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Evaluation of Medicines for Human Use

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Thymus vulgaris L., *Thymus zygis* L., herba

ASSESSMENT REPORT FOR THE DEVELOPMENT OF COMMUNITY MONOGRAPHS AND FOR INCLUSION OF HERBAL SUBSTANCE(S), PREPARATION(S) OR COMBINATIONS THEREOF IN THE LIST

DISCUSSION IN HMPC MLWP	October 2006 March 2007 May 2007 October 2007
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ASSESSMENT REPORT

FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH TRADITIONAL USE

***Thymus vulgaris* L., *Thymus zygis* L., herba**

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Thymus vulgaris* L., *Thymus zygis* L., herba[1]
Herbal preparation(s)	A) Liquid extract (1:1), extraction solvent ethanol 24% (v/v) B) Liquid extract (1:1.16), extraction solvent glycerol 85% (m/m): ethanol 25% (m/m) (0.1:2) C) Liquid extract (1:2-2.5), extraction solvent ammonia solution 10% (m/m) : glycerol 85% (m/m) : ethanol 90% (v/v) : water (1:20:70:109) D) Tincture (1:5 or 1:10), extraction solvent ethanol 70% E) Soft extract (5-7:1), extraction solvent ethanol 25% (v/v) F) Liquid extract from fresh herb (1:1.5-2.5), extraction solvent water G) Dry extract (6-10:1), extraction solvent ethanol 70% (v/v) H) Comminuted herbal substance for tea preparation
Pharmaceutical forms	Liquid and solid dosage forms for oral use
Rapporteur	Heribert Pittner
Assessors	Johann Krisper Reinhard Länger

[1] The dry material complies with the Ph. Eur. monograph (ref. 01/2005:0865)

1 INTRODUCTION

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

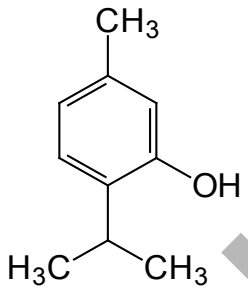
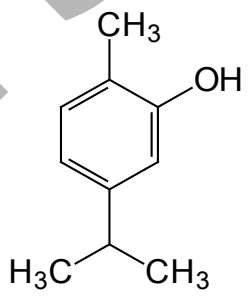
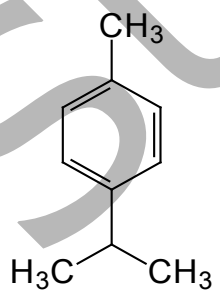
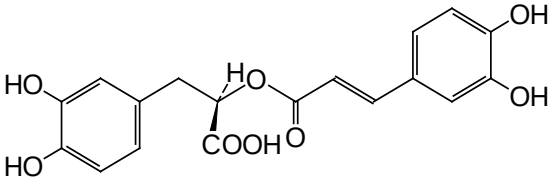
Herbal substance[2],[3]

Thymi herba (European Pharmacopoeia)

Whole leaves and flowers separated from the previously dried stems of *Thymus vulgaris* L. or *Thymus zygis* L. or a mixture of both species. Minimum content of essential oil: 1.2% with minimum 40% thymol + carvacrol.

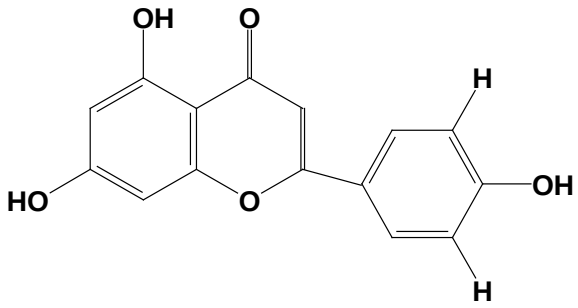
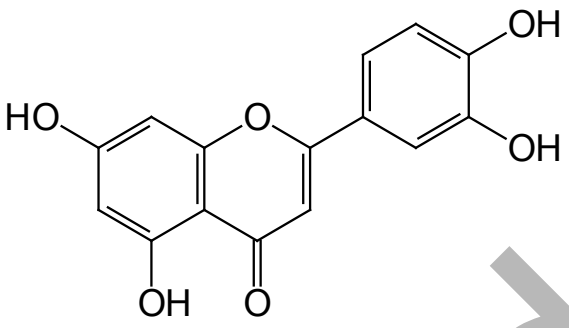
Constituents (Czygan FC *et al* (2004), Hänsel R *et al* (1994)):

- Essential oil: there are at least 6 chemotypes of *Thymus vulgaris* (Thompson JD (2003)) with different compositions of the essential oil; only the 'thymol'-type with thymol as predominant compound complies with the definition in the European Pharmacopoeia. The dried herbal substance contains up to 2.5% essential oil; the main components are thymol, carvacrol, p-cymene, γ-terpinene, linalool, β-myrcene, terpinen-4-ol. Some compounds occur partly as glycosides (e.g. p-cymene-9-ol (Takeuchi H *et al* (2004), Kitajima J *et al* (2004)).
- Flavonoids: flavones (e.g. apigenin, luteolin, 6-hydroxyluteolin) and their glycosides, methylated flavones (e.g. cirsilineol, eriodictyol, thymonin)
- Caffeic acid, rosmarinic acid
- Carbohydrates: up to 8% polysaccharides, app. 1% free monosaccharides
- Triterpenes: derivatives of ursolic and oleanolic acid

	
Thymol	Carvacrol
	
p-Cymene	Rosmarinic acid

[2] According to "Note for guidance on Quality of herbal medicinal products" (CPMP/QWP/2819/00)

[3] According to "Note for guidance on Specifications: Test procedures and acceptance criteria for herbal drugs, herbal preparations and herbal medicinal products" (CHMP/QWP/2820/00)

	
Apigenin	Luteolin

Herbal preparation(s)

Plant preparation to be specified for the individual finished product:

A) Thyme liquid extract (Austrian Pharmacopoeia ÖAB, current edition, monograph unchanged at least from 1960 onwards): DER 1:1 prepared with 24% v/v ethanol, ethanol content in the finished product min. 33% v/v; 1 ml corresponds to 1 g herbal substance. This particular extract is prepared by exhaustive percolation and subsequent evaporation of parts of the solvent. Therefore it can be assumed, that the liquid extract ÖAB contains twice the amount of active compounds compared to the liquid extract DAB.

B) Thyme liquid extract (Czech Pharm.), DER 1:1.16, solvent 25% v/v ethanol; 1 ml corresponds to 0.86 g herbal substance.

C) Thyme liquid extract (DAB 7 onwards), DER 1:2-2.5, prepared with a mixture of ammonia 10% (1 part), glycerol 85% (20 parts), ethanol 90% v/v (70 parts), purified water (109 parts); A minimum content of phenolic compounds of 0.03% is required. The description of the manufacturing process of this extract has been improved over the years. The tradition of herbal preparations which are manufactured in accordance with the monographs from the DAB 7 onwards can be accepted.

D) Tincture (Van Hellemont J (1988)) 1:10, 70% ethanol); 1 ml corresponds to 0.1 g herbal substance. Also tinctures with a DER 1:5 have been traditionally used.

E) Soft extract (5-7:1), extraction solvent ethanol 25% (v/v)

F) Liquid extract from fresh herb (1:1.5-2.5), extraction solvent water

G) Dry extract (6-10:1), extraction solvent ethanol 70% (v/v)

H) Comminuted herbal substance for tea preparation. The comminuted herbal substance is also currently available in solid dosage forms on the market (capsules containing the powder). However, this type of administration cannot be considered as traditional.

Dry extracts prepared from aqueous herbal preparations can be considered as a corresponding product to a herbal infusion, if similarity in the qualitative and quantitative composition can be demonstrated.

<u>Further preparations not discussed in the assessment report:</u>

Dry extract: DER 5-7:1, solvent: 25% methanol

Less than 30 years of tradition, therefore not included as traditional preparations.

No clinical data published, therefore not suitable for well established use.

Soft extract (DER 1.7-2.5:1): prepared with a mixture of ammonia 10% (1 part), glycerol 85% (20 parts), ethanol 90% v/v (70 parts), purified water (109 parts); 1 ml corresponds to approximately 2.1 g herbal substance (mean value).

Less than 30 years of tradition, therefore included as traditional preparations.

No clinical data published, therefore not suitable for well established use.

There are numerous other preparations on the market (e.g. extracts prepared with water [DER 9-11:1, DER 1:7-14]). No published data could be found which would support evidence on tradition, indication or posology.

Combinations of herbal substance(s) and/or herbal preparation(s)[4]

Thyme extracts are used in combination with many other herbal substances / herbal preparations. This monograph refers exclusively to Thymi herba.

Vitamin(s)[5]

Not applicable

Mineral(s)[5]

Not applicable

2 TRADITIONAL MEDICINAL USE

2.1 Information on period of medicinal use in the Community regarding the specified indication

Thyme has been in medicinal use for many decades and references are available dating back to 1938 (Madaus G (1938)). Therefore, for Thymi herba, a period of at least 30 years in medical use, as required by Directive 2004/24 EC for qualification as a traditional herbal medicinal product, is easily fulfilled.

The above mentioned liquid preparations have been included in pharmacopoeias and standard text books of phytotherapy for many decades. Soft extracts and dry extracts have also been marketed for more than 30 years.

2.2 Type of tradition, where relevant

European tradition

2.3 Bibliographic/expert evidence on the medicinal use

2.3.1 Evidence regarding the indication/traditional use

The following indications have been reported for Thyme:

Respiratory, thoracic and mediastinal disorders:

catarrh of the upper respiratory tract, bronchial catarrh	ESCOP (2003), Commission E (1998), Fintelmann V *et al* (2002)
Symptoms of bronchitis	Commission E (1998)
Cough with spasms	Fintelmann V *et al* (2002)

General disorders and administration site conditions

Stomatitis	ESCOP (2003)

[4] According to the Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations (EMEA/HMPC/166326/2005)

[5] Only applicable to Community monographs

Further traditional indications:

Digestive disorders	Czygan FC *et al* (2004)
Halitosis	ESCOP (2003)

The HMPC agreed not to include reference to "pertussis" as a therapeutic indication, because according to current knowledge, expectorants have little or no benefit in the treatment of pertussis.

Provisional wording for indications (based on standard text books of phytotherapy, not considering the assessment of pharmacological data):

Indication A:
Traditional herbal medicinal product used as an expectorant in cough associated with cold.
The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

Indication B:
Traditional herbal medicinal product for the topical treatment of inflammations of the gums and the mucous membranes of the oral cavity or the throat. The product is a traditional herbal medicinal product for use in the specified indications exclusively based upon long-standing use.

2.3.2 Evidence regarding the specified posology

Posology indication A (oral use):

Posology for adolescents, adults and elderly:
Herbal substance and comminuted herbal substance for tea preparation:

	single dose	daily dose
ESCOP (2003)	1-2 g, several times daily	no detailed data published
Commission E	1-2 g, several times daily	no detailed data published
Hänsel R *et al* (1994)	1-2 g, several times daily	no detailed data published
Fintelmann V *et al* (2002)	2 teaspoons (= 2.8 g), several times daily	no detailed data published

'Several times' could be interpreted as '3-4 times daily.

Herbal preparations

	single dose	daily dose
A) Liquid extract (ÖAB)	30-60 drops 2 g (ÖAB)	60-180 drops (Van Hellemont J (1988)) 6 g (calculated)
B) Liquid extract (Czech Pharm.)	no detailed data published	no detailed data published
C) Liquid extract (DAB 2006)	3-4 x 1,7 ml	equivalent 2.4-3.2 g herbal substance
D) Tincture	40 drops	120 drops (ESCOP (2003))
E) Soft extract	50 mg	300 mg (according to the dosage of authorized products)
F) Liquid extract from fresh herb	10 ml	30 – 40 ml (according to the dosage of authorized products)
G) Dry extract	75 – 200 mg	225 – 600 mg (according to the dosage of authorized products)

Assessor's comments:

Liquid extract according to DAB 7 onwards: Traditionally, the particular liquid extract has been used in a low dosage: single dose 1-2 g, daily dose 1-4 g, which is in agreement with the

monograph of the German commission E. The scientific research on this type of extract (Gaedcke F (2004)) as well as the improvement of the manufacture, which can be tracked in the editions of the German pharmacopoeia, revealed that the content of some active marker compounds is less than could be assumed from the DER of 1:2-2.5. Therefore the German national competent authority recommended a higher dosage than the traditional one. The proposed posology in this assessment report for this liquid extract has included both the traditional dosage and the higher one, which is based on the DER:

Proposed posology for adolescents, adults and elderly (indication A, oral use):

	single dose	daily dose
Herbal substance	1-2 g	3-8 g
A) Liquid extract (ÖAB)	1-2 ml	3-8 ml
B) Liquid extract (Czech Pharm.)	1.2-2,4 ml	3.5-9.3ml
C) Liquid extract (DAB 2006)	1-4 g	1-14 g
D) Tincture	40 drops	120 drops
E) Soft extract	50 mg	300 mg
F) Liquid extract from fresh herb	10 ml	30 – 40 ml
G) Dry extract	75 – 200 mg	225 – 600 mg

Posology for children (indication A, oral use)
Herbal substance- literature references:

	single dose	daily dose
ESCOP (2003)	children up to 1 year: 0.5-1 g children >1-adolescent: 1-2 g	no detailed data published
Dorsch W *et al* (2002)	children up to 1 year: 0.5-1 g children >1-adolescent: 1-2 g	no detailed data published

Herbal preparations – literature references

	single dose	daily dose
A) Liquid extract (ÖAB)	From 4 years: 1-2 g to be calculated as the herbal substance	1-6 g (Czygan FC *et al* (2004)) to be calculated as the herbal substance (ESCOP (2003))
All other herbal preparations	no detailed data published	no detailed data published

<u>Observational studies in children with Thymi herba (reported from the German national competent authority):</u>
Studies with the liquid extract type C) according to DAB 7 onwards:
Dethlefsen (1997, not published, data obtained from German national competent authority):

Study medication: Preparation containing 16.95% Thyme liquid extract (DAB), 1 ml corresponds to 75 mg herbal substance.
Indication: acute upper respiratory tract infection, symptoms of a bronchitis or pertussis
Average duration of treatment: 11.1 days

age	number of children	posology	single dose liquid extract	daily dose liquid extract
< 2 years	18	3-4 x 1.25 ml	0.21 ml	0.63-0.84 ml
2-6 years	105	3-4 x 2.5 ml	0.42 ml	1.27-1.68 ml
7-10 years	19	3-4 x 5 ml	0.85 ml	2.54-3.39 ml

No adverse events were observed.

Schlaps (1997, not published, data obtained from German national competent authority)

Study medication: Preparation containing 49.67% Thyme liquid extract (DAB); 1 ml corresponds to 0.22 g herbal substance.
Indication: acute upper respiratory tract infection, symptoms of bronchitis
Average duration of treatment: 9.57 days

age	number of children	posology	single dose liquid extract	daily dose liquid extract
< 2 years	48	3 x 1.2 ml	0.6 ml	1.8 ml
2-4 years	121	3 x 1.5 ml	0.75 ml	2.25 ml
4-6 years	123	3 x 1.7-2.0 ml	0.84-1.0 ml	2.53-3.0 ml
6-8 years	68	3 x 2.0 ml	1.0 ml	3.0 ml
8-12 years	77	3 x 2.0-2.3 ml	1.0-1.14 ml	3.0-3.4 ml
12-16 years	9	3 x 2.7-3.0 ml	1.3-1.5 ml	4.0-4.5 ml

One patient suffered from nausea because of the bad taste, no further adverse events were observed.

Graubaum (2004, not published, data obtained from German national competent authority)
Study medication: Preparation containing 9% Thyme liquid extract (DAB 2006), 1 ml corresponds to 50 mg herbal substance.
Indication: acute upper respiratory tract infection, symptoms of bronchitis
Average duration of treatment: 8.8 days

age	number of children	posology	single dose liquid extract	daily dose liquid extract
1-5 years	171	2-3 x 10 ml	0.9 ml	1.8-2.7 ml
6-11 years	80	3 x 15ml	1.35 ml	4.05 ml

Adverse events: a 2-year-old child showed repeating vomiting about 1 1/2 hours after administration of the preparation; a 5-year-old child showed repeating vomiting. A 1-year-old child revealed repeated diarrhoea, another 1-year-old child showed an exanthema of the neck and neckline.

Kaas PJ (2003)
Study medication: Preparation containing 8% Thyme liquid extract (DAB), 1 ml corresponds to 40 mg herbal substance.
Indication: acute upper respiratory tract infection, symptoms of bronchitis
Maximum duration of treatment: 14 days.
100 children in the age between 1 and 16 years.

age	posology	single dose liquid extract	daily dose liquid extract
<6 years	2.5 ml every 3 hours	0.2 ml	0.6-1.2 ml
6-12 years	5 ml every 3 hours	0.4 ml	1.2-2.4 ml
>12 years	10 ml 3-6 times daily	0.8 ml	2.4-4.8 ml

No adverse events reported.

Dentinox (1997, cited in ESCOP (2003)):

In an open, multicentre study, 154 children aged 2 months to 14 years (mean 4.4 years) with bronchial catarrh or bronchitis were treated daily with 15 – 30 ml of thyme syrup, containing 97.6 mg of thyme liquid extract (2 – 2.5 : 1) per ml, for a period of 7-14 days (mean 7.9 days); 46 patients did not receive any co-medication. Compared to the start of the treatment an improvement in the intensity of coughing was reported in 93.5 % of patients.

Study medication: Syrup containing 10% Thyme liquid extract (2-2.5:1), 1 ml corresponds to 220 mg herbal substance.
Indication: bronchial catarrh, symptoms of bronchitis
Average duration of treatment: 7.9 days

age	number of children	posology	single dose herbal substance	daily dose herbal substance
2 months – 14 years	154	15-30 ml daily		1.5-3.0 ml

No adverse events are published.

Assessor's comment: the mentioned herbal medicinal product contains the liquid extract according DAB. Therefore it may be concluded that the DER mentioned in the ESCOP monograph should be corrected to 1:2-2.5.

Study with the liquid extract from fresh herb type F)

PädiSolvan (2001, not published, data obtained from German national competent authority):

Study medication: Preparation containing 75% liquid extract from fresh herb, 1 ml corresponds to 1.1 g herbal substance.

Indication: acute upper respiratory tract infection, symptoms of bronchitis

Duration of treatment: 9-12 days

age	number of children	posology	single dose liquid extract	daily dose liquid extract
< 1 years	32	2 x 5 ml	3.75 ml	7 ml
1-4 years	34	2-3 x 5 ml	3.75 ml	7-10 ml
4-10 years	37	2 x 10 ml	7 ml	14 ml
10-12 years	28	3 x 10 ml	7 ml	21 ml

Two adverse events were observed: a 5-year-old child had vomiting and soft faeces on the fourth day of treatment; a 4-year-old child had soft faeces from the beginning of the treatment.

Schmidt (2002, not published, data obtained from German national competent authority):

Study medication: Preparation containing 3.347% Thyme soft extract (DER 1.7-2.5:1), 1 ml corresponds to 70 mg herbal substance.

Indication: acute upper respiratory tract infection, symptoms of bronchitis

Duration of treatment: 10 days

age	number of children	posology	single dose herbal preparation	daily dose herbal preparation
1-4 years	34	2 x 5 ml	0.17 ml	0.33 ml
4-10 years	35	3 x 5ml	0.17 ml	0.50 ml
10-12 years	34	3 x 10 ml	0.33 ml	1.0 ml

Adverse events: a 5-year-old child had a facial rash on the first treatment day; a 4-year-old child had bronchitis and a 14-month-old child had otitis media.

Assessor's comment: insufficient information was available for evaluation of the traditional use of the soft extract, therefore this type of extract is not considered in the monograph.

Studies with combination products:

There are several studies published on combinations of thyme with other expectorants in children (e.g., Ismail C *et al* (2003), Nauert C *et al* (2006), Fasse M *et al* (2006)).

Assessor' comments on posology in children:

Although numerous clinical trials provide evidence on the safe use of the liquid extract (DAB) and the expressed juice, the treatment of cough in children below 4 years of age needs supervision by a doctor. Furthermore, since traditional herbal medicinal products are intended to be used without medical supervision the oral use of thyme preparations should be restricted to children over 4 years of age.

Proposed posology for children (indication A, oral use):

Data from observational trials refer only to the liquid extract type C (DAB 2006). The lower limit of age should be set to 4 years.

Children 4-12 years of age:

C) Liquid extract:

Single dose: 0.5-0.9 ml

Daily dose: 2.5 – 4 ml, divided into 3-4 single doses.

F) Liquid extract from fresh herb:

Single dose: 7-10 ml

Daily dose: 14-30 ml, divided into 2-3 single doses.

As a general precaution ethanol-free preparations should be preferred for children.

Posology indication A (topical use):

5% infusion for poultice (Czygan FC *et al* (2004)).
At least 0.004 g essential oil per litre for preparation of a full bath, preparations on the market recommending a concentration of 0,001% in the bath water.
In unctions in concentrations up to 10% (Hänsel R et al (1994))
No data are available concerning semi-solid preparations.

No data on the topical use of herbal preparations of thyme in children are available.

Posology for indication B:

Strength of the preparations:
5 % infusion as a gargle or mouth wash (Basch E *et al* (2004).
3 % infusion as mouth-water (Van Hellemont J (1988))
No data available concerning the dosage and frequency of application.

Special warnings and special precautions for use

If the symptoms persist longer than 1 week, a doctor or a qualified health care practitioner should be consulted.
When dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted.

Herbal preparations type C (liquid extract DAB) and type F (liquid extract from fresh herb):

The use in children under 4 years of age is not recommended. The treatment of cough in this age group needs medical supervision.

Herbal substance and all other herbal preparations:

The use in children below 12 years of age is not recommended. No data on the safe use are available.

2.3.4 Evidence regarding the route of administration

The oral administration is the only route of administration for Thyme herb preparations in the traditional indications discussed in this assessment report.

2.3.5 Evidence regarding the duration of use

No restriction on the duration of use has been reported for Thymi herba and herbal preparations. The duration of use in clinical studies and observational studies was up to 14 days. However, in these studies the use was under medical supervision. Without supervision the duration of use should be restricted to 1 week.

2.4 Assessor's overall conclusion on the traditional medicinal use

Preparations from Thymi herba have been used for the relief of symptoms of the upper respiratory tract in coughs and colds for many decades. The traditional medicinal use is made plausible by pharmacological data, comparative and observational clinical studies.

2.5 Bibliographic review of safety data of the traditional herbal medicinal substances

2.5.1 Patient exposure

No exact data on patient exposure are available.

2.5.2 Adverse events

Hypersensitivity:
ESCOP (2003):
In very rare cases hypersensitivity reactions have been reported.

Czygan F-C *et al* (2004):
"Thyme and preparations thereof are normally without risk and only very rarely allergens. Cross-sensitivity has been observed for plants of the Lamiaceae family, so allergic reactions cannot be ruled out."
Benito M *et al* (1996) reported that plants belonging to the Lamiaceae family seem to show cross-sensitivity.
In very rare cases allergic reactions may occur due to the content of thymol (Hänsel (1994)).

Adverse events due to thymol:
Thymol has been used orally in folk medicine as a vermifuge at therapeutic doses (0.3 – 0.6 g, max. 1 g). Thymol in these concentrations caused abdominal pain and transient collapse (Czygan F-C *et al* (2004)).
Assessor's comment: The symptoms described above may also be due to the worm infections. The doses of thymol correspond to 62 – 208 g herbal substance. These doses exceed the recommended daily doses by far. With the recommended amounts of thyme preparations only approximately 38 mg of thymol are administered. The proposed dosage of the pure essential oil (25 drops per day) corresponds to approximately 300 mg thymol. However, no adverse reactions from the oral use of the essential oil are published.

Essential oil:
In concentrations higher than 8% in Vaseline irritation of the skin may occur. The daily application in gargles, mouthwashes and toothpastes over a longer period (no exact data available) may cause allergic reactions (Hänsel R *et al* (1994)).

Thyme dust:
Thyme dust, which may occur during processing of the herbal substance, can cause contact dermatitis and asthma (Lemiere C *et al* (1996), Spiewak R *et al* (2001)).

Case reports:
Germany has received 17 case reports for allergic reactions (urticaria, skin rashes, bronchospasm, asthma attack, anaphylactic shock)

Austria: In the pharmacovigilance database of AGES PharmMed no adverse events concerning Thymus vulgaris are reported.

Proposed wording:

Undesirable effects:

Oral application:

Hypersensitivity reactions and stomach disorders have been observed. The frequency is not known.

2.5.3 Serious events and deaths

One case of anaphylactic shock has been reported.

2.5.4 Safety in special populations and situations

2.5.4.1 Intrinsic (including elderly and children)/extrinsic factors

None known

2.5.4.2 Drug-drug interactions and other interactions

None reported

Foster BC *et al* (2003) report that an aqueous thyme extract significantly inhibited in vitro several iso-forms of CYP 450. These findings seem to have no practical consequences on the medical use of Thymi herba since in the same experiment an extract of *Hypericum perforatum* showed also a pronounced inhibition, while it is known that in humans these enzymes are stimulated by St. John's wort.

2.5.4.3 Use in pregnancy and lactation

Thyme essential oil consisting of 48% p-cymene and 24% thymol (0.25% essential oil in the feed over 2 weeks and during 4 days of pregnancy, n=15, number of embryos: 126) showed no influence on the growth and development of mouse embryos in vivo (Domaracky M *et al* (2006)).

Assessor's proposal:
Safety during pregnancy and lactation has not been established. No adverse effects have been reported from the use of Thyme herb as a medicinal product during pregnancy and lactation.
In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

2.5.4.4 Overdose

None reported

2.5.4.5 Drug abuse

None known

2.5.4.6 Withdrawal and rebound

None known

2.5.4.7 Effects on ability to drive or operate machinery

None known

2.5.4.8 Contraindications

Hypersensitivity to the active substance or to other members of the Lamiaceae family.

2.5.5 Non-clinical safety data

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

Acute toxicity

A concentrated extract produced decreased locomotor activity and slight slowing down of respiration in mice in an acute toxicity test. Oral doses were 0.5 – 3.0 g extract/kg body weight corresponding to 4.3 – 26.0 g dried plant material and these effects were produced at all dose levels (Qureshi S *et al* (1991)). The LD50 of the essential oil p.o. is 2.84 g/kg body weight in rats (Von Skramlik E (1959)).

Subchronic toxicity

An increase in liver and testes weight was observed after oral administration of a concentrated 95 % ethanolic extract of plant material to mice. A dose corresponding to 0.9 g dried plant was administered daily for three months. 30 % of the male animals died while in the female and control group only 10 % died (Qureshi S *et al* (1991)).

A diet containing 10% leaves of *Thymus vulgaris* was fed to Wistar rats for 6 weeks. No toxic effects could be observed (Haroun EM *et al* (2002)).

Mutagenicity

Thyme essential oil had no mutagenic or DNA-damaging activity in either the Ames or Bacillus subtilis rec-Assay (Zani F *et al* (1991)).
Thymol did not show mutagenicity in Salmonella typhimurium strains TA97, TA98 and TA100, with and without S9 metabolic activation and 20 minutes standard preincubation time (Azizan A *et al* (1995)).

Concentrations of thymol and γ-terpinene above 0.1 mM significantly induced DNA damage in human lymphocytes, however, below these concentration thymol and carvacrol significantly reduced the oxidative DNA damage induced by H_2O_2 (Aydin S *et al* (2005)) or imidazolquinoline and mitomycin C (Aydin S *et al* (2005a)).

Thymol and carvacrol reduced the level of DNA-lesions caused by H_2O_2 in HepG2 and colonic Caco-2 cells (Horvathova E *et al* (2006)).

Thymol in concentrations up to 520 µMol did not increase the frequencies of chromosome aberrations in Syrian hamster embryo cells compared to the control cells (Hikiba H *et al* (2005)).

Rosmarinic acid did not show DNA damage in rat brain tissue in concentrations up to 8 mg/kg (Pereira P *et al* (2005)).
Assessor's comment: the herbal substance contains approximately 3% of hydroxycinnamic acid derivatives (calculated as rosmarinic acid).

Reproduction toxicity:

Thyme essential oil showed no influence on the growth and development of mouse embryos in vivo (Domaracky M *et al* (2006)).

Assessor's proposal:
Thyme extracts are not toxic in acute toxicity and subchronic toxicity tests.
Thyme oil, thymol and rosmarinic acid are not toxic in reproduction toxicity and in vitro genotoxicity tests.

Assessor's comment:
Tests on genotoxicity have been performed with the essential oil and with isolated substances (thymol, rosmarinic acid) only; no data are available on total extracts. Therefore the requirements for a list entry are not fulfilled.

2.5.6 Assessor's overall conclusions on safe use

The oral administration of Thyme herb preparations can be regarded as safe, especially at therapeutic doses proposed.

3 PHARMACOLOGICAL PROPERTIES

3.1 PHARMACODYNAMIC PROPERTIES

In vitro experiments:

Spasmolytic activity:

Van den Broucke CO et al (1980, 1981, 1982, 1983) focussed in several publications on flavonoids. An ethanolic extract (DER 1:2), as well as isolated flavonoids (thymonin, cirsilineol, luteolin and 8-methoxy-cirsilineol) exhibited spasmolytic activity in the guinea-pig ileum and trachea in a dose dependent manner.
The flavones and thyme extracts were found to be non-competitive antagonists to specific agonists (acetylcholine, histamine, noradrenaline) and unspecific agonists (barium chloride). Inhibition of calcium - induced contractions on potassium – depolarised smooth muscles suggests inhibition of availability of calcium for muscle contraction. Flavones induce relaxation of the carbachol contracted tracheal strip without stimulation of the beta – adrenoceptors. The tracheal relaxing effect of the flavones (pD_2 value) was about 3 decades less than that of the beta- adrenergic agonist isoprenaline.

An ethanolic extract (ethanol 70%, DER not mentioned, content of thymol 0.072%, carvacrol 0.005%) of Thymi herba exhibited dose dependently, a strong antispasmodic activity on the isolated guinea-pig trachea (spasmogens: $BaCl_2$, carbachol, histamine, $PGF_{2\alpha}$) (Meister A *et al* (1999).

A soft extract (DER 1.7-2.5:1, extraction solvent ammonia solution 10% (m/m): glycerol 85% (m/m): ethanol 90% (v/v): water (1:20:70:109)) was tested on the effect on β_2-receptors and mucociliary clearance (Wienkötter N *et al* (2007)). The authors conclude that there is evidence for an influence of the thyme extract on β_2-receptors by both binding studies and biological effects. An at least indirect interaction in rat uteri and trachea is revealed by a decreased antagonism of propranolol on the relaxing effect of isoprenaline by the plant extract. The mucociliary clearance is improved in vivo in mice; the mechanism has still to be elucidated.

Aqueous extracts of Thymus vulgaris (macerate and extract of 50 g herbal substance in 300 ml water, final concentration 10% herbal substance) were also tested in precontracted tracheal chains of the guinea-pig. The thyme extracts showed dose dependently (0.25-1%) relaxant effects which were similar to those of theophylline (in concentrations from 0.25-1 mM) (Boskabady MH *et al* (2006)).

Thymol has in vitro an agonistic effect on α_1-, α_2- and β-adrenoreceptors; the spasmolytic activity is detectable in concentrations > 10^{-6} M. In a concentration of 10^{-4} M, thymol

suppresses the spontaneous contractile activity of the non striated muscles of the stomach of the guinea-pig. In higher concentrations thymol exhibits a spasmolytic activity in the ratio of 1:10 compared to papaverine (Beer AM *et al* (2007)).

Antibacterial, antifungal activity

The essential oil is highly antibacterial and antifungal, when tested on Gram-positive and Gram-negative bacteria, fungi, and yeasts, e.g. Candida albicans. The activity is mainly attributed to thymol and carvacrol (e.g., Simeon de Bouchberg M *et al* (1976), Janssen AM *et al* (1986), Menghini A *et al* (1987), Patakova D *et al* (1974), Allegrini J *et al* (1972), Janssen AM (1989), Farag RS *et al* (1986), Lens-Lisbonne C *et al* (1987), Vampa G *et al* (1988), Chalchat JC *et al* (1991), Giordani R (2004)). Oils with higher percentage of phenolic compounds show higher inhibitory activity (Penalver P *et al* (2005)). In a screening of the activity of plant extracts against Clotrimazole-resistant Candida albicans the methanolic extract from *Thymus vulgaris* exhibited highest activity with a MIC of 0.62 mg/ml. Even the vapour of thyme essential oil (3-12 mg/litre air) is highly effective against respiratory tract pathogens (Inouye S *et al* (2001)). Correlations between concentrations of thymol and MIC and minimal bactericidal concentration suggest that the formation of membrane perforations is the principal mode of action of thymol against oral bacteria (Shapiro S *et al* (1995)).

Further activities:

Thymol was shown to inhibit the experimentally induced release of neutrophil elastase. The authors concluded that thymol may have a helpful effect in the control of inflammatory processes present in many infections (Braga PC *et al* (2006)).

Thyme oil inhibits prostaglandin biosynthesis (Wagner H et al (1986)). Rosmarinic acid has anti-inflammatory activity due to inhibition of classical complement pathway in rats and inhibition of some human PMN functions, when tested at several dosage levels and by several application methods in vitro (Englberger W *et al* (1988), Gracza L *et al* (1985))

Rosmarinic acid shows a strong antiangiogenic potential, which might be related to its anti-oxidative activity, which further resulted in the inhibition of ROS (reactive oxygen species) - associated VEGF (vascular endothelial growth factor) expression and IL-8 release (Huang SS et al (2006)). Rosmarinic acid exhibited also antiapoptotic effects on H_2O_2 induced cell injury (Gao LP et al (2005)).

Radical scavenging potential: Many compounds from the leaves of *Thymus vulgaris* showed radical scavenging properties: Rosmarinic acid, eriodictyol, taxifolin, luteolin, p-cymene, thymol carvacrol and others (Haraguchi H *et al* (1996), Dapkevicius A et al (2002)). In a model using CCl_4-induced hepatotoxicity the essential oil of *Thymus zygis* (thymol-type) showed a notable activity combined with a marked scavenger activity (Jimenez J *et al* (1993)):

Thymol is a positive allosteric modulator of the GABA(A) receptor; it enhances the GABA-induced chloride influx at concentrations lower than those exhibiting direct activity in the absence of GABA (Garcia DA *et al* (2006)).

In vivo experiments:

Rosmarinic acid exhibited inhibitory activity in three in vivo models in which complement activation plays a role: Reduction of oedema induced by cobra venom factor in the rat; inhibition of passive cutaneous anaphylaxis; impairment of in vivo activation by heat-killed Corynebacterium parvum of mouse macrophages. Rosmarinic acid did not inhibit t-butylhydroperoxide- induced paw oedema in rat, indicating selectivity for complement-dependent processes (Englberger W *et al* (1988)).

A diet containing thyme (up to 2%) as well as oral thymol and carvacrol (200 mg/kg) given once a day over 7 days induced the activity of phase I and phase II enzymes in the mouse liver up to 90% (Sasaki *et al* (2005)).

Mosquito control:
Thymol and carvacrol are potent repellents in concentrations of about 0.055 in topical treatment (Choi WS *et al* (2002), Park BS *et al* (2005)).

Clinical studies

Indication A (cough associated with cold, oral application):

Studies with thyme preparations as the only active ingredient:

In a randomized, double-blind, comparative study, 60 patients with productive cough complaints resulting from uncomplicated respiratory infections were treated with thyme syrup (3 x 10 ml daily, n=31) or a bromhexine preparation (n=29) for 5 days. No significant difference was observed between thyme syrup and bromhexine in self-reported alleviation of the complaints on days 2 and 5 of treatment (Knols G *et al* (1994))

Assessor's comments:

This study was performed in a small population. Due to the small number of patients and due to the lack of a placebo group, this study alone cannot qualify the use of thyme syrup for a well-established use indication.

In an open, multicentre study (Dentinox 1997, cited in ESCOP (2003)), 154 children aged 2 months to 14 years (mean 4.4 years) with bronchial catarrh or bronchitis were treated daily with 15 – 30 ml of thyme syrup, containing 97.6 mg of thyme liquid extract (2 – 2.5: 1) per ml, for a period of 7-14 days (mean 7.9 days); 46 patients did not receive any co-medication. Compared to the start of the treatment an improvement in the intensity of coughing was reported in 93.5 % of patients.

Assessor's comments:

This company report is typical for an open study sponsored by the marketing authorization holder. The extract is stated to be a liquid extract but this seems unlikely in view of the DER. It is assumed that the liquid extract according to the DAB (with a DER of 1: 2-2.5) has been tested. Nevertheless this open study on the use of thyme syrup in young children contributes to the documentation of the safe use of thyme syrup as traditional herbal medicinal product in general.

Koch U (2003): In this observational study children were treated with Aspecton Hustensaft and Aspecton Hustentropfen.

Assessor's comments:

In the publication it is mentioned that both preparations contain a thyme fluid-extract, which would indicate the liquid extract according to the DAB. However, according to the current 'Rote Liste' both products contain a soft extract (DER 1.7-2.5:1, extraction solvent ammonia solution 10% (m/m) : glycerol 85% (m/m) : ethanol 90% (v/v) : water (1:20:70:109). Because of the lack of information on the actual active ingredient this study results cannot be evaluated.

The findings of the observational studies mentioned in section "2.3.2 Evidence regarding the specified posology" support the use of preparations of Thymi herba in the indication 'cough associated with cold'. They do not fulfil the criteria necessary for placing the respective preparations in the 'well established use' category.

Studies with combinations:

Study on Bronchipret film coated tablets (60 mg dried extract of Primulae radix DER 6-7:1, solvent ethanol 47.4% v/v; 160 mg dried extract of Thymi herba DER 5.9-10:1, solvent ethanol 70% v/v) (Ernst E *et al* (1997):

> In this controlled multi-center study the medication was compared to other pharmacotherapeutical options for acute bronchitis (e.g. ivy extract, ambroxol). 7783 patients have been included. The study was neither randomized nor placebo-controlled. The findings imply that a risk/benefit evaluation would favour the thyme-primula combination over synthetic drugs for acute bronchitis.

Combination of thyme preparations with ivy or Primula extracts (Ismail C *et al* (2003))

> In this multicentric cohort study more than 7000 patients with acute bronchitis were included. Different pharmaceutical forms of the product Bronchipret were tested against ambroxol or N-acetyl-cystein. The authors conclude superiority of the herbal preparations. The study was not randomized and not blinded.

Combination of thyme liquid extract (1:3, solvent not known) and primrose root tincture (1:5) [Bronchicum drops] compared to placebo (Gruenwald J *et al* (2005)):

> Double-blind, randomized, placebo-controlled, multicenter, prospective study; 150 outpatients suffering from acute, previously not treated bronchitis. Duration of treatment: 7-9 days. Compared to placebo, the combination resulted in a clinically relevant and more pronounced decrease of the bronchitis symptoms and in shortening the duration of acute bronchitis. The medication was well tolerated; in the verum group 2 minor adverse events occurred.

Combination of thyme liquid extract (1:3, solvent not known) and primrose root tincture (1:5) [Bronchicum drops] compared to a combination of thyme liquid extract and primrose root liquid extract (1:1) [Bronchicum Elixier S] (Gruenwald J *et al* (2006)):

> Single blind, randomized, bi-centric, prospective study; 189 outpatients suffering from acute, previously not treated bronchitis. Duration of treatment: 7-9 days. No differences in the efficacy between the medications, From a total of 10 adverse events only 5 minor ones could be considered as possibly or probably related to the study medications.

Combination of Thyme liquid extract and ivy liquid extract (Bronchipret liquid) (Kemmerich B *et al* (2006)):

> Double blind, randomized, multicenter, placebo-controlled, prospective study; 361 outpatients suffering from acute bronchitis. Duration of treatment: 11 days. Study medication was superior to placebo in terms of efficacy. No differences in frequency of adverse events between placebo and verum group. Medication was well tolerated, no severe or serious adverse events occurred.

Open trial to assess aspects of safety and efficacy of a combined herbal cough syrup with ivy and thyme (Büechi S *et al* (2005)):

> 62 patients were treated from 13 general practitioners with a syrup containing (per 5 ml) 0.07 g dry extract of Hederae folium (DER 4-8:1), 1.7 g decoction of Thymi herba and Anisi fructus (DER 1:3.5-4 in relation to thyme), aniseed should only enhance the flavor. The authors conclude that this syrup was well tolerated and alleviated the symptoms of cough associated with common cold, bronchitis or respiratory tract diseases with formation of mucus.

Fasse M *et al* (2006): Treatment of acute cough and cold in children – results of an observational trial with a combination of thyme and Primula.

This observational trial with Phytobronchin liquid including 300 children up to 12 years of age demonstrated the safe use of the combination in children.

Indication A (cough associated with cold, topical application, inhalation):

No clinical data could be found which support the topical use of preparations or the essential oil of thyme for the treatment of cough associated with cold. The lipophilic nature of the components of the essential oil makes absorption via the skin plausible. It is also plausible that absorption of volatiles occurs after inhalation of the essential oil when applied in semi-solid dosage forms on the skin, in a bath or directly with an inhalation apparatus.

In semi-solid preparations usually a combination of several essential oils is used, not thyme oil alone.

Assessor's overall comments indication A:

The published data on pharmacology and from observational trials support evidence level 3 for Thymi herba and preparations for oral use for the treatment of cough associated with cold. Since randomized, placebo-controlled clinical trials for preparations with thyme as the only active ingredient are not published, the herbal substance and liquid dosage forms have to be assigned to 'traditional use'.

Pharmaco-therapeutic group: Expectorants
ATC code: R05CA

Thyme is acting as an expectorant.
In vitro the essential oil has antibacterial and antifungal activity, when tested on Gram-positive and Gram-negative bacteria, fungi, and yeasts. The activity is mainly attributed to thymol and carvacrol. Components of the essential oil as well as flavonoids exhibit spasmolytic activity in several experimental models with non striated muscle tissue.
The expectorant effects of thyme preparations have long been recognised empirically. The use is made plausible by pharmacological data, comparative and observational clinical studies (level of evidence 3).

Indication B (stomatitis):

There is evidence that thymol is active against cariogenic and periodontopathogenic bacteria (e.g. Shapiro S *et al* (1995)).

A comparison of different mouthrinses (containing thymol, chlorhexidine, povidon + H_2O_2) showed no differences in the papillary bleeding score and in plaque index between the treatment with thymol and water (Maruniak J *et al* (1992)).

The application of a combination of thymol, menthol, methyl salicylate and 1,8-cineol over 6 months did not show statistically significant differences between the vehicle and the essential oil group. Neither development of bacterial resistance nor emergence of opportunistic pathogens could be observed (Charles CH *et al* (2000)).

Many clinical trials are published which investigate the efficacy of combinations of chlorhexidine and thymol (e.g., Twetman S *et al* (1999)). The contribution of thymol to the overall efficacy cannot be estimated.

Assessor's overall comments indication B:

Since clinical evidence is only poorly documented for isolated compounds of the thyme essential oil or for combinations with other essential oils and synthetic antiseptic drugs the traditional use of Thymi herba, its preparations and its essential oil in oromucosal preparations cannot be supported.

3.2 PHARMACOKINETIC PROPERTIES

Thymol:
After application of a single dose of a thyme dry extract (corresponding to 1.08 mg thymol) only the sulfate could be detected in the human plasma, but not the free thymol nor the glucuronide. The sulfate could be detected 20 minutes after application; maximum plasma levels were reached after about 2 hours. Thymol can be detected in the plasma up to 38 hours; renal elimination was completed within 24 hours. Elimination half-life was determined as 10.2 hours (Kohlert C *et al* (2002)).

Rosmarinic acid:
After oral administration of rosmarinic acid (50 mg/kg rat) the peak concentration is reached within 0.5 hours. Rosmarinic acid is present in plasma as conjugate or in the methylated form. The main metabolites are free or glucuronide conjugates. Orally administered rosmarinic acid is also degraded to caffeic acid, ferulic acid and m-coumaric acid, the majority of these degradation products is eliminated within 8 hours after oral administration (Baba S *et al* (2004)).

4 USE IN MEMBER STATES

AT

In Austria the following preparations are authorised:

Thymus vulgaris as only active ingredient:

- Thyme tincture

- Thymus "ratiopharm" bronchial balsam - authorised 1995
- Thymus "ratiopharm" cough drops - authorised 1995

In addition numerous combination products are authorized containing the herbal substance, liquid extracts, dry extract, soft extract, tincture, syrup or the essential oil.

BE

In Belgium the following preparations are authorised:

	Medicinal product
Herbal substance Herbal preparation	▪ Herb ▪ liquid extract hydro-alcoholic 22% V/V (1:1)
Pharmaceutical form	Tea, oral solution (syrup)
Indication(s)	▪ Tea : unclear, is ingredient in combination products with trademarks "Enterofal, Pulmofal" ▪ For the soothing of mouth and throat in case of common cold, and as expectorant (serious pathologies excluded)
Method of administration	oral
Posology (per day, unless otherwise stated)	▪ Teas: combination product, 50-100mg /g, no posology available ▪ Oral solution : thyme liquid extract 92mg/ml in combination with wild thyme liquid extract 92mg/ml. Posology: children 3-7 y : 5ml 4 times a day; children 7-12y: 10ml 4 times a day; children >12y and adults: 15 ml 4 times a day ▪ Oral solution : thyme liquid extract 1.66mg/ml in combination with aconitum tincture, belladonna tincture, ephedrine HCl, sodium benzoate, Adiantum capillus veneris liquid extract (*see* ***** *note below*)
Date of grant of marketing authorization / date of notification (food supplements)	1961-1962
Other information	***** this oral solution is reformulated (MAA will be granted in the next coming months) and will contain 65mg thyme liquid extract/g (=one active component; DER: 1 : 1.1-1.3; EtOH 31.5% V/V). Posology : children 2-6 y : 5ml 3-6 times a day; children 6-12y: 15ml 2-4 times a day; children >12y and adults: 15 ml 3-6 times a day

DE

Since 1996 a standard marketing authorization exists in Germany for the herbal substance. It is defined as herbal tea.

In Germany the following herbal preparations are authorized:

- liquid extract from *Thymus vulgaris* (1:2-2.5); ammonia solution 10 % (m/m); glycerol 85 % (m/m); ethanol 90 % (V/V): water (1:20:70:109)
- expressed juice from *Thymus vulgaris* (1:1,5 – 2,4)
- dry extract from *Thymus vulgaris* (6-10:1), ethanol 70 (V/V)
- soft extract from *Thymus vulgaris* (1,7 – 2,5:1); ammonia solution 10 % (m(m); glycerol 85 % (m/m); ethanol 70 % (V/V); water (1:20:70:109)
- thyme oil

Some of these preparations are on the market since 1978.
Furthermore there are 72 medicinal products authorized that contain *Thymus vulgaris* (drug or extract) in combination with other active substances like e.g. Primula, Anisi aetheroleum, Foeniculum, Liquiritiae, Plantago.

Pharmaceutical forms:
Oral liquid, syrup, liquid extract, pastille, expressed juice, oral gum, lozenge, film-coated tablet, bath additive, hard capsule

Posology:
Oral: 1 – 5 x daily 1 – 5 ml extract
1 – 4 x daily 126 mg – 4.4 g extract
Children 1 – 3 years: 0.25 g extract every 3 hours
3 – 4 x daily 10 ml expressed juice
As a bath additive: 1,69 g oil / 100 l water
Infants > 6 months: 0.19 g oil / 30 l water

Indications:
For the relief of symptoms in coughs and colds with viscous mucilage.
Indications dealing with bronchitis or pertussis are no longer accepted for well-established use.

DK

Denmark has had several products with Herba Thymi as medicinal products, but most of them have been withdrawn due to low sales. Denmark still has Bronchosan drops, a combination product.

IR

Ireland has no authorised products containing *Thymus vulgaris* L. and has no ADRs reported in association with its use on the national ADR database.

IT

In Italy no herbal or conventional medicinal products containing only Thymi herba or its preparation as an active substance are currently authorised or registered.

LV

1. Bronchial fix, Species 2 g.
   Herba Thymi, Herba Violae, Flores Chamomillae etc.
2. Bronchicum Elixir, solution
   Tinct. herbae Thymi, Tinct. herbae Grindeliae, Tinct. rad. Pimpinellae, Tinct. rad. Primulae, Tinct. corticis Aspidospermae.
3. Bronchicum Hustensirup, Sirup.
   Herba Grindeliae, Radix Pimpinellae, Radix Primulae, Flores Rosae, Herba Thymi.
4. Bronchicum Pastillen, Lozenges.
   Extractum Thymi fluidum.
5. Hustagil Cold Balsam, Ointment.
   Thymi aetheroleum, Pini aetheroleum, Eucalypti aetheroleum, Flores Caryophylli.
7. Hustagyl Thyme Cough Syrup, Syrup.
   Extractum herbae Thymi.
8. Pectoral, Syrup.
   Extr. Plantaginis fluidum, Extr. Primulae fluidum, Extr. Senegae fluidum, Extr. Thymi fluidum.
9. Stoptussin Fito, Syrup.
   Extr. Thymi, Extr. Serpylli, Extr. Plantaginis.
10. Syrup against Cough with Marsh Mallow, Thyme and Vitamin C for Children, Syrup.
    Extr. Althaeae, Extr. Thymi, Acidum ascorbicum.
12. Tymsal Spray, Spray.
    Extractum Thymi fluidum, Tinctura Salviae**.**

UK

Bio-Strath Thyme Formula (Ingredients: Extract of Primula root, Extract of Thyme leaves, Candida Yeast Plasmolysate); oral liquid for the temporary relief of coughs. Authorised since 1980.

5 ASSESSOR'S OVERALL CONCLUSIONS

The expectorant effects of thyme preparations have long been recognised empirically. The use is made plausible by pharmacological data (level of evidence 3), comparative and observational clinical studies.

In conclusion, Thyme herb preparations can be regarded as traditional herbal medicinal products. The available clinical studies are not satisfactory for qualifying preparations from Thyme herb for well-established use indications.