Module 2.5
Clinical Overview

THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml

Sirop

Table of Contents

List of Abbreviations

AUC	area under the concentration-time curve;
CL	clearance
C_{max}	peak plasma concentration
CYP	cytochrome P450
DER	Drug Extract Ratio
EMA	European Medicines Agency
ESCOP	European Scientific Cooperative on Phytotherapy
MAT	mean absorption time
MRT	mean residence time
$t_{1/2}$	elimination half-life
t_{max}	time to reach C_{max}
Vdss	volume of distribution at steady state
WHO	World Health Organization

List of Tables

2.5.1 Product Development Rationale

The purpose of this document is to support an application for marketing authorization of *THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop* with an abridged dossier as allowed under Article 16a(1) (traditional-use registration) of Directive 2001/83/EC: *Thymus vulgaris* L. liquid extract has been on the market in the European Community for several decades.

2.5.1.1 Pharmacological Class of the Medicinal Product

The use of thyme extract is described in pharmacopoeias and in traditional systems of medicine.

Thyme extract has been used orally to treat; coughs due to colds, bronchitis and pertussis; laryngitis and tonsillitis (as a gargle); and dyspepsia and other gastrointestinal disturbances. Topical applications of thyme extract have been used in the treatment of minor wounds, the common cold, disorders of the oral cavity, and as an antibacterial agent in oral hygiene. Both the essential oil and thymol are ingredients of a number of proprietary drugs including antiseptic and healing ointments, syrups for the treatment of respiratory disorders, and preparations for inhalation (1).

2.5.1.2 Description of the Clinical/Pathophysiological Condition that the Medicinal Product is Intended to Treat, Prevent or Diagnose / Claimed Indication

THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop is a traditional herbal medicinal product used as an expectorant for relief of productive cough associated with common colds.

2.5.1.3 Summary of the Scientific Background that Supported the Investigation of the Medicinal Product for the Indications that were Studied

THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop has been on the market in the European Community for several decades.

This medicinal product will be registered as a traditional herbal medicinal product as defined in Directive 2001/83/EC under Article 16a(1) (traditional-use registration) and as such this section is not applicable.

2.5.1.4 Brief Description of the Clinical Development Program of the Medicinal Product, including Planned and Ongoing Clinical Studies

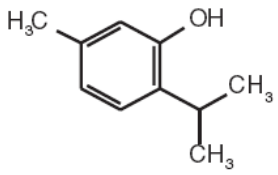
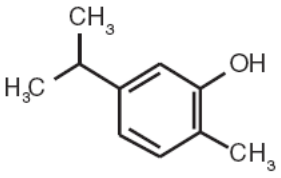
Not applicable.

2.5.2 Overview of Biopharmaceuticals

Herba Thymi is the dried leaves and flowering tops of *Thymus vulgaris* L. (Lamiaceae) which is an aromatic perennial sub-shrub, 20–30 cm in height, with ascending, quadrangular, greyish brown to purplish brown lignified and twisted stems bearing oblong-lanceolate to ovate-lanceolate greyish green leaves that are pubescent on the lower surface (1).

The plant material of interest are leaves and flowering tops separated from the previously dried stems of *Thymus vulgaris* L. Herba Thymi contains about 2.5% but not less than 1.0% of volatile oil. The composition of the volatile oil fluctuates depending on the chemotype under consideration. The principal components of Herba Thymi are thymol and carvacrol (up to 64% of oil) (see Table 1), along with linalool, *p*-cymol, cymene, thymene, α-pinene, apigenin, luteolin, and 6-hydroxyluteolin glycosides, as well as di-, tri- and tetramethoxylated flavones, all substituted in the 6-position, and an arabinogalactan (1, 2). Some compounds occur partly as glycosides (e.g. p-cymene-9-ol (3, 4).

Table 1: Main components of Herba Thymi

Name: Thymol	**Name:** Carvacrol
IUPAC name: 5-methyl-2-propan-2-ylphenol	**IUPAC name:** 2-methyl-5-propan-2-ylphenol
Formula: $C_{10}H_{14}O$	**Formula:** $C_{10}H_{14}O$
Molecular Weight: 150.2 g/mol	**Molecular Weight:** 150.2 g/mol
CAS number: 89-83-8	**CAS number:** 499-75-2
Structure: 	**Structure:** 

THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop is a traditional herbal medicinal product used in productive cough associated with cold. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

For *THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop* the following preparation is used:

Liquid extract (DER 1:2-3), extraction solvent mixture of ammonia 10% (1 part), glycerol 85% (20 parts), ethanol 90% v/v (70 parts), purified water (109 parts). This liquid extract has been used in Germany in medicinal products since 1977.

Regulatory status overview

Traditional use registration in Austria, Belgium, Bulgaria, Germany, Latvia, Lithuania, and Poland (includes information as of November 2013) (5).

2.5.2.1 Bioequivalence Study Performed by the Applicant

Not applicable.

2.5.3 Overview of Clinical Pharmacology

2.5.3.1 Pharmacokinetic Properties

After oral administration of a tablet or capsule containing thyme extract (70% ethanol, 6-10:1) to healthy volunteers, first traces of thymol were detected in the exhaled air after 30 and 60 minutes respectively; after 140 minutes thymol was no longer detectable in the exhaled air. The increase in concentration of thymol in the exhaled air matched the blood concentration (2).

Kohlert et al (6) determined the systemic availability and the pharmacokinetics of thymol after oral application to humans in a clinical trial (12 healthy volunteers). Each subject received a single dose of a tablet. After the single oral dose of Thyme dry extract (corresponding to 1.08 mg thymol) only the sulphate could be detected in the human plasma, but not the free thymol nor the glucuronide. The thymol sulphate could be detected 20 minutes after dosing; peak plasma concentrations were 93.1 ± 24.5 ng/ml and were reached after 2.0 ± 0.8 hours. The mean terminal elimination half-life was 10.2 hours. Thymol sulphate was detectable up to 41 hours after administration. Urinary excretion could be followed over 24 hours. The amount of both thymol sulphate and glucuronide excreted in 24-hour urine was 16.2% ± 4.5% of the dose.

Table 2 summarises the established pharmacokinetic parameters of thymol after a single oral dose of 1.08 mg thymol.

Table 2: Pharmacokinetic data of total thymol absorption and elimination in human plasma after single oral administration

	Mean	*SD*	Minimum Value	Median	Maximum Value	Geometric Mean	Number
Dose (mg)	1.08						
C_{max} (ng/ml)	93.11	24.47	55.90	99.01	125.82	90.04	11
t_{max} (h)	1.97	0.77	0.80	2.03	3.13	1.81	11
$t_{1/2}$ (h)	10.2	1.4	8.3	9.9	12.9	10.1	11
$AUC_{0 \rightarrow clast}$ (ng h/ml)	837.3	278.5	456.7	835.8	1281.6	793.6	11
MRT_{abs} (h)	12.6	2.1	8.1	12.5	15.2	12.4	11
MAT (h)	0.53	0.04	0.46	0.54	0.59	0.53	11
CL_{tot}/f (L/h)	1.2	0.3	0.8	1.1	1.8	1.2	11
Vdss/f (L)	14.7	5.1	6.1	13.8	23.3	13.9	11
Vd_{area}/f (L)	17.7	5.6	10.8	17.2	29.5	16.9	11

C_{max}, peak plasma concentration; t_{max}, time to reach C_{max}; $t_{1/2}$, elimination half-life; $AUC_{0 \rightarrow clast}$, area under the concentration-time curve from time 0 to clast; MRT_{abs}, mean residence time after extravascular administration; MAT, mean absorption time; CL_{tot}/f, total body clearance with respect to unknown bioavailability f; Vdss/f, volume of distribution at steady state with respect to unknown bioavailability f; Vd_{area}/f, volume of distribution during the elimination phase with respect to unknown bioavailability f. Taken from (6).

2.5.3.1.1 Pharmacokinetic Interactions

No data available.

2.5.3.2 Pharmacodynamics

2.5.3.2.1 Primary Pharmacodynamics

***In vitro* and animal studies**

Antitussive, expectorant and antispasmodic actions are considered to be the major pharmacological properties of thyme, and have been associated with the volatile oils (e.g. thymol, carvacrol) and flavonoid constituents (1, 7).

2.5.3.2.2 Secondary Pharmacodynamics

***In vitro* studies**

In vitro studies have shown that both thyme essential oil and thymol have antifungal activity against a number of fungi, including *Cryptococcus neoformans*, *Aspergillus*, *Saprolegnia*, and *Zygorhynchus* species. Both the essential oil and thymol had antibacterial activity against *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, and a number of other bacterial species. As an antibiotic, thymol is 25 times as effective as phenol, but less toxic (1).

2.5.3.2.3 Pharmacodynamic Drug Interactions

Thyme oil, thymol, and carvacrol all induced some phase I and phase II enzymes in mice (8). This suggests that thyme given simultaneously with some drugs may lead to reduced drug efficacy due to increased metabolism. Human trials are warranted to determine if this is a real problem.

Thymol and carvacrol at low concentrations blocked the genotoxic and lymphocyte suppressive effects of the chemotherapy drug mitomycin C *in vitro*, while higher concentrations caused DNA damage (9).

2.5.4 Overview of Efficacy

The efficacy of *Thymus vulgaris* L. liquid extract has been well documented over many years of widespread traditional use as herbal medicine.

According to the assessment report on *Thymus vulgaris* L., *vulgaris zygis* L., herba" from the European Medicines Agency (EMA) (5), *"the published data on pharmacology and from observational trials support the safe traditional oral use of herbal preparations of Thyme for the treatment of cough associated with cold"*.

2.5.4.1 Clinical Efficacy of Thyme Preparations in the Treatment of the Proposed Indications

In a randomised, double-blind, comparative study, 60 patients with productive cough complaints resulting from uncomplicated respiratory infections were treated with Thyme syrup (3×10 ml daily, n=31, no details regarding DER, extraction solvent and amount of herbal preparation in the syrup) 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 (10). However, no power calculation was conducted prior to the study, and it is conceivable that the sample size was too small to detect significant differences between groups. Without a placebo arm, these results cannot be discriminated from the natural course of disease.

The results from following company report are cited in (2):

In an open, multicenter 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 fluid 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.

2.5.4.2 Efficacy of Thyme Preparations in Other Indications

Not applicable.

2.5.4.3 Posology

2.5.4.3.1 Reconstitution and Administration

Oral administration.

2.5.4.3.2 Dosage

2.5.4.3.2.1 Adult Dosage

Using the measuring cup provided 15 ml of syrup, 4 times per day.

2.5.4.3.2.2 Paediatric Dosage

Children over 12 years: Using the measuring cup provided 15 ml of syrup, 4 times per day.

Children between 4 and 12 years: Using the measuring cup provided 10 ml of syrup, 4 times per day.

THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop is not recommended for use in children under 4 years of age

2.5.4.4 Conclusions

These claims are consistent with the spectrum of activity reported in standard references and published literature, and also with the traditional use as herbal medicine. The description of the efficacy profile of the drug and the dosage recommended correspond accurately with that described in standard reference works.

2.5.5 Overview of Safety

Based on historical use and clinical anecdote, thyme flower and leaves appear to be safe in limited medicinal and in culinary use. However, caution is warranted with the use of thyme oil, which should not be taken orally and should be diluted for topical administration due to potential toxic effects (11).

Safety data of several unpublished clinical trials in children with Thyme herbal preparations from Thyme as the only active ingredient are mentioned in the *"Assessment report on Thymus vulgaris L., vulgaris zygis L., herba"* from the EMA (5):

- Most of the trails reported no adverse events.
- One patient suffered from nausea because of the bad taste, no further adverse events were observed.
- In one of the trials, following adverse events were reported: a 2-year-old child showed repeating vomiting about 1½ hours after administration of the preparation; a 5-year-old child showed repeating vomiting; a 1-year-old child had repeated diarrhoea, another 1-year-old child showed an exanthema of the neck and neckline.
- In another trial in children, 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.

Safety data were also reported in clinical trials with herbal preparations from Thyme in combination herbal medicinal products.

In the trial reported by Ernst et al (12),160 mg dry extract Thyma herba was combined with 60 mg dry extract of *Primulae radix*. The rate of adverse events was below 1% (in 3140 adults 0.64%, in 1490 children 0.60%).

Kemmerich et al (13) combined liquid extract from Thyme with liquid extract from ivy leaves. No differences in frequency of adverse events between placebo and verum group. Medication was well tolerated, no severe or serious adverse events occurred.

In the trial reported by Kemmerich (14), dry extracts from Thyme and from *Primula* root were investigated in comparison to placebo. No difference in the frequency or severity of adverse events was observed. Severe or serious adverse events were not reported. In the verum group one case with Eustachian tube disorder and one case of back pain were labelled as moderate, one case of otitis externa as mild.

Gruenwald et al (15) reported after application of liquid extract from Thyme (combined with tincture from Primula root no serious adverse events. Five adverse events occurred in the placebo group, two in the verum group (stomach ache and nausea were considered to be related to the study medication).

In an open trial assessing the safety of syrup combining *Thymus vulgaris* leaf infusion with *Hedera helix* leaf extract, *Pimpinella anisum* seed decoction, and *Althaea officinalis* root mucilage, no significant adverse effects were reported in 61 adult patients (16).

2.5.5.1 Adverse Effects Characteristic for the Pharmacological Class

2.5.5.1.1 Immune System Disorders

Patients sensitive to birch pollen or celery may have a cross-sensitivity to thyme (2).

2.5.5.1.2 Gastrointestinal Disorders

Gastrointestinal effects such as nausea or gastric pain can occur (7).

2.5.5.1.3 Skin and Subcutaneous Tissue Disorders

Contact dermatitis has been reported (2).

2.5.5.2 Precautions

2.5.5.2.1 General Precautions

Patients with a known sensitivity to plants in the Lamiaceae (Labiatae) should contact their physician before using thyme preparations (2).

Patients sensitive to birch pollen or celery may have a cross-sensitivity to thyme (2).

2.5.5.2.2 Precautions in Special Population

The liquid thyme extract in this medicinal product contains ethanol, resulting in 2.2 vol% in the syrup. This corresponds for the highest dose (15 ml) to 0.26 g ethanol which is equivalent to 6.6 ml of beer or wine per 2.8 ml dose. This has to be considered for paediatric patients and patients with alcohol dependence and/or liver disease.

2.5.5.3 Contraindications

Hypersensitivity to the active substances (i.e. thymol and carvacrol), to other members of the Lamiaceae family or to any of the excipients.

2.5.5.4 Use in Pregnancy and Breastfeeding

The safety of *Thymus vulgaris* L. liquid extract during pregnancy or lactation has not been established. As a precautionary measure, the drug should not be used during pregnancy or lactation except on medical advice. However, widespread use of *Thymus vulgaris* L. liquid extract has not resulted in any safety concerns (2).

The liquid thyme extract in this medicinal product contains ethanol, resulting in 2.2 vol% in the syrup. This corresponds for the highest dose (15 ml) to 0.26 g ethanol which is equivalent to 6.6 ml of beer or wine per 2.8 ml dose. This has to be considered during pregnancy and breastfeeding.

2.5.5.5 Drug Interactions

None reported.

Foster et al (17) reported that an aqueous Thyme extract significantly inhibited several isoforms of CYP 450 *in-vitro*.

Thyme oil, thymol, and carvacrol all induced some phase I and phase II enzymes in mice (8). This suggests that thyme given simultaneously with some drugs may lead to reduced drug efficacy due to increased metabolism. Human trials are warranted to determine if this is a real problem.

According to Aydin et al (9) thymol and carvacrol at low concentrations block the genotoxic and lymphocyte suppressive effects of the chemotherapy drug mitomycin C *in vitro*.

2.5.5.6 Effects on the Ability to Drive or Operate Machinery

None known (2).

2.5.5.7 Overdose

No toxic effects reported (2).

2.5.5.8 Tolerance / Potential for Dependence / Rebound Phenomena / Abuse

None known.

2.5.6 Benefits and Risk Conclusions

The claimed therapeutic indications for *THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop* are consistent with the spectrum of activity reported in standard references and published literature. The data related to the clinical properties of *THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop* are collected from and based upon a careful and extensive literature search.

Documented pharmacological actions support the traditional medicinal use of herbal preparations of Thyme for the treatment of cough associated with cold. The pharmacological actions have been principally attributed to the volatile oil and flavonoid constituents.

Thyme is a potent spasmolytic, used particularly for productive cough associated with common colds.

Data from clinical trials support the safe use of herbal preparations of Thyme in the proposed indication 'cough associated with cold'. The reported adverse events are mild. Therefore a positive benefit-risk-ratio can be assumed.

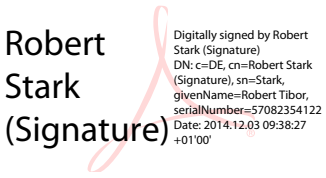
Taken together, the claimed expectorant effects of Thyme preparations have long been recognised empirically. The use in cases of productive cough is made plausible by pharmacological data, comparative and observational clinical studies.

In conclusion, herbal preparations of Thyme can be regarded as traditional herbal medicinal products.

In summary, the data presented concerning the use of *THIOPECTOL THYM SANS SUCRE EDULCORE AU MALTITOL, 6.5 g/100 ml, sirop* has been summarised in the product literature which forms part of this licence application / for which references are provided on the next pages. The information presented confirms the suitability and efficacy of the product when used as recommended.

Mechelen, 2014-12-03

Name of expert: Robert Stark



2.5.7 Literature References

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