clinical data on the combination of Thyme and Primula root

Nauert *et al.* (2005) investigated the influence of extracts of Primula root, Thyme and of their combination on the LPS-induced release of interleukin-8 in primary human monocytes in concentrations between 0.001% and 1%. Primula root extract inhibited dose-dependently the release in the range of the extract concentration between 0.1% and 1%. Thyme extract did not show an effect. The combination of both extracts had a more pronounced effect compared to the sum of the single extracts. The authors are of the view that this effect might contribute to the mucolytic effect of the extracts.

Assessor's comment: No data are provided on the type of the extracts (DER, extraction solvent). Therefore the relevance of these findings for the therapeutic use of the combination cannot be evaluated.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No non-clinical data on pharmacokinetics are available.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

No non-clinical safety data on genotoxicity, carcinogenicity and reproductive toxicity are published for the combination.

3.4. Overall conclusions on non-clinical data

The non-clinical data support the plausibility of the use of the combination of Thyme and Primula root as an expectorant. The therapeutic effects observed in clinical trials may be explained by the results of pharmacological testing.

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Kohlert *et al.* (2002) determined the systemic availability and the pharmacokinetics of thymol after oral administration of a single dose of 160 mg dry extract from Thyme (DER 6-10:1), extraction solvent ethanol 70% V/V and 60 mg dry extract from Primula root (DER 6-7:1), extraction solvent ethanol 47.4% V/V. Thymol sulfate and thymol glucuronide were found in urine and only thymol sulphate in plasma. The mean terminal elimination half-life was 10.2 hours. Thymol sulphate was detectable up to 41 hours after administration. No unchanged thymol could be found in plasma or urine.

4.2. Clinical Efficacy

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

In most of the clinical trials the bronchitis severity score (BSS) was defined as an important tool for the evaluation of the efficacy of the study medication. The BSS documents the symptoms cough, sputum, rales/rhonchi, chest pain during coughing and dyspnoea. Each symptom is assessed by the investigator using a verbal rating scale: 0=absent; 1=mild; 2=moderate; 3=severe; 4=very severe. The score was retrospectively properly validated (Matthys & Kamin 2013, Kardos *et al*. 2014).

Efficacy and tolerability of a fixed combination of Thyme and Primula root in patients with acute bronchitis (Gruenwald *et al.* 2005)

Study: Double-blind, placebo-controlled, randomised, multicentre, prospective clinical trial including 150 outpatients (≥ 18 years of age).

Preparation: 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 (corresponds to herbal preparation WEU a) and TU g) in the monograph)

100 g (= 92.081 ml) liquid contain 40 g liquid extract from Thyme and 20 g tincture from Primula root

Inclusion criteria: acute, not previously treated bronchitis, lasting less than 48 hours; BSS ≥ 5 points.

Exclusion criteria: obstructive or non-obstructive chronic bronchitis; allergic asthma bronchiale; simultaneous treatment with or indication for antibiotic treatment; treatment with antibiotics during the past 4 weeks; concomitant treatment with corticoids, beta-2-mimetics, theophylline, expectorants or antitussives or treatment with these medications during the past 7 days prior to the study; clinically relevant deviations in laboratory parameters due to severe organ or systemic diseases; patients with cancer or HIV; pregnancy and lactation; chronic alcohol abuse, medication or drug dependency. Concomitant medications without influence on the results were allowed (e.g. paracetamol, maximum 3 g per day).

Duration of treatment: 7-9 days

Posology: 30 drops (= 1 ml) 5 times daily

	Thyme liquid extract	Corresp. Thyme	Primula tincture	Corresp. Primula root
Single dose	0.43 g	0.19 g	0.21 g	0.042 g
Daily dose	2.15 g	0.95 g	1.05 g	0.21 g

Primary endpoint: decrease of the BSS

Results: 17 patients were excluded from the per-protocol collective because of withdrawal from the trial (n=2) or violations regarding examination time points and/or intake of the study medication (n=15). BSS decreased in the verum group from 12.0 ± 4.4 to 1.0 ± 2.1; in placebo group from 11.7 ± 4.3 to 6.5 ± 4.8. The difference between these groups is highly significant (p≤ 0.001). At the end of the study significantly more patients were symptom free in the verum group (58.7%) compared to the placebo group (5.3%).

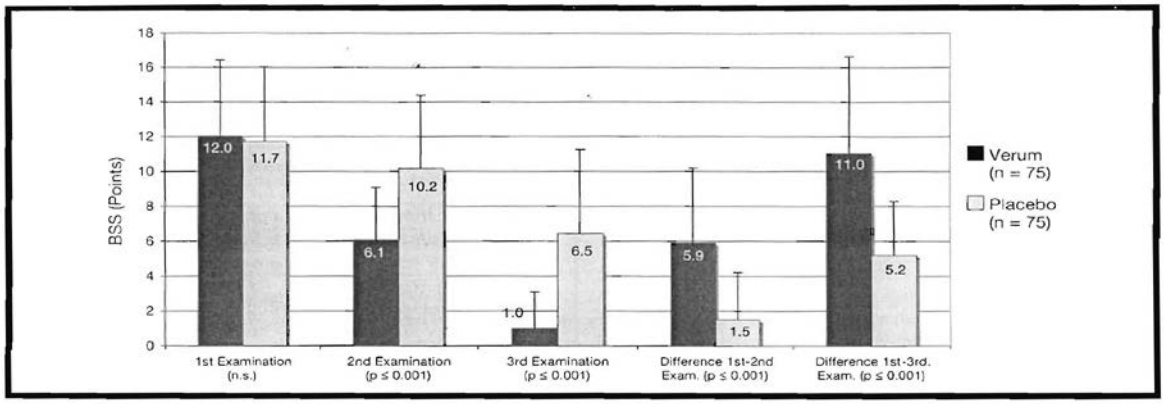

Fig. 1: Bronchitis severity score (BSS, x ± s) after 3–5 (2nd examination) and 7–9 days (3rd examination) of treatment (ITT population, n = 150).

Figure from Gruenwald *et al.* (2005)

A subgroup analysis revealed that patients with more severe symptoms benefit more from the study medication compared to patients with less pronounced symptoms.

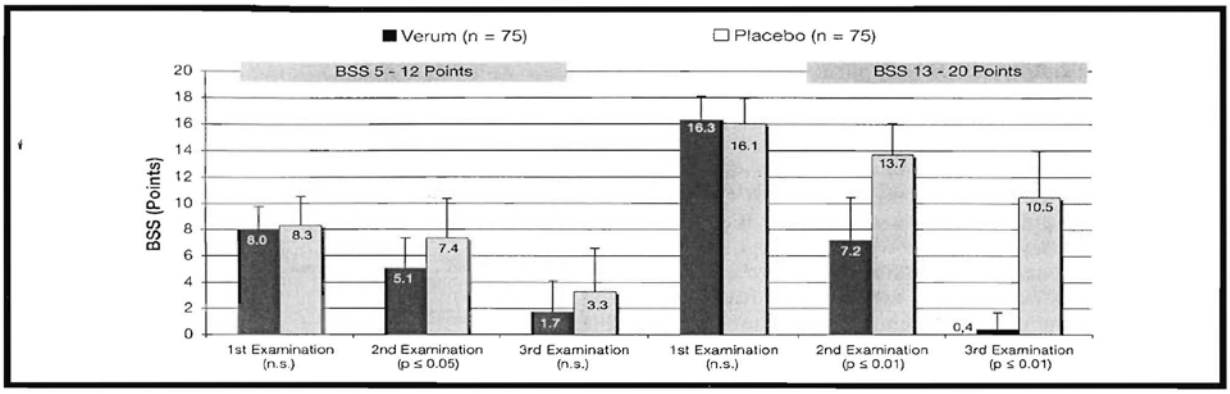

Fig. 2: Bronchitis severity score (BSS, x ± s) based on Severity Grade (ITT population, n = 150) after 3–5 (2nd examination) and 7–9 days (3rd examination) of treatment.

Figure from Gruenwald *et al.* (2005)

The mean reported onset of the treatment was in the verum group at day 3.4, in the placebo group at day 5.6.

No serious adverse events were observed. 5 adverse events occurred in the placebo group, 2 in the verum group (stomach ache and nausea were considered to be associated with the study medication).

Evaluation of the non-inferiority of a fixed combination of Thyme fluid and Primula root extract in comparison to a fixed combination of Thyme fluid extract and primrose tincture in patients with acute bronchitis (Gruenwald *et al*. 2006)

Study: Single-blind, randomised, bi-centric, prospective study including 189 outpatients (≥ 18 years of age).

Preparation: 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)
(corresponds to herbal preparation WEU b) and TU h) in the monograph)

100 g (=75.36 ml) liquid contain 5 g liquid extract from Thyme and 2.5 g liquid extract from Primula root

Inclusion criteria: acute, not previously treated bronchitis, lasting less than 48 hours; BSS ≥ 5 points.

Exclusion criteria: obstructive or non-obstructive chronic bronchitis; allergic asthma bronchiale; simultaneous treatment with or indication for antibiotic treatment; treatment with antibiotics during the past 4 weeks; concomitant treatment with corticoids, beta-2-mimetics, theophylline, expectorants or anti-tussives or treatment with these medications during the past 7 days prior to the study; clinically relevant deviations in laboratory parameters due to severe organ or systemic diseases; patients with cancer or HIV; pregnancy and lactation; chronic alcohol abuse, medication or drug dependency. Concomitant medications without influence on the results were allowed (e.g. paracetamol, maximum 3 g per day).

Duration of treatment: 7-9 days

Posology: herbal preparation WEU b): 5 ml 6 times daily

	Thyme liquid extract	Corresp. Thyme	Primula liquid extract	Corresp. Primula root
Single dose	0.33 g	0.15 g	0.165 g	0.073 g
Daily dose	1.98 g	0.88 g	0.99 g	0.44 g

or herbal preparation WEU a): 30 drops 5 times daily

	Thyme liquid extract	Corresp. Thyme	Primula tincture	Corresp. Primula root
Single dose	0.43 g	0.19 g	0.21 g	0.042 g
Daily dose	2.15 g	0.95 g	1.05 g	0.21 g

Primary outcome criterion: change of the BSS at study endpoint compared to baseline.

Results: 72 patients were excluded from the per-protocol collective because of either withdrawal from the trial (n=1) or violations regarding examination time points and/or intake of the study medication (n=71). Reduction of bronchitis severity score from baseline 11.0 ± 5.0 to 2.6 ± 4.6 in the group treated with herbal preparation WEU b) compared to a decrease from 11.0 ± 4.8 to 2.5 ± 4.2 in the group treated with herbal preparation WEU a). The mean onset of the treatment effect was at day 4 in both groups.

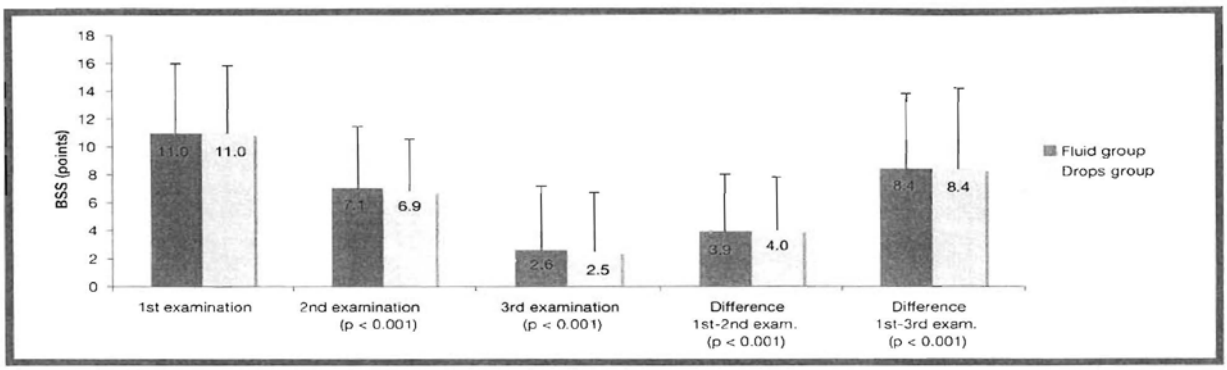

Fig. 1: Bronchitis Severity Score (BSS; x ± s) after 3–5 (2nd examination) and 7–9 days (3rd examination) of treatment (ITT population, n = 189). ■ Bitte < prüfen. ■

Figure from Gruenwald *et al.* (2006)

A statistically significant intergroup difference was not observed at any time point. The authors conclude that the study medications showed comparable results regarding their efficacy.

Evaluation of efficacy and tolerability of a fixed combination of dry extracts of Thyme herb and Primula root in adults suffering from acute bronchitis with productive cough (Kemmerich 2007)

Study: Placebo-controlled, double-blind multicentre phase IV study; 361 outpatients (adults only), 23 study centres.

Preparation: 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
(corresponds to herbal preparation WEU c) in the monograph)

Inclusion criteria: acute bronchitis with ≥ 10 coughing fits per day, onset of bronchial mucus production up at a maximum of 2 days prior to recruitment, bronchitis severity score ≥5, maximum BSS 20 points.

Exclusion criteria: concomitant fever (>39°C), pneumonia, history of chronic bronchial or pulmonary disease such as chronic bronchitis, chronic obstructive pulmonary disease (including acute episode), bronchiectasis, bronchial asthma, mucoviscidosis, history of clinically relevant chronic cardiovascular, kidney, gastrointestinal or liver disease, malignant growth, any severe somatopathic, neurological and/or psychiatric disease, pregnancy, lactation.

Responders were defined as patients with no or improved symptoms at visit 2 and 3 compared to visit 1. Patients whose symptoms were unchanged or deteriorated were classified as 'non-responders'.

Duration of treatment: 11 days

Posology: 1 tablet 3 times daily

	Thyme dry extract	Corresp. Thyme	Primula dry extract	Corresp. Primula root
Single dose	160 mg	1.28 g	60 mg	0.39 g
Daily dose	480 mg	3.84 g	180 mg	1.17 g

Baseline examination, control examinations on day 4 and day 10/end of treatment.

Evaluation: Manual count of coughing fits per day by the patients.

Investigator's assessment of the bronchitis severity score (at baseline: 7.9 in the verum group, 7.6 in the placebo group).

Primary outcome criterion: change in mean frequency of coughing fits during the daytime of days 7 to 9 as documented in the patient diary divided by the baseline value of day 1.

Secondary outcome criteria: reduction in coughing fits during daytime within 9 days of investigational treatment; time to 50% reduction in coughing fits during daytime compared to day 1; proportion of patients with no coughing fits on day 9; relative reduction in mean frequency of coughing fits at day 9; response to treatment assessed by the investigator; change in mean BSS score; change in the ability to cough up mucus during daytime; change in sleep disturbances induced by coughing; change in patient's general well-being.

Results: 6 patients of the verum group and 7 patients from the placebo group prematurely discontinued the study participation. Additionally 2 patients from the verum group and 1 patient from the placebo group stopped participation due to complete healing.

Reduction of coughing fits compared to baseline: 67.1% in verum vs. 51.3% in placebo group. A 50% reduction of coughing fits was reached in the verum group 2 days earlier compared to placebo group.

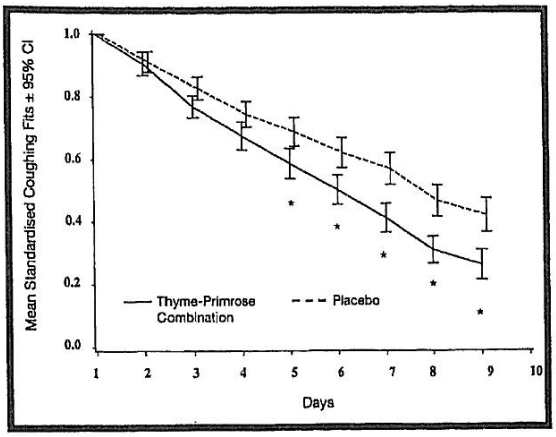

Fig. 1: Time course of coughing fits (standardised coughing fits ± 95% confidence intervals [CI]) (FAS: N = 353; 7 patients not evaluable due to missing values at baseline). Significant difference on α-level = 0.05 (*) between thyme-primrose combination and placebo (Mann-Whitney-Wilcoxon test adjusted for centres, p < 0.0001).

Figure from Kemmerich *et al.* (2007)

The bronchitis severity score improved in both groups rapidly, but responder rates were higher in the verum group (visit 2: verum 77.5%, placebo 60.1%; visit 3: verum 92.9%, placebo 75.8%)

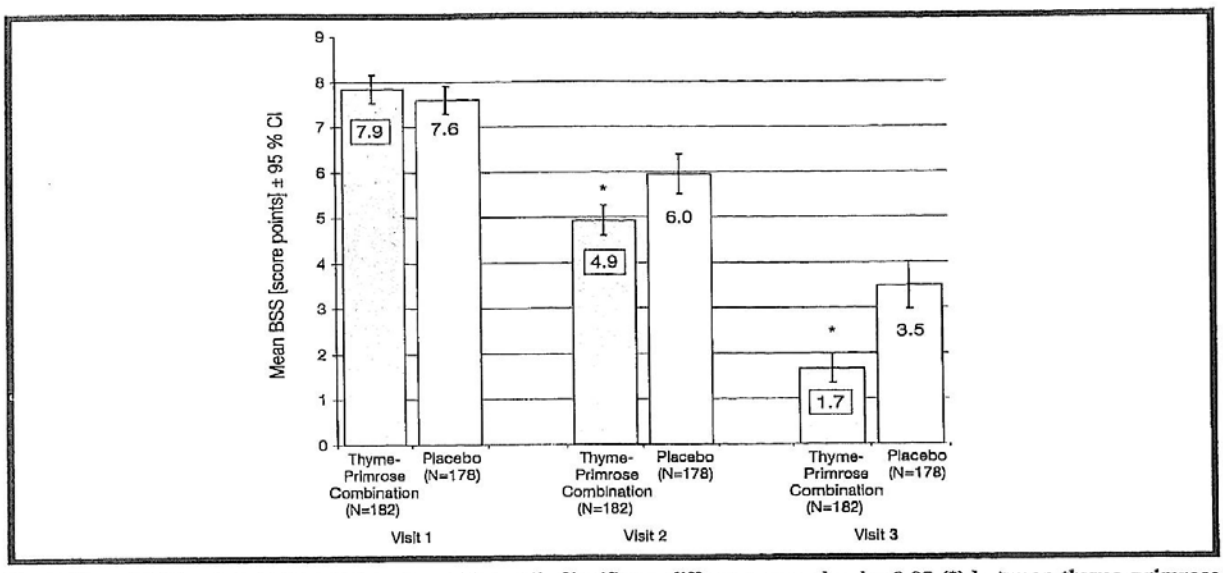

Fig. 5: Mean BSS [score points] ± 95% CI (FAS: N = 360). Significant difference on α-level = 0.05 (*) between thyme-primrose combination and placebo at Visit 2 (Mann-Whitney-Wilcoxon test adjusted for centres, p < 0.0001) and Visit 3 (Mann-Whitney-Wilcoxon test adjusted for centres, p < 0.0001).

Figure from Kemmerich *et al.* (2007)

No difference in the frequency or severity of adverse events was observed. Severe or serious adverse events were not reported. In the verum group 1 case with Eustachian tube disorder and 1 case of back pain were labelled as moderate, 1 case of otitis externa as mild.

A controlled multi-centre study of herbal versus synthetic secretolytic drugs for acute bronchitis (Ernst *et al.* 1997)

Study: Controlled, multi-centre (771 general physicians), post-marketing surveillance study with 7,783 patients included.

Preparation: 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 (corresponds to herbal preparation WEU c) in the monograph)

1,490 children 5.7 ± 2.9 years of age and 3,139 adults 40.9 ± 18.6 years of age were included in the study group which received the fixed combination of Thyme and Primula root. The other patients received Ambroxol (n=479 children, 590 adults), N-Acetylcysteine (n=299 children, 1044 adults) or other herbal medicinal products (n=207 children, 183 adults, e.g. extracts of Hederae folium, Thyme, combination of essential oils).

The study was neither randomised nor placebo-controlled.

The calculation of the odds ratios revealed that for any parameter (e.g. auscultation, coughing during day/night, pain while coughing, quantity of sputum, viscosity of sputum) the treatment was better with the fixed combination of Thyme and Primula root compared to the other groups. This was true for both age groups.

The rate of adverse events was clearly below 1% (in adults 0.64%, in children 0.60%).

4.3. Clinical studies in special populations (e.g. elderly and children)

Treatment of acute cold in children – results of an observational study with a Primula – Thyme – preparation (Fasse *et al.* 2006)

Study: Non-interventional study in 98 children (0 - <3 years of age), 112 children (≥3 - ≤6 years of age), and 90 children (>6 - ≤12 years of age).

Preparation: 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 soft extract from Primula root (DER 1-2:1), extraction solvent ethanol 55% V/V
(corresponds to herbal preparation TU c) in the monograph)

100 g (=77.5 ml) contain 12 g liquid extract of Thyme and 1.8 g soft extract of Primula root

Posology:

<3 years: 3 times daily 2.5 - 3 ml

3-6 years: 3 times 5 ml

6-12 years: 3 - 4 times 5 ml

Side effects: No data; the authors state an 'excellent tolerability'. In 4 children vomiting occurred (2 children <3 years, 1 in group 3-6, 1 in group 6-12).

Assessor's comment: No control group, therefore no evaluation of the efficacy of the treatment was possible.

Treatment of acute cold in children – results of an observational study with a Primula – Thyme – preparation (Bässler & Zieseniß 2005)

Assessor's comment: No control group, therefore no evaluation of the efficacy of the treatment was possible. This study is published as a congress abstract only. This paper seems to be the abstract of the paper by Fasse *et al.* (2006, see above).

Efficacy and tolerability of liquid dosage forms of a fixed combination of Thyme and primrose in children with acute bronchitis (Nauert & Grünwald 2005, Grünwald *et al.* 2006a)

Study: Non-interventional study in 110 children (6-12 years of age).

Preparation: 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
(corresponds to herbal preparation WEU a) and TU g) in the monograph)

100 g (=92.081 ml) liquid contain 40 g liquid extract from Thyme and 20 g tincture from Primula root

Posology: 25 drops up to 6 times daily.

The authors state an 'excellent tolerability' of the herbal preparation.

Assessor's comment: This study is published as congress abstract only. No control group was included. Therefore no judgement of the efficacy of the treatment is possible. However, the study can be used for the demonstration of safety of the herbal preparation in children from 6 years up.

Efficacy and tolerability of liquid dosage forms of a fixed combination of Thyme and primrose in children with acute bronchitis (Nauert & Grünwald 2005, Grünwald *et al.* 2006a)

Study: Non-interventional study in 111 children (1-4 years of age) and 109 children (5-12 years of age).

Preparation: 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)
(corresponds to herbal preparation WEU b) and TU h) in the monograph)

100 g (=75.36 ml) liquid contain 5 g liquid extract from Thyme and 2.5 g liquid extract from Primula root

Posology:

1-4 years: 2.5 ml up to 6 times daily

4-12 years: 5 ml up to 6 times daily

The authors state an 'excellent tolerability' of the herbal preparation.

Assessor's comment: This study is published as a congress abstract only. No control group was included, therefore no judgement of the efficacy of the treatment is possible. However, the study can be used for the demonstration of safety of the herbal preparation in children from 1 year up.

Fixed combination of Thyme liquid extract and Primula root liquid extract for the oral treatment of children with cough and bronchial catarrh (Nauert & Eckert 2003, Grünwald *et al.* 2006a)

Study: Non-interventional study in 312 children (1-4 years of age) and 324 children (4-12 years of age).

Preparation: 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)
(corresponds to herbal preparation WEU b) and TU h) in the monograph)

100 g (=75.36 ml) liquid contain 5 g liquid extract from Thyme and 2.5 g liquid extract from Primula root

Posology:

1-4 years: 2.5 ml 6 times daily

4-12 years: 5 ml 6 times daily

The onset of the treatment effect was observed at day 3-4.

The authors state an 'excellent tolerability' of the herbal preparation.

Assessor's comment: This study is published as congress abstract only. No control group was included, therefore no evaluation of the efficacy of the treatment was possible. However, the study can be used for the demonstration of safety of the herbal preparation in children from 1 year up.

A fixed combination of Thyme and primrose for the treatment of cough (Schmidt 2008)

Study: Non-interventional study in 199 children 6-12 months of age.

Preparation: 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)
(corresponds to herbal preparation WEU b) and TU h) in the monograph)

100 g (=75.36 ml) liquid contain 5 g liquid extract from Thyme and 2.5 g liquid extract from Primula root

Posology: 1 ml 6 times per day

Mean duration of treatment: 6.4 days

Inclusion criterion: acute disorders of the upper respiratory tract with cough, catarrh and mucous obstruction of the bronchia.

Rating of symptoms like 'severity of cough', 'number of coughing fits per day', 'number of coughing fits during night', 'impairment of sleep quality'.

Side effects: 1 adverse event with possible causal relationship to the study medication (perioral eczema). 1 adverse event (vomiting, diarrhoea) was interpreted as correlated with the underlying disease.

Ethanol: 1 ml of the study medication results in a blood ethanol concentration of 0.008 ‰ . The metabolism in children in this age group is about 0.06 ‰ -0.09 ‰ per hour. Therefore no accumulation is to be expected.

Assessor's comment: No control group was included, therefore no evaluation of the efficacy of the treatment is possible. Although the ethanol content is very low, the herbal preparation is not recommended for children below 2 years of age (according to the 'Reflection paper on ethanol content in herbal medicinal products and traditional herbal medicinal products used in children', EMA/HMPC/85114/2008, published in January 2010).

Compliance, tolerability and efficacy of a fixed combination of Thyme and Primula (T+P) in 200 infants with acute bronchitis (Nauert & Bentley 2008)

Study: 200 infants (6-12 months of age) treated in 6 centres in Germany.

Posology: The study medication was given in a dosage of 1 ml, 6 times daily.

Duration of treatment: The study medication was given over a period of 7 days.

The authors state an 'excellent tolerability' of the herbal preparation.

Assessor's comment: This study is published as a congress abstract only. No control group was included. Therefore no evaluation of the efficacy of the treatment is possible. This paper appears to be the abstract of the paper by Schmidt (2008, see above).

Assessor's general comments on the studies with the fixed combination (herbal preparation WEU a) including children: Parts of the studies are published as abstracts. Grünwald *et al.* 2006a combined the data obtained until 2006. The numbers of included children differ between the publications.

A controlled multi-centre study of herbal versus synthetic secretolytic drugs for acute bronchitis (Ernst *et al.* 1997)

Study: Controlled, multi-centre (771 general physicians), post-marketing surveillance study.

1,490 children 5.7 ± 2.9 years of age were included in the study group which received the fixed combination of Thyme and Primula root. The other patients received Ambroxol (n=479 children), N-Acetylcysteine (n=299 children) or other herbal medicinal products (n=207 children, e.g. extracts of Hederae folium, Thyme, combination of essential oils).

The study was neither randomised nor placebo-controlled.

Preparation: Dry extract from Thyme (DER 6-10:1), extraction solvent ethanol 70% V/V and dry extract from Primula root (DER 6.0-7.0:1), extraction solvent ethanol 47.4% V/V (corresponds to herbal preparation WEU c) in the monograph).

Clinical endpoints: Body temperature, auscultation, auscultation during coughing, coughing during daytime, coughing during the night, pain during coughing, quality of cough, quantity of sputum, viscosity of sputum, patient judgement. All parameters were assessed on a 3 point rating scale except body temperature.

The calculation of the odds ratios revealed that for any parameter (e.g. auscultation, coughing during day/night, pain while coughing, quantity of sputum, viscosity of sputum) the treatment was better with the fixed combination of Thyme and Primula root compared to the other groups.

The rate of adverse events was clearly below 1% (in 1,490 children 0.60%).

Assessor' comments on the proposed age limit for the monograph:

Traditional use:

Although there are data available on the safe use of some fixed combinations even in children below 1 year of age, the age limit should be set at 4 years for those fixed combinations where data on the safe use in the paediatric population are available (monograph TU part preparations c), g), h)). Medicinal products containing such a fixed combination will be available without prescription; therefore the use will be without medical supervision. For safety reasons, the use of expectorants in children below 4 years of age has to be restricted, the treatment has to be performed under medical control. Moreover, recent guidelines for the management of cough in children recommend a 'wait, watch, review' approach instead of an intervention by medication (Kelley & Allen 2007). Traditional fixed combinations should be limited for use in children between 4 and 11 years of age, adolescents above 12 years of age, adults and elderly like it was agreed for the European Union herbal monographs on the single active ingredients Thyme and Primula root.

Well-established use:

Herbal preparations WEU a) and WEU b): As children and adolescents below 18 years of age were not included in controlled clinical trials the combinations under well-established use are restricted to adults and elderly. However, as stated above, these combinations may be used in traditional herbal registrations for the age group of children from 4-11 years and adolescents from 12 – 18 years as sufficient data from non-interventional studies confirm the safety of the use in this age group.

Herbal preparation WEU c): Although a considerable number of children was included in the study of Ernst *et al.* (1997) the efficacy of the combination is still insufficiently documented for children and adolescents due to the lack of a placebo group and due to the lack of a validation of the score used. Consequently the well-established use of this combination is restricted to adults and elderly. As this combination does not fulfil the criteria for traditional use with regard to the minimum period of 30

years medicinal use (thereof 15 in the EU) a traditional use for the paediatric population cannot be proposed.

4.4. Overall conclusions on clinical pharmacology and efficacy

The benefit of cough medicines has been the focus of controversial discussion. Although not mentioning explicitly herbal medicinal products and not specifically considering 'acute bronchitis', a Cochrane review on OTC medications for cough (Smith *et al.* 2008), the guideline on diagnosis and treatment of cough from the German Society for General and Family Medicine (DEGAM 2008) as well as the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines conclude that currently there is insufficient evidence to support the use of expectorants for the treatment of acute cough. In contrast, the guideline of the German society for pneumology and respiratory medicine (Kardos *et al*. 2010) strongly recommends the combination of Thyme and Primula in the case of acute cough.

Currently, there is no 'gold standard' for endpoints used in clinical trials with the indication 'cough'. However, the BSS symptom score, which was used in some of the clinical trials, seems to be an appropriate instrument.

The inclusion criterion 'acute bronchitis' remains unclear. Acute bronchitis is not well defined. 'Acute bronchitis' is considered inappropriate terminology and should be read as 'common cold with productive cough'. Also in current therapeutic guidelines these terms are used synonymously. Under the heading 'acute and chronic cough' in the *Guideline of the German Respiratory Society for Diagnosis and Treatment of adults suffering from acute or chronic cough (*Kardos *et al.* 2010*)* it is mentioned: 'the spontaneous course of cough in case of acute bronchitis…' From this statement it can be concluded that at least in Germany, where the clinical trials for thyme/primula have been carried out, acute bronchitis and acute cough are used as synonyms. According to the guideline #11 of the German Society for General and Family Medicine (DEGAM 2008) common cold and acute bronchitis are defined as subchapters of 'acute cough'. When applying this guideline a diagnosis of acute bronchitis can be stated retrospectively only considering the time course of improvement of symptoms. Therefore the inclusion criterion 'acute bronchitis' appears debatable as the time course of the development of symptoms cannot be predicted. Taken together, the differences in the wording between inclusion criteria in the clinical trials and the proposed indication for the monograph cannot be regarded as differences in the clinical sense.

Although there are some shortcomings in the published randomised, placebo-controlled clinical trials, the overall scientific conclusions are that the studies of Gruenwald *et al.* 2005 (supporting herbal preparation WEU a), Gruenwald *et al.* 2006 (supporting herbal preparation WEU b) and Kemmerich 2007 (supporting herbal preparation WEU c) are of suitable quality in terms of design and performance.

Taking all of the clinical trials together, the HMPC was of the opinion that for three fixed combinations the quality of the studies was sufficient to demonstrate efficacy (i.e. well-established use is demonstrated). Children and adolescents below 18 years of age were not included in the controlled clinical trials of sufficient quality. Therefore the combinations under well-established use are restricted to adults and elderly.

The data from the clinical trials also support the traditional use of other fixed combinations and support the plausibility of the use in the proposed indication. The safety data generated in non-interventional clinical trials support the safe use of the herbal preparations TU c), g) and h) in adolescents and children from 4 years of age.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

No data available.

5.2. Patient exposure

The fixed combinations included in the monograph have been in medicinal use at least since 1976. Beside the numbers of patients included in the clinical trials mentioned above no further data on patient exposure are available.

5.3. Adverse events, serious adverse events and deaths

No serious adverse events or deaths were either observed during the clinical trials or reported from the medicinal use of the fixed combinations.

During clinical trials stomach ache, nausea, vomiting, diarrhoea and perioral eczema were observed and interpreted as possibly caused by the study medication.

For the monograph, section 4.8 'Undesirable effects' will include: 'Gastric disorders and nausea may occur. The frequency is not known.'

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No serious adverse events or deaths were either observed during the clinical trials or reported from the medicinal use of the fixed combinations in children.

During clinical trials in children gastrointestinal complaints such as vomiting and diarrhoea as well as skin reactions such as pruritus and perioral eczema were observed and interpreted as possibly caused by the study medication.

Fertility

No fertility data available.

Use during pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

5.6. Overall conclusions on clinical safety

No serious adverse events or deaths were either observed during the clinical trials or reported from the medicinal use of the fixed combinations.

In clinical trials only mild to moderate undesirable effect were reported.

As children and adolescents below 18 years of age were not included in controlled clinical trials of sufficient quality the combinations under well-established use are not recommended for this age group because of lack of data on efficacy.

Although the data from clinical trials suggest that use of some of the fixed combinations might be safe in children down to 6 months of age, the traditional use of these fixed combinations (monograph TU part preparations c), g), h)) as expectorants without supervision by a doctor should be restricted to children over 4 years of age. In younger children the diagnosis should be performed by a doctor and treatment should be only under medical supervision.

No special risks are known for the single active ingredients or for the combination. Therefore the use of the fixed combination of Thyme and Primula root can be considered as safe when administered at the specified posology.

6. Overall conclusions (benefit-risk assessment)

Based on the documented traditional medicinal use for fixed combinations of thyme and primula the indication 'Traditional herbal medicinal product used as an expectorant in cough associated with cold' is proposed. The medicinal use in this indication is plausible in view of the long-standing use as well as the pharmacological properties of Thyme and Primula root and the results of clinical trials. All fixed combinations proposed for traditional use have been in medicinal use for at least 30 years and fulfil all criteria for traditional herbal medicinal products as defined in Article 16a of Directive 2001/83/EC as amended. For three combinations safety data for children are available. Therefore the traditional use of these combinations is proposed for children from 4-11 years of age and for adolescents.

For three combinations the clinical trials report beneficial effects in the treatment of acute bronchitis (which should be translated as 'productive cough'). The quality of the studies was considered as sufficient to support these combinations for well-established use in the indication 'Herbal medicinal product used as an expectorant in case of productive cough'. Data on efficacy in children and adolescents are lacking for the use of these combinations according to the well-established use is restricted to adults and elderly.

No special risks are known for the single active ingredients or for the combinations. The nature and severity of adverse events which were observed during clinical trials do not give cause for safety concerns. Therefore the use of the fixed combinations of Thyme and Primula root can be considered as safe when administered at the specified posology.

The benefit of the medicinal use in the specified indication is adequately demonstrated for the combinations under well-established use and plausible for the combinations under traditional use and no special risks are known; the benefit-risk balance is clearly positive.

Due to the lack of adequate data on genotoxicity, a European Union list entry is not proposed.

Annex

List of references