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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Melilotus officinalis* (L.) Lam., herba Final

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Melilotus officinalis</i> (L.) Lam., herba
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance c) Liquid extract, ratio of herbal substance to extraction solvent 1:3, extraction solvents: ethanol 70% (V/V) and rapeseed oil
Pharmaceutical form(s)	a) Comminuted herbal substance as herbal tea, infusion, for oral use b) Herbal substance in solid dosage forms for oral use d) Herbal preparations in semi-solid dosage forms for cutaneous use
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1. Introduction

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

- Herbal substance(s)

Melilotus officinalis (L.) Lam., herba^{1, 2}

The European Pharmacopoeia provides the following definition for melilot (*Meliloti herba*): Whole or cut, dried aerial parts of *Melilotus officinalis* (L.) Lam. Content: minimum 0.3 per cent of coumarin (C₉H₆O₂; M_r 146.1) (dried herbal substance).

The definition formerly given by the Pharmacopée Française was as follows: "melilot consists of the dried flowering tops of *Melilotus officinalis* Desr." was changed in 2005 to the above mentioned definition of the European Pharmacopoeia. Similarly, the former German DAB and DAC definitions of melilot were replaced by the current European Pharmacopoeia melilot monograph.

The main characteristic constituents of melilot are cinnamic acid/coumarin derivatives (HagerROM, 2014). Coumarin is contained in the herbal substance in quantities of 0.3–0.9%. The European Pharmacopoeia requires of herbal substance min 0.3% of coumarin. The main coumarin derivative contained in dried melilot herb is melilotoside, o-glycosid of coumaric acid, which is present in dry melilot herb in a quantity of 0.4% (Bradley, 2006) up to 6% (HagerROM, 2014). Coumarin is formed from cis- and trans-o-hydroxycinnamic acid glucosides during drying of fresh plant material. The hydrolysis of cis-o-hydroxycinnamic acid glucosides to free coumarinic acid is catalyzed by β-glucosidase. The coumarinic acid spontaneously lactonises to free coumarin. Other cinnamic acid derivatives are dihydrocoumarin (melilotin), scopoletin, umbelliferone and acids: dihydro-o-coumaric acid (melilotic acid, 0.17%), caffeic acid (0.085%), ferulic acid (0.44%), o-coumaric acid (0.03%), p-coumaric acid 0.04% and small amounts others among them salicylic acid (HagerROM 2014). Melilot herb also contains oleanane type saponins: soyasapogenin I, astragaloside VIII, vistariasaponin D, melilotus-saponin, azukisaponin V carboxylate, with sapogenols soyasapogenol B and E and melilotigenin. Flavonoids are robinin (kaempferol 3-rhamno-[1→6 galactosid 7-rhamnoside) and its quercetine glycoside clovin and kampferol 3-galacto-gluco-arabino-rhamnoside (Kang, 1988; Bradley, 2006; HagerRom, 2014). The characteristic aroma of the dried melilot herb (synonym sweet clover) is caused by coumarins and about 80 other aromatic substances including alcohols like benzylalcohol, borneol, 2-butanol, ketons like Artemisia ketone, 2-butanon, carvon, dihydrocarvon, decanal; esters like bornyl acetate, ethyl dihydrocoumarate, ethyl hexadecanoate; hydrocarbons like β-cymene, eicosane, heneicosane; lactones, mainly 3,4-dihydrocoumarin (up to 1 mg/kg); carboxylic acids like butyric, decanoid, dodecanoic and phenols like anethol, carvacrol (HagerRom, 2014).

Dicoumarol and the antifungal isoflavonoid medicarpin, can be formed in melilot due to fungal infection and spoilage (Bradley, 2006).

¹ According to Guideline on quality of herbal medicinal products (CPMP/QWP/2819/00 Rev. 2)

² According to Guideline on specifications: test procedures and acceptance criteria for herbal preparations and herbal medicinal products/traditional herbal medicinal products (CHMP/QWP/2820/00 Rev. 2)

- Herbal preparation(s)
 - a) Comminuted herbal substance
 - b) Powdered herbal substance
 - c) Liquid extract, ratio of herbal substance to extraction solvent 1:3, extraction solvents: ethanol 70% (V/V) and rapeseed oil.

The preparation methodology of the liquid extract c) was described in monograph Emplastrum Meliloti in Farmakopea Polska III (1954) and in, Farmakopea Polska IV, Vol 2 (1970). According to the description Herba Meliloti is wetted with ethanol 70% (V/V) (2 parts of ethanol to 10 parts of herbal substance, = 16% of wetted herbal substance). After 2 hours rapeseed oil is added and the mixture is heated on a water bath for 2–3 hours. Then the oil extract is pressed and filtered through paper filter. The filtrate is used to prepare cutaneous patches.

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Meliloti herba and preparations thereof are often used in combinations with other herbal substances/ herbal preparations or various chemically defined substances. Although bibliographic data on combinations were discussed in the former assessment report from 2008, the current monograph refers exclusively to Meliloti herba.

1.2. Search and assessment methodology

In 2008 the assessment report reviewed the scientific data available for Meliloti herba and had taken into account the literature presented by the ESCOP to the monograph “Meliloti herba”, the French *Avis aux fabricants* and the German list of traditional medicinal products according to § 109 a AMG. Previous search for methodology was based on keywords “Melilotus” and “human” from 1900 in all text fields, melilot, coumarin, melilotoside, melilotin, 3,4-dihydrocoumarin and scopoletin. Additionally all Member States were asked to give information about what kind of products containing *Melilotus officinalis* are on their market including pharmaceutical forms, indications, posology and methods of administration.

After review of newly available data this revised assessment report is focused on data on melilot preparations and safety. It takes into account compounds contained in melilot herb which are important for safety of the herbal substance or its preparations assessed.^{3, 4}

Search engines used: Google, Google Scholar

Scientific databases: SciFinder, SCOPUS, ScienceDirect

Medical databases: PubMed, Medline

Toxicological databases: TOXLINE

³Data on human use of medicinal products, containing individual substances derived from *Melilotus officinalis*, herba (like coumarin), or their combinations with other substances, which were contained in the assessment report from 2008, does not fulfill criteria for herbal medicinal products and they are not included in this assessment report.

⁴ One herbal combination product present on EU market contains 20 mg dry extract from Hippocastani semen and 30 mg dry extract from Meliloti herba and have to regarded as fixed combination of both extracts.

Pharmacovigilance resources: WHO Global ICSR database, VigiBase. Drugs searched: Melilot, Melilotus spp. Status 01.2017

Data from EU and non-EU regulatory authorities: In this review, information was obtained from the following EU countries: Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Great Britain, Greece, Latvia, Netherlands, Poland, Slovakia, Slovenia and Spain.

Other resources: Bibliography collected in 2008⁵

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 2: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form, Posology, Duration of use	Regulatory Status
<i>Melilotus officinalis</i> , herba, comminuted	<p>Orally, in leg heaviness connected to mild venous circulation disturbances.</p> <p>Topically on a skin in discomfort and feeling of heaviness of legs, associated with mild venous circulation disturbances.</p> <p>Topically on areas of the skin after injuries, bruises, sprains.</p>	<p>Herbal tea, infusion.</p> <p>0.25–1 g (1/2 to 1½ teaspoons) with 200 ml of boiling water.</p> <p>3 times daily 200 ml of freshly-prepared infusion.</p> <p>Orally: Adults and elderly from 1/2 to 1½ teaspoons (0.25–1 g) pour a cup of boiling water, infuse covered for about 10 minutes. Then strain. Drink 3 times a day a glass of fresh infusion.</p> <p>Topically: Adults and elderly 3 to 6 teaspoons (2–4 g) poured with 150 ml of warm water, boiled 10 minutes and strained. Warm decoction is used</p>	<p>4 products registered Certificates since 15.03.1995</p> <p>Registration since 15.09.1998</p> <p>Poland</p>

⁵ Bibliographic sources from 2008 not included in this revised assessment report, can be found in Addendum I to the List of references.

Active substance	Indication	Pharmaceutical form, Posology, Duration of use	Regulatory Status
		incompressess on affected skin.	
<i>Melilotus officinalis</i> , herba, comminuted, liquid extract, drug solvent ratio (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil.	Topically on skin inflammations, sores.	Cutaneous patch (<i>Emplastrum Meliloti</i>) One 10 g patch contains 3 g of <i>Melilotus officinalis</i> , herba, liquid extract, drug solvent extract (1:3), extraction solvents ethanol 70% (V/V), rapeseed oil. For topical use on affected skin. Put on the patch on the affected skin. Usually used once a day. Duration of use was not limited.	National registration (Drug Institute Certificate) 21.02.2002 Poland
<i>Melilotus officinalis</i> , herba, powdered	Traditional herbal medicinal product used in haeviness of legs, related to minor venous circulatory disturbances.	Capsules, hard, containing 250 mg of powdered <i>Melilotus officinalis</i> herb. Posology: 3 times daily one capsule.	Registered in Spain in August 1992. Corresponding product reported to be sold in France in 1986.

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

The following preparations listed in the HMPC monograph published in 2008 were found not to be on the EU market: dry extract (3-5:1), extraction solvent water; liquid extract (DER 1:1) extraction solvent ethanol 30% V/V; dry extract (DER 5-7:1) ethanol 50% V/V; dry extract (DER 4-8:1), extraction solvent ethanol 25% m/m; dry extract (DER 5-7:1) extraction solvent ethanol 50% V/V; dry extract (DER 4-8:1) extraction solvent 35% V/V; dry extract (DER 6-9:1), extraction solvent ethanol 90% V/V; dry extract (DER 7-9), extraction solvent methanol 30% V/V. Consequently, they are no longer included in the revised monograph nor discussed in the assessment report.

Information on relevant combination medicinal products marketed in the EU/EEA

Belgium

In Belgium there are two combination herbal medicinal products containing *Melilotus officinalis* herb:

1. Herbal tea

Cnicus benedictus, herb, 0.03 mg/g

Frangula, cortex, extract 0.05 mg/g

Foeniculum, fruit, essential oil 0.03 mg/g
Mallow, flower 0.01 mg/g
Melilotus officinalis, (flowering stems) 0.08 mg/g
Pimpinella anisum, fruit 0.03 mg/g
Peppermint, leaf 0.27 mg/g
Senna, leaf, 0.35 mg/g
Rosmarinus, leaf, Tincture 0.04 mg/g
Tilia sylvestris/cordata, flower, Dry Extract 0.04 mg/g
Althaeae Flos/Radix 0.06 mg/g
Calendula officinalis, flower 0.01 mg/g
Indication: for gastric juice and bile secretion stimulation
Posology: unknown
On the market since 1962 to 2013;

2. Eyes drops, solution

Centaurea cyanus, flower, 0.05 ml/ml
Melilotus officinalis, (flowering stems), 0.05 ml/ml
Rosa, flowers, fluid extract 0.1 ml/ml
Procaine 1.0 mg/ml
Oxychinoli Sulfas 0.02 mg/ml
Boric acid 4.2 mg/ml
Amylocaine 0.5 mg/ml
Zinc sulfate (Heptahydrate) 2.0 mg/ml
Indication, Posology: No data
On the market since 1961 to 1997.

France

In France there are two combination products containing *Melilotus officinalis* extracts:

1. Cream, containing *Ruscus aculeatus* dry extract, extraction solvent: water, DER unknown and *Melilotus officinalis* liquid extract, extraction solvent: ethanol 30% (V/V). Content of extracts in the cream 2 g/100 g. The product has been on the market since 1974.
2. Hard capsules, containing: *Crataegus* (*Crataegi folium cum flore*, powder) 120 g, *Eschscholzia californica* (*herba*, powder) 120 mg, *Melilotus officinalis* (*herba*, powder) 120 mg; traditionally used in the "symptomatic treatment of neurotonic conditions of adults and adolescents, notably in cases of mild disorders of sleep". The product has been on the market since 1992.

Germany

In Germany, there is one combination product containing extract of *Melilotus officinalis*, herba:

Capsules, soft, containing:

20 mg dry extract from *Hippocastani semen* (5.5-6.5:1), extraction solvent: methanol 80% (V/V) and

30 mg dry extract from Meliloti herba (7-9:1), extraction solvent: methanol 30% (V/V)

Indication: To relief symptoms of discomfort and heaviness of legs, as reconstituent for the venous system.

Posology: 1 capsule, soft 2–3 times daily

On the market since 1976, Traditional Use Registration 30.07.2013.

Latvia

There is one combination product on the market:

Tablets

1 tablet contains:

150 mg Crataegi folium cum flore, powdered, 150 mg

Crataegi fructus, powdered, 30 mg

Leonuri cardiaca herba, powdered 100 mg

Meliloti herba, powdered, 40 mg

Indication: as additional treatment of functional disorders of heart function and blood system

Posology: 1-2 tablets 2-3 times per day

The product has been on the market since 1999.

Poland

One combination product is on the market (the same as in Latvia). One tablet contains 0.02–0.5 mg of coumarin. The product has been on the market since 20.03.1992.

Comments

Two combination herbal teas were used in Belgium, where Meliloti herba was a minor component. One of them has been used in gastrointestinal complaints (in combination with Sennae folium, Frangulae cortex, Anisi fructus, Foeniculi fructus, Cnici benedicti herba and others) but it seems not to be a key component. The second combination product in form of eye drops, where Meliloti herba was one minor additive to combination of boric acid, zinc sulphate, procaine and amylocaine (4.2 mg/ml + 2 mg/ml + 1 mg/ml 0.5 mg/ml) was used in eye irritation or discomfort due to various causes (smoky atmospheres, sustained visual effort, swimming in the sea or swimming pools). A herbal cream, containing extracts of *Ruscus aculeatus* rhizome and the *Melilotus officinalis* herb extracts has been on the French market since 1974. It is used for mild venous insufficiency. The concentration of extracts is not known.

One combination product, containing 120 mg of Crataegi folium cum flore (powdered), Eschscholziae californicae herba (powdered 120 mg) and Meliloti herba (powdered 120 mg), has been on the market in France since 1992. It was traditionally used in symptomatic treatment of “neurotonic conditions” and sleep disorders. Another combination product, containing: Crataegi folium cum flore (powdered, 150 mg); Cratagi fructus (powdered, 30 mg); Leonuri cardiaca herba (powdered, 100 mg) and Meliloti herba (powdered, 40 mg), has been on the market in Poland and Latvia since 1992. It is used in the indication: supporting the heart and circulatory system. The quality of melilot herb in the product indicates that it is not a key component.

Information on other products marketed in the EU/EEA (where relevant)

Austria

There are combination products, manufactured and sold by pharmacies, that contain liquid extracts of *Melilotus officinalis* but there are no details available about the extracts. The products are used for the treatment of venous insufficiency.

2.1.2. Information on products on the market outside the EU/EEA

A herbal preparation made of *Melilotus officinalis* flowering herb, was developed in Iran for use as a supplement to treat diabetic foot ulcers (Abdollahi *et al.* 2008, Farzamfar *et al.* 2008, Heshmat *et al.* 2008, Bahrami *et al.* 2008, Larijani *et al.* 2008).

2.2. Information on documented medicinal use and historical data from literature

According to Madaus, Hippocrates had used melilot flowers externally for septic ulcers and Bock (1551) summarized the use of melilot extracts as constricting, softening and analgetic agent externally for ulcers of the eyes, earache, "hardening and swelling of uterus" (Madaus, 1938). Traditional formulas under the name of *Emplastrum Meliloti*, were used in many European countries in the 18th century. They were for example listed in *Dispensatorium fuldense tripartitum* (von Schlereth FA, 1787); *Pharmacopoea Rossica* (1799) or *Pharmacopoea Gandavensis* (1786) (*Emplastrum e Meliloto five Emolliens*). The *Emplastrum* was contained in many dispensatorias and manuals until the 20th century (Madaus, 1938). There were two kinds of melilot plasters, the monocomponent, containing as only active component a preparation of the flowering herb of melilot (*Pharmacopoea Gandavensis*, 1786; *Pharmacopoea Hispana*, Editio tertia, 1803; *Pharmacopoea Rossica*, 1799); and combination products described mostly in manuals, containing, apart from *Herba Meliloti*, also additional components like *Flores Chamomillae*, *Baccae Lauri* and others. *Emplastrum Meliloti* and *Emplastrum Meliloti comp.* were mentioned first in "Neues Pharmazeutisches Manual" dated 1904 (Dieterich, 1924). *Herba Meliloti* and *Emplastrum Meliloti* were also included in the "Deutsche Arzneitaxe" from 1936 and *Herba Meliloti* in the (DAB 6, 1926, 1957). The example of the *Emplastrum Meliloti*, combination type, was mentioned in Madaus manual, 1938. This combination melilot plaster was used in arthritis and rheumatoidal swelling (Madaus, 1976). *Emplastrum Meliloti* has been used externally in skin ulcers, varices, skin inflammations, superficial burns, as anti-inflammatory and to accelerate of healing of wounds and as wounds cleaning agent (Ożarowski, 1976, Hager, 1976). More recent sources have indicated its use for the treatment of ulcers (sores) and inflammations of the subcutaneous tissue like furunculosis and pimples (Chruściel & Gibiński, 1991, Grosse Enzyklopädie der Heilpflanzen, 1994). It is still used as anti-inflammatory in sores and skin inflammations.

Roeske (1955) mentions use of 10% infusions of *Meliloti herba*, taken 4-6 spoons a day in adults or 4-6 teaspoons in children as: *sedativum*, *hypnoticum*, *antispasmodicum* and *diureticum*. Leclerc (1976), lists melilot among antispasmodics and recommends its use for insomnia in children and elderly.

Hagers Handbuch der Pharmazeutischen Praxis (1938, 1949, 1976), lists the medical and folk uses of melilot herb including varices, hemorrhoids, ulcer cruris, edemas, brachalgias, thrombophlebitis, in thrombosis prophylaxis, as a diureticum and as deodorant. Also, the traditional use of herbal pillows in swelling, ulcers and rheumatism is mentioned as well use as antispasmodic and carminative remedies. There are no data on preparations used in the mentioned indications and on their posologies.

Madaus (1938, 1976) lists the topical use of melilot herb for ulcers and even tumors as an agent “softening” tissues around, promoting purulence and in arthritis, rheumatoid swelling (in a form of preparations like *Emplastrum Meliloti*). Topically melilot herb was used in inflamed breasts of breastfeeding women; in the case of earaches such as otitis and otorrhoea (in combination with *Flos Malvae arboreae*, *Folium Althaeae*, *Flos Chamomillae* and *Semen Lini* for preparation of “earmuffs” form for ear evaporation). In combination products it’s being used in oesophageal ulcers (Species Emollientes contained: *Folium Althaeae*, *Folium Malvae*, *Herba Meliloti*, *Flos Chamomillae*, *Semen Lini*). The author also mentioned the use of the herb in insomnia and in a form of herbal pillows in swellings. The monograph of German Kommission E: *Steinklee Kraut* (published March 13 1986; revised March 13 1990) contained following indications for internal use:

1. Problems arising from chronic venous insufficiency, such as heaviness in legs, night cramps in the legs, itching and swelling,
2. For the supportive treatment of thrombophlebitis, post-thrombotic syndromes, haemorrhoids and lymphatic congestion, and
3. For external use: Contusions, sprains, and superficial effusion of blood (Monographie: *Meliloti herba* (*Steinklee Kraut*), 1986, 1990).

In the ESCOP monograph are assigned for *Meliloti herba* following indications: Symptomatic treatment of problems related to varicose veins, such as painful and heavy legs, nocturnal cramps in the legs, itching and swelling (ESCOP, 2003).

The British Herbal Compendium lists following indications for internal use: for the treatment of complaints arising from chronic venous insufficiency in the legs, such as varicose veins and associated pains, swelling, nocturnal cramp, itching and feeling of heaviness. Also oral uses mentioned are: treatment of lypoedema arising from various causes of cutaneous capillary fragility, such as ecchymoses or petechiae; haemorrhoids; phlebitis; indigestion and flatulence; minor sleep disorders; rheumatic pains; and burns, based on experience and tradition as well as external use in bruises and superficial bleeding, were regarded by the author to be based only on experience and tradition (Bradley, 2006).

Melilot monopreparations for oral use are licensed in Poland and Spain. One cutaneous patch preparation for topical use, *Emplastrum Meliloti*, is present on the Polish market (see in 2.1.1).

The 2008 HMPC monograph included a number of melilot extracts: dry extract DER (5-7:1), extraction solvent water, dry extract DER (4-8:1) extraction solvent ethanol 50% V/V, dry extract DER (4-8:1), extraction solvent ethanol 25% m/m, dry extract DER (4-8:1) extraction solvent methanol 50% V/V, dry extract DER (4-8:1) extraction solvent ethanol 25% m/m or methanol 50% V/V or ethanol 35% V/V, fluid extract DER (1:1), extraction solvent ethanol 30% V/V. The traditional use of these preparations could not be confirmed during the revision of the monograph. The 2008 monograph also included melilot extracts (dry extract DER (6-9:1) extraction solvent ethanol 90% V/V and dry extract DER (7-9) extraction solvent methanol 30% V/V) which were found to be used only in combinations with other herbal preparations or isolated substances. Therefore these preparations are no longer included in the revised monograph.⁶

⁶ Bibliography for the combination products containing isolated herbal substances not included in this revised assessment report can be found in Addendum I to the List of references.

Table 3: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form, Posology, Duration of use	Reference
<i>Melilotus officinalis</i> (L.) Lam., herba, liquid extract, drug solvent ratio (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil.	Externally. Anti-inflammatory	One cutaneous patch, 10 g, contains 3 g of <i>Melilotus officinalis</i> (L.) Lam., herba, liquid extract, drug solvent ratio (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil.	Farmakopea Polska IV, 1970
<i>Melilotus officinalis</i> (L.) Lam., herba, liquid extract, drug solvent ratio (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil.	Anti-inflammatory, astringent, softens tissue, accelerates the healing of ulcers, Indications: Externally in sores, inflammatory states of subcutaneous tissue	One cutaneous patch, 10 g, contains 3 g of <i>Melilotus officinalis</i> (L.) Lam., herba, liquid extract DSR (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil. Put on the patch on the affected skin.	Poradnik Terapeutyczny, 1975
Comminuted herbal substance for herbal tea, infusion	Used mainly as a venous remedy in the form of tea in complaints of chronic venous insufficiencies, such as pains, heaviness of legs, night cramps itching and swelling and as diuretic. Also in treatment of sores and haemorrhoids.	Orally: herbal tea, infusion. Single dose: 1–2 teaspoons (1.6–3.2 g), 2–3 times daily (Daily dose: 3.2–9.6 g) Externally, cataplasm of a poultice of the herbal substance, thoroughly soaked with the same amount of hot water, wrapped in linen, and placed on the affected part. Strength of the extract and posology are unknown.	Wichtl, 1984
Comminuted herbal substance	Cough, rheumatism and gout, venous disorders, thrombosis prophylaxis	Orally: herbal tea, infusion. Single dose 2–4 g	Fisher & Krug, 1984
Comminuted herbal substance	Venous and lymphatic circulation disturbances	Orally: herbal tea, infusion. Single dose infusion of 1–2 teaspoons. Daily dose: 3–4 times a day.	Weiss, 1985
<i>Melilotus officinalis</i> (L.) Lam., herba, liquid extract, drug solvent ratio (1:3), extraction	For topical use on sores and skin with inflammation symptoms.	One cutaneous patch, 10 g, contains 3 g of <i>Melilotus officinalis</i> (L.) Lam., herba, liquid extract drug solvent	Leksykon Leków. Chruściel & Gibiński, 1991

Herbal preparation	Documented use / Traditional use	Pharmaceutical form, Posology, Duration of use	Reference
solvents: ethanol 70% (V/V), rapeseed oil.	Indications: sores, inflammatory states of subcutaneous tissue.	ratio (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil. Put on the patch on sores or on the inflammatory skin.	
<p>Infusion of 5 g herbal substance in 100 ml of water.</p> <p>Infusion of 1 g of herbal substance in 100 ml of water.</p> <p>Infusion of 2 g of herbal substance in 100 ml of water.</p>	<p>Skin inflammations, mild burns, furunculosis, pimples, inflammation of mucosa.</p> <p>Eyelids inflammations.</p> <p>Skin eruptions, inflammations of mouth, gums and throat.</p> <p>Insomnia, neuralgia, migraine, digestive disorders.</p>	<p>Compresses of the infusion</p> <p>Washings</p> <p>Orally: herbal tea, infusion. 1-2 cups daily</p>	Die Grosse Enzyklopädie der Heilpflanzen, 1994
<p>Comminuted herb for infusions and other galenical forms (preparations not specified) for oral use.</p> <p>Comminuted herbal substance for herbal tea.</p> <p>Not specified preparations for rectal use.</p> <p>Not specified preparations for external use.</p>	<p>Internal: Problems arising from chronic venous insufficiency, such as pain and heaviness in legs, night cramps in the legs, itching, and swelling.</p> <p>For the supportive treatment of hemorrhoids.</p> <p>External: Contusions and superficial effusions of blood.</p>	<p>Herbal tea, infusion</p> <p>Herbal substance or preparations in amounts corresponding to 3–30 mg coumarin.</p> <p>Herbal tea, infusion. Strength and posology not specified.</p> <p>Ointments and suppositories for rectal use Strength not specified.</p> <p>Ointments, liniments cataplasms and herbal sachets for external use. Strength not specified.</p>	Commission E Monograph Steinkleekekraut, Blumenthal, 1998
<i>Melilotus officinalis</i> (L.) Lam., herba, liquid extract, drug solvent ratio (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil.	Externally, healing promoting	One cutaneous patch, 10 g, contains 3 g of <i>Melilotus officinalis</i> (L.) Lam, herba, liquid extract, drug solvent ratio (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil.	Farmakopea Polska VI 2002 (PI)

Herbal preparation	Documented use / Traditional use	Pharmaceutical form, Posology, Duration of use	Reference
<p>Preparations for oral use not specified.</p> <p>Extracts for external use not specified.</p>	<p>Symptomatic treatment of problems related to varicose veins, such as painful and heavy legs, nocturnal cramps in the legs, itching and swelling.</p>	<p>The amount of herbal substance or herbal preparation corresponding to 3–30 mg coumarin</p>	<p>ESCOP 2003</p>
<p>Preparations for oral use, not specified.</p> <p>External use: Extracts in semi-solid preparations, not specified.</p>	<p>Oral use: Complaints arising from chronic venous insufficiency in the legs, such as varicose veins and associated pains, swelling, nocturnal cramp, itching and feeling of heaviness.</p> <p>Traditional use: orally in lymphoedema arising from various causes including lymphadenectomy, symptoms of cutaneous capillary fragility, such as ecchymoses or petechiae, haemorrhoids, phlebitis, indigestion and flatulence, minor sleep disorders, rheumatic pains and burns.</p> <p>Traditionally used externally in bruises, sprains and superficial bleeding.</p>	<p>Daily doses in adults: Preparations containing the equivalent of up to 10 g of dried herb, in divided doses.</p> <p>Preparations (not defined) of known coumarin content, the equivalent of up to 30 mg of coumarin, up to 1 mg/kg body weight.</p>	<p>Bradley P British Herbal Compendium 2006</p>

Based on the available literature, herbal monographs and the use in EU Member States, the following indications are proposed for the HMPC monograph for traditional use:

Oral use:

Traditional herbal medicinal product to relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances.

Topical use:

- Traditional herbal medicinal product to relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances.
- Traditional herbal medicinal product used for the treatment of minor inflammations of the skin

The traditional use in ulcers was not endorsed by the HMPC, because this may require medical supervision.

The tradition to use infusions in complaints of chronic venous insufficiencies is documented (Wichtl, 1984)

The traditional use in hemorrhoids is mentioned by Hagers (1976), however, the information on preparations is incomplete. Wichtl (1984) mentions the use of cataplasms prepared of comminuted melilot herb for ulcers and hemorrhoids, but the details of the preparations are lacking. In the Commission E monograph for *Melilotus officinalis* two preparations are mentioned: infusion for oral use or other preparations in quantities corresponding to 3–30 mg of coumarin or unguenta and suppositoria for rectal use. None of these products is on the market and there are no data on the preparations, their strength and posology.

Single bibliographical sources mention the use of melilot tee, infusion, in insomnia, neuralgia, migraine, digestive disorders, cough and cold but the use of these preparations could not be confirmed with other bibliography.

2.3. Overall conclusions on medicinal use

The traditional use of melilot preparations is plausible by the consistent and long-standing use in European countries. They are licensed with traditional indications in Poland and Spain, for oral use and in Poland for topical use. Combination products containing melilot preparations are registered in Germany and France.

There are no authorised medicinal products on the market for longer than 10 years in the EU for melilot mono preparations that are suitable for well-established use acceptance. The medicinal use of Meliloti herba preparations has to be regarded as traditional with available documentation of at least 30 years.

Table 4: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
<i>Melilotus officinalis</i> (L.) Lam., herba, liquid extract, drug solvent ratio (1:3), extraction solvents: ethanol 70% (V/V), rapeseed oil.	Externally in inflammations of the skin.	One 10 g patch contains 3 g of liquid extract of 1 g <i>Melilotus officinalis</i> , herba. Usually used once a day. (Duration of use was not specially regulated nor limited)	Poland, 1970- 2002 Poland, before 1975
Comminuted herbal substance	Used as a venous remedy in the form of tea in complaints of	Orally: herbal tea Single dose: 1 level teaspoon (1.0–1.2 g), 2 times daily	Wichtl, 1984

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
	chronic venous insufficiencies, such as pains, heaviness of legs, night cramps itching and swelling.	(Daily dose: 2–2.4 g)	
<i>Melilotus officinalis</i> , herba, powdered	Traditional herbal medicinal product used in heaviness of legs, related to minor venous circulatory disturbances.	Capsules, hard, containing 250 mg of powdered <i>Melilotus officinalis</i> herb. Posology: 3 times daily one capsule.	In Spain registered in 1992 base on a corresponding product reported to be sold in France since 1986.

Assessor's comments:

The tradition to use infusions in complaints of chronic venous insufficiencies is documented (Wichtl, 1984). However the daily dose given by the author (up to 6 teaspoons) exceeds the level of coumarin once recommended by the Commission E (30 mg a day) and also the tolerable daily intake for coumarin from food as established by EFSA (see section 5.1). For safety reasons the oral dose of melilot herb may therefore be reduced to 2.0–2.4 g (corresponding to two level teaspoons a day and 10 mg of coumarin a day).

The proposed indications for melilot preparations are:

For oral use: in symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances.

The justification of the traditional use of herbal teas in this indication is based on bibliography and former national regulations. It was accepted in 2008 by HMPC as indication for *Melilotus officinalis* based of its use in EU countries.

For topical use:

- in symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances
- for the treatment of minor inflammations of the skin

Although the duration of topical use of melilot oil extract had never been limited traditionally, in the opinion of the HMPC it is reasonable to limit the use of the product to one week. If a product does not prove to be effective enough, it is advised to consult a doctor.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Melilot extracts

Constituents responsible for therapeutic activity of the melilot preparations are not known. Historically, antioedematous activity of melilot preparation was attributed to its coumarin content (Pabst & Klemm, 1960).

Melilot extract (details of the extract unknown) was administered to rats at a dose of 2.5 g/kg, intraperitoneally or subcutaneously, 4 hours before the thermal injury. The effect of intraperitoneal injection of melilot extract on the rate of swelling was compared to that of saline. Both methods of administration of melilot extract gave significant differences with saline control, diminishing swelling rate, i.p. gave more intensive effect on swelling. In another experiment the extract was administered immediately after applying the burns and after 2 hours and 4 hours, by single and multiple injections. Both single and multiple injections of melilot extract (2.5 g/kg), immediately, 2 hours after, 4 hours after thermal injury gave statistical reduction of swelling rate (Nishikawa *et al.*, 1983). The histological observation of massive infiltration of neutrophils and macrophages 6 to 24 hours after the subcutaneous injection of *Melilotus officinalis* extract suggested its reducing effect on thermal injuries and rat model experiment indicate that lymphatic circulation is not involved in this effect. The observed effect was similar to the effects of coumarin in experimental oedemas (see below).

Pleşca-Manea *et al.*, (2002) observed that the extracts of *M. officinalis* and coumarin influenced the inflammatory response. In further experiments the authors studied the influence of an aqueous-ethanolic (1:1) extract of *Melilotus officinalis* flowering herb, standardized to 0.25% coumarin (containing 0.25% coumarin, 0.38% flavones and 1.20% polyphenols), on an experimental model of acute inflammation, induced with turpentine oil, in male rabbits. The effects of 10 ml/kg melilot extract administered intraperitoneally to rabbits, were compared with those from a group treated with hydrocortisone sodium hemisuccinate. The effects were evaluated by measuring serum citrulline, test of *in vitro* phagocytosis, total leukocyte count and differential leukocyte count expressed as percentage. The extract had antiinflammatory effects reducing the activation of circulating phagocytes and lowering citrulline production. These properties were similar to those of hydrocortisone sodium hemisuccinate and coumarin. In the bone marrow acute phase response, melilot extract had an inhibitory activity, lower than that of hydrocortisone sodium hemisuccinate and similar to coumarin. The authors concluded that their findings suggest that the tested melilot extract has an antiinflammatory effect, by decreasing the number of phagocytosed *E. coli* with an intensity smaller than that of hydrocortisone but comparable to that of coumarin. The melilot extract decreased also NO synthesis similarly to hydrocortisone and coumarin and reduced the bone marrow acute phase response, decreasing the neutrophil percentage. This effect was smaller than that of hydrocortisone but comparable to that of coumarin.

Coumarin possesses weak anti-inflammatory and antiedematous activities. After intraperitoneal injections of 50 mg/kg in rats the effect of coumarin decreased carragen-induced paw edema by 42% (after 4 hours) and by 33% (after 6 hours) in contrast to the effect of injection of normal saline, and could be compared to that of 1.5 mg of flufenamic acid (Földi-Borcsök *et al.*, 1971).

The antiedematous activity of coumarin was studied by Piller & Casley-Smith (1975); Piller (1976) and Piller & Clodius (1986).

Scopoletin contained in melilot may also contribute to the anti-inflammatory activity of the melilot preparations. Its anti 5-lipoxygenase activity was found to be fifty times more potent than nordihydroguaiaretic acid with $IC_{50} = 0.34 \pm 0.01 \mu\text{g/ml}$ compared to $85.23 \pm 0.02 \mu\text{g/ml}$ of NDHGA (Mogana *et al.*, 2013). This compound was earlier observed to exhibit protective effects on cultured rat hepatocytes, pretreated with CCl_4 and radical scavenging ability (Kang *et al.*, 1998).

3.1.2. Secondary pharmacodynamics

Some coumarin derivatives present in melilot extract were recorded to possess antiprotozoal activities. Melilotoside (cis-O-coumaric β -glucoside) was found to be active against *Giardia lamblia* (IC_{50} 12.5 and 16.8 $\mu\text{g/ml}$) (Calzada *et al.*, 2003). However, it wasn't ~~been~~ studied if it ~~s active to have~~ has an *in vivo* effect (inside the animal intestine lumen). Also scopoletin was identified to be antileishmanial and to have anti-acetylcholinesterase activity ~~other-after~~ bio-guided isolation from an ethanol extract from the leaves of another plant species *Canarium patentinervium* Miq. ~~leaves-~~ (Mogana *et al.*, 2014).

In contrast to ~~the~~ coumarin and its simple derivatives, naturally occurring in *Meliloti herba*, which are devoid of effect on coagulation, 4-Hydroxycoumarin-hydroxycoumarin and its dimeric derivatives appear in plant material only as a result of fungal infection.

The dimeric 4-hydroxyderivatives of coumarin are reported to possess anticoagulant activities (Campbell & Link, 1941) and their discovery had initiated the development of a new class of synthetic oral anticoagulants.

3.1.3. Safety pharmacology

The data are not available.

3.1.4. Pharmacodynamic interactions

There are no data.

3.1.5. Conclusions

There are only limited data on pharmacodynamic properties of melilot mono-preparations. Available data show an antioedematous effect (Nishikawa *et al.*, 1983) and a mild anti-inflammatory effect lower than that of hydrocortisone sodium hemisuccinate (Pleşca-Manea *et al.*, 2002). All available pharmacological data are from experiments where the active substance was administered intraperitoneally. It is unknown whether these results can be extrapolated to oral or topical use.

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

Melilot extracts

There are no data on pharmacokinetic properties of melilot preparations. There is one study on human skin absorption of coumarin from cutaneous patches containing melilot extract, applied on skin of volunteers and human skin permeation (*ex vivo*), see part. 4.1.2.

A combination product containing coumarin and rutin has been used in pharmacokinetic studies in humans, but only the kinetic behaviour of coumarin has been studied (the product is not regarded as herbal medicinal product).

Coumarin

Coumarin in animals 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).

Distribution of coumarin in rats, after single intraperitoneal injections, was studied by Piller (1977). Coumarin binds readily with serum albumins and after injection the level of free compound is greatly reduced what delays its excretion and metabolism. About 40% of coumarin is eliminated in the faeces and the remainder excreted in the urine. The major hydroxy derivative in rats was found 3-hydroxycoumarin, followed by 4-hydroxycoumarin (3–4%) and smaller amounts of 6, 7-hydroxyderivatives. The main metabolite present in faeces is *o*-hydroxyphenylacetic acid. The distribution of [3-¹⁴C] coumarin in rat tissues, after single intraperitoneal injection of 250 mg, was observed in: blood, brain, heart, kidneys, liver, lung, thigh muscle, skin in thigh region, small intestine and spleen samples. In skin, after initial level of 20 µg/g a rapid decline to 5 µg/g was observed followed by a gradual increase to 15 µg/g at 40 hours and then a decline to 1.5 µg/g at 200 hours. The distribution profiles in muscles and small intestine contained similar maxima between 10–50 hours and 20–30 hours after single dose injection. The pharmacokinetic profile of coumarin in rats differs from that in humans but the affinity to connective tissue is similar.

In primates, coumarin and its principal metabolite 7-hydroxycoumarin (which are relatively lipid soluble) are rapidly absorbed from the intestine. 7-hydroxycoumarin is readily glucuronidated, probably already in the gut and finally in the liver. The first-pass metabolism is quick and extensive in most species. Bioavailability of coumarin is dependent on the activity of the 7-hydroxylation pathway in a given species. The pathway is very active in the liver in man and no or only very few unchanged coumarin passes into the systemic circulation. Readily detectable metabolites in blood in primates are free and conjugated 7-hydroxycoumarin. On this basis it has been claimed, that 7-hydroxycoumarin is actually the active principle of therapies with synthetic coumarin anticoagulants (Raunio *et al.*, 2001). Its role in therapies with traditional herbal medicinal products is not known.

Percutaneous absorption and distribution of [4-¹⁴C] coumarin, applied via 70% aqueous ethanol solution on the skin, was studied in rats and volunteers. The human dose was 0.77 mg/kg. Coumarin was quickly absorbed; half-life in humans was 1.7 hours and in rats 5 hours. After 6 hours of exposure total absorption (to receptor fluid) in humans was 60% and in rats 72% of the dose. There is no evidence for coumarin metabolism in skin (Yourick & Bronaugh, 1997).

7-hydroxycoumarin and its glucuronide are excreted via urine (80–90% of the absorbed coumarin) and the glucuronidated form is a main subject of the active transport by multidrug resistance-associated proteins. This was regarded as a main way of transport from liver to kidneys (Wittgen *et al.*, 2012).

The relative contribution of the two major metabolic pathways, which are catalysed by different P450 enzymes, is highly variable between species. The ring-opening one, predominating in rodents, proceeds via an epoxide intermediate is thought to be a necessary prerequisite for toxic effects. Species differences in toxicity are thought to be related to differences in the detoxification of the reactive intermediate. Recent findings indicate that possible final toxicity outcome is dependent on a balance between the formation of the epoxide metabolite and their inactivation via acetaldehyde dehydrogenase (Vasallo *et al.*, 2004). Coumarin is very specifically metabolized by CYP2A6, and being inducible P450 enzyme is susceptible to be affected by a number of exogenous and host factors, so the elimination of coumarin is expected to be affected accordingly (Pelkonen *et al.*, 2000).

The frequency of CYP2A6 poor metabolizer phenotype due to a loss of functional enzyme in the Caucasian population is below 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>). 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, meantime other metabolic pathways such as 3-hydroxylation and ring-opening may be still present. The global metabolism of coumarin and pharmacokinetic characteristics in individuals homozygous for CYP2A6 gene deficiencies has not yet been investigated.

There are no available data on scopoletin or umbelliferone pharmacokinetic properties.

Assessor's overall conclusions on pharmacokinetics

There are no data on absorption and distribution of other compounds, contained in melilot extract after oral use and through animal skin. There is only data on distribution of radiolabelled coumarin, after intraperitoneal administration to rats.

Comparatory data on absorption and metabolism of labelled coumarin, administered on human skin showed quick absorption and metabolism mainly through a pathway of 7-hydroxycoumarin and elimination mainly as active transport of the glucuronates. The distribution studies showed a special affinity of radiolabelled coumarin to connective tissue, mainly skin, where coumarin is not metabolised. In humans, data on absorption of coumarin from patches containing melilot extract comes from stripping experiment on volunteers, and from experiment with ex vivo permeation of coumarin through human skin. 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 so far. Because the coumarin content in melilot preparations is rather small, clinically significant consequences are unlikely.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single dose toxicity

Toxicity of a liquid ethanolic extract of *Melilotus officinalis* (DER and extraction solvent concentration not specified), diluted with saline (1:5), was tested on BALB/c mice after IM and IP administration and in Wistar rats after ip administration. LD₅₀ was found to be in range 44–52 ml/kg. There was no significant difference between IM and IP toxicity. LD₅₀ in rats was 42–44 ml/kg. The administration in doses close to LD₅₀ was accompanied with depression, narcosis and sleep in animals. The pictures of intoxication of mice and rats were similar to the intoxication by ethanol. Therefore, the authors concluded the toxicity and observed effects were due to the extraction solvent (Abdollahi *et al.*, 2008).

There are no available data on toxicity on melilot extract containing no alcohol.

Endell & Seidel (1978) tested single dose toxicity of coumarin in male DBA/2J mice and male CH3/HeJ mice. They have estimated oral toxicities in CH3/HeJ 420 (394-448) mg/kg and in DBA/2J 780 (748-813) mg/kg.

LD₅₀ values (mg/kg body weight) reported for coumarin are: mice (196 mg/kg (oral); 20 mg/kg (IP); 242 mg/kg (subcutaneous); for rats 293 mg/kg (oral) and guinea pigs 202 mg/kg (oral) (Lewis, 1992). Several extensive assessments concerning coumarin toxicity have been published during the past years (Lake, 1999; IARC, 2000; NTP, 2004).

3.3.2. Repeat dose toxicity

Melilotus preparations

A liquid ethanol extract of *Melilotus officinalis* in dilution (prepared in proportion 1:5, DER and ethanol concentration not specified) was tested on rats in two doses: 0.07 and 0.21 ml/kg during a period of 3 months. The administration had no effect on body weight, general state of animals and their behavior. The authors did not detect any significant changes in hematological and biochemical parameters: total serum proteins, bilirubin, glucose content, triglycerides, cholesterol, blood urea, creatinine in tested and control groups receiving dissolute extract in both doses. Mean body weights of rats in both groups were not significantly different from control animals (Abdollahi *et al.*, 2008).

A liquid ethanol extract of *Melilotus officinalis* in dilution (1:10, DER and ethanol concentration unknown) was tested in one month study on 8 male and 8 female dogs, divided into two 4 animals groups. The diluted extract was administered in dose 0.07 ml/kg once a day, while the control group received 0.9% sodium chloride. During the test following parameters were monitored: general state of the animals including body weight changes, appetite, motor activity and behavior, hair condition, ECG parameters, rectal temperature of animals and data of hematological and biochemical tests were monitored for signs of toxicity and side-effects. Finally, morphological and histological analyses were performed using standard methods. Hematological and biochemical analyses were conducted at the baseline of the study and in the end, and one month after first administration; on blood samples from subcutaneous vein of each animal. The authors did not detect any significant changes in: serum proteins, serum bilirubin, serum glucose, triglycerides, cholesterol, blood urea and creatinine, hepatic enzymes nor difference in physiological range of these parameters. Body weights and rectal temperatures of animals were not significantly different from those of controls. Pathomorphological examination did not show any changes of the internal organs nor irritating effects. The authors concluded that the study provides evidence for good tolerance and safety of the preparation (Farzamfar *et al.*, 2008).

Repeat dose toxicity data for extract not containing ethanol are lacking.

Coumarin

16-days toxicity studies were carried out in the program of NTP coumarin carcinogenicity study (NTP, 1993, Lake, 1999). The NTP toxicity studies were conducted by administering coumarin to groups of male and female F344/N rats and B6C3F₁ mice in doses 400 mg/kg and 600 mg/kg. At day 16th all female rats and mice were dead. Some of the male rats receiving 400 mg/kg, were still alive.

In a 13-week study, rats and mice were given 150 and 300 mg coumarin per kg body weight. At higher dose levels, serum liver enzymes were increased, the absolute and relative liver weights were significantly higher than those of the controls. Also centrilobular hepatocellular hypertrophy and/or degeneration and/or necrosis, chronic active inflammation, and bile duct hyperplasia were observed.

In a 2-year study, to 70 male and female rats were administered coumarin doses of 0, 25, 50, or 100 mg/kg and 70 male and female mice were administered (gavage, corn oil) coumarin doses of 0, 50, 100, or 200 mg/kg body weight. After 15 months, 10–20 animals from each group were evaluated. In male rats of both of groups a marked mortality was observed (males of high-dose groups died prematurely, primarily due to exacerbation of renal disease), while the survival of female rats was similar to the control. The principal lesions occurred in the liver, kidney, and forestomach. The hepatic lesions were seen in all male rats, and only in the 50 and 100 mg/kg females. The lesions included hepatocellular necrosis, fibrosis, cytologic alteration, and increased severity of bile duct 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 the controls. The incidences of syncytial alteration in all male dose groups and in 200 mg/kg females

were also significantly greater than those in the controls. There was a substance-related increase in the average severity of nephropathy in all dosage groups of male and female rats. The incidences of forestomach ulcers in groups of male and female rats, in dose 100 mg/kg, were significantly more frequent than those of the controls. The hepatic lesions caused by 9 or 15 months exposure, were reversible. Opposite to the liver lesions, the nephropathies in male rats following the recovery period were more significant than those of males examined at the 9- and 15-month interim evaluations. The main target organs of coumarin toxicity, identified by (Lake, 1999), were liver and lung.

Assessor's conclusions

In summary, there are no data on toxicity melilot extracts not containing ethanol. Data obtained indicate that coumarin causes: 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 is also associated with centrilobular hypertrophy, syncytial alteration, and eosinophilic focus in the liver. Coumarin is contained in melilot herb in only 0.3–0.8 per cent and the properties of other substances contained in the herbal substance may influence the toxicity.

3.3.3. Genotoxicity

Ethanollic melilot extract (DER unknown) was tested in three genotoxicity tests. In an Ames test conducted on 3 *Salmonella typhimurium* strains: TA98, TA100, TA1537, with or without metabolic activation, no increase of revertants over a normal range (1.0–1.6) was observed. In the chromosomal aberration test conducted on mice given 10 x diluted extract was administered (0.7 ml/kg) for 4 consecutive days, no induction of aberrations in bone marrow cells was observed. Also a dominant lethal mutation test was conducted on mice. The extract (1:10 diluted) was injected in the male mice which were then paired with virgin females. Administration of the extract did not increase the number of lethal mutations in implants and embryos (Khorram Khorshid, 2008).

Genotoxicity of coumarin has been studied in a number of relevant tests (NTP, 1993; 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 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 genotoxic agent. However, there are some inconsistencies in the data from different species, which should be kept in mind. On this basis it can be concluded provisionally, that coumarin is not a genotoxic carcinogen.

3.3.4. Carcinogenicity

Data on human carcinogenicity of melilot preparations are not available.

The IARC Working group ~~concluded~~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 (IARC monograph, 2000). The overall evaluation was that coumarin is *not classifiable as to its carcinogenicity to humans (Group 3)*. The U.S. Environmental Protection Agency came to the same conclusion.

Carcinogenicity of coumarin was found to be non-linear. Tumour formation, observed at high doses, is associated with hepatic and pulmonary toxicity (Lake, 1999). This suggests that coumarin is a non-genotoxic carcinogen in only those animal species in which it causes (metabolically induced) tissue toxicity.

3.3.5. Reproductive and developmental toxicity

There are no data on melilot preparations.

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 has shown no increase in malformation rates compared to controls, nor increased number of resorptions or fetal mortality (Grote & Weinmann, 1973).

The developmental toxicities of coumarin, 4-hydroxycoumarin and 7-hydroxycoumarin were observed in Frog Embryo Teratogenic Assay on *Xenopus* (FETAX) test in two concentrations, with and without metabolic activation. In the experiment without metabolic activation coumarin, 4-hydroxycoumarin and 7-hydroxycoumarin were developmentally toxic with following EC₅₀ (malformations) 0.08 mg/ml (TI=2); 0.18 mg/ml; 0.04 (TI=2.8). The use of metabolic activation increased developmental toxicity of coumarin and increased toxic potential of 4-hydroxycoumarin, while 7-hydroxycoumarin toxic potential remained unchanged. The authors suggested that highly epoxide intermediates formed by cytochrome P-450 oxidation and epoxide hydrolase may play a role in detoxification of the metabolites (Fort *et al.*, 1998).

The experiments with influence of coumarin on frog zebrafish embryos development (Weigt, 2012) indicate its possible embryotoxic potential. This effect was observed with doses higher than the blood concentrations that are obtained at therapeutic doses of melilot extracts.

3.3.6. Local tolerance

No studies on melilot extracts were available.

3.3.7. Other special studies

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 both hepatocytes or liver slices from rats, mice, rabbits and guinea-pigs, whereas monkey and human cells and/or slices appear to be resistant. By 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).

Local tolerance

No studies on melilot extracts were available.

3.3.8. Conclusions

Only limited toxicity data are available for melilot preparations. These data do not indicate any serious toxicity in normal therapeutic conditions. However, tests on reproductive toxicity have not been performed for melilot extracts.

The genotoxicity and carcinogenicity of defined herbal preparations have not been performed. Coumarin toxicity has been extensively studied; its primary target organ in rats and mice is the liver. However, toxicity was also observed in kidneys and lungs. Approximate no effect levels in rats and mice are in a range of 10–50 mg/kg regarding tissue toxicity. Thus, toxic effects occur at high doses of coumarin, which are not attained in normal use of melilot preparations. 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.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on the anti-inflammatory activity of melilot extract, to support the proposed indications are limited. The activity of coumarin is weaker than that of hydrocortisone. Coumarin was quickly absorbed from the melilot patches placed on skin (see below in 4.1.2). The distribution profiles in tissues show its special affinity to skin and connective tissues.

Non-clinical data on antiedematous activity of melilot extracts support their traditional use in venous circulatory swellings. The activity of the extracts was compared with the activity of coumarin. The stimulation of macrophages migration by coumarin was observed in edematous, injured or inflamed tissues. The mechanism of the reaction is not clarified.

Laboratory animal tissues showed after exposure to melilot extracts morphological effects such as decreased edema volume after burns.

Data on pharmacokinetics are only available from experiments with intraperitoneal radiolabelled coumarin administration and skin melilot extract or radiolabelled coumarin administration.

Data on interactions are not available.

Non-clinical information on the safety of melilot extracts is scarce.

There is no information on reproductive and developmental toxicity for melilot preparations used in humans. However, coumarin possesses some embryotoxic potential which is observed in fish and frog embryos at higher concentrations than blood levels obtained after therapeutic use of herbal medicinal products containing melilot preparations. For this reason (and in the absence of sufficient data from women), the use of these preparations during pregnancy and lactation cannot be recommended.

Genotoxicity and carcinogenicity studies have not been performed with melilot preparations.

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. (For safety data in humans see chapter 5.1)

Assessor's comments:

Assuming a hepatotoxic risk of coumarin doses above 90 mg/day and taking into account potential toxic doses above a cut point of 25 mg coumarin/day., the TDI level of 0.1 mg coumarin/body

weight/day given by EFSA, 2004, 2008 may also be used for herbal medicinal products (see also section 5.1).

4. Clinical Data

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

There are no special data on pharmacodynamics, regarding melilot herbal preparations.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

There are no pharmacokinetic data on melilot preparations after oral use.

In volunteers receiving an oral 60 ml dose of syrup (containing 17.6 mg of coumarin, 1.1 mg of o-coumaric acid and 8.9 mg kanurenoic acid) no peak absorption in serum was observed until 600 min after syrup administration. The limit of coumarin detections in plasma was 3 ng/ml (Gasparetto *et al.*, 2015). To obtain pharmacokinetic data the authors had to use a syrup with a higher amount of coumarin added. After 100 mg of coumarin had been added a peak of 8 ng/ml with appeared max 180 min after administration.

Pharmacokinetic data on coumarin skin permeation from cutaneous patches containing melilot extract are available (Minghetti *et al.* 2000). The authors studied, in two experiments, the permeation of coumarin from melilot extract patches through the skin. Samples of 2.54 cm² patches were first analysed on coumarin content and then dissolution tests were performed. The authors prepared 4 patches: containing melilot extract in two concentrations 0.95 g (1A) and 1.28 g (2A) in 100 g or coumarin 0.16 g (1B) and 0.22 g (2B) in 100 g. The content of coumarin was the same in patches with extract and with coumarin. The original melilot dry extract used for preparation of patches contained 17% to 20% of coumarin (w/w). The skin permeation was studied in two ways. *Ex vivo* permeation through human skin (stratum corneum and epidermis, from 3 different donors) was quicker from the patch containing lower concentration of melilot extract; after 5 hours about 25% of content of patch 1A and about 13% from 2A was absorbed; after 10 hours about 45% from patch 1A and 25% from 2A and after 24 hours over 80% of content of patch 1A and more than 50% from 2A. For patch 1A, containing $20.9 \pm 0.9 \mu\text{g}/\text{cm}^2$ of coumarin, the release rate was $\text{h}^{-0.5} 0.19 \pm 0.02$ and Flux $1.22 \pm 0.12 \mu\text{g}/\text{cm}^2 \cdot \text{h}$. For patch 2A, containing $23.4 \pm 1.6 \mu\text{g}/\text{cm}^2$ of coumarin, the release rate was $\text{h}^{-0.5} 0.17 \pm 0.01$ and Flux $0.79 \pm 0.07 \mu\text{g}/\text{cm}^2 \cdot \text{h}$. Using a stripping technique, the residue of coumarin in melilot patches placed on forearms skin of volunteers was measured. The permeation profile was nearly linear. Absorption of coumarin from both patches was similar: after 5 hours the coumarin content was about $2.5 \mu\text{g}/\text{cm}^2$, after 10 hours it was about $5 \mu\text{g}/\text{cm}^2$ and after 24 hours it was about $13 \mu\text{g}/\text{cm}^2$. Every hour $0.5 \mu\text{g}$ of coumarin diminished of the patches. There was no statistical difference in the quantity of coumarin permeated. Coumarin flux was not influenced by other components in the melilot extract. The authors observed a correlation between skin permeation in volunteers with the permeation recorded in *ex vivo* model on human SCE skin.

4.2. Clinical efficacy

4.2.1. Dose response studies

There are no dose-finding studies available. In the case of topical use (Minghetti *et al.*, 2000), there was no difference between intensity of coumarin permeation from 2.5 cm² patches with two coumarin concentrations of tested melilot extract.

4.2.2. Clinical studies (case studies and clinical trials)

Venous circulatory disturbances with feelings of heavy legs itching and swelling

Melilot mono preparations

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

Aloisi & Scondotto (1999) studied 4536 patients suffering from chronic venous insufficiency of various causes, treated with a daily dose of 4 to 8 mg of a melilot extract standardized to 20% coumarin for 3 to 8 months in the years 1995 to 1998. 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. According to the authors, 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%).

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. Subjective symptoms, e.g. pain and tension, and objective measurements, e.g. leg circumference/ultrasonography were scored at the beginning and after 90 and 180 days of treatment. An improvement of all variables was seen; however it is not possible to assess the contribution of melilot extract on treatment effects (Martignani *et al.*, 1997).

Due to the lack of an acceptable control group and of objective measurement of efficacy, the available data are not sufficient to propose an indication for well established medicinal use. However, the data supports a traditional use melilot preparation for venous disturbances like symptoms of heavy legs, oedemas, and nocturnal cramps.

Sprains, bruises

Melilot monopreparations

The efficacy of a product in form of sugar coated tablets, containing 25 mg of melilot extract (no specification given, coumarin content 0.25 mg), was assessed in a group of 80 patients with post-traumatic swellings. The authors observed that the addition of the melilot extract tablets to the conventional treatment, for 7 days after traumas, remarkably diminished symptoms of inflammation, pain and swellings in comparison to the group treated conventionally (Yang *et al.*, 2010, abstr.).

No clinical data are available from Europe.

The available clinical data for melilot preparation in treatment of sprains and bruises are only preliminary observation.

Therefore the data are not sufficient to propose a well-established use indication for the monograph.

Secondary indications

Melilot monopreparations

Anti-ulcer activity

A 3 center, controlled, randomized trial was conducted on 25 patients suffering from diabetic foot ulcers. Sixteen patients received intravenous infusions of a product, containing an extract of *Melilotus officinalis* (specification not available), additionally to the conventional treatment used in the ulceration. Nine patients (control group) received conventional therapy. The inclusion criteria were: diabetes mellitus (type 1 or 2) on medication; age 18–75 years; foot ulcers, open, without improvement for more than 2 weeks. Excluded were patients with severe heart failure, symptoms of chronic and severe ischemia, other situations that impair ulcer improvement. The patients were randomized in every study center. Patients received intravenously 4 cm³ of the product for 28 days, diluted in 50–100 cm³ of saline. In both groups conventional treatments were used: betaine baths, antibiotic therapy, pressure decompression. The primary recorded parameters were: ulcer diameters in planimetric evaluation and steadiness of regression. After 28 days of treatment a 64% regression of the ulcer surfaces in treated group, compared to 25% in conventional therapy group, which received saline infusions instead of the melilot extract (Larijani *et al.*, 2008).

The study was conducted on a small patients group and verum and placebo groups were not balanced. The authors admitted that further studies on larger population are required. Neither there are details on the strength of the product nor its standardisation.

Mastalgia

In an open clinical trial 50 patients with cyclic or non-cyclic mastalgia were treated with oral doses of high concentration melilot extract (no specification given, no dosage given) for 2 periods of months followed by a washout of 1 month. After 6 months the efficacy was assessed by clinical examination and a compilation of a symptom-related questionnaire for self-evaluation (name of questionnaire not mentioned). Therefore the measurement of efficacy remains unclear and can't be assessed. Efficacy was measured on 31 patients and for safety assessment 43 patients were included. 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).

4.3. Clinical studies in special populations (e.g. elderly and children)

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

Clinical pharmacology trials with *Melilotus officinalis* herba preparations were not performed.

The results of open clinical trials on use of melilot extract preparations in patients with symptoms of venous insufficiency, like feeling of heavy legs, lymphoedema of lower limbs, due to the lack of control groups and of objective efficacy measures are not sufficient to demonstrate efficacy at a level required for well established medicinal use. However, the results support the traditional use for the relieve symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances.

The use of melilot extracts in diabetic food ulcers was a subject of clinical trials in Asia. The indication and the method of administration used in the this study are not suitable for traditional use because they require medical supervision.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

There are no available clinical safety data on humans for melilot preparations.

Coumarin contained in herbal medicinal products is metabolized in humans predominantly via 7-hydroxylation by CYP2A6 and they seem to be generally less susceptible to hepatotoxicity than other species. Due to genetic polymorphisms, a high interindividual variability exists. Case reports of hepatotoxicity in humans are predominantly reported in daily doses above 90 mg coumarin, but a few case reports after a daily intake of 25 to 90 mg coumarin are also documented. Some authors pointed that data from patients treated with medicinal products revealed a few percent subgroup of human population being more sensible for the coumarin hepatotoxic effect (Abraham *et al.*, 2010). 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 1–6% (Caucasians) and 25–50% (Orientals) (Nakajima *et al.*, 2006).

In 2004, EFSA established a tolerable daily intake (TDI) for coumarin for 0.1 mg/kg body weight, based on available hepatotoxicity data. The proposed TDI was maintained in 2008 after reassessment of data and taking into account metabolism of coumarin human CYP2A6 population (EFSA 2008).

5.2. Patient exposure

Aside from market presence and data from studies, there are no data concerning patient exposure.

5.3. Adverse events, serious adverse events and deaths

Adverse events

In general melilot preparations were well tolerated in clinical trials. In some studies adverse events as gastrointestinal complaints, allergic reactions and photosensitivity are mentioned. So far, adverse events in Member States that have preparations on the market have not been recorded.

Data from WHO database Vigilyze Monitoring Center

The Vigilyze database contains data of 32 reports on adverse reactions observed in years 1994–2014 in patients, who have used products containing *Melilotus officinalis* L., herba (melilot) preparations. Most of the adverse reactions (27) were recorded from South Korea, 20 of them after parenteral administration (which is not used in Europe); 4 from France and 1 from Germany.

Eleven reactions were observed after oral use of *Melilotus officinalis* (melilot) extracts and only 1 reaction was recorded after topical use. 3 of the Korean cases were adverse reactions for oral or topical use forms, relevant to Europe. The reactions relevant to oral or topical preparations used in Europe were as follows: vomiting, nausea, contact eczema rhinitis, conjunctivitis, pruritus, rash, urticaria and ecchymosis.

For a cutaneous patch (*Emplastrum Meliloti*) of the European market, that contains oil extract of Meliloti herba and a colophony as additive, no adverse reactions have been reported. However, the colophony (rosin) is known to cause allergic skin reactions after occupational exposure.

Serious events and deaths

None are known for Meliloti herba and preparations thereof ~~for~~used by oral or topical administration.

5.4. Laboratory findings

There are no data on melilot preparations' influence on laboratory findings in humans. Sometimes transaminases elevation is attributed to interaction with coumarin contained in different products.

5.5. Safety in special populations and situations

So far, there were no reports on human embryotoxicity or teratogenicity caused by herbal medicinal products containing melilot preparations. For animal embryotoxicity and teratogenicity data on coumarin, see in 4.2.

5.5.1. Use in children and adolescents

None known. Preparations used orally are not suitable for children.

5.5.2. Contraindications

Hypersensitivity to melilot or to coumarin.

5.5.3. Special warnings and precautions for use

The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

Use to relieve symptoms of discomfort and heaviness of legs:

If the symptoms of thrombophlebitis or subcutaneous induration, sudden swelling of one or both legs, cardiac or renal insufficiency appear during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

Use for minor skin inflammation:

If symptoms of skin inflammation worsen or signs of skin infections occur during the use of the medicinal product for the treatment of minor skin inflammations, a doctor or a qualified health care practitioner should be consulted.

5.5.4. Drug interactions and other forms of interaction

There are no data on interactions of monocomponent medicinal products containing melilot preparation with other products.

There are only data on products containing melilot preparations in combination with other herbal preparations or substances of herbal origin.

Tamura *et al.*, (2012) reported a case of transaminases elevation in a 23 year-old woman with multiple sclerosis who has taken supplements with lutein (dose not specified) and a melilot supplement containing coumarin at a dose of 10 mg/day. She suffered two relapses and was admitted to the hospital with symptoms of jaundiced palms but without hyperbilirubinemia. Her ALT was only slightly elevated (41 IU/l). The patient was given subcutaneous injections of interferon beta 1-b at doses elevated from 4 MIU to 8 MIU. Fourteen day after the start of the interferon therapy the AST and ALT

levels rised markedly (235 and 681 IU/l accordingly). After the discontinuation of IFN-1b therapy and supplement intake, AST and ALT returned to normal levels. There was no evidence of hepatosis. Later the patient was given intramuscular injection of interferon beta-1a injection at 1.5 MIU weekly and the IFN-1a dose was gradually increased to 6 MIU without supplements intake and was able to continue the interferone treatment without signs of impaired liver function. The authors suggested that combination of interferone beta-1b and melilot supplement could cause severe liver dysfunction. The dose taken by the patient was twice the recommended tolerable daily intake. There is no data on the amount of lutein consumed together with melilot supplement. Excess amounts of lutein may cause jaundice symptoms, therefore this supplement component may have played a role in this case.

In two clinical studies intravenously administrated combination of melilot extract and rutoside did not affect parameters of blood clotting (prothrombin time respectively "coagulation analysis", details not given) (Völkner, 1961; Mayer & Sukthaworn, 1963).

There is one case report of a young woman in whom hemorrhagic diathesis (abnormal clotting function and mild menometrorrhagia) occurred as a result of drinking large amounts of a "seasonal tonic" herbal tea, for approximately 2 months. 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. A 66 year-old woman with cardiac arhythmia 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 for venous insufficiency, 3 times daily, the INR increased from 2 to 5.82. Either treatment was discontinued the INR returned to the usual values. Seven month later, a rechallenge with the crème was attempted. After one week the INR had again increased from 2.56 to 4.06. The patient denied any changes in treatment or alimentation. She did not use occlusive dressing but she massaged her legs 3 times per day when two times per day is recommended (Chiffolleau *et al.*, 2000, 2001).

5.5.5. Fertility, pregnancy and lactation

There are no human fertility data for melilot preparations.

Embryotoxic potential of 7-hydroxycoumarin and coumarin was recorded in animal tests. It is suggested to refrain from oral intake of large amounts of melilot preparations, during the first trimester of pregnancy. For animal embryotoxicity and teratogenicity data on coumarin, see in 4.2.

No influence on bleeding time, thrombelastogram and prothrombin time was seen in 2 clinical trials with combination of 60 mg coumarin daily with troxerutin, given to pregnant and breastfeeding women (Krajnovic *et al.*, 1974, 1977a, 1977b).

Because safety during pregnancy and lactation has not been established systematically and in the absence of sufficient data, the use during pregnancy and lactation is not recommended.

5.5.6. Overdose

Hager's Handbuch cites information that intake of 4 g of melilot extract triggered nausea, vomiting, headache and weakness. However the information could not be confirmed.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

None known

5.5.8. Safety in other special situations

Not applicable

5.6. Overall conclusions on clinical safety

There are no clinical safety data with herbal medicinal products, containing melilot preparations as single active ingredient.

6. Overall conclusions (benefit-risk assessment)

Clinical trials on use of melilot extract in patients with symptoms of venous insufficiency are not sufficient to show efficacy at a level required for well established medicinal use, because of lack of an acceptable control group and of objective efficacy measures. However, these studies support the traditional use of melilot preparations for ~~the~~ relieve of symptoms of discomfort and heaviness of legs related to minor venous circulatory disturbances.

Emplastrum Meliloti, containing melilot herb oil extract, has a long tradition of use for skin inflammations and mild sores. The use in skin inflammations could be considered plausible because melilot extract exhibited antiinflammatory properties in pre-clinical studies.

Due to the lack of sufficient safety data the use of melilot herb cannot be recommended during pregnancy and breast-feeding.

As no data from the use in children are available, the use of melilot herb preparations is not recommended in children.

Coumarin was considered to contribute to the activity of the melilot herb preparations as an active marker, although its pharmacological role among other substances possessing pharmacological activities has not been clarified. Therefore, neither constituents with known therapeutic activity nor active markers contributing to the therapeutic activity could be recognized by the HMPC.

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

Annex

List of references