2.7.4 Summary of Clinical Safety

2.7.4.1 Exposure to the Drug

2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

As *Thymus vulgaris* L. liquid extract has been developed before the current guidelines of clinical and preclinical research and as this report is based on a review of published scientific data, there is no structured overall safety evaluation plan.

The safety of the products has been evaluated over many years and a large number of patients has been exposed to this product.

Safety data were obtained from clinical studies, reviews and spontaneous case reports.

2.7.4.2 Adverse Events

2.7.4.2.1 Safety Data from Published Literature

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 (9).

Safety data of several unpublished clinical trials in children with Thyme herbal preparations from Thyme as the only active ingredient are mentioned in the *"Assessment report on Thymus vulgaris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 (10),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 (11) 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 (12), 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 (13) 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 (14).

2.7.4.2.1.1 Immune System Disorders

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

2.7.4.2.1.2 Gastrointestinal Disorders

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

2.7.4.2.1.3 Skin and Subcutaneous Tissue Disorders

Contact dermatitis has been reported (2).

2.7.4.2.2 Spontaneous Case Reports on Adverse Reactions

The applicant has not received any spontaneous case reports on adverse reactions.

2.7.4.2.3 Narratives

This section is not applicable as there have been no cases of fatalities, other serious adverse events and other significant events deemed to be of special interest or of clinical importance other than those described in the preceding paragraphs.

2.7.4.3 Clinical Laboratory Evaluations

No abnormal laboratory results attributed to *Thymus vulgaris* L. liquid extract have been reported.

2.7.4.4 Vital signs, Physical Findings and Other Observations Related to Safety

No such findings have been reported.

2.7.4.5 Safety in Special Groups and Situations

2.7.4.5.1 Drug Interactions

None reported.

Foster et al (15) 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 (16). 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 (17) thymol and carvacrol at low concentrations block the genotoxic and lymphocyte suppressive effects of the chemotherapy drug mitomycin C *in vitro*.

2.7.4.5.2 Use in Pregnancy and Lactation

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.

2.7.4.5.3 Use in Paediatric Patients

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.

2.7.4.5.4 Overdose

No toxic effects reported (2).

2.7.4.5.5 Drug Abuse

Thymus vulgaris L. liquid extract has no potential for drug abuse.

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 d patients with alcohol dependence and/or liver disease.

2.7.4.5.6 Withdrawal and Rebound

None known.

2.7.4.5.7 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

None known (2).

2.7.4.6 Post marketing data

See 2.7.4.2.2.