



9 July 2013
EMA/HMPC/130038/2010 *Corr.*¹
Committee on Herbal Medicinal Products (HMPC)

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

This document was valid from 24 September 2012 until April 2016. It is now superseded by a [new version](#) adopted by the HMPC on 5 April 2016 and published on the EMA website.

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Thymus vulgaris</i> L. and <i>Thymus zygis</i> L., herba and <i>Primula veris</i> L. and <i>Primula elatior</i> (L.) Hill, radix
Herbal preparation(s)	Dry, liquid and soft extracts, tinctures
Pharmaceutical form(s)	Solid and liquid dosage forms for oral use
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Assessor(s)	R. Länger

¹ Correction on page 5 concerning herbal preparation F



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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 und Primula root and their preparations have been discussed in the assessment reports on thyme (Doc. Ref. EMEA/HMPC/234113/2006) thyme essential oil (Doc. Ref EMEA/HMPC/131901/2009) Primula root (Doc. Ref. EMA/HMPC/113577/2012).

- Herbal preparation(s)

Tschiggerl & Bucar (2011) investigated the influence of saponins of *Primulae radix* 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, Czech Republic and Slovakia.

1.2. Information about products on the market in the Member States

According to the information provided by the National Competent Authorities²

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
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 y: 2 x daily 1 capsule ≥ 12 y: 3 x daily 1 capsule
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 y: 3 x daily 35 drops (=1.5 g)

² Data are collected using the template entitled 'Document for information exchange for the preparation of the assessment report for the development of Community monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the list' (EMA/HMPC/137093/2006)

Code in AR and monograph	Composition	On the market	Posology
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) and 1.8 g soft extract from Primula root (DER 1-2:1), extraction solvent ethanol 55% v/v	at least since 1976	1-3 y: 3 x daily 3 ml 3-6 y: 3 x daily 5 ml 6-12 y: 3-4 x daily 5 ml ≥ 12 y: 4 x daily 7.5 ml
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 y: 3 x daily 8 ml (=3.28 g) granules prepared as tea
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 y: 3-5 x daily 36 drops (=1.8 ml)
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 6-10:1), extraction solvent water	at least since 1976	1-6 y: 2 x daily 5 ml 7-12 y: 2-3 x daily 5 ml ≥ 12 y: 3-4 x daily 5 ml
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 y: 3-5 x daily 25 drops ≥ 12 y: 5 x daily 30 drops

Code in AR and monograph	Composition	On the market	Posology
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) and 2.5 g liquid extract from Primula root (DER 1:2-2.5), extraction solvent ethanol 70% m/m	at least since 1976	6-12 m: 6 x daily 1 ml 1-4 y: 6 x daily 2.5 ml ≥ 5 y: 4 x daily 7.5 ml
not considered in monograph	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 <i>et al.</i> (1997) the dry thyme extract contains essential oil.	since 1993	≥ 12 y: 3 x 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 from Primula root (1:5), extraction solvent ethanol 70% v/v	since 2007	≥ 12 y: 5 x daily 75 drops (ca. 2.3 ml)

Poland

A combination of Extractum compositum spissum (3:1; aq.) ex: Thymi herba et Primulae radix 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
I	<p>Liquid extract from the mixture of thyme (DER 1:3.3) and Primula root (DER 1:2-4.6), extraction solvent water</p> <p>5 ml (single dose) of the finished product contains 3.08 g of the liquid extract.</p>	Since 1981	<p><i>Adolescents, adults and elderly</i></p> <p>Single dose: 3.08 g of an aqueous extract which is equivalent to 0.22–0.51 g of Primula root and 0.62 g of thyme. Daily dose: 4 times daily</p> <p><i>Children between 4 and 12 years of age</i></p> <p>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</p>

Regulatory status overview

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

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

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

1.3. 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. Historical data on medicinal use

The historical use of thyme and primrose has been discussed in the assessment reports on *Thymi herba* and *Primulae radix* (Doc. Ref. EMEA/HMPC/234113/2006 and EMA/HMPC/113577/2012, respectively).

2.1. Information on period of medicinal use in the Community

The fixed combination of thyme and primrose is a European tradition. All combinations of herbal preparations included in the monograph are in medicinal use in the EU at least since 1976. The combinations A-H are in medicinal use in Germany, combination I in Slovenia. 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, since 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.

Therefore the criteria of at least 30 years for traditional use are fulfilled for all of the combinations included in the monograph.

2.2. Information on traditional/current indications and specified substances/preparations

The traditional indication as well as the current indication of thyme, *Primula* and combinations thereof is the use as 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 recommended for traditional herbal medicinal products containing a fixed combination of these two herbs.

In the clinical trials the inclusion criterion was 'acute bronchitis'. The treatment of acute bronchitis needs medical supervision and is therefore not suitable for traditional herbal medicinal products (see also section 4.3.).

2.3. 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 Thymi herba and Primulae radix.

Results from clinical trials indicate an onset of the treatment effect on days 3 to 5. The use of combinations of thyme and Primula shall be restricted to 7 days as it was agreed for the Community herbal monographs for the single active ingredients.

Route of administration

Oral administration.

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. EMEA/HMPC/234113/2006)
thyme essential oil (Doc. Ref. EMEA/HMPC/131901/2009)
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 relevant substance for the quality of thyme, does not contribute to the spasmolytic activity (Engelbertz *et al.* 2008).

Antimicrobial activity: the essential oil exhibits a strong antibiotic activity.

Primula root

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

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 suppose 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 make the use of the combination of thyme and Primula root as an expectorant plausible. 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 application 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.

No data on a validation of the score are published.

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, multicenter, 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 (correspond to herbal preparation 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 anti-tussives or treatment with these medications during the past 7 days prior to the study; clinical 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: 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 ($p \leq 0.001$). 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%).

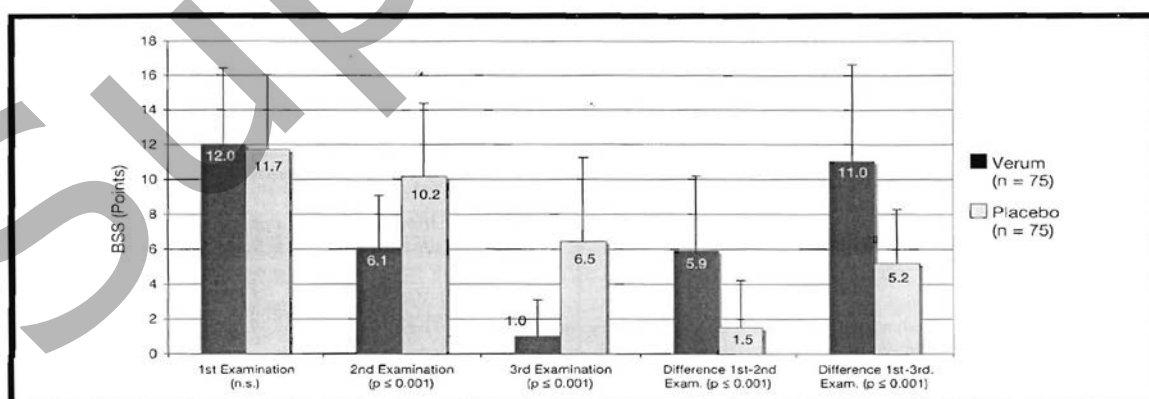


Fig. 1: Bronchitis severity score (BSS, $x \pm s$) after 3–5 (2nd examination) and 7–9 days (3rd examination) of treatment (ITT population, n = 150).

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.

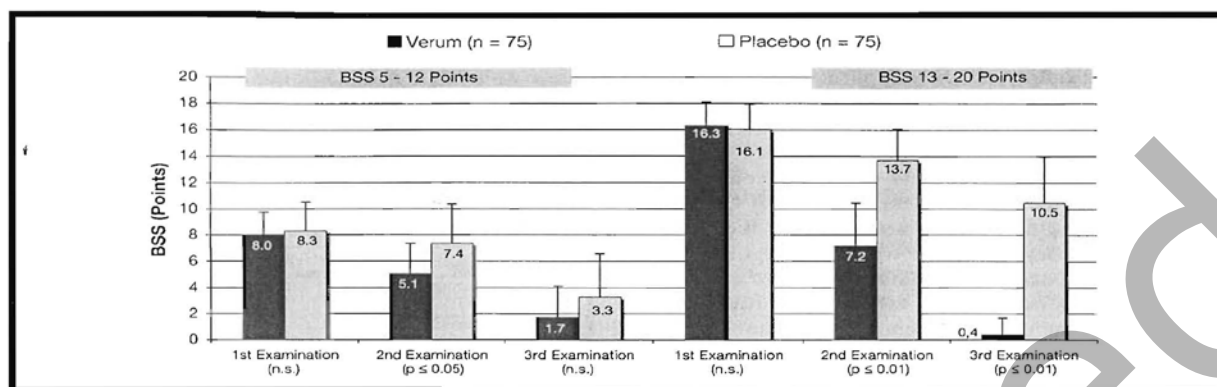


Fig. 2: Bronchitis severity score (BSS, $\bar{x} \pm s$) based on Severity Grade (ITT population, n = 150) after 3–5 (2nd examination) and 7–9 days (3rd examination) of treatment.

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 in possible connection to 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 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; clinical 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 H: 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 G: 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:

Reduction of bronchitis severity score from baseline 11.0 ± 5.0 to 2.6 ± 4.6 in the group treated with herbal preparation H compared to a decrease from 11.0 ± 4.8 to 2.5 ± 4.2 in the group treated with herbal preparation G. The mean onset of the treatment effect was at day 4 in both groups.

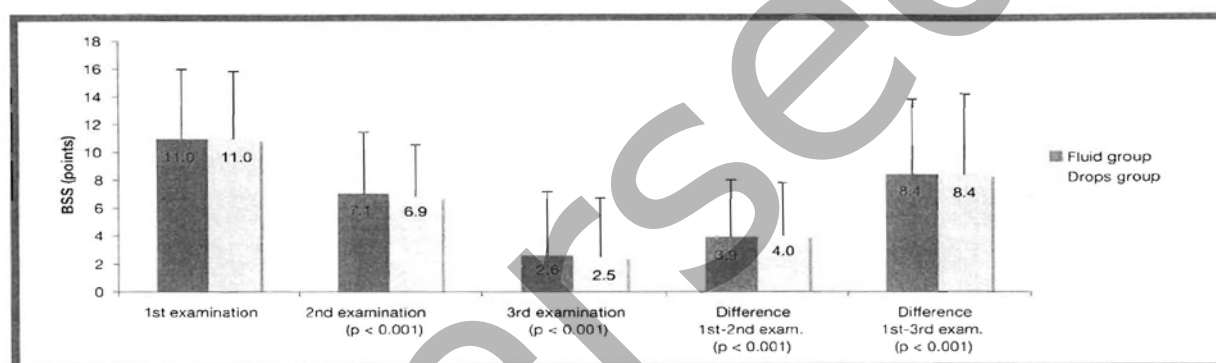


Fig. 1: Bronchitis Severity Score (BSS; $\bar{x} \pm s$) after 3–5 (2nd examination) and 7–9 days (3rd examination) of treatment (ITT population, $n = 189$). ■ Bitte < prüfen. ■

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 primrose 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

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 ($> 39^\circ\text{C}$), 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.

Results:

Reduction of coughing fits compared to baseline:

67.1% in verum, 51.3% in placebo group.

A 50% reduction of coughing fits was reached in the verum group 2 days earlier compared to placebo group.

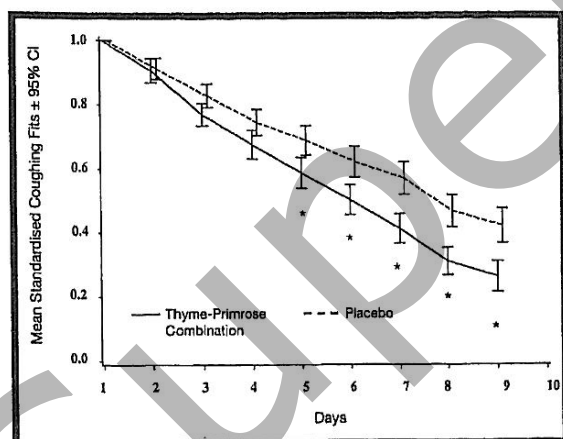


Fig. 1: Time course of coughing fits (standardised coughing fits \pm 95% confidence intervals [CI]) (FAS: N = 353; 7 patients not evaluable due to missing values at baseline). Significant difference on α -level = 0.05 (*) between thyme-primrose combination and placebo (Mann-Whitney-Wilcoxon test adjusted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

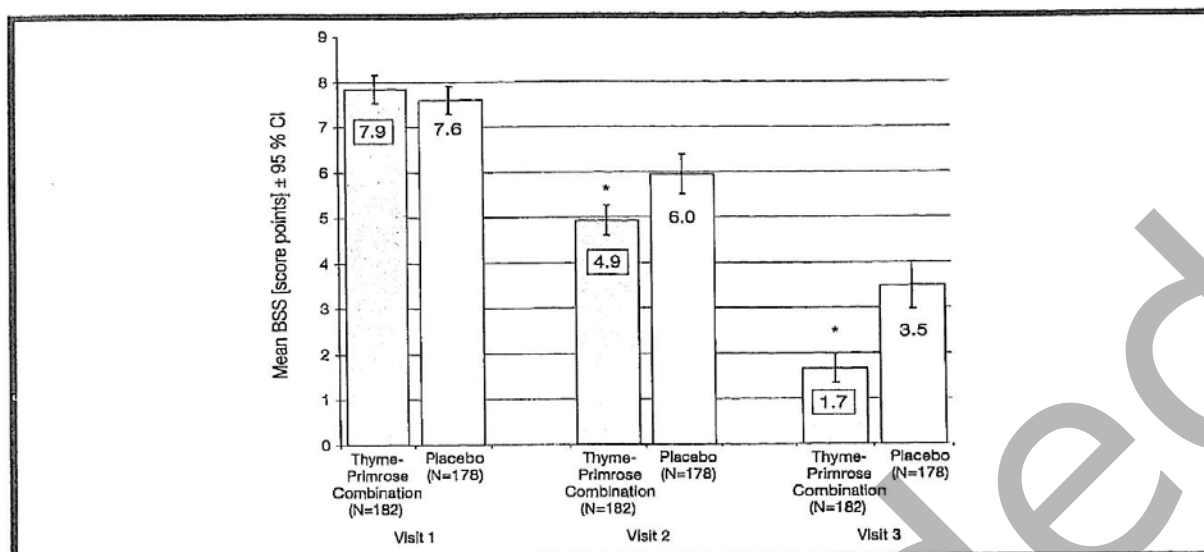


Fig. 5: Mean BSS [score points] \pm 95% CI (EAS: N = 360). Significant difference on α -level = 0.05 (*) between thyme-primrose combination and placebo at Visit 2 (Mann-Whitney-Wilcoxon test adjusted for centres, $p < 0.0001$) and Visit 3 (Mann-Whitney-Wilcoxon test adjusted for centres, $p < 0.0001$).

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

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 *Hederæ 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%).

4.2.3. 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 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 judgement of the efficacy of the treatment 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 judgement of the efficacy of the treatment possible. This study is published as 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 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 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 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 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 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.

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 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: 6 times 1 ml 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 judgement 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 congress abstract only. No control group was included. Therefore no judgement of the efficacy of the treatment is possible. This paper seems 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 G) 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.

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:

Although there are data on the safe use of some fixed combinations even in children below 1 year of age available the age limit should be set with 4 years for those fixed combinations where data on the safe use in the paediatric population are available. 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 12 years of age, adolescents above 12 years of age, adults and elderly like it was agreed for the Community herbal monographs on the single active ingredients thyme and *Primula* root.

4.3. Overall conclusions on clinical pharmacology and efficacy

Although there are promising results from randomised, placebo-controlled clinical trials published for three fixed combinations, the scientific discussion led to the conclusion that efficacy is still not sufficiently proven. A major deficiency of the trials is the lack of validation of the bronchitis severity score. Additionally the validity of the criterion 'number of coughing fits' taken from patient diaries or manual counts is questioned in scientific literature (Irwin *et al.* 2006, Morice *et al.* 2007).

Although not mentioning explicitly herbal medicinal products and not speaking specifically of 'acute bronchitis', a recent 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 medicine and family medicine (DEGAM 2008) as well as the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines conclude that there is at the moment no sufficient evidence for the use of expectorants for the treatment of acute cough provoked by different reasons. In contrast, the guideline of the German society for pneumology and respiratory medicine (Kardos *et al.* 2010) recommends the combination of thyme and *Primula* strongly in the case of acute cough.

At the moment there is no 'gold standard' for endpoints used in clinical trials with the indication 'cough'. The BSS symptom score, which was used in some of the clinical trials, is a non-validated score. Even when positive signals were detected for the total score as well as for the single symptoms, the lack of validation remains a critical deficiency. This score should be translated into fewer lost days of work and less inappropriate antibiotic use, which could be a strong and useful primary outcome.

Moreover the inclusion criterion 'acute bronchitis' remains unclear. Acute bronchitis is not well defined. 'Acute bronchitis' is an inappropriate wording and should be read as 'common cold with productive cough' according to comments by interested parties. However, the total set of symptoms of common

cold was not considered in the clinical trials. For the support of well-established use it is impossible to replace inclusion criteria from clinical trials with different wordings.

Taking all facts of the clinical trials together, the HMPC was of the opinion that the quality of the studies was not of sufficient level to prove efficacy (i.e. well-established use is not demonstrated).

However, the data from the clinical trials support the traditional use of fixed combinations and make the use in the proposed indication plausible.

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 are in medicinal use at least since 1976. No concrete data on patient exposure are available.

5.3. Adverse events and 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 like vomiting and diarrhoea as well as skin reactions like 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, transient gastrointestinal complaints or skin reactions occurred.

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 use of this fixed combination as an expectorant without supervision of a doctor should be restricted to children older than 4 years of age. In younger children the diagnosis should be performed by a doctor, also the 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

Both thyme and Primula root are traditionally used as expectorants in cough associated with cold. This indication is also recommended for traditional herbal medicinal products containing a fixed combination of these two herbs. The medicinal use in this indication is plausible due to the long-standing use as well as the pharmacological properties of thyme and Primula root and in view of the results of clinical trials. Although the clinical trials report beneficial effects of some fixed combinations in the treatment of acute bronchitis, the quality of the studies was not of sufficient level to prove efficacy. The main reason is the lack of validation of the parameters used for the evaluation of the efficacy (e.g. the bronchitis severity score BSS). Therefore all fixed combinations with evidence of at least 30 years of medicinal use as defined in Article 16c(1)(c) of Directive 2001/83/EC as amended are rated as traditional herbal medicinal products.

For all combinations which are included in the monograph concrete data on the posology are available.

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

Since the benefit of the medicinal use in the specified indication is plausible and no special risks are known, the benefit-risk balance is clearly positive.

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

Annex

List of references