22 November 2011
EMA/HMPC/353910/2011
Committee on Herbal Medicinal Products (HMPC)

# Overview of comments received on Community herbal monograph on *Plantago lanceolata* L., folium (EMA/HMPC/437858/2010)

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Plantago lanceolata* L., folium as released for public consultation on 15 January 2011 until 15 April 2011

| | **Organisations and/or individuals** |
|---|---|
| 1 | AESGP, Brussels, Belgium |
| 2 | Kooperation Phytopharmaka, Bonn, Germany |

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Table 2: Discussion of comments

## General comments to draft document

| Interested party | Comment and Rationale | Outcome |
|---|---|---|
| AESGP | AESGP in principle welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for *Plantaginis lanceolatae folium*-containing products, should facilitate mutual recognition in Europe. We have the following comments:<br><br>There are some products in the German market containing ribwort plantain dry extract (DER 3-5:1), extraction solvent: ethanol 20% m/m, which have been authorised as well-established medicinal use products in Germany, but cannot prove a 30-years tradition for each product. | |

## SPECIFIC COMMENTS ON TEXT

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| **2. Qualitative and quantitative composition** | AESGP | **Traditional use:**<br><br>**1. Dry extract (DER 3-5:1), extraction solvent: ethanol 20 % m/m:**<br><br>We propose to add the following extract: Dry extract (DER 3-5:1), extraction solvent: ethanol 20% m/m. | Endorsed. The justification given by AESGP with reference to the soft extract already introduced into the monograph is reasonable. |

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| | | This extract is correctly mentioned in the draft HMPC Assessment Report (page 7, Well-established use, product 1 and 2, effervescent tablets), but this is unfortunately not reflected in the draft monograph. We can agree with the Rapporteur that considering the current requirements established by the HMPC, existing data is no longer sufficient to support the well-established use in the monograph.<br>Although according to the legislation, Community monographs do not bear a direct influence on existing well-established use marketing authorisations, by measure of precaution, we would ask that these preparations be transferred to the traditional use column of the monograph.<br><br>This is justified since a very similar preparation with the same extraction solvent is already defined in the draft monograph under traditional use:<br><br>e) Soft extract (DER 1.5-1.7:1); extraction solvent: ethanol 20% m/m<br><br>A soft extract is the direct precursor of a dry extract, the only difference is that a soft extract still contains relevant amounts of water (not ethanol, this is almost removed during concentration of the primary liquid extract under reduced pressure), whereas the corresponding dry extract directly results by further concentration to dry residue and contains only negligible amounts of water < 5%.<br>The native extract (and this is the virtual “active ingredient” of | |

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| | | a corresponding soft and dry extract) is identical.<br><br>Therefore the preparation e) of the monograph in principle already covers the dry extract we propose to add, but for the sake of certainty, we would like to see the dry extract being reflected as well.<br><br>Also the liquid extract preparation d) in the draft monograph *d) Liquid extract (DER 1:0.8-1.2); extraction solvent: ethanol 20-40% V/V* justifies the inclusion of the proposed dry extract, since the range of extraction solvent 20–40 % ethanol V/V covers the extraction solvent ethanol 20 % m/m, and the posology is comparable, too (see comments under 4.2). Therefore the preparation d) of the monograph in principle also already covers the dry extract. However, in order to avoid doubts, we would prefer to mention the dry extract itself as well.<br><br>**2. Liquid extract 1:5.8-5.9, extraction solvent: water**<br><br>We propose to include the 'liquid extract 1:5.8-5.9, extraction solvent: water' into the monograph. This extract is marketed in Germany as Gebauers Spitzwegerich Sirup, so far authorised according to section 109a of the Medicines Law (see encl 1), registration according to section 39a has been applied for (ENR 2177303). | Endorsed. The details of the proof of tradition have been checked and they do support the traditional use of this herbal preparation. |

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| | | **3. Herbal extracts from fresh plantago leaves (final ethanol content 45%V/V)**<br><br>**Comments:**<br>Preparations for oral and cutaneous use have been reported (see Weleda vademecum 1968 and 1992).<br>The preparation is a herbal extract (solvent ethanol) from fresh Plantago leaves (final ethanol content 45% *V/V*). The preparation is for oral use or in solid dosage (ointment) form for cutaneous use. These preparations should therefore be included in the monograph.<br><br>**Proposed changes:**<br>Insertion of the liquid dosage form from 10% ethanolic extracts from fresh *Plantago lanceolata* L. leaves for oral use and the solid dosage form (ointment containing 10% of the ethanolic extract) for external use. | Not endorsed.<br>The cream containing 10% Plantaginis lanceolatae folium is an anthroposophic medicinal product and its registration as homeopathic medicinal product was refused in 2005. The cutaneous use is not plausible based on the data summarised in the AR.<br>According to the data records of the German NCA an application for registration of the fluid was submitted in 1978. In 1991 this application was withdrawn. The tradition is not proven for a period of 30 years. |
| **3. Pharmaceutical form** | AESGP | In line with our request for addition of herbal extracts from fresh plantago leaves (final ethanol content 45% V/V), we would like to see 'cutaneous use' added in the pharmaceutical forms, as follows:<br><br>*"Comminuted herbal substance as herbal tea, powdered herbal substance in a solid dosage form and other herbal preparations in liquid or solid dosage forms for oral ~~and/or~~, oromucosal and/or cutaneous use."* | Not endorsed. See above. |

| Section number and heading | Interested party | Comment and Rationale | Outcome |
|---|---|---|---|
| **4.2 Posology** | AESGP | **Traditional use:**<br><br>**1. Dry extract (DER 3-5:1), extraction solvent: ethanol 20 % m/m:**<br><br>*Adolescents, adults and elderly*<br><br>For the dry extract (DER 3-5:1), extraction solvent: ethanol 20 % m/m we propose to add:<br><br>300 mg 3-4 times daily. One single dose of 300 mg is equivalent to 900–1500 mg of herbal drug (average: 1200 mg).<br>This corresponds perfectly to the posology of preparation e) where 804 mg of soft extract (DER 1.5–1.7:1) is defined as single dose, which corresponds to 1206–1366 mg of herbal drug equivalents (average 1286 mg).<br>The proposed dosage 3–4 times 300 mg dry extract is fully in line with the marketing authorisation granted by German BfArM for products 1+2 mentioned in the assessment report and additionally is comparable to the dosage stated in the HMPC draft monograph for the soft extract preparation e).<br><br>The posology of the liquid extract (DER 0.8–1.2:1 / average: 1.0) fully covers the proposed posology for the dry extract. A single dose of 0.4 to 1.9 g liquid extract DER 1:1 corresponds to 400–1900 mg herbal drug, which includes the proposed 1200 mg herbal drug equivalents (average) resulting from 300 | Partially endorsed. The posology for children from 3-4 years of age is adapted to the posology of the corresponding soft extract. |

<table>
<tr><th>Section number and heading</th><th>Interested party</th><th>Comment and Rationale</th><th>Outcome</th></tr>
<tr><td></td><td></td><td>mg dry extract DER 3-5:1.<br><br>Children<br>Since for the corresponding soft and liquid extracts preparations d) and e) the use in children from 5-11 years and from 3-4 years is recognised, the same should apply for the dry extract as well, as the native extracts in all three preparations are identical.<br><br>Therefore it should read:<br>5-11 years of age 3 times 300 mg of dry extract<br>3-4 years of age 2-3 times 300 mg of dry extract<br><br>Use in children under 3 years is not recommended.<br><br>2. Liquid extract 1:5.8-5.9, extraction solvent: water<br><br>The liquid extract 1:5.8-5.9, extraction solvent: water, is marketed as Gebauers Spitzwegerich Sirup with the following posology:<br><br><table><tr><td>Age</td><td>Single dose</td><td>Daily dose</td></tr><tr><td>Children < 1 year of age</td><td>n.a.</td><td></td></tr><tr><td>Children 1 – 4 years of</td><td>2 ml (=2.6 g) Gebauer's®</td><td>4-6 ml Gebauer's® Spitzwegerichsirup</td></tr></table></td><td>Partially endorsed. The posology is introduced for children from 3 years of age in parallel to other herbal preparations in the monograph.</td></tr>
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| Section number and heading | Interested party | Comment and Rationale | Outcome |
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| | | | |
|---|---|---|---|
| age | Spitzwegerichsirup (corr. to 0.18 g herbal substance) | (corr. to 0.360-0.54 g herbal substance) (2-3 times daily 2 ml Gebauer's® Spitzwegerichsirup |
| Children 5 – 12 years of age | 3 ml (=3.9 g) Gebauer's® Spitzwegerichsirup (corr. to 0.27 g herbal substance) | 6–12 ml Gebauer's® Spitzwegerichsirup (corr. to 0.54-1.09 g herbal substance) (2-4 times daily 3 ml Gebauer's® Spitzwegerichsirup) |
| Adolescents from 12 years onwards and adults | 4 ml (=5.2 g) Gebauer's® Spitzwegerichsirup (corr. to 0.36 g herbal substance) | 12–20 ml Gebauer's® Spitzwegerichsirup (corr. to 1.09-1.82 g herbal substance) (3-5 times daily 4 ml Gebauer's® Spitzwegerichsirup) |

The package leaflet is attached **(encl. 2).**

**3. Herbal extracts from fresh plantago leaves (final ethanol content 45% V/V)**

Insertion of the usual posology: "oral use: 10-15 drops per take, 2 to 3 takes a day. Cutaneous use: rub the ointment 1-3 times a day on the chest".

Not endorsed. See above.

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|---|---|---|---|
| Page 23, Lines 49-51<br>Page 24, Line 1 | Kooperation Phyto-pharmaka | It is correct that about 30% of patients with pollinosis are allergic to pollen from *Plantago lanceolata* (Wüthrich *et al.* 1977, Horak and Jäger 1980), 28% out of 82 patients with a clinical history of seasonal, respiratory allergy were skin test positive to plantain pollen extract.<br>This however does not mean that patients are allergic to leaf extract from *Plantago lanceolata*, as these preparations do not contain pollen and patients do not inhale the extracts. Also allergies after intake of Plantago preparations were not reported so far. | The remark will be considered in the wording of the AR. |
| Page 24, third line from the bottom | Kooperation Phyto-pharmaka | In the study cited only 593 patients were treated, not 598. | The remark will be considered in the wording of the AR. |

**References (cited by AESGP):**

Weleda vademecum 1968 and 1992

The complete German Commission C monographs - Blumenthal, Busse, Goldberg, Gruenwald, Hall, Klein, Riggins & Rister, 1998

Anthroposophische Arzneimittel – Commission C