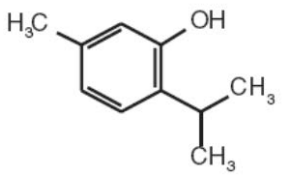
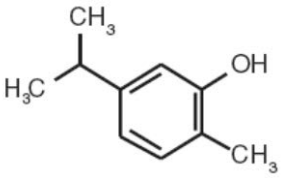
2.7.2 Summary of Clinical Pharmacology Studies

2.7.2.1 Background and Overview

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).

2.7.2.2 Summary of Results of Individual Studies

Not applicable as no such studies have been performed.

2.7.2.2.1 Special populations

2.7.2.2.2 Analysis of Clinical Information Relevant to Dosing Information

The dosage recommended by the applicant corresponds accurately with that described in standard reference works.

2.7.2.3 Comparison and Analysis of Results Across Studies

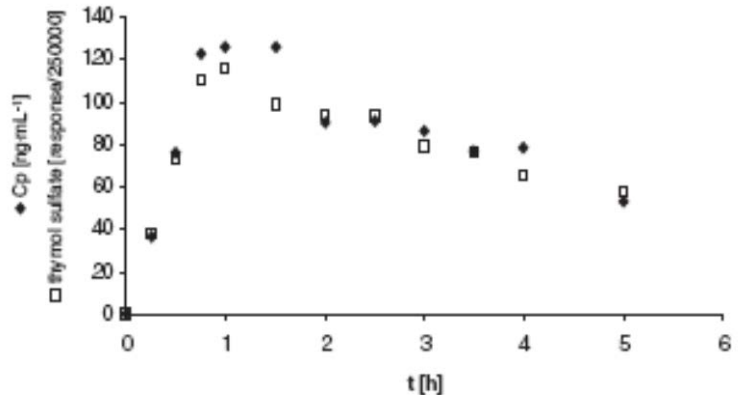
2.7.2.3.1 Pharmacokinetics

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.

Free thymol could not be detected in human plasma. By means of LC-MS/MS analysis, only thymol sulphate but not the glucuronide was identified in human plasma. The plasma concentration versus time curves of thymol sulphate (measured by LC-MS) and total thymol concentrations after enzymatic hydrolysis of plasma (measured by HS-SPME) showed parallel profiles (Figure 1). Hence, the quantification of thymol in plasma was based on the total thymol concentration after enzymatic hydrolysis of the sulphate.

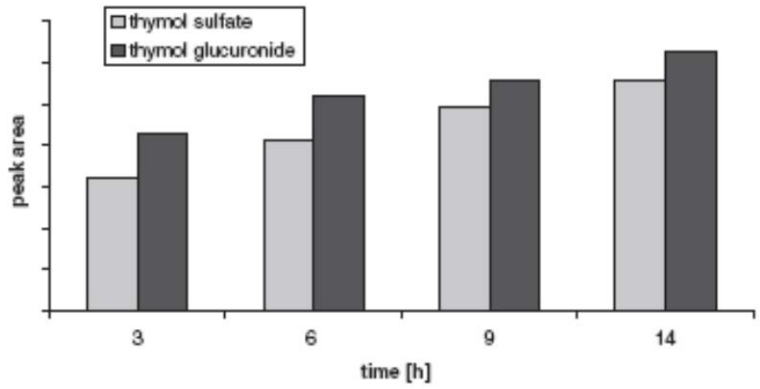
Figure 1: Thymol plasma concentration



Thymol plasma concentration determined after enzymatic hydrolysis of plasma (♦) and thymol sulphate measured by LC-MS in 1 subject (□).Taken from (6).

No free thymol was found in urine either. Instead, two phase II conjugates were identified by LC-MS/MS as thymol sulphate and thymol glucuronide. The ratio of peak areas of thymol sulphate and thymol glucuronide was constant over the different urine fractions (Figure 2).

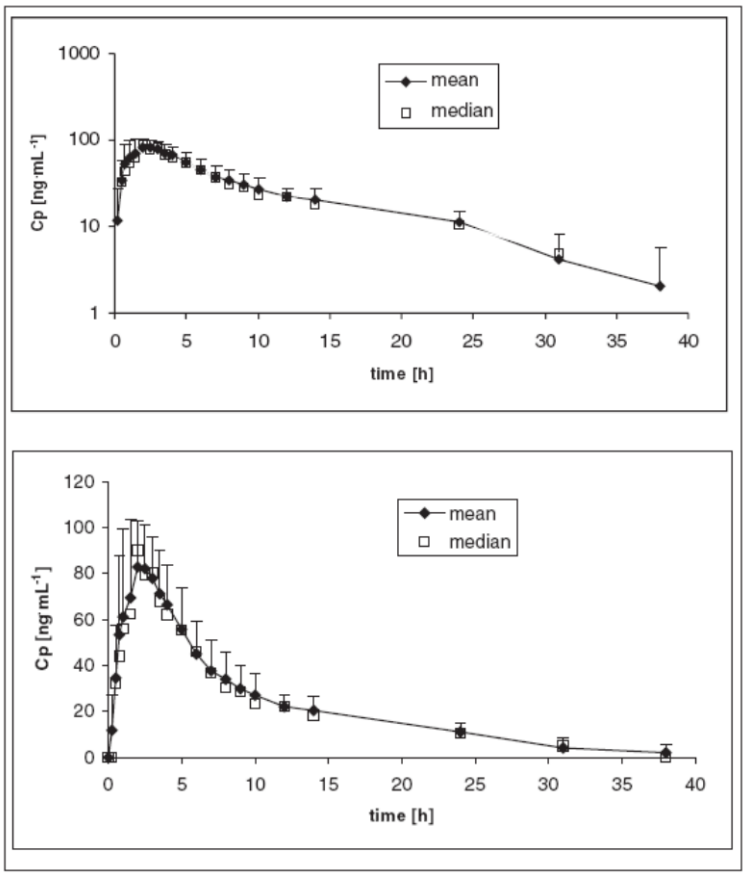
Figure 2: Cumulative renal excretion of thymol sulphate and thymol glucuronide



Excretion data based on one subject. Taken from (6).

The time course of the total thymol concentrations in human plasma is shown in Figure 3: Time course of thymol concentration in plasma. Thymol was rapidly absorbed. Thymol sulphate could be detected in plasma 20 minutes after application. Maximum plasma levels of 93.1 ± 24.5 ng/ml (mean ±SD) were reached after 1.97 ± 0.77 hours (mean ±SD) plasma concentration versus time profile was biphasic, subdivided into a distribution phase and a slow terminal elimination phase beginning at about 10 hours after administration and lasting up to an average of 38 hours. Elimination half-life was calculated to be 10.2 ± 1.4 hours (mean ±SD) (Table 2).

Figure 3: Time course of thymol concentration in plasma



Thymol concentration (after enzymatic cleavage) in plasma (mean ±SD; median) of 11 volunteers after administration of one tablet (1.08 mg thymol). Taken from (6).

In urine, the elimination of thymol conjugates was detectable for the first 24-hour interval, with most being eliminated after 6 hours. The combined amount of both thymol sulphate and glucuronide excreted in 24-hour urine was 16.2% ± 4.5% of intake. The renal clearance was calculated to be 0.271 ± 0.7 l/h.

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).

2.7.2.3.2 Pharmacodynamics

Based on *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).

Other pharmacodynamic actions have been demonstrated *in vitro*. 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).

2.7.2.4 Special Studies

Not applicable as no such studies have been performed.