



European Medicines Agency
Evaluation of Medicines for Human Use

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**OVERVIEW OF COMMENTS RECEIVED ON
'COMMUNITY HERBAL MONOGRAPH ON *PEUMUS BOLDUS* MOLINA, FOLIUM'**

Table 1: Organisations providing comments on the draft 'Community herbal monograph on *Peumus boldus* Molina, folium' as released for consultation on 8 May 2008 until 15 September 2008.

Organisation	
1	Association of the European Self-Medication Industry (AESGP)
2	European Scientific Cooperative on Phytotherapy (ESCOP)

Table 2: Discussion of comments

Comment and Rationale	Outcome
The interested party welcomes, in principle, the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for <i>Boldi</i> -containing products, should facilitate mutual recognition in Europe.	Endorsed
The interested party in principle, welcomes the preparation of the above-mentioned Community herbal monograph which may provide harmonised assessment criteria for herbal medicinal products in Europe.	Endorsed

Paragraph no. line no.	Comment and Rationale	Outcome
<p>2. Qualitative and Quantitative Composition'</p>	<p>We suggest adding the following under ii) Herbal preparations:</p> <p>- Dry extract (5:1; water) Justification: Such preparation is referred to in the literature listed in annex. It corresponds to the medicinal product named "Elusanes Boldo" which has been marketed in France since 1987.</p> <p>- Tincture (1:10) of dried leaves, extraction solvent ethanol 55% (V/V) Justification: The following speciality with <i>Boldi folium</i> has been marketed in France since 1965: Tincture Nature of the drug substance used: tincture (ethanol 55% V/V) Ratio drug/solvent: 1:10 Posology: 50-150 drops daily, as a single dose up to 1-4 times Therapeutic indications: herbal medicinal product traditionally used in the treatment of dyspeptic complaints. Date of first marketing: 1965</p>	<p>Endorsed. Inclusion of the dry aqueous extract is considered acceptable as ascaridole has low solubility in water. However, applicants would have to address ascaridole levels.</p> <p>Not endorsed.</p> <p>Tinctures are likely to have higher levels of ascaridole than aqueous extracts. In the absence of supporting data usage of ethanolic extracts is not considered acceptable.</p>

Different herbal preparations are described in the literature beside comminuted herbal substance for tea preparation. The following herbal preparations should be also considered:

- Powdered herbal substance
- Tincture (1:10, ethanol 60% v/v [[1,5] or 1:5, ethanol 80% v/v [2-4]
- Fluid extract (1:1, ethanol 45% v/v [1] or ethanol 80% v/v [4,6]) [5]

The BHP 1976 did not specifically describe ‘powdered herbal substance’ nor limit particle size in any way under Preparations and Dosage; it stated ‘Dried leaves. Dose 60-200 mg or by infusion...’ Relatively coarse particles, as implied by comminuted herbal substance for tea preparation’ would be suitable for an infusion, but the BHP statement implies that the dose of 60-200mg can also be taken orally as the dry herbal drug, for which ‘powdered herbal substance’ would be the most appropriate form.

The description of certain of those herbal preparations has been reiterated in more recent literature (eg.[7,8]) and also in the ESCOP monograph ‘Boldo folium’.

Additionally, the following herbal preparation should also be considered based on traditional registrations granted in France (see below 4.2 Posology):

- Dry extract (5:1) extraction solvent: water

Powdered herbal substance: Not endorsed.

Powdered herbal substance is not considered acceptable due to potential presence of ascaridole.

Ethanolic extracts: Not endorsed.

Ethanolic extracts (tincture, fluid extracts) are not considered acceptable as they are likely to have higher levels of ascaridole.

Paragraph no. line no.	Comment and Rationale	Outcome
2. Qualitative and Quantitative Composition'	According to the comment included under '2. Qualitative and Quantitative Composition' it is proposed to read: "Herbal substance or herbal preparations as herbal tea in solid or liquid dosage forms for oral use."	Partially endorsed: "Herbal substance or herbal preparations for oral use as herbal tea or in solid dosage forms.
Paragraph no. line no.	Comment and Rationale	Outcome
4.1. Therapeutic indications	<p>The following indications should be added:</p> <ul style="list-style-type: none"> - Traditional herbal medicinal product for hepatobiliary dysfunction - <p>Justification: see references in annex</p> <ul style="list-style-type: none"> - Traditional herbal medicinal product used in the treatment of dyspeptic complaints - <p>Justification: in accordance with the indication of the Boldo preparation above.</p>	<p>Not endorsed – as this is not suitable for self-medication as required for traditional registration.</p> <p>Endorsed – however, dyspepsia is already included as part of the proposed traditional indication.</p>
4.2 Posology and method of administration	<p>The following posologies should be added in accordance with the above:</p> <ul style="list-style-type: none"> - Dry extract (5:1; water): 400 mg per day in 2 intakes - Tincture: 50-150 drops of tincture in ethanol 55% V/V (1:10) daily, as a single dose up to 1-4 times daily 	<p>Inclusion of the dry aqueous extract is considered acceptable as ascaridole has low solubility in water. However, applicants would have to address ascaridole levels.</p> <p>Not endorsed:</p> <p>Tinctures are likely to have higher levels of ascaridole than aqueous extracts. In the absence of supporting data usage of ethanolic extracts is not considered acceptable.</p>

	<p>Posology described in the literature for the different herbal preparations:</p> <p>Single dose:</p> <ul style="list-style-type: none"> • Powdered herbal substance : 60 – 200 mg [1] • Tincture (1:10, ethanol 60% v/v: 0.5-2ml [1,5] • Fluid extract (1:1, ethanol 45% v/v: 0.1-0.3ml [1] <p>To be taken 3 times daily.</p> <p>Only as a single daily dose:</p> <ul style="list-style-type: none"> • Tincture (1:5, ethanol 80% v/v: 1-3ml [3,4] • Fluid extract (1:1, ethanol 80% v/v: 0.5-1ml [4] <p>Additionally, traditional use registrations have been granted in EU countries for: Encapsulated powdered boldi folium, each single dose containing either 200 mg (Spain) or 260 mg(France) (to be taken 3 times daily)</p> <p>Encapsulated dry aqueous extract (5:1), each single dose containing either 160 mg (to be taken 2 times daily) (France).</p> <p>We propose to complete the daily dosage of herbal preparations, based on the same daily dosage posology scheme, as follows:</p> <p>Single dose:</p> <ul style="list-style-type: none"> • Powdered herbal substance : 60 – 260 mg • Dry extract (5:1, aqueous): 160 mg 	<p><u>Powdered herbal substance: Not endorsed.</u></p> <p>Powdered herbal substance is not considered acceptable due to potential presence of ascaridole.</p> <p>Ethanollic extracts: Not endorsed.</p> <p>Ethanollic extracts (tincture, fluid extracts) are not considered acceptable as they are likely to have higher levels of ascaridole.</p> <p>Ascaridole is soluble in organic solvents and has low solubility in water. However, applicants would have to address ascaridole levels.</p> <p>Encapsulated powdered herbal substance is not considered acceptable due to potential presence of ascaridole..</p>
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	<ul style="list-style-type: none"> • Tincture (1:5, ethanol 80% v/v): 0.5-1ml • Tincture (1:10, ethanol 60% v/v): 0.5-2ml • Fluid extract (1:1, ethanol 80% v/v): 0.2-0.4ml • Fluid extract (1:1, ethanol 45% v/v): 0.1-0.3ml • <p>To be taken 2 to 3 times daily.</p> <p>Dosages already included in the ESCOP monograph “Boldi folium” are in line with these recommendations.</p>	<p>Inclusion of the dry aqueous extract is considered acceptable as ascaridole has low solubility in water. However, applicants would have to address ascaridole levels.</p> <p>One interested party has proposed 160 mg of aqueous extract 2-3 times daily (total 480 mg) whereas the other interested party has proposed 400 mg 2 times daily (total 800mg). The following is accepted:</p> <p>Dry extract (5:1, aqueous): up to 400 mg 2 times daily.</p> <p>Ethanollic extracts (tincture, fluid extracts) are not considered acceptable as they are likely to have higher levels of ascaridole.</p>
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