Melilotus officinalis (L.) Lam., herba

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

*Melilotus officinalis* (L.) Lam., herba

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

<table>
<thead>
<tr>
<th>Herbal substance(s) (binomial scientific name of the plant, including plant part)</th>
<th><em>Melilotus officinalis</em> (L.) Lam., herba</th>
</tr>
</thead>
</table>
| **Herbal preparation(s)** | Comminuted herbal substance  
Powdered herbal substance  
Dry extracts (3 - 5:1), water  
Fluid extracts (1:1), ethanol 30 % V/V  
Dry Extracts (5-7:1), ethanol 50 % V/V  
Dry extracts (4-8:1), ethanol 25 % m/m  
Dry extracts (4-8:1), methanol 50 % V/V  
Dry extracts (4-8:1), ethanol 35 % V/V  
Dry extracts (6-9:1), ethanol 90 % V/V  
Dry extracts (7-9:1), methanol 30 % V/V |
| **Pharmaceutical forms** | Oral use:  
Tea infusion, liquid or solid preparations  
Topical use:  
Tea infusions for external use  
Emplastrum Meliloti |
| **Rapporteurs** | Dr. Ulrike Wissinger-Gräfenhahn  
Prof. Olavi Pelkonen  
Dr. Konstantin Keller |
1 INTRODUCTION

This assessment report reviews the scientific data available for Meliloti herba. We also take into account the literature presented by the ESCOP to the monograph “Meliloti herba”, the WHO monograph, and regarding the traditional use the French Avis aux fabricants and the German list of traditional medicinal products according to § 109 a AMG. Additionally all Member States were asked to give information about what kind of products containing Melilotus are on their market including pharmaceutical forms, indications, posology and methods of administration.

Database search

This document is based on publications supplied by ESCOP and a DIMDI-based data search (xtoxlitall and xmedall) with the keywords “Melilotus” and “human” from 1900 in all text fields. The databases searched are listed in Appendix I.

Market situation in the Member States

Not in all Member States melilot containing herbal medicinal products are on the market. In some Member States melilot is only used in homeopathic medicinal products. Melilot also seems to be quite popular as a food supplement. Detailed information is given in section 4.

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

Herbal substance(s)¹²

Melilot (Meliloti herba)

The European Pharmacopoeia (01/2008:2120) monograph Meliloti herba (melilot) provides the following definition: Whole or cut, dried aerial parts of Melilotus officinalis (L.) Lam. Content: minimum 0.3 per cent of coumarin (C9H6O2; Mr 146.1) (dried drug).

The definition formerly given by the Pharmacopée Francaise was as follows:

Melilot consists of the dried flowering tops of Melilotus officinalis Desr.

The main characteristic constituents of melilot are cinnamic acid / coumarin derivates /(Hager 1994) (see table 1). Dicoumarol and the antifungal isoflavonoid medicarpin, which can be formed in melilot due to fungal infection and spoilage, should be absent from properly dried material (British Herbal Compendium).

Table 1: Main characteristic constituents of melilot

<table>
<thead>
<tr>
<th>Constituent</th>
<th>Abundance</th>
<th>Aspects with relevance for the benefit / risk assessment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cis-O-coumaric β-glucoside</td>
<td>0.5 %</td>
<td>Lactonises to coumarin after hydrolysis</td>
<td>Not assessed as such (in vivo exposure is actually as coumarin)</td>
</tr>
<tr>
<td>(melilotoside)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumarin</td>
<td>0.9 % (min. 0.3 % Ph.Eur.)</td>
<td>Because of an almost complete first-pass effect in humans, 7-hydroxycoumarin is thought to be “the active principle”</td>
<td>Assessed in this monograph</td>
</tr>
</tbody>
</table>

¹ According to “Note for guidance on Quality of herbal medicinal products” (CPMP/QWP/2819/00)
² 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)
<table>
<thead>
<tr>
<th>Substance</th>
<th>Toxicological activity</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>3,4-Dihydrocoumarin</td>
<td>Toxicologically less active than coumarin <em>in vitro</em> and animal studies</td>
<td>Not assessed*</td>
</tr>
<tr>
<td>(melilotin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopoletin</td>
<td></td>
<td>Not assessed*</td>
</tr>
<tr>
<td>7-Hydroxycoumarin</td>
<td>At least in primates, the primary <em>in vivo</em> exposing substance of coumarin. Umbelliferone is rapidly glucuronidated during first pass.</td>
<td>Not assessed as such</td>
</tr>
<tr>
<td>(Umbelliferone)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaempferol glycosides</td>
<td>Rapid hydrolysis in GI-tract</td>
<td>Not assessed*</td>
</tr>
<tr>
<td>Quercetin glycosides</td>
<td>Rapid hydrolysis in GI-tract</td>
<td>Not assessed*</td>
</tr>
</tbody>
</table>

*a minor component with probably no toxicological significance, or is rapidly inactivated or converted to another derivative.

Problems in risk assessment of other substances than coumarin

It is difficult to treat Cinnamic acid derivates / “coumarins” as a homogeneous group from pharmacology and toxicology point of view. Even relatively small structural changes result in considerable changes in kinetics and dynamics. A case in point is a difference between coumarin and its dimeric 4-hydroxyderivatives. Many oral anticoagulants are dimeric 4-hydroxycoumarin derivatives, whereas coumarin and many of its simple derivatives are devoid of effect on coagulation. The same is true in kinetic comparisons. These differences lead to a necessity to deal with different derivatives on their own rights.

Herbal preparation(s)\(^1,2\)

i) Preparations corresponding to a known coumarin content for oral and topical use (Commission E, ESCOP, British Herbal Compendium). On the basis of the data given by the Member States so far a clear definition of the preparations on the market is not possible.

ii) Emplastrum Meliloti: prepared by extraction of 10 parts of pulverized drug, wetted with 2 parts of ethanol, to 90 parts of semi-solid base (Rapae oleum, Cera flava, Colophonium) Final DER 0,11:1. (Polish Pharmacopoeia, VI edition)

Combinations of herbal substance(s) and/or herbal preparation(s)\(^3\)

Meliloti herba and preparations thereof are mainly used in combinations with other herbal substances / herbal preparations or various chemically defined substances. Although bibliographic data to combinations were assessed in the assessment report to some extent this monograph refers exclusivity to Meliloti herba.

Vitamin(s)\(^4\)

Not applicable

Mineral(s)\(^3\)

Not applicable

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\(^1\) According to the Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations (EMEA/HMPC/166326/2005)

\(^2\) Only applicable to Community monographs
TRADITIONAL MEDICINAL USE

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

References regarding use in folk medicine are going back to Plinius and Hippokrates. Emplastrum Meliloti, Emplastrum Meliloti comp. and Oleum Meliloti are mentioned in “Neues Pharmazeutisches Manual” dated 1904 (Dieterich, 1904). Herba Meliloti and Emplastrum Meliloti are also included in the “Deutsche Arzneitaxe” from 1936 and in the DAB 6 (1951).

Melilot and preparations thereof are licensed as traditional medicinal products in Germany, France, Latvia and Poland for oral and topical use. Therefore for melilot and the mentioned preparations a period of at least 30 years in medical use as requested by Directive 2004/24 EC for qualification as a traditional herbal medicinal product is fulfilled.

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 Meliloti herba:

| Symptomatic treatment of problems related to haemorrhoids (topical use) | German Commission E (1986) |
| External use: Bruises, sprains and superficial bleeding | German Commission E (1986) |

Use in folk medicine:

Plinius summarizes the use of melilot as constricting and softening agent for hot tempered ulcera of eyes, anus and genitals. Orally taken it was used against stomach ache, gastric ulcer and disorders of uterus and liver.

Hippokrates used melilot flowers externally for septic ulcers.

Fuchs (1543) mentions external use of melilot in honey for facial spots as well as oral use of chopped drug in vine for bladder disorders.

Bock (1565) summarizes the use of melilot as constricting, softening and analgetic agent externally used for ulcers of the eyes, earache, hardening and swelling of uterus.

Matthiolus (1626) describes external use of melilot in case of stomach ache or headache and skin rash due to mycosis.

Leclerc (1976) numbers melilot to be among antispasmodics and recommends it in case of insomnia in children or elderly.

Hager (1938, 1949, 1975) mentions external use of melilot in herbal pillows, as constricting agent for ulcers and rheumatic disorders, internal use as a diuretic agent as well as use as aromatic adjuvant internal use for varices, thrombotic diseases, haemorrhoids, leg ulcer, oedema and brachialgia is added.

Madaus (1938) summarizes the external use of melilot on ulcers, tumours, swelling of rheumatic joints and inflamed breasts of breastfeeding women.
According to Wichtl (1984), Hoppe (1977) and Berger (1949) melilot was also used as a diuretic in folk medicine. Additionally, the use of melilot as an expectorant is described by Karsten, Weber, Stahl (1962).

Melilot is also widely used in homeopathic medicinal products in the Member States.

The indications currently on the market in the Member States are tabled in Annex 4.

Based on the available literature and the known actions of coumarins, the following text on the indication is recommended:

**Internal use**
1) “Traditional herbal medicinal product to relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances. The product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.”

**Topical use**
2) “Traditional herbal medicinal product to relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances. The product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.”

3) “Traditional herbal medicinal product used for external use of symptomatic treatment of bruises and sprains. The product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.”

4) “Traditional herbal medicinal product used for symptomatic treatment of insect bites. The product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.”

The use of eye drops in case of eye irritation or discomfort due to various causes (smoky atmospheres, sustained visual effort, swimming in the sea or swimming pools) cannot be supported because no data on exposure or on local tolerance are available. The safety of eye drops with Melilotus infusions can not be assessed for this reason.

The use in digestive disorders seems to be no longer claimed by any preparation on the EU market.

### 2.3.2 Evidence regarding the specified strength

Preparations for oral use are quantified on 0.3 % to 20 % coumarin or on a certain content of coumarin varying from 3 mg to 15 mg coumarin. Extracts should be quantified for coumarin and the total exposure in adults should not exceed 5 mg coumarin/day.
### 2.3.3 Evidence regarding the specified posology

#### Posology in adults:

##### Dried herb

<table>
<thead>
<tr>
<th>Source</th>
<th>Single dose</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madaus (1938)</td>
<td></td>
<td>4.0 g</td>
</tr>
<tr>
<td><strong>Orally</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>add 2 teaspoons of chopped drug in 2 cups of cold water and let it extract for 8 hours. To drink during daytime in case of insomnial.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Externally</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ear vapouration</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 tablespoonful of mixture per ½ 1 water. In case of otitis and otorhoe for ear vapouration.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herba Meliloti</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Flores Malvae arboreae</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Flores Chamomillae</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Herba Equiseti</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Wichtl M (1984)</td>
<td>2 - 4 g</td>
<td>4 – 12 g</td>
</tr>
<tr>
<td><strong>Orally</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - 2 teaspoons of finely chopped drug per cup of decoction, 2 – 3 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Externally</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For sores and haemorrhoids and as a poultice: the drug is thoroughly soaked with the same amount of hot water, wrapped in linen, and placed on the affected part.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weiß RF (1985)</td>
<td>2 - 4 g</td>
<td>6 – 16 g</td>
</tr>
<tr>
<td><strong>Orally</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>in herbal teas 1 – 2  teaspoons per cup of decoction, 3- 4 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Commission E (1986)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Orally</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to 3 – 30 mg coumarin (based on a content of 0.5% coumarin this would correspond to 0.6-6 g of herbal drug)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESCOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Orally</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to 3 – 30 mg coumarin (see above)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAB VI</td>
<td>0.8 g</td>
<td></td>
</tr>
<tr>
<td>2 tablespoonful per 2 cups of decoction (10-15 minutes). Used for gargling and as a poultice.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• <strong>Species emmollientes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Folia Altheae</td>
<td>20 g</td>
<td></td>
</tr>
<tr>
<td>Foliæ Malvae</td>
<td>20 g</td>
<td></td>
</tr>
<tr>
<td>Herba Meliloti</td>
<td>20 g</td>
<td></td>
</tr>
<tr>
<td>Flores Chamomillae</td>
<td>20 g</td>
<td></td>
</tr>
<tr>
<td>Semen Lini</td>
<td>20 g</td>
<td></td>
</tr>
<tr>
<td>Polish Pharmacopoeia VI edition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 – 3 g of pulvered drug per 200 – 300 ml of boiling water for infusions</td>
<td>2.5 - 3 g</td>
<td></td>
</tr>
<tr>
<td>Source</td>
<td>Preparations</td>
<td>Single dose</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Commission E (1986)</td>
<td>Preparations for oral use</td>
<td></td>
</tr>
<tr>
<td>ESCOP (2003)</td>
<td>Preparations for oral use</td>
<td></td>
</tr>
<tr>
<td>Hager 1938 / 1949, Madaus 1938</td>
<td><em>Emplastrum Meliloti</em></td>
<td>melilot 15%</td>
</tr>
<tr>
<td></td>
<td>Cerae flavae 500</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olei olivi 45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Res. Pini 45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sebi ovilis 45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Res. Gumm. Ammon. sol. in Oleum Terebinthini</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Herba Meliloti pulv. 125</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Herba Absinthii pulv. 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flor. Chamomillae pulv. 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fol. Lauri nob. pulv. 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M.f. Unguentum 8</td>
<td></td>
</tr>
<tr>
<td>British Herbal Compendium</td>
<td>Preparations containing the equivalent of up to 10 g dried herb; For preparations of known coumarin content.</td>
<td>Up to 10 g in divided doses Up to 30 mg of coumarin (see above) or up to 1 mg/kg body weight (based on a content of 0.5% coumarin for a person of 70 kg b w this would correspond to 1.4-14 g of herbal drug)</td>
</tr>
<tr>
<td>(Bradley 2006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polish Pharmacopoeia, VI edition</td>
<td><em>Emplastrum Meliloti</em> is prepared by extraction of 10 parts of pulverized drug, wetted with 2 parts of ethanol, to 90 parts of semi-solid base (Rapae oleum, Cera flava, Colophonium) Final DER 0,11:1.</td>
<td>For single use</td>
</tr>
</tbody>
</table>
### Preparations on the German Market

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Concentration/Volume (v/v)</th>
<th>Dosage Unit</th>
<th>Dosage (mg/3 times daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid extracts (1:1), ethanol 30%</td>
<td>1:1, ethanol 30% V/V</td>
<td>1.14 g</td>
<td>1.14 mg coumarin</td>
</tr>
<tr>
<td>Dry Extracts (5-7:1), ethanol 50%</td>
<td>50% V/V</td>
<td>160 mg</td>
<td>160 mg extract (1.1 mg coumarin)</td>
</tr>
<tr>
<td>Dry extracts (4-8:1), ethanol 25%</td>
<td>25% m/m</td>
<td>100 mg</td>
<td>100 mg extract (7.3 - 10.1 mg coumarin)</td>
</tr>
<tr>
<td>Dry extracts (4.2-7.5:1), methanol</td>
<td>50% V/V</td>
<td>200 mg</td>
<td>200 mg extract</td>
</tr>
<tr>
<td>Dry extracts (4-8:1), ethanol 35%</td>
<td>35% V/V</td>
<td>252 mg</td>
<td>252 mg extract (3-5 mg coumarin)</td>
</tr>
<tr>
<td>Dry extracts (6-9:1), ethanol 90%</td>
<td>90% V/V</td>
<td>24 mg</td>
<td>24 mg extract (3-5 mg coumarin)</td>
</tr>
<tr>
<td>Dry extracts (7-9:1), methanol 30%</td>
<td>30% V/V</td>
<td>30 mg</td>
<td>30 mg extract (3-5 mg coumarin)</td>
</tr>
</tbody>
</table>

### Preparations on the French Market

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Concentration/Volume</th>
<th>Dosage Unit</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powdered herbal substance</td>
<td>1 g</td>
<td>250 mg</td>
<td>3 times daily</td>
</tr>
<tr>
<td>Powdered herbal substance (suspension)</td>
<td>1.6 g</td>
<td>1.6 g</td>
<td>Once daily</td>
</tr>
<tr>
<td>Powdered herbal substance</td>
<td>1 g</td>
<td>500 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Dry extract with water (3-5:1)</td>
<td>1 g</td>
<td>200 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Tea infusion (1 g/100 ml) for eye drops</td>
<td>1-2 drops</td>
<td>1-2 drops</td>
<td>3-4 times daily</td>
</tr>
</tbody>
</table>

**Posology in children:**
There are no data for internal and external use of melilot in children.

According to the “NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION” (CPMP/ICH/2711/99) of 27 July 2000 and other monographs age limit for children should be determined to “adolescents over 18 years of age” for oral and topical administration.

### 2.3.4 Evidence regarding the route of administration

Oral and topical administrations of melilot and preparations thereof are used in the recommended traditional indications. Parenteral use is documented but it is not suitable for traditional herbal medicinal products.
2.3.5 Evidence regarding the duration of use

No restriction on the duration of use has been reported for Meliloti herba. As persistent symptoms require medical diagnosis and supervision, the use is limited to 2 weeks. In case of insect bites, medical diagnosis is requested if symptoms persist for more than 3 days.

2.4.1 Assessor’s overall conclusion on the traditional medicinal use

Meliloti herba and preparations thereof have been used orally and topically for symptomatic treatment of problems related to varicose veins, such as painful and heavy legs, nocturnal cramps in the legs, itching and swelling, for gastric upsets in oral dosage forms and for external use in blunt traumata for many decades. The traditional use is made plausible by the consistent, long-standing use and, with some limitations, by the pharmacological data regarding to coumarin and to a minor degree to Melilotus extracts.

Melilot or preparations thereof are licensed with a traditional indication in Germany, France, Latvia and Poland for oral and topical use.

Since the clinical documentation for melilot as a mono preparation is poor and no controlled clinical studies are available, the use of Meliloti herba preparations has to be regarded as traditional.

2.5.1 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

In general melilot was well tolerated in clinical trials. In some studies adverse events as gastrointestinal complaints, allergic reactions and photosensitivity are mentioned. Adverse events in Member States that have preparations on the market have not been recorded so far. However, a precise question for adverse events was not included in the request for information from the Member States.

2.5.3 Serious events and deaths

None known for Meliloti herba and preparations thereof for oral or topical administration.

Due to reports of hepatotoxicity associated with coumarin intake (for details see below) pharmacovigilance action was taken in 1997 in Germany for herbal and homeopathic medicinal products for oral use containing preparations of melilot, woodruff or tonka beans. After assessing the data the BfArM concluded in 1998 that there is no evidence of an increased hepatotoxic risk for these herbal or homeopathic medicinal products if certain limits with respect to coumarin are guaranteed. Melilot and preparations thereof for oral use are included in the German traditional list according to § 109 a AMG up to doses corresponding to 5 mg coumarin per day. With a content of 0.3 to 1 % of coumarin in the herbal drug this amount would correspond to 0.5 to 1.5 g of herbal drug and thus would be far less than the posology used traditionally.

During the consultation phase this issue has been raised by interested parties. Several options were considered by the HMPC:

a) to reduce the posology to exclude exposures of more than 5 mg Coumarin under a worst-case scenario,

b) not to accept or to go below the minimum specification of Ph.Eur.,

c) to require additional release / extraction data or accept only herbal substance with a low-content of coumarin.
As restriction of the posology just to "5 mg of Coumarin" is not acceptable, because Coumarin is not a substance with generally accepted therapeutic activity in the traditional indications of melilot.

It was concluded that both requirements (amount of herbal preparation and limit for coumarin) have to be fulfilled. If no herbal drug with a lower content in the range of 0.3% Coumarin can be found, or if no data are presented that demonstrate that the finished dosage form or preparation taken by the patient, e.g. tea infusions, contains less than 5 mg of coumarin, the daily dose of the herbal preparation needs to be reduced to the minimum daily dose or single dose of the herbal preparation.

**Coumarin**

Treatment of humans in connection with various clinical conditions (lymphoedema, various cancers) has been associated with cases of hepatotoxicity. In 1997 up to 82 case reports of liver damage possibly associated with Coumarin intake were published. However, a clear relationship between the dose of coumarin and the hepatotoxic responses observed has not been established. It is important to note that in the majority of cases coumarin doses have been from 90 mg to several grams but in 5 cases a daily dosage of 25 to 30 mg coumarin is reported. Pharmacovigilance action was taken by Germany, France, Switzerland, Luxemburg and Australia followed by withdrawal of marketing authorizations for Coumarin preparations in different member states (e.g. Australia 1995, France 1997, Germany 1998).

In 1994 a threshold value of a daily intake of coumarin in food was set by 0.5 mg/kg bw by the European Commission (Scientific Committee for Food 1997). The use of coumarin in food was re-evaluated by EFSA in 2004. Regarding hepatotoxicity the Panel concluded from recent comparative studies that liver toxicity is not directly correlated to coumarin 3,4-epoxide/ortho-hydroxy phenyl acetic acid, but rather the balance between bioactivation and detoxification likely dictates the susceptibility of the animal species to coumarin-mediated liver toxicity. The Panel came to the conclusion that the data now available allow the derivation of a Tolerable Daily Intake (TDI); a TDI of 0 – 0.1 mg coumarin/kg body weight was established (EFSA 2004). According to this a daily intake of 7 mg coumarin corresponding to approx. 1.5 g of herbal drug would be acceptable for a person with 70 kg of body weight. Taking into account the additional exposure through food, a limit 5 mg Coumarin / day provides sufficient safety for traditional use.

2.5.4.1 Intrinsic (including elderly and children)/extrinsic factors

None known

2.5.4.2 Drug-drug interactions and other interactions

There is one case report of a young woman in whom hemorrhagic diathesis (abnormal clotting function and mild menometrorrhagia) caused by drinking large amounts of a “seasonal tonic” herbal tea for approximately 2 months occurred. The major ingredients of the patients tea were tonka beans (1/2 lb), melilot (2 oz), and sweet woodruff (3 oz). Natural coumarins are found in all three of them with the highest content in tonka beans (1 to 3 % coumarin). Additionally the patient was taking medications, which might potentiate the effect of oral anticoagulant drugs, e.g. propoxyphene, vitamin A in “fairly large daily doses” and bromelain (Hogan (1983).

There is also a report of a possible interaction between oral anticoagulant treatment and topical treatment with a cream containing extracts of ruscus and melilot (Cyclo 3®). A 66 year-old woman with cardiac arrhythmia received acebutolol 200 mg/day and acenocoumarol 3 tab/day for years. She also had a current treatment with thyroxine 100 mg/day. 10 days after she started topical treatment with Cyclo 3® for venous insufficiency, 3 times daily, the INR increased from 2 to 5.82. Cyclo 3® was discontinued and the INR returned to the usual values. Seven month later, a rechallenge with Cyclo 3® Crème was attempted. After one week the INR was again increasing from 2.56 to 4.06. The patient denied any changes in treatment or alimentation. She did not use occlusive dressing but she strongly massaged her legs 3 times per day when two time per day is recommended (Chiffoleau et al (2000).
In 2 clinical studies an influence of melilot extract administered intravenously on parameters of blood clotting (prothrombin time respectively “coagulation analysis”, details not given) was not seen (Völker 1961, Mayer and Sukthaworn (1963). Additionally no influence on bleeding time, thrombelastogram and prothrombin time was seen in 2 clinical trials with 60 mg coumarin daily given to pregnant and breastfeeding women (Krajnovic et al. 1974 /1977a/1977b).

Taking into account that in the above mentioned case reports combination products and/or co-medication which might potentiate the effect of oral anticoagulant drugs was taken a causal relationship of melilot can not be unequivocally deduced. Although there is no mechanistic basis for interactions with anticoagulants, i.e. coumarin is not an inhibitor of CYP 2C9 responsible for warfarin clearance and coumarin itself is not an anticoagulant, Meliloti herba contain a number of coumarin derivates which might affect coagulation. However, taking into account the use of melilot in a setting of self-medication a concomitant anticoagulant therapy should be a contraindication with respect to patients’ safety.

2.5.4.3 Use in pregnancy and lactation

Safety during pregnancy and lactation has not been established systematically. Use of melilot extracts in combinations is mentioned by various authors. No adverse effects have been reported from the use of these combinations as a medicinal product during pregnancy and lactation. Information about the delivered babies is lacking. As there are no appropriate data available, use is not recommended during pregnancy and lactation.

2.5.4.4 Overdose

According to Hager’s Handbuch intake of 4 g of melilot extract triggers nausea, vomitus, headache and weakness. Data on the extract and on details are missing.

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 Contra indications (hypersensitivity and allergic potential to be both covered)

Hypersensitivity to melilot or to coumarin.

Not to be used together with anticoagulant therapy.

2.5.5 Non-clinical safety data

For the most part, coumarin is dealt with here, because a large database exists. Other constituents are mentioned only sporadically, because less useful studies are available in the literature.

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

(e.g. single/repeat dose toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicity, local tolerance, other special studies)
Melilot and combinations

Single dose toxicity

No data available (ESCOP 2003). The ip LD50 of a melilot/rutin preparation in mice was too high to be determined (ESCOP 2003).

Repeated dose toxicity

No data available (ESCOP 2003).

Reproductive toxicity

The teratogenic effects of a combination of coumarin and rutin have been investigated in white New Zealand rabbits. Iv administration of either coumarin alone or a coumarin/rutin combination at 10 and 100 times the therapeutic dose did not result in any increase in malformation rates compared to controls, nor increased number of resorptions or fetal mortality (ESCOP 2003).

Tests on reproductive toxicity, genotoxicity and carcinogenicity of clearly defined herbal preparations have not been performed.

Coumarin

Several extensive assessments concerning coumarin toxicity have been published during the past few years (Lake 1999; IARC 2000; NTP 2004).

Single dose toxicity

LD50 values (mg/kg body weight) for coumarin have been determined for mice (oral 196; ip 220; subcutaneous 242), rats (oral 293) and guinea pigs (oral 202) (ESCOP 2003).

Repeat dose toxicity

An in-depth survey of coumarin toxicity was carried out in connection with the NTP coumarin carcinogenicity study (NTP 2004) and these studies are summarized below.

NTP toxicity and carcinogenicity studies were conducted by administering coumarin (97% pure) in corn oil by gavage to groups of male and female F344/N rats and B6C3F1 mice for 16 days, 13 weeks, and 2 years.

In 16-day dose-finding studies in rats and mice, all female rats and most male rats receiving 400 mg/kg, and all mice receiving 600 mg/kg died. There were no clinical signs of organ-specific toxicity, and the mean body weight gains and final mean body weights of surviving dosed male and female animals were similar to those of the controls.

13-week study in rats and mice liver seemed to be the principal target for toxicity at the higher dose levels (150 and 300 mg per kg body weight). Serum enzymes indicating liver involvement were increased, the absolute and relative liver weights were significantly greater than those of the controls, and centrilobular hepatocellular hypertrophy and/or degeneration and/or necrosis, chronic active inflammation, and bile duct hyperplasia were observed.

2-year study in rats and mice. Groups of 60 male and 60 female rats were administered coumarin in corn oil by gavage at doses of 0, 25, 50, or 100 mg per kg body weight. Groups of 70 male and 70 female mice were administered coumarin in corn oil by gavage at doses of 0, 50, 100, or 200 mg per kg body weight. After 15 months, 10-20 animals from each group were evaluated. Male rats in two high-dose groups died prematurely primarily due to chemical-related exacerbation of spontaneously occurring renal disease. The principal lesions occurred in the liver, kidney, and forestomach. While the hepatic lesions were seen in all groups of male rats, they occurred only in the 50 and 100 mg/kg females. The lesions consisted of a spectrum of changes including hepatocellular necrosis, fibrosis, cytologic alteration, and increased severity of bile duct hyperplasia.
hyperplasia. The principal toxic lesions to mice occurred also in the liver. The incidences of centrilobular hypertrophy in 100 and 200 mg/kg males and 200 mg/kg females were significantly greater than those of controls. The incidences of syncytial alteration in all male dose groups and in 200 mg/kg females were also significantly greater than controls.

There was a chemical-related increase in the average severity of nephropathy in all groups of dosed male and female rats. There were corresponding increased incidences of parathyroid gland hyperplasia in all groups of dosed males, probably as a result of compromised renal function. The incidences of forestomach ulcers in all groups of dosed male rats and in 100 mg/kg female rats were significantly greater than those of the controls. The hepatic lesions produced by 9 or 15 months of exposure were reversible. In contrast to the liver lesions, the severity of nephropathy in male rats following the recovery period was significantly greater than that of males examined at the 9- and 15-month interim evaluations.

In summary, the administration of coumarin to rats was also associated with an increased severity of nephropathy in the kidney and of bile duct hyperplasia in the liver, increased incidences of ulcers of the forestomach, and necrosis, fibrosis, and cytologic alteration of the liver. Administration of coumarin to mice was also associated with centrilobular hypertrophy, syncytial alteration, and eosinophilic focus in the liver.

Genotoxicity

Genotoxicity of coumarin has been studied in a number of relevant tests (NTP 2004; IARC 2000). Coumarin did not induce micronuclei in mice in vivo and was not mutagenic in Drosophila melanogaster. It was weakly positive in induction of micronuclei in human cells in vitro, but failed to induce unscheduled DNA synthesis in human liver cells in vitro. Coumarin induced sister chromatid exchanges without metabolic activation and chromosomal aberrations with metabolic activation, but not micronuclei or gene mutations in mammalian cells in vitro. It was mutagenic in only two out of 11 Salmonella typhimurium strains tested, with metabolic activation. Coumarin was antimutagenic in various assays, but also had co-mutagenic properties.

The weight of evidence suggests that coumarin is not a clear genotoxicant. However, there are some inconsistencies in the data basis, which should be kept in mind. On this basis it can be concluded provisionally, that coumarin is not a genotoxic carcinogen.

Carcinogenicity

No data on human carcinogenicity are available. However, coumarin has been adequately tested by oral administration in two experiments in mice and in one experiment in rats. In mice of one strain, it produced increases in lung tumours (adenomas and carcinomas) in both males and females and in hepatocellular adenomas in females. There was no increase in tumour incidences in another strain of mouse. In one study in rats, coumarin produced a low incidence of renal tubule adenomas in males, seen only after step-sectioning of the kidney. Three other studies in rats could not be evaluated (IARC 2000). The IARC Working group concluded, that no epidemiological data relevant to the carcinogenicity of coumarin were available, whereas there is limited evidence in experimental animals for the carcinogenicity of coumarin. The overall evaluation was that coumarin is not classifiable as to its carcinogenicity to humans (Group 3). EPA became to the same conclusion (NTP 2004).

Regarding the potency of coumarin, the dose-response relationships for coumarin-induced toxicity and carcinogenicity are non-linear, with tumour formation only being observed at high doses which are associated with hepatic and pulmonary toxicity (Lake 1999). The tentative conclusion regarding the carcinogenicity mechanism and potency of coumarin is that it is a non-genotoxic carcinogen in only those animal species in which it can cause tissue toxicity because of its peculiar species-specific metabolic features (see below).

Species differences in toxicity

The target organs for coumarin toxicity are primarily the liver in rats and the liver and lung in mice. There are marked species differences in these responses, with the mouse being particularly susceptible to coumarin-induced Clara cell injury. Coumarin is hepatotoxic in rats and mice. Hamsters and gerbils are resistant to acute coumarin-induced hepatotoxicity. In vitro, coumarin is toxic in either hepatocytes or liver slices from rats, mice, rabbits and guinea-pigs, whereas monkey and human cells and/or slices appear to be resistant.
and large, these species differences seem to be associated with metabolic differences, i.e. those species with predominant ring-opening pathway and postulated epoxide formation seem more susceptible to tissue damage than species with 7-hydroxylation predominating (Lake 1999), although also the rate of detoxification of a putative reactive intermediate seems to be of importance (Vasallo et al. 2004).

Reproductive and developmental toxicity

No studies were available.

Local tolerance

No studies were available.

Assessor’s overall conclusions on toxicology

Only general information is available concerning melilot preparations. These data do not indicate any serious toxicities. However, tests on reproductive toxicity, genotoxicity and carcinogenicity of clearly defined herbal preparations have not been performed. Toxicity of coumarin has been studied rather extensively. The primary target organ in rats and mice is liver. In addition, coumarin causes toxic manifestations in kidneys and lungs. Approximate no effect levels (if they can be reliably calculated) in rats and mice are in a range of 10-50 mg/kg regarding tissue toxicity. Thus, toxic outcomes are due to relatively high doses of coumarin. It seems probable that the mechanism of coumarin-induced tumour formation in rodents is associated with metabolism-mediated tissue toxicity only at very high doses.

2.5.6 Assessor’s overall conclusions on safe use

Humans are one of the species with predominating 7-hydroxylation by CYP2A6 and therefore seem in general less susceptible to hepatotoxicity due to coumarin intake. However, a high interindividual variability in coumarin 7-hydroxylation is documented in humans, partially due to genetic polymorphisms. Case reports of hepatotoxicity in humans are predominantly reported in doses above 90 mg coumarin/day. However, a few case reports after a daily intake of 25 to 90 mg coumarin are documented as well. It is not known if these are cases of “poor metabolizers” with limited 7-hydroxylation. The frequency of CYP 2A6 poor metabolizers (complete lack of activity) is dependent on ethnic background and is reported to be between 6 % (Caucasians) and 25 - 50 % (Orientals). Assuming a hepatotoxic risk of coumarin doses above 90 mg/day a safety factor of 18 is given to the proposed dosage of melilot and preparations thereof according to a maximum of 5 mg coumarin per day. The safety factor is reduced to 5 taken into account potential toxic doses above a cut point of 25 mg coumarin/day. Basically this threshold also complies with the TDI given by EFSA in 2004.

2.6 PHARMACOLOGICAL PROPERTIES

2.6.1 Overview of pharmacological effects of herbal substance(s), herbal preparation(s) and relevant constituents thereof on the basis of long-standing use and experience

Melilot

There are many studies with combinations of coumarin and rutosid that are, historically, linked to melilot preparations. The combinations derived from studies with the extract and were thought to represent the “active principles”. At least these studies might come closer to melilot than those dealing with coumarin as a single ingredient.

Coumarin

Because of a large volume of investigations, old and newer, this chapter is based on mostly secondary sources (see reviews of Egan et al. 1990: O’Kennedy and Thornes 1997). Coumarin and its principal

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5 Not required as per Article 16c(1)(a)(ii) of Directive 2001/83/EC as amended
metabolite 7-hydroxycoumarin have been studied in a large number of experimental systems and numerous effects on many functions have been observed (see table 2).

Table 2. Some pharmacological properties of coumarin and 7-hydroxycoumarin in in vitro, cellular and animal investigations (see O’Kennedy and Thornes 1997)

<table>
<thead>
<tr>
<th>Action</th>
<th>Implicated mechanism(s) of action based on preclinical investigations</th>
<th>Effective concentrations</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-oedematous action</td>
<td>increased proteolysis by macrophages; lymphokinetic properties</td>
<td>minimally effective about 150 uM up to 1 mM</td>
<td>Casley-Smith’s in op.cit.</td>
</tr>
<tr>
<td>Immunomodulatory action</td>
<td>effects on monocytes and macrophages</td>
<td>about 50 uM</td>
<td>Zlabinger in op.cit.</td>
</tr>
<tr>
<td>Cellular signaling</td>
<td>gap junction communication; migration</td>
<td>about 500 uM</td>
<td>Zänker in op.cit.</td>
</tr>
<tr>
<td>analgesic and anti-inflammatory action</td>
<td>prostaglandin and leukotriene production</td>
<td>very high</td>
<td>see Weinmann in op.cit.</td>
</tr>
<tr>
<td>Vasodilator activity</td>
<td>haemorheological properties</td>
<td>not known</td>
<td>see Weinmann in op.cit.</td>
</tr>
<tr>
<td>endothelial protection</td>
<td>no information</td>
<td>not known</td>
<td>see Weinmann in op.cit.</td>
</tr>
<tr>
<td>choleretic action</td>
<td>no information</td>
<td>not known</td>
<td>see Weinmann in op.cit.</td>
</tr>
<tr>
<td>Diuretic action</td>
<td>no information</td>
<td>not known</td>
<td>see Weinmann in op.cit.</td>
</tr>
<tr>
<td>spasmodyltic action</td>
<td>no information</td>
<td>not known</td>
<td>see Weinmann in op.cit.</td>
</tr>
<tr>
<td>sedative and hypnotic</td>
<td>no information</td>
<td>not known</td>
<td>see Weinmann in op.cit.</td>
</tr>
<tr>
<td>antimicrobial activity</td>
<td>no information</td>
<td>not known</td>
<td>see Weinmann in op.cit.</td>
</tr>
</tbody>
</table>

Assessor’s overall conclusions on pharmacology

Although numerous pharmacological effects on various cellular and tissue function have been unraveled in in vitro, cellular or animal experiments, concentrations in these studies have been rather high, from tens to hundreds of micromolar (see table 2), which makes it questionable whether many of these actions could be demonstrated in in vivo situations. The best studied and documented effect both in vitro and in vivo seems to be the anti-oedematous action, which could be used as a basis of traditional medicinal use.

2.6.2 PHARMACOKINETIC PROPERTIES

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

Melilot

There are no data on pharmacokinetic properties of melilot as a mono preparation. A combination product of coumarin and rutin (Venalot®) has been used in pharmacokinetic studies in humans, but only the kinetic behaviour of coumarin has been studied.

Coumarin

Pharmacokinetics of coumarin has been very thoroughly characterized since 1960’s and 1970’s and several reviews have been published on different aspects of coumarin pharmacokinetics (Pelkonen et al. 1997; Raunio et al. 2001). Coumarin and its principal hydroxylated metabolite (in primates) 7-hydroxycoumarin
are relatively lipid soluble and they are rapidly absorbed from intestine. However, 7-hydroxycoumarin is readily glucuronidated, probably already in the gut if appropriate UGT isoenzymes are present there and finally in the liver. Thus, its first-pass metabolism is quick and extensive in most species. Bioavailability of coumarin is dependent on the activity of 7-hydroxylation pathway in a given species. If this pathway is very active in the liver (as in man or other primates), very little or no unchanged coumarin passes into the systemic circulation. Readily detectable metabolites in blood in those species are free and conjugated 7-hydroxycoumarin. If this pathway is relatively minor, as it is in rats, the half-life of coumarin is greatly increased to even 1 to 2 days. On this basis of an extensive first-pass metabolism of coumarin to 7-hydroxycoumarin in humans, it has been claimed that 7-hydroxycoumarin is actually the active principle of coumarin therapy.

Metabolism of coumarin has been extensively studied since the 1960s. Coumarin undergoes a very extensive metabolism along two major pathways, 7-hydroxylation and 3-hydroxylation (3,4-epoxidation) followed by ring-opening to ortho-hydroxyphenylacetaldehyde (Cohen 1979; Pelkonen et al 1997). There are numerous minor metabolites, many of which are secondary products from the primary metabolites. The relative contribution of these two major pathways, which are catalysed by different P450 enzymes, is highly variable between species. Ring-opening predominates in rodents, while 7-hydroxylation is particularly evident in humans. Ring-opening proceeds via an epoxide intermediate, which is thought to be a necessary prerequisite for toxic effects. However, species differences in toxicity are thought to be due to differences in the detoxification of the reactive intermediate. Thus, recent findings indicate that probably it is not the formation of the reactive epoxide per se, which is of importance for hepatotoxicity, but the inactivation of the epoxide via acetaldehyde dehydrogenase (Vasallo et al. 2004). Consequently the final toxicity outcome is dependent on a complex balance between the formation of the epoxide metabolite and the activity of detoxifying enzymes.

Both in vitro and in vivo human studies have shown that coumarin is very specifically metabolized by CYP2A6, and coumarin is thus used as a preferred in vivo probe drug for phenotyping for CYP2A6 (Pelkonen et al 2000). Because CYP2A6 is an inducible P450 enzyme and it is affected by a number of exogenous and host factors, the elimination of coumarin is expected to be affected accordingly (Pelkonen et al, 2000).

Several herbal compounds have been tested for their inhibitory effects on the CYP2A6 enzyme in vitro. Compounds that have been found to be relatively potent, although not necessarily highly selective CYP2A6 inhibitors include methoxsalen (8-methoxypsoralen), menthofuran and pilocarpine (Pelkonen et al. 2000). Of these inhibitors, methoxsalen can be used to suppress CYP2A6 function in vivo.

The frequency of CYP2A6 poor metabolizer phenotype due to a complete loss of functional enzyme in the Caucasian population is <1%. The frequency is much more common in Orientals, up to 25% of the Japanese, Korean or Chinese population (Nakajima et al 2006). More than 20 variant alleles of the CYP2A6 gene have been characterized, including SNPs and whole gene deletion, with variable effects on enzyme activity (http://www.cypalleles.ki.se/).

Recent studies have shown that the pharmacokinetics of coumarin is altered in individuals carrying the variant CYP2A6 alleles (Nakajima et al. 2006). In vitro studies with human liver microsomes have indicated that the coumarin 7-hydroxylation is practically absent in individuals with deletion or defective genotypes. Other metabolic pathways such as 3-hydroxylation and ring-opening are still present, but the global metabolism of coumarin and pharmacokinetic characteristics in individuals homozygous for a CYP2A6 gene deficiencies have not yet been investigated.

Assessor’s overall conclusions on pharmacokinetics

In humans, a relatively thorough knowledge of coumarin pharmacokinetics and the enzyme determining the elimination has been worked out. Coumarin elimination is affected significantly by inducers, inhibitors and genetic factors controlling the activity of CYP2A6, but it is not known whether any clinically or toxicologically significant outcomes from coumarin elimination would ensue. The role of CYP2A6 poor metabolizer status in coumarin hepatotoxicity is purely conjectural thus far. Because the coumarin content of Melilot preparations is rather small, clinically significant consequences are unlikely.
2.6.3 PHARMACODYNAMIC PROPERTIES

Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

There are just a few pharmacodynamic studies conducted with extracts of melilot in combination with ruscus or vitamins. In most of the publications the pharmacodynamic effects of benzopyrones or coumarin (5,6-benzo—alpha-pyrene) are reported.

In part of the studies Esberiven® ampoules were investigated. In “older” trials Esberiven® ampoules are defined as a combination of melilot extract and “vitamin P”. In more recent studies the declaration was changed from “vitamin P” to “rutin”. The term “vitamin P” does not comply with accepted terminology. It is not clear if this change is just a change in declaration or a change in composition. Therefore the term “vitamin P” is kept in quotation marks where applicable.

Melilot extracts in combinations

In a randomized, placebo-controlled, double-blind study in cross-over design the effects of a single application of 11.5 g cream containing 184 mg melilot extract and 184 mg ruscus-extract on transcutaneous vеноconstriction and oedema protection in 20 healthy male volunteers was investigated by measuring the venous capacity and filtration rate using the venous occlusion plethysmography. A specification of the extracts is not given. During the 2-hours registration period venous capacity and filtration rate were reduced about 20% by the active cream, whereas under placebo the parameters slightly increased (approx. 5%). The difference was statistically significant. Similar effects could be seen as a trend in the untreated leg (Rudofsky 1989). The contribution of melilot to the observed effect cannot be assessed.

Mayer and Sukthaworn (1963). tested the influence of 8 – 10 ml of an melilot extract (extract with water, standardized on coumarin) or Esberiven ampoules (melilot extract with water, standardized on 0.1 % coumarin, “vitamin P”) or an melilot extract with water, standardized on 0.1 % coumarin, combined with “vitamin P” and B1, on circulation in the lower extremities of injured patients. All preparations are reported to improve circulation determined by a quotient of two values of “decholin time” obtained by measurements in the elbow and in the foot following i.v. application. Additionally a coagulation analysis was done and showed no signs of coagulotropic effects (Mayer and Sukthaworn, 1963).

Völkner studied the influence of an injection of 2 ml Esberiven (melilot extract with water, standardized on 0.1 % coumarin, “vitamin P”) on cardiac and circulation performance in 18 volunteers. He noticed an increase of ventricular end-diastolic volume and a decrease of tonicity in peripheral veins; blood pressure and heart rate remained unchanged. The changes were within the standard deviation of the method of measurement. The author concludes that melilot does not primarily influence cardiac performance but the peripheral circulation with secondary adaptation of cardiac performance. The i.v. administration was well tolerated, in single cases a short-term feeling of warmth was noticed. Additionally the influence of the melilot preparation on clotting of the blood was measured and no influence on parameters of blood clotting was seen (Völker 1961).

Venalot (melilot extract with water standardized to 3 mg coumarin, 50 mg rutin) or rutin were administered endolymphatically, i.v., and by i.v.-infusion to 390 patients and examined pharmacolymphographically (dosage not given). The “lymphotropic” effects of the drugs in lymphogram were compared with a control group of 100 patients. Both drugs improved representation of peripheral lymphatic drugs and of central lymph nodes and improved the diagnostic statement. The authors mention that an “essential increase of the complication rate” was not seen; details are not given (Schmidt and Keilacker 1985).

Seidel investigated the effects of “Venalot”(composition and dosage not given) or benzaron therapy during 6 weeks on lipometabolism of 41 patients. Distribution of lipometabolic parameters corresponded with the ones of the normal population. “Venalot” showed no effect on lipometabolism (Seidel 1985).
Blätter and Schoch (1994) tested six herbal drug preparations used in phlebology (e.g. “Venalot”, may be ampuoles= melilot extract with water standardized to 3 mg coumarin, 50 mg rutin?) and extracts of hop and valerian for neuronal and mitochondrial benzodiazepine receptor binding activity in vitro. All phlebotropic drug preparations interacted weakly with central and/or peripheral benzodiazepine receptors in vitro. Their diazepam-equivalent concentrations were, however, too low to be of pharmacological relevance. No binding activity was recovered in the blood of volunteers pretreated with phlebotropic drugs. The authors concluded that the positive influence of the tested phlebotropic drugs on the subjective symptoms of venous disease is not mediated through benzodiazepine receptors.

**Coumarin**

The reducing effect of benzopyrones on high protein oedemas was in extenso investigated by Casley-Smith, Piller and Földi (e.g. Piller 1976); Casley-Smith: (1982); Casley-Smith 1976; Földi-Böresök, Bedall and Rahlfs 1971).

**Assessor’s overall conclusions on pharmacodynamics**

There are no data on pharmacodynamic properties of melilot as a mono preparation. Except for the study of Rudofsky (1989) the pharmacodynamic trials with melilot extracts in combination are of poor quality. Additionally the relevance of studies where coumarin alone or coumarin combined with rutosid was investigated for the assessment of the pharmacodynamic profile of melilot can not be assessed. The contribution of melilot to the effects of combinations can also not be assessed.

### 2.6.4 CLINICAL EFFICACY STUDIES

Part of the following trials deal with coumarin in combination with other substances. Under the trademarks „Esberiven®“ and „Venalot®“ composition is depending on the pharmaceutical form, e.g. some pharmaceutical forms contain „melilot extracts“ while others contain „coumarin“. From the literature it is not always clear which pharmaceutical form / composition was investigated. Additionally in some publications observed results are not differentiated between the varying pharmaceutical forms. For the reason of safety these data are assessed here too.

#### 2.6.4.1 Dose response studies

There are no dose-finding studies available.

#### 2.6.4.2 Clinical studies (case studies and clinical trials)

**Venous insufficiency**

With a prevalence of 10-15% in men and up to 25% in women, chronic venous insufficiency (CVI) is one of the most common conditions afflicting humans. The standard treatment for CVI is compression therapy, but compliance is often poor. Therefore, amongst the therapeutic approaches available phlebotropic drugs are proposed to treat signs and symptoms of CVI and to prevent worsening of the disease.

**Melilot mono preparations**

In an open study patients suffering from chronic venous insufficiency 20 were treated with 200 mg dry extract of melilot daily (no specification given), another 15 by ozontherapy and 20 with combined therapy for 15 days. Melilot therapy significantly reduced malleolar oedema, nocturnal cramps and feelings of heaviness and was superior to ozontherapy. An influence on the symptoms “pain”, “paraesthesia” and “hyperthermia” was not seen. Details regarding the extent of the observed effects are not given. Ozontherapy is not an accepted “gold standard”. The clinical relevance of the observed effects is doubtful (Stefanini et al 1996).

Aloisi and Scanditto (1999) treated 4536 patients suffering from chronic venous insufficiency of various causes with 4 to 8 g of a melilot extract standardized to 20 % coumarin daily for 3 to 8 months in the years 1995 to 1998. Subjective symptoms, e.g. feeling of heavy legs, pain, nocturnal cramps, oedema and pruritus, as well as assessment of oedema were assessed on a 3 level symptom score. Details regarding the extent of the observed effects are not given. Good results were seen in 70 % of the patients. The symptom score is not
validated. An objective measurement of efficacy is missing. Side effects, predominantly gastrointestinal complaints, were seen in 55 patients (1.2%). Allergic reactions occurred in 12 patients (0.25%) (Aloisi and Scondotto 1999).

Melilot extracts in combinations

30 patients with venous insufficiency were treated with Esberiven drinking ampoules (1 ml contains 0.100 g melilot extract, 0.025 g rutin, 0.0265 ml alcohol 95 %) 9 to 12 times a day for 10 to 20 days. In 23 of these cases compression therapy and/or others (no details given) was added. Based on the symptoms feeling of heavy legs, pain, oedema and pruritus efficacy was judged good or very good in 24 of 29 cases. Oedema disappeared or improved in 27 from 28 patients and in 7 from 7 patients treated with melilot only. Pain (feeling of heavy legs / pruritus) disappeared or improved in 21 (25 / 6) from 22 (25 / 7) patients and in all patients (n= 3 / 7 / 1) treated with melilot only. Details regarding the extent of the observed effects are not given. An objective measurement of efficacy is not mentioned. The preparation was well tolerated in 29 patients. Vomiting was observed in 1 patient who was excluded from efficacy assessment. Only a very small number of patients were treated with melilot only. It is not possible to assess the contribution of melilot on treatment effects of the combination with compression therapy and/or others (Babilliot 1977 ; Desmons and Simons 1975).

In another double-blind study 44 patients with chronic venous insufficiency were treated with a compression bandage in the first 4 weeks followed by 10 Venalot injections of 10 ml (15 mg coumarin, 250 mg rutosid) versus a control solution of weak concentration (2 mg coumarin, 100 mg rutosid) during 3 weeks. Compression stockings were stopped and Venalot depot coated tablets or placebo tablets were taken 3 times a day in the following 3 weeks. At the end of the trial the therapeutic results of the verum group, e.g. reduction of oedema and refilling time in phlebodynamometry as well as physicians assessment, were more pronounced than in the control group. Details on symptoms are not given. The author states that, however, higher case rates will be needed to prove efficacy (Blume 1994).

1458 patients with various venous diseases were treated with a combination of a melilot extract, standardized to 0.05% coumarin, and 50 mg “vitamin P” administered 10 to 60 times i.m. or orally (dosage not given). The overall therapeutic results were given as “satisfactory”. Details on symptoms are not given. An objective measurement of efficacy is not mentioned (Klein 1967).

24 patients with varicosis with the symptoms cramps in the calf at night time and pretibial oedemas were treated with Esberiven (melilot extracts standardized on 0.1 % coumarin, “vitamin P” and B1 (coated tablets only) orally or rectally or in severe cases at the beginning intravenously for at least 4 weeks. A decrease in cramps was seen by 20 patients and oedemas were reduced (quantity not given). An objective measurement of efficacy is not mentioned. The author mentioned that in some patients with Brachalgia paraesthetica nocturna an improvement of symptoms after oral treatment could be seen. Treatment of leg ulcer with oral and topical Esberiven preparations was not always successful (Völker 1961).

For prevention of thrombosis 75 patients were treated with Esberiven ampoules: 6 to 8 drinking ampoules (1 ml contains 0.100 g melilot extract, 0.025 g rutin, 0.0265 ml alcohol 95 %) or 3 injections per day (2 ml contain melilot extract standardized to 1 mg coumarin, 50 mg rutin) up to 3 days after operations of various causes. In three cases an anticoagulant had to be added. The preparation in both dosage forms was well tolerated. Details on symptoms are not given. (Descottes 1975).

Lacativa reports of the therapeutic use of Venalot administered orally, i.m. or i.v. in 7900 patients with various indications like venous insufficiency, lymphatic oedemas, thrombosis, post operations, hematoma, leg ulcer, restless legs, hemi- and paraplegia. Patients with a weight greater than 50 kg were treated with 3-4 coated tablets daily (1 coated tablet contains 15 mg coumarin, 90 mg troxerutin) in the beginning. Dosage was decreased continuously up to 3 coated tablets a week for 6 month. Patients with severe thrombosis were treated with 1 ampoule i.v. per day (1 ampoule 2 ml/5 ml: 10 mg /25 mg melilot extract with water standardized to 3 mg / 7.5 mg coumarin, 50 mg/ 125 mg rutin). To avoid local irritation of the veins the ampoules were diluted with 0.9 % NaCl. An objective measurement of efficacy is not mentioned. Details on symptoms are not given. Treatment was well tolerated. Approx. 1 % of the patients reported gastrointestinal adverse events and approx. 1 % weak allergic reactions and photosensitivity (Lacativa 1980).

Coumarin in combination with other substances
In a randomized placebo controlled trial 231 patients suffering from chronic venous insufficiency were treated with medical compression stockings and 90 mg coumarin and 540 mg troxerutin per day or medical compression stockings and placebo for the first 4 weeks. Compression stockings were stopped and the coumarin-troxerutin combination tablets or placebo tablets were taken for the following 12 weeks. The primary efficacy endpoint was the lower leg volume measured by water plethysmometry. 226 patients were evaluated. Lower leg volume decreased in both medication groups under compression therapy. After ceasing compression therapy an oedema protective effect was seen under verum by a recurrence of leg volume increase of $6.5 \pm 12.1$ ml versus $36.7 \pm 12.1$ ml under placebo. However, the difference between verum and placebo has no clinical relevance (Vanscheidt et al 2002).

In a six-week double blind study 41 patients with chronic venous insufficiency with and without leg ulcer were treated with daily 3 x 2 coated tablets Venalot depot (1 coated tablet contains 15 mg coumarin, 90 mg troxerutin) or benzaron for 6 weeks. Difference of circumference at noon, circumference of leg ulcer, phlebometric measurements and subjective criteria like pain, nocturnal cramps, feeling of heavy legs were evaluated at the beginning, after 2 and 6 weeks. In both treatment groups a statistically relevant decrease in objective and subjective parameters was seen. The question of clinical relevance of the observed effects is not discussed (Bosse, Drieschner and Klose 1985).

In an open clinical trial 200 patients with venous insufficiency were treated with 3 x 1 coated tablet Venalot depot (a 15 mg coumarin, 90 mg troxerutin) or 3 x 1 capsule Calcium dobesilate (a 500 mg). Both medications improved the subjective symptoms. The combination of coumarin and troxerutin appeared to be superior to calcium dobesilate regarding overall efficacy and the symptom heaviness of legs. 15 patients reported side-effects, mainly gastro-intestinal symptoms and 1 case of generalized itching (Berson and Geiser 1980).

**Conclusion**

Due to the lack of an acceptable control group and of objective measurement of efficacy the 2 clinical studies investigating the effects of melilot as a single preparation are not sufficient to show efficacy in the treatment of symptoms of venous insufficiency. Clinical studies with melilot extracts in combinations, mostly with flavonoids, are also of poor quality. In clinical trials with coumarin in combination with other substances using objective measurements of efficacy the observed effects had no clinical relevance. Overall the data are not sufficient to show efficacy of melilot in a well-established use. However, the data can be accepted for establishing “plausibility” of the traditional use.

**Haemorrhoidal conditions**

Melilot mono preparations
No data available.

Melilot extracts in combinations

50 patients with haemorrhoidal conditions were treated with 6 to 8 Esberiven drinking ampoules (melilot extract, rutin) per day (40 cases) or in combination with other local or surgical treatment (10 cases) for 10 to 28 days. Symptoms like anal pain and pruritus disappeared in most of the cases. The treatment was generally well tolerated. The following side effects are given: 3 x bad taste, 1 x epigastric discomfort, 1 x head ache, 1 x decrease of libido. An objective measurement of efficacy is missing. It is not possible to assess the contribution of melilot on treatment effects (Mot 1976).

**Conclusion**

Due to the lack of data to melilot as a mono preparation and only insufficient data to a combination the data is not sufficient to show efficacy of melilot in haemorrhoidal conditions. Additionally there is no traditional use of melilot as a single substance documented in this indication.

**Lymphoedema**

Melilot mono preparations

In an open clinical trial 20 patients with lymphoedema of the lower limbs, stage I-II, were treated with 200 mg melilot extract (no specification given) daily in combination with compression therapy for 6 months.
A clinical score for assessment of subjective symptoms, e.g. pain and tension, and objective measurements, e.g. circumference/ultrasonography were assessed at the beginning and after 90 and 180 days of treatment. An improvement of all variables was seen. It is not possible to assess the contribution of melilot on treatment effects (Martignani et al. 1997).

In an open clinical trial 25 women with lymphoedema of the upper limbs due to axillary lymphadenectomy for breast cancer were treated with 20 mg melilot extract standardized to 20% coumarin (daily dose equivalent to 4 mg of coumarin, no further specification given) for 12 weeks. Circumferences of the diseased and the contra lateral arm were measured at the level of the armpit, arm, elbow, forearm, wrist and hand, before and after 6 and 12 weeks of treatment. A statistically significant decrease in limb volume at all levels (approx. 0.5 to 1 cm) was seen at week 6 and 12. The reductions of up to 11 cm shown in figures 1 and 2 are not in line with the data shown in tables I and II. The clinical relevance of the findings is not discussed. Adverse events were not reported (Muraca and Baroncelli 1999).

Melilot extract combinations

In an open clinical trial 21 women with chronic lymphoedema of the upper limbs due to axillary lymphadenectomy for breast cancer were included. According to the English abstract a melilot monopreparation was given but according to the data under “Pazienti e Metodi” a combination product was investigated. Of these patients 14 were treated with 2 capsules of a combination of melilot dry extract and rutin once a day (daily dose: 400 mg melilot dry extract standardized to 20% coumarin -> equivalent to 8 mg of coumarin, no further specification given, declaration does not seem to be correct; 60 mg rutin) for 6 months, 4 patients were controls (no treatment?). 3 patients were lost to follow up; it is not mentioned, which treatment they received. Circumferences of the diseased arm and the contra lateral arm were measured at 5 defined points before and after 3 and 6 months of treatment and a symptom-related questionnaire for self-evaluation was taken at every clinical control (name of questionnaire not mentioned, validated?). From these 14 patients the median reduction in upper arm circumference was about 5% compared to initial values; however, looking at the individual data only 1 patient showed a relevant reduction of circumferences (20%), 10 had only minimal changes and 3 showed no change. Lymphoedema of the 4 controls worsened during that time (Pastura et al., 1999).

In a randomized study the effect of Venalot intravenously (5 ml contain 25 mg melilot extract with water standardized to 7.5 mg g coumarin, 125 mg rutin) compared to standard treatment without Venalot for the prophylaxis of oedema following gastric operations (e.g. Billroth I / II) was investigated. From the patients surviving the operation all 25 patients in the Venalot group were able to eat on their own latest on day 5 whereas in the control group only 15 from 21 where able to do so. The author concludes that the medication positively influences the function of the gastric anastomosis by reducing the volume of oedema (Kriz 1978).

In another randomized investigation 24 patients with an acute hemorrhagic-necrotic pancreatitis were treated with 10 ml Venalot intravenously 3 times daily or aprotinin (starting dose 500.000 unit followed by 2.000.000 unit daily) for 10 days combined with standard treatment for the prophylaxis of oedema following pancreatic operation. All patients survived in the Venalot group, 4 died in the aprotinin group. The stay in hospital was shorter in the Venalot group (24 days versus 34.5 days) (Vida 1977).

In an open study 30 women with lymphoedema due to mastectomy and radiation were treated in the beginning with 2 ml Venalot intravenously per day (10 mg melilot extract with water standardized to 3 mg g coumarin, 50 mg rutin) for 10 days followed by 2 x 2 coated tablets (15 mg Coumarin, 90 mg troxerutin) orally. A decrease in the circumference of the arm was seen in 14 women; in 7 patients no effect and in 9 an increase of circumference was seen (El-Shammah 1976).

Coumarin and combinations with other substances

Casley-Smith et al reported that coumarin was effective in reducing the volume of oedema fluid and lowering skin temperature in 31 women with postmastectomy lymphoedema of the arm and 21 men and women with lymphoedema of the leg of various causes (Casley-Smith, Morgan and Piller (1993). Similar findings were reported by Eggert on 17 women with postmastectomy lymphedema (Eggert et al., 1977).
In contrast to these findings Loprinzi did not find that coumarin had any benefit in reducing arm volume or treating symptoms or that the frequency of infections was similar during coumarin and placebo. In his prospective, double-blind, randomized, crossover design study he investigated the effects of 2 x 200 mg oral coumarin or placebo for six months followed by 6 months of the other therapy in 140 women with unilateral lymphoedema attributed to earlier local or regional treatment of breast cancer on the average volume of the affected arm. The outcome of treatment was evaluated by detailed measurements of arm volume and a questionnaire completed by each patient. Coumarin was well tolerated, except that it resulted in serologic evidence of liver toxicity in 6% of the women (Loprinzi et al., 1999; Ganz 1999).

In a randomized double-blind study 3 x 2 Venalot retard coated tablets (15 mg Coumarin, 90 mg troxerutin) and suppositories (30 mg coumarin, 180 mg troxerutin) per day were tested against placebo regarding reduction of the postreconstructive oedema of the lower extremities in 56 patients. A statistically significant reduction of the postreconstructive oedema in the verum group could only be seen in the subgroup with a very distinct oedema (femoropopliteal bypass) (Becker, Niedermaier and Orend 1985).

In a prospective and double-blind investigation 134 women receiving an episiotomy after otherwise normal deliveries were treated with 3 x 1 coated tablet Venalot depot (15 mg coumarin, 90 mg troxerutin) or placebo for 7 days post partum. Significantly less local oedema was found in the verum group but no effects were observed on the patient’s subjective complaints (Pedersen AKO, Kristensen OK, Gram-Hansen J 1982). In a double-blind study the effects of the above mentioned combination in 3 different dose levels (2 x 1, 2 x 2, 3 x 2 coated tablets), its active components separately and of placebo in 560 women following medio-lateral episiotomy were investigated. The efficacy of the combination on oedema, rubor around the incision wound, posttraumatic pain as well as consumption of analgesics was superior to the components applied separately (Pethö 1981).

In a double-blind trial the effect of Venalot depot coated tablets (1 coated tablet contains 15 mg coumarin, 90 mg troxerutin) or placebo for the prophylaxis of oedema following operation for phimosis was investigated. Medication started with 2 x 2 tablets the day prior operation followed by 3 x 2 coated tablets for 7 days; for patients under the age of 15 dosage was reduced to 1 tablet 3 times a day. Significantly less oedema under verum was observed on the first postoperative day but no difference was seen on the seventh postoperative day. No differences in the amount of pain and discomfort were recorded and no side-effects nor changes in blood chemistry were observed (Nielsen and Rokkjaer 1980).

148 patients with euthyroid endocrine ophthalmopathy were treated with 4 different therapies: 1. levothyroxine alone, or 2. levothyroxine and prednisone, or 3. levothyroxine, prednisone and retrobulbar X-radiation, or 4. levothyroxine, prednisone, retrobulbar X-radiation and Venalot Depot (15 mg Coumarin, 90 mg troxerutin) assuming that endocrine eye symptoms are manifestations of local myxoeedema. No single drug was found to be superior to any of the others (Horster and Wildmeister 1983).

Bider et al. report shortly of favourable results on the use of 3 x 2 coated tablets Venalot depot per os (1 coated tablet contains 15 mg coumarin, 90 mg troxerutin) in the treatment of traumatic and postoperative hemophalmia, retinal hemorrhage and turbidity of the vitreous body (Bider et al., 1975).

In a prospective, randomized, placebo-controlled, double-blind study the effects of a coumarin /troxerutine combination (Venalot depot) for protection of salivary glands during a head and neck irradiation on 48 radiotherapy patients (60 Gy) with head and neck cancer were investigated. During radiotherapy the salivary glands were located in the core irradiation field. Primary efficacy parameters were sialometry, quantitative salivary gland scintigraphy and clinical evaluation of early effects of radiotherapy (RTOC-score). All data were assessed at 6 visits starting 1 week pre-radiation, at start, half-time and end of irradiation, and 8 and 28 days after the end of irradiation. Early clinical effects of irradiation (RTOG-score) were less pronounced in the active treatment group than under placebo, but the sample size was too low to show statistically significant differences with the szintigraphic method. In the authors opinion sialometry seems not suitable for the assessment of early radiation effects (Grötz et al., 1999).

Conclusion
The clinical data on treatment of lymphoedema from various causes show inconsistent effects of melilot preparations or combination products. Even if statistically significant reductions of lymphoedema were seen in some of the studies the clinical relevance of the observed effects is missing. Therefore the data are not
sufficient to show efficacy in a well-established use. The indication is not acceptable for a traditional use as medical intervention is always required.

**Blunt Traumata**

Melilot monopreparations
No data available.

Melilot extracts in combinations
In a randomized and double-blind investigation 48 patients with distorsions and contusions of the lower leg or feet were treated with 4 g Phlebodril ointment (100 g contains 1.6 g ethanolic dry extract of ruscus standardized on 25 mg ruscogenin, 1.6 g ethanolic liquid extract of melilot standardized on 0.32 mg coumarin) or placebo three times daily for a period of 14 days. Concomitant analgetic or antiphlogistic medication and physical therapy was not allowed. Difference of circumference, skin temperature, painless muscle force between injured and healthy leg and changes of pain symptomatics (pain at rest, pain in motion, pain on tension) on days 3 to 5 and 14 were taken as target criterion. During treatment symptoms decreased in both groups but faster in the verum group. It is not possible to assess the contribution of melilot on treatment effects (Böhmer and Ambrus 1989; 1990; N.N 1990).

Coumarin in combination with other substances
174 patients with sprained ankles attending a casualty department were treated with Venalot depot coated tablets (15 mg coumarin, 90 mg troxerutin) or placebo in varying doses. In addition, rapid mobilisation was recommended. Regarding to swelling, pain on weight-bearing, sensation of instability and days of sick-leave no effect could be demonstrated. The incidence of side-effects was low (Jensen, Jensen 1980).

Conclusion
There are no data for melilot as a single preparation in external treatment of blunt traumata. Data from a randomized, double blind and placebo controlled trial of a combination of extracts of ruscus and melilot give some evidence of efficacy of the combination studied but it is not possible to assess the contribution of melilot on treatment effects. Therefore the data are not sufficient to show efficacy in a well-established use. As traditional external use of melilot on bruises and sprains is well documented and plausible from pharmacological data a traditional indication is acceptable.

**Mastalgia**

Melilot monopreparations
In an open clinical trial 50 patients with cyclic or non-cyclic mastalgia were treated daily with a melilot extract for oral use (no specification given, no dosage given) for 2 periods of months with an interval of 1 month. After 6 months efficacy was assessed by clinical examination and a compilation of a symptom-related questionnaire for self-evaluation (name of questionnaire not mentioned, validation of the questionnaire is questionable). Measurement of efficacy remains unclear and can’t be assessed. 31 patients were evaluable for response; 43 for safety assessment. It is not clear from the paper why 19 patients were not assessed for efficacy (drop out due to lack of efficacy may have occurred) In 23 of the cases melilot was effective, 8 had no benefit from the treatment. Side effects are not mentioned (Mazzocchi et al.,1997).

Melilot extracts in combinations
In an open clinical trial 20 patients with mastalgia were treated with 5 drinking ampoules Esberiven (1 ml contains 0.100 g melilot extract, 0.025 g rutin, 0.0265 ml alcohol 95 %) daily on days 15 to 25 of menstruation cycle for 3 months. Overall good therapeutic results were seen in 15 patients, side effects were not seen (Giraud 1984).
In two overviews the use of angiotonic drugs, e.g. Esberiven, in the treatment of fibrocystic mastopathy or mastodynia is shortly mentioned. Details are not given (Gorins 1994; et al., 1993).

Conclusion
Due to the lack of controlled studies and objective measurements of efficacy the data is not sufficient to show efficacy of melilot in mastalgia. Additionally there is no traditional use of Melilot documented in this indication.

**Others**

**Melilot extracts in combinations**

In an open study 25 patients with rosacea were treated with a cream containing extracts of melilot (2%, no specification of extracts given) and ruscus aculeatus (8%) twice daily for 3 months. In each patient telangiectasias were studied by optic videocapillaroscopy (number of venous ansas by field, diameter of ansas) and the intensity of erythema by colometry was assessed at the beginning, every two weeks during treatment and at the end of treatment. During treatment a gradual and continuous improvement of telangiectasias (number and diameter) and erythema was observed, while papules and pustules remained unchanged. After an 8-month follow-up slight relapses of erythema and telangiectasias were observed. The author states that topical treatment with melilot extract cream can give a reduction of vassal lesions of rosacea. Side effects were not observed (Iurassich, Bianco and Pascarella 1999).

Older literature gives a short overview about medical use of medicinal products containing melilot extracts standardized on 0.1 % coumarin, vitamin P and B1 for oral use in solid and liquid dosage forms, creams and suppositories for melilot in patients with various indications like thrombosis, venous insufficiency, haemorrhoids, haematomas, arthritis, apoplex, heart attack, endangitis obliterans, bursitis and tendovaginitis. Duration of treatment varied from 10 up to 240 days. 2 patients reported gastric complaints. An objective measurement of efficacy is missing in all given indications (von Blumröder 1960; Becker 1956).

An overview about the therapeutic use of Esberiven drinking ampoules in gynaecology is given by Cluzan and Kieffer (1979). 308 women with dysmenorrhoea, pelvipathia, premenstrual syndrome, venous insufficiency, haemorrhoids and others were treated with 6 drinking ampoules (1 ml contains 0.100 g melilot extract, 0.025 g rutin, 0.0265 ml alcohol 95 %) per day or i.v. injections (2 ml contain melilot extract standardized to 1 mg coumarin, 50 mg rutin; dosage per day not given) from 3 weeks up to 2 months with good or excellent results in about 70% of the patients. An objective measurement of efficacy is missing in all given indications. Side effects were seen in 5 patients (1.6%).

According to an English abstract of a Japanese publication 55 patients with chronic prostatitis were given Esberiven (content, dosage form and dose not mentioned) with or without Cotrimoxazole daily for more than 8 weeks. Efficacy was evaluated by improvement of subjective symptoms and objective findings including transrectal ultrasonography and urodynamic measurements. An overall therapeutic effect of Esberiven alone was seen in 12 of 16 cases (75 %) in contrast to 35 from 39 cases (87 %) treated with the combination. Because detailed information is not included in the abstract an evaluation of the data is not possible (Akiyama et al., 1980).

**Conclusion**

The fragmentary data given in the overviews are not sufficient to show efficacy of melilot in the studied combinations in any of the mentioned indications. Additionally it is not possible to assess the contribution of melilot on the reported treatment effects.

**Clinical studies in special populations (such as elderly and children)**

**Use in children**

There are no clinical data for use of melilot in children.

**Conclusion**

According to the “NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION” (CPMP/ICH/2711/99) of 27 July 2000 and other monographs age limit for children should be determined to “adolescents over 18 years of age”.

**Use during pregnancy and lactation**

a) **Pregnancy**
Melilot extracts in combinations
Leng treated 25 pregnant women with venous insufficiency and thrombosis with Esberiven drinking ampoules and 5 patients post partum with Esberiven injections, i.m. 2 times daily, for 6 to 7 days. (melilot extracts standardized on 0.1 % coumarin, “vitamin P”). In 17 cases out of 25 pregnant women an improvement of symptoms was noticed, in 5 cases no change and in 3 cases the medication was judged to be ineffective. Tolerance was good in all cases. An objective measurement of efficacy is missing. Information about the delivered babies is lacking (Leng et al., 1974).

Oral use and topical application of melilot combinations in pregnancy is also mentioned by various authors (Lacativa 1980; N.N. 1990; Eyraud 1982; Tran 1981; Krajnovic 1977a). Detailed information, especially on the outcome of the delivered babies, is missing in these reports.

Coumarin combinations
10 healthy pregnant women were treated with 4 Venalot depot coated tablets (15 mg coumarin, 90 mg troxerutin) starting approx. 2 weeks before delivery to 4 days post partum. All women delivered without complications. Haemoglobin, bleeding time, thrombelastogram and prothrombin time of the women and their infants were within normal range before and after treatment (Krajnovic, Vranes and Djuric 1974).

b) Lactation
Melilot
There is no data available.

Coumarin combinations
The influence of daily 4 Venalot depot coated tablets (15 mg coumarin, 90 mg troxerutin) for 3 weeks on hematological parameters of 20 breastfeeding mothers and their infants was investigated. Erythrocytes, haemoglobin, thrombocytes, thrombelastogram, prothrombin time, blood-clotting and bleeding time were within normal range before and after treatment. (Krajnovic 1977a).

Assessor’s overall conclusions on clinical efficacy
There are just few clinical data for melilot or preparations thereof as a single ingredient. However, a wide use of melilot is documented in literature and there is some evidence of efficacy of some melilot containing combination products that have been evaluated in various indications. In the majority of the studies combinations of Meliloti herba with rutosid, troxerutin, extracts with Horse chest nut or Ruscus aculeatus and vitamins were investigated.

In most of the publications the declaration of the investigated medicinal products is incomplete or missing, e.g. the drug-extraction-ratio or the extraction solvent is not given. Usually the preparations were investigated in different dosage forms and several indications under “real life conditions” and not in a controlled clinical trial setting. In the majority of the studies an objective measurement of efficacy is missing or not mentioned.

Therefore, the published clinical studies available on melilot as a single preparation are not convincing and not sufficient to demonstrate a well-established use.

Due to the hepatotoxic potential of coumarin in daily doses from 30 mg to several grams the content of coumarin in melilot preparations should not exceed 5 mg coumarin per day. This limit takes into account additional exposure through food and the additional exposure to other cinnamic acid derivates that have not yet been fully investigated. Because pharmacodynamic effects have been described after topical use and because the systemic availability of coumarin after topical application has not been studied, the same limit is recommended for topical use. To minimize potential risks children and adolescents up to the age of 18 years as well as pregnant and breastfeeding women should not take melilot or preparations thereof.
<table>
<thead>
<tr>
<th>Member State</th>
<th>Medicinal product</th>
<th>Food supplement</th>
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<tbody>
<tr>
<td>Austria</td>
<td>Only in homeopathic</td>
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<tr>
<td>Belgium</td>
<td><strong>Melilotus officinalis:</strong></td>
<td></td>
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<tr>
<td></td>
<td><strong>Herbal substance</strong></td>
<td></td>
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<tr>
<td></td>
<td>o <strong>Pharmaceutical form:</strong> 2 teas</td>
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<tr>
<td></td>
<td>(combination products; registrations dating for the ’60s)</td>
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<tr>
<td></td>
<td>o <strong>Posology:</strong> containing 150mg/g and 0.08mg/g, respectively</td>
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<tr>
<td></td>
<td>o <strong>Indication:</strong> bronchopulmonary, stomach/biliary function, respectively</td>
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</tr>
<tr>
<td>Bulgaria</td>
<td>One medicinal product, containing Melilotus extract is on the Bulgarian market (<strong>Cyclo 3</strong>, cream, (Pierre Fabre Medicament). <strong>Herbal preparation:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>o <strong>Pharmaceutical form:</strong> cream</td>
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</tr>
<tr>
<td></td>
<td>o <strong>Composition:</strong> dry extract of the roots of <em>Ruscus aculeatus</em> and liquid extract of the herb of <em>Melilotus officinalis</em> .</td>
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<tr>
<td></td>
<td>o <strong>Posology:</strong></td>
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<tr>
<td></td>
<td>o <strong>Indication:</strong> for treatment of varicose veins (ATC: C05C “Capillary tonic preparations”)</td>
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<td>Denmark</td>
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<tr>
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<td>Finland</td>
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© EMEA 2008 28/38
<table>
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<th>France</th>
<th>France</th>
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</table>
| **Herbal substance:**  
4 products containing only melilot,  
12 products containing melilot and other herbals | No information |
| **Herbal preparation:**  
1 product containing only Melilotus,  
10 products containing Melilotus and other herbals | |
| *Pharmaceutical form:* capsule, hard, herbal tea, oral solution, oral suspension, coated tablet, eye drops and cream | |
| *Composition:* - | |
| *Indication:*  
**A) Oral use**  
- Traditionally used in symptomatic treatment of functional disorders of cutaneous capillary fragility, such as ecchymosis petechias, etc...  
- Traditionally used in subjective signs of venous insufficiency, such as heavy legs, in haemorrhoidal symptoms.  
- Traditionally used in the symptomatic treatment of digestive upsets such as epigastric distension, slow digestion, eructation, flatulence.  
- Traditionally used as an adjuvant treatment for painful component of functional digestive disorders.  
- Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.  
**B) Topical use**  
- Traditionally used in symptomatic treatment of functional disorders of cutaneous capillary fragility, such as ecchymosis petechias, etc...  
- Traditionally used in subjective signs of venous insufficiency, such as heavy legs.  
- Traditionally used in haemorrhoidal symptoms.  
- Traditionally used in cases of eye irritation or discomfort due to various causes (smoky atmospheres, sustained visual effort, swimming in the sea or swimming baths, etc...). |
<table>
<thead>
<tr>
<th>Country</th>
<th>Status</th>
<th>Description</th>
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</table>
| Germany | License | 5 medicinal products with a traditional indication according to § 109a AMG are licensed. Two of them are combinations with extracts of horse chestnut.  
*Pharmaceutical form*: capsules, tablets, solutions for oral use  
*Composition*: hydroethanolic or hydromethanolic dry or fluid extracts of the herb of *Melilotus officinalis*. DEV from 1:1 to 5:8  
*Posology*: The daily dosage contains 1 to a maximum of 5 mg Coumarins  
*Indication*: Traditionally used for relief of the feeling of heavy legs. |
| Hungary | License | There are two tea-mixtures on the market as paramedicines which contain Meliloti herba (*Melilotus officinalis*).  
*Pharmaceutical form*: herbal tea  
*Posology*: 200 or 700 mg Meliloti herba in one dose corresponding to about 5-19 mg coumarin/day.  
*Indication*: Helps to protect the liver against toxic materials. They can be used after hepatitis, or to complement the drug treatment. |
| Iceland | Not on the market | No information |
| Ireland | Not on the market | No information |
| Italy | Not on the market | *Herbal substance*: whole, leaves, apical flowers  
*Pharmaceutical form*: capsules, tablets, scirop, solutions, herbal tea for oral use  
*Composition*: hydroethanolic dry or fluid extracts of the herb of *Melilotus officinalis*.  
*Posology*: each product has a different posology (see attached list)  
*Indication*: *Melilotus* increases blood vessels permeability, therefore it can treat varicose veins and haemorrhoids. Use of the plant also helps to reduce the risk of phlebitis and thrombosis. The flowering plant is also used as antispasmodic, aromatic, carminative, diuretic, emollient, mildly expectorant and mildly sedative. In form of... |
infusion is used in the treatment of sleeplessness, nervous tension, neuralgia, palpitations, varicose veins, painful congestive menstruation, in the prevention of thrombosis, flatulence and intestinal disorders.

<table>
<thead>
<tr>
<th>Country</th>
<th>Information</th>
<th>No information</th>
</tr>
</thead>
</table>
| Latvia    | In Latvia Melilotus officinalis is authorized in 3 medicinal products for oral use. Species pro gynaecologicum morbum  
  o **Composition:** 11 medicinal plants, Melilotus 8%  
  o **Posology:** 1 tablespoon of mixture to glass of boiling water for infusion.  
  ½ glass of infusion twice daily: in the morning – before meal, in the evening – before bedtime.  
  o **Indication:** traditional medicinal tea on inflammation in gynecology.  
  Species anticlimactericae  
  o **Composition:** 14 medicinal plants, Melilotus 10%  
  o **Posology:** 1 tablespoon of mixture to glass of boiling water for infusion.  
  ½ glass of infusion twice daily: in the morning – before meal, in the evening – before bedtime.  
  o **Indication:** traditional medicinal tea to prevent climacteric symptoms.  
  Toning up tablets  
  o **Composition:**  
    - Flores Crataegi 150 mg  
    - Fructus Crataegi 30 mg  
    - Herba Leonuri 100 mg  
    - Herba Meliloti 40 mg  
  o **Posology:** 3 tablets a day  
  o **Indication:** Restorative on blood circulation. |                |
| Lithuania | No reply                                                                                                                                     |                |
| Luxembourg| There is 1 product registered in Luxembourg containing Melilotus (ARKOGELULES MELILOT 190mg capsules).  
  **Pharmaceutical form:** capsules for oral use  
  o **Composition:** -  
  o **Posology:** 3 capsules per day (1 in the morning, 1 at noon, 1 in the evening) together with the meal and 1 glass of water. Maximum 5 capsules per day. |                |
**Indication:** (French original text):"Traditionnellement utilisé dans le traitement symptomatique des troubles fonctionnels de la fragilité capillaire cutanée, tel que ecchymoses, pétéchies. Traditionnellement utilisé dans les manifestations subjectives de l'insuffisance veineuse telles que jambes lourdes et dans la symptomatologie hémorroidaire."

<table>
<thead>
<tr>
<th>Country</th>
<th>Status</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td>No reply</td>
<td>No information</td>
</tr>
<tr>
<td>Malta</td>
<td>Not on the market</td>
<td>No information</td>
</tr>
<tr>
<td>Poland</td>
<td>Meliloti Herba is described in Polish Pharmacopoeia (ed.VI). According to the pharmacopoeia it contain dried herb of Melilotus officinalis (L.) Desrousseaux or M. altissima Thuilier, (Leguminosae). Meliloti Herba can be distributed as pharmaceutical raw material for use in pharmacies. The common pharmacopoeial prescription is Emplastrum Meliloti described by Polish Pharmacopoeia V. It is traditionally used topically, in a form of poultice on furuncles as a medium improving lymph circulation in tissues surrounding. It is also used in oedemas after injuries. Emplastrum Meliloti can be also registered in Poland according to Regulation from 9.06.2003. All other products containing Meliloti Herba preparations have to be authorised. Pharmaceutical form: tablets and herbal tea for oral use, emplastrum and infusion for topical use. Composition: powdered drug for oral use; Meliloti emplastrum, according to last VI edition of Polish Pharmacopoeia is prepared by extraction of 10 parts of pulverized Meliloti herba, wetted with 2 parts of ethanol, to 90 parts of semi-solid base (Rapae oleum, Cera flava, Colophonium). Final DER in Meliloti emplastrum is (0,11:1). Posology: Infusions are prepared of 2,5 - 3 g of Meliloti herba in 200 - 300 ml of boiling water.</td>
<td>No information</td>
</tr>
</tbody>
</table>
- Oral use: traditionally as a component improving symptoms of chronic venous insufficiency and peripheral circulation insufficiency.
- Topical use: Emplastrum is used as facilitating of skin healing. Infusions of *Meliloti herba* are used traditionally externally, on skin, in a form of warm poultice (cataplasms) for purulent skin inflammations or furunculosis. Infusions were also used traditionally on eyelid inflammations (fresh prepared warm infusion on gauze swab) but this indication is under revision.

<table>
<thead>
<tr>
<th>Country</th>
<th>Information</th>
<th>Orthodox Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portugal</td>
<td>Not on the market</td>
<td>No information</td>
</tr>
<tr>
<td>Romania</td>
<td>No reply</td>
<td>No information</td>
</tr>
</tbody>
</table>
| Slovak Republic | *Pharmaceutical form*: granules, tablets, oral drops, oral solution, powder for oral use. Ointment and suppository for topical use.  
  o *Composition*: -  
  o *Posology*: depends on physician  
  o *Indication*: - | No information    |
| Slovenia      | In Slovenia the following medicinal product containing *Melilotus* is on the market:  
  o *Pharmaceutical form*: gel for cutaneous application  
  o *Composition*: 1 g gel contains 0.35 g of liquid extract of horse-chestnut seed (*Hippocastani seminis extractum fluidum*) (stand. to 10.5 mg of aescin) and 0.02 g of liquid extract of melilot (*Meliloti herbae extractum fluidum*) 1:1.  
  o *Posology*: cutaneous application more times daily  
  o *Indication*: symptomatic treatment of varicose veins | No information    |

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Spain  | We have one old herbal medicinal product "MELILOTO ARKOCAPSULAS" registered by ARKOCHIM.  
| o Pharmaceutical form: hard capsules  
| o Composition: 190 mg of powdered flowers of Melilotus officinalis L.  
| o Posology: 1-2 caps, 3 times a day  
| o Indication: Short-term relief of symptoms associated to chronic venous insufficiency.  

| Sweden  | Not on the market  | No information  
| UK  | Not on the market  | No information  

**Additional data from France and Germany (October 2007)**

**GERMANY**

<table>
<thead>
<tr>
<th>Extract</th>
<th>Pharmaceutical Form</th>
<th>Posology</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 g melilot fluid extract DER (1:1), Extraction solvent: ethanol 30%(V/V) / 100 g medicinal product</td>
<td>solution</td>
<td>Oral: 3 x 40 drops (40 drops=1,14 g FE= 1,14 mg coumarin</td>
</tr>
<tr>
<td>80 mg melilot dry extract DER (5-7:1), Extraction solvent: ethanol 50% (V/V) / tablet</td>
<td>tablet</td>
<td>Oral: 3 x 2 tablets (0,55 mg coumarin/tablets)</td>
</tr>
<tr>
<td>8,4-11,7 g melilot dry extract DER (4-8:1), Extraction solvent: ethanol 25% (m/m) / 100 g medicinal product</td>
<td>solution</td>
<td>Oral: 3 x 1 ml (≈ 7,3 – 10,1 mg coumarin/ml)</td>
</tr>
<tr>
<td>100 mg melilot dry extract DER (4,2-7,5:1), Extraction solvent: Methanol 50% (V/V) / tablet</td>
<td>tablet</td>
<td>Oral: 3 x 2 tablets (daily dose 3 - 5 mg coumarin)</td>
</tr>
<tr>
<td>252 mg melilot dry extract DER (4-8:1), Extraction solvent: ethanol 35% (V/V) capsule</td>
<td>Soft capsule</td>
<td>Oral: 1x1 capsule (daily dose 3 - 5 mg coumarin)</td>
</tr>
<tr>
<td>4 g melilot fluid extract (1:1), Extraction solvent: ethanol 3 0% (V/V) / 100 ml medicinal product</td>
<td>solution</td>
<td>Oral: 3 x 20 ml (daily dose &lt; 3 mg coumarin)</td>
</tr>
<tr>
<td>24 mg melilot dry extract (6-9:1), Extraction solvent: ethanol 90% (V/V)/ tablet</td>
<td>tablet</td>
<td>Oral: 2-3 x 1 tablet( daily dose 1-1,5 mg coumarin)</td>
</tr>
<tr>
<td>30 mg melilot dry extract (7-9:1), Extraction solvent: methanol 30% V/V / Kapsel</td>
<td>Soft capsule</td>
<td>Oral: 2-3 x 1 capsule (daily dose 1,5 mg coumarin)</td>
</tr>
</tbody>
</table>
### FRANCE

<table>
<thead>
<tr>
<th>Well-Established Use</th>
<th>Traditional Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparations</strong> (kind of extract, extraction solvent, DER)</td>
<td></td>
</tr>
<tr>
<td>1) Powdered</td>
<td>1) Powdered</td>
</tr>
<tr>
<td>2) Powdered</td>
<td>2) Powdered</td>
</tr>
<tr>
<td>3) Powdered</td>
<td>3) Powdered</td>
</tr>
<tr>
<td>4) Dry aqueous extract</td>
<td>4) Dry aqueous extract</td>
</tr>
<tr>
<td>5) Infusion</td>
<td>5) Infusion</td>
</tr>
</tbody>
</table>

### SINCE WHEN ARE THE PREPARATIONS ON THE MARKET?

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) 1989</td>
</tr>
<tr>
<td>2) 1990</td>
</tr>
<tr>
<td>3) 1990</td>
</tr>
<tr>
<td>4) 1987</td>
</tr>
<tr>
<td>5) 1991</td>
</tr>
</tbody>
</table>

### Pharmaceutical form (Standard Terms)

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) hard capsule</td>
</tr>
<tr>
<td>2) oral suspension, single dose container</td>
</tr>
<tr>
<td>3) oral solution, ampoule</td>
</tr>
<tr>
<td>4) hard capsule</td>
</tr>
<tr>
<td>5) eye drops</td>
</tr>
</tbody>
</table>

### Posology (Route of administration in Standard Terms + daily dosage)

<p>| |</p>
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1) 1 hard capsule (250 mg) three times daily</td>
</tr>
<tr>
<td>2) 10ml daily (containing 1614 mg)</td>
</tr>
<tr>
<td>3) 2 ampoules daily (1 containing 500 mg /5 ml)</td>
</tr>
<tr>
<td>4) 1 hard capsule (200 mg) twice daily</td>
</tr>
<tr>
<td>5) 1 to 2 drops three to four times daily (5 ml of eye drops containing 50 mg of herbal)</td>
</tr>
</tbody>
</table>
### Indications

|   | Traditionally used in the symptomatic treatment of functional disorders of cutaneous capillary fragility, such as ecchymosis, petechias, etc.  
|   | Traditionally used:  
|   | - in subjective signs of venous insufficiency, such as heavy legs  
|   | - in haemorrhoidal symptoms. |
| 1) |  
| 2) | Traditionally used:  
|   | - in subjective signs of venous insufficiency, such as heavy legs  
|   | - in haemorrhoidal symptoms. |
| 3) | Traditionally used in cases of eye irritation or discomfort due to various causes (smoky atmospheres, sustained visual effort, swimming in the sea or swimming baths, etc.). |
| … |  
| 4) | Traditionally used:  
|   | - in subjective signs of venous insufficiency, such as heavy legs  
|   | - in haemorrhoidal symptoms. |
| 5) | Traditionally used in cases of eye irritation or discomfort due to various causes (smoky atmospheres, sustained visual effort, swimming in the sea or swimming baths, etc.). |
### Risks (adverse drug effects, literature)

<table>
<thead>
<tr>
<th></th>
<th>1)</th>
<th>2)</th>
<th>3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the Herbal Substance on the market?</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Authorised products</td>
<td>Registered products</td>
<td>Food supplements</td>
<td></td>
</tr>
</tbody>
</table>

Were pharmacovigilance actions taken on medicinal products containing the herbal substance? Yes | No

#### a. Combination products

- The herbal substance is only available in combination products.
- Average number of combination substances: 2-3, 3-5, >5
- What are the main combination substances?
- Other information on relevant combination products:

#### b. Combination products

- The herbal substance is only available in combination products.
- Average number of combination substances: 2-3, 3-5, >5
- What are the main combination substances?
- Other information on relevant combination products:

Date: 04/10/2007

Additional comments:
4. ASSESSOR'S OVERALL CONCLUSIONS

Melilot and preparations thereof have been widely used in different member states for several decades. The anti-oedematous effects of melilot preparations have long been recognised empirically; the uses are made plausible by pharmacological data on coumarin and the long-standing use of melilot in those indications. Since the clinical documentation for melilot as a mono preparation is poor and no controlled clinical studies are available, the use of Meliloti herba preparations has to be regarded as traditional.

In conclusion, Meliloti herba and preparations thereof can be regarded as traditional herbal medicinal products.

Appendix I.

T165 - XTOXLINE copyright NLM 2006
CC00 - CCmed copyright ZBMD
CDSR93 - Cochrane Library - CDSR copyright Cochrane
DAHTA - DAHTA-Datenbank copyright Bundesministerium für Gesundheit
AR96 - Deutsches Ärzteblatt copyright DAEB
GA03 - gms copyright gms
GM03 - gms Meetings copyright gms
HG05 - Hogrefe-Verlagsdatenbank und Volltexte copyright Hogrefe-Verlag
KR03 - Karger-Verlagsdatenbank copyright Karger-Verlag
KP05 - Krause & Pachernegg Verlagsdatenbank copyright KuP
CDAR94 - NHS-CRD-DARE copyright Cochrane
INAHTA - NHS-CRD-HTA copyright NHS CRD 2004
SM78 - SOMED copyright LOEGD 2002
SPPP - Springer-Verlagsdatenbank PrePrint copyright Springer-Verlag
SP97 - Springer-Verlagsdatenbank copyright Springer-Verlag
TV01 - Thieme-Verlagsdatenbank copyright Thieme-Verlag
VV00 - VVFM copyright editworks GbR
CCTR93 - Cochrane Library - Central copyright Cochrane
ME66 - MEDLINE copyright NLM
ME60 - OldMEDLINE copyright NLM 2004
ME0A - MEDLINE Alert copyright NLM
ZT00 - AnimAlt-ZEBET copyright BfR (ZEBET) 2005
MK77 - MEDIKAT copyright ZB MED
ED93 - ETHMED copyright IDEM 2005
GE79 - GeroLit copyright DZA 2002
HN69 - HECLINET copyright IFG 2002
CV72 - CAB Abstracts copyright CAB
CB85 - AMED copyright THE BRITISH LIBRARY 2003
NHSEED - NHS-EED copyright NHS EED 2003
AZ72 - GLOBAL Health copyright CAB
IA70 - IPA copyright Thomson Scientific 2005
BA70 - BIOSIS Previews copyright Thomson Scientific
EM74 - EMBASE copyright 2006 Elsevier B.V.
DH64 - Derwent Drug Backfile copyright Derwent Information
EA08 - EMBASE Alert copyright 2006 Elsevier B.V.
DD83 - Derwent Drug File copyright 2005 Thomson Derwent
IT78 - ISTPB + ISTP/ISSHP copyright Thomson Scientific
IS74 - SciSearch copyright Thomson Scientific 2003

5 COMMUNITY MONOGRAPH ON MELILOTUS OFFICINALIS (L.) LAM, HERBA