European Medicines Agency
Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON 'COMMUNITY HERBAL MONOGRAPH ON *MELILOTUS OFFICINALIS* (L) LAM., HERBA' (EMEA/HMPC/220828/2008)

Table 1: Organisation(s) that commented on the draft 'Community herbal monograph on *Melilotus officinalis* (L.) Lam., herba' as released for consultation on 31 October 2007 until 15 February 2008.

	Organisation
1	The Association of the European Self-Medication Industry (AESGP)
2	The European Scientific Cooperative on Phytotherapy (ESCOP)
3	Kooperation Phytopharmaka, Germany

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Table 2: Discussion of comments

GENERAL COMMENTS TO DRAFT DOCUMENT
An interested party appreciates the above-mentioned draft document prepared by the Herbal Medicinal Products Committee (HMPC) as it provides harmonised and sound criteria which should facilitate the granting of marketing authorisation of product containing this plant in Europe. However, they consider that some modifications are necessary.
Another interested party welcomes in principle the preparation of the above-mentioned Community herbal monograph which may provide harmonized assessment criteria for herbal medicinal products in Europe.
SPECIFIC COMMENTS ON TEXT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
"Dry extracts (4.2-7.5:1), methanol 50 % V/V"	Should be given as integral number: e.g. 4 – 8 : 1 Decimals suggest accuracy which cannot be realised.	Accepted

4. CLINICAL PARTICULARS		
Paragraph no. line no.	**Comment and Rationale**	**Outcome**
4.1 Therapeutic indications	Oral use Bibliographic references and existing medicines on the market (cf. table) substantiate the traditional use of melilotus in the following indications: - to relieve symptoms of haemorrhoids - to relieve symptoms associated with chronic venous incompetence, in particular, painful and heavy legs, nocturnal cramps, pruritus and oedema - for symptomatic treatment of capillary vessels brittleness We would like these 3 indications to be added. *((Table with products and indications is provided))*	*Not accepted. The examples provided by AESGP have been marketed since 1987, 1990, 1994 and 2001. No evidence on 30 years of traditional use has been provided.*

4.2 Posology and method of administration	**Posology** **We agree with the daily dose of 5mg coumarin.** However, the definition of the European Pharmacopoeia monograph on "Meliloti herba" states that the herbal substance contains a '*minimum 0.3% of coumarin'* (i.e. 1.7 g of herbal substance with the lower content of 0.3 per cent coumarin, corresponds to 5mg coumarin). Hence, the daily doses of herbal drug preparations are conflicting with the maximum daily dose of coumarin. They should be modified accordingly. **Duration of use** For indications 1 and 2, the duration of use should be modified as follows: "There is no restriction. A long-term administration may be advisable. If the symptoms persist for more than 4 weeks during the use of the medicinal product, a doctor or qualified health care practitioner should be consulted." **Duration of use:** An additional sentence should be inserted before the items relating to specific indications: "No restriction; long-term use may be advisable"	See comment below. Not accepted. Such a situation needs medical advice for further diagnosis and follow up.

4.2 Posology and method of administration	The European Pharmacopoeia requires the herbal substance, Meliloti herba (dried drug), to contain **not less than 0.3 per cent of coumarin**. Taking into account that the coumarin content of the herbal substance is usually in the range **0.3-0.8 per cent** [1], the statement under *Adults and the elderly* that "The daily dose should not exceed 5 mg of coumarin in the final preparation" may be incompatible with some of the daily dosage levels recommended for the herbal preparations. For example, the amount of coumarin present in daily doses of the herbal substance (recommended immediately below the heading Oral use) could be within the following ranges: i) In 0.75-3 g of herbal substance (as an infusion), 2.25-24.0 mg of coumarin. Coumarin solubility: 1 g dissolves in 400 ml of cold water, 50 ml of boiling water [2]. ii) In 0.75-1.6 g of powdered herbal substance, 2.25-12.8 mg of coumarin. Among the extract dosages listed, if we consider extracts prepared from Meliloti herba with a coumarin content of 0.8 per cent, potentially the highest daily dose of coumarin would be present in: Dry extracts (4.2-7.5:1), methanol 50% V/V. Single dose: 200 mg of extract, 3 times daily. This corresponds to up to 4.5 g of herbal substance daily. With 100% extraction of coumarin, the daily dose could potentially contain up to 36 mg of coumarin. Even if the specification of the starting material, Meliloti herba, were to include a maximum content of coumarin, major inconsistencies may arise between the limit for coumarin (5 mg per day) and the daily doses recommended for herbal preparations. In these circumstances it seems pointless to specify precise dosages for eight different and very specific extracts; the majority of the stated dosages are unlikely to have a coumarin content within the daily limit.	Both requirements have to be fulfilled. If no herbal drug with a lower content can be found, or if no data are presented that demonstrate that the finished dosage form or preparation, e.g. tea infusions contains max. 5 mg of coumarin, the daily dose needs to be reduced to the minimum daily dose or single dose. Limit can be held, if coumarin content is close to the minimum or extraction is not 100%.

4.2 Posology and method of administration	**To avoid conflicting information we suggest a more general and flexible approach to daily doses of herbal preparations, with the maximum daily dose of 5 mg of coumarin as the primary criterion.** In any case, dosages relating to four types of dry extract have been duplicated in the text and one set should be deleted **Posology** *Adults, elderly* Daily dosage The daily dose should not exceed 5 mg of coumarin in the ~~final preparation.~~ herbal medicinal product. Maximum coumarin concentration should be measured by use of the HPLC method. **Remarks:** A daily dose of 3 – 30 mg coumarin is proposed by ESCOP (2003). In a clinical study, a dry extract of Meliloti containing 8 mg coumarin was given for 6 months (Pastura et al., al., 1999). …Liquid extracts (1:1), ***Extraction solvent:*** ethanol 30 % V/V: Single dose: 1.14 g, 3times daily. Dry extracts (5 – 7 : 1), ***Extraction solvent:*** ethanol 50 % V/V: Single dose: 160 mg extract, 3 times daily. ***For other extracts analogously.*** Dry extracts (4 - 8:1), ethanol 25 % m/m: Single dose: 100 mg extract, 3 times daily. ~~Dry extracts (4.2 – 7.5:1), methanol 50 % V/V:~~ Single dose: 200 mg extract, 3 times daily. Dry extracts (4 - 8:1), ethanol 35 % V/V: Single dose: 252 mg extract; once daily. ***Duplication of extracts mentioned before.***	Not accepted; final preparation intends to address the situation of herbal teas, where the concentration in the tea infusion is the relevant parameter, not the amount e.g. in the tea bag (herbal medicinal product). Safety is not fully established for higher phonologies. Addition of "extraction solvent" is not required Not accepted The extracts covered by the monograph have to be clearly defined. Text maintained (see above) Agreed.

4.3 Contraindications	According to literature search, no data support the statement "hypersensitivity to the active substance" as contraindication. Hence, this statement should be deleted. Unlike coumadin and other coumarin derivatives, coumarin has **no anti-coagulant activity**. So, no interactions between anticoagulants and melilotus-containing medicinal products can be suspected. It is proposed to delete the statement "Not to be used concomitantly with anticoagulant therapy".	Standard wording maintained.
	No data or information to support the statement "hypersensitivity to the active substance(s)" was found in our literature search. **We propose deletion of this statement**. Unlike warfarin, dicoumarol and certain other coumarin derivatives, coumarin itself is not an anticoagulant. We know of no reason to anticipate or suspect interactions between anticoagulants and preparations of Meliloti herba, nor to include the statement "Not to be used concomitantly with anticoagulant therapy". **We propose deletion of this statement.**	Standard wording maintained.

4.5 Interactions with other medicinal products and other forms of interaction	In line with our comments under section 4.3, it is proposed to delete the statement "Interactions between anticoagulants and Melilotus-containing medicinal products have been reported". See comments under 4.3. **We propose deletion of the statement "Interactions between anticoagulants and Melilotus-containing medicinal products have been reported"** **Kooperation Phytopharmaka** ~~Interactions between anticoagulants and Melilotus-containing medicinal products have been reported.~~ **Remark:** No interactions between anticoagulants and Melilotus-containing products have been found in the literature. However, interactions with anticoagulants are possible due to the coumarin compounds contained in Meliloti herba.	There are reports on possible interactions with products containing Melilotus extracts, even when used topically. Although a causal relationship cannot be established, a contraindication seems appropriate, because traditional melilotus products are intend to be used without any medical advice.
4.9 Overdose	According to literature search, the side effects "nausea, vomits, headache and weakness" seem to refer to coumarin overdose and not to meliloti herba overdose. From our literature search, the side effects "nausea, vomits, headache and weakness" appear to refer to overdoses of coumarin and not of Meliloti herba.	According to handbooks, such effects have been observed after taking 4 g of the herb (see assessment report).