



European Medicines Agency  
Evaluation of Medicines for Human Use

London, 4 September 2008  
Doc. Ref. EMEA/HMPC/102215/2008

**OVERVIEW OF COMMENTS RECEIVED ON  
'COMMUNITY HERBAL MONOGRAPH ON *SOLIDAGO VIRGAUREA* L., HERBA'  
(EMEA/HMPC/285758/2007)**

Table 1: Organisations providing comments on the draft 'Community herbal monograph on *Solidago virgaurea* L., herba' as released for consultation on 31 October 2007 until 15 February 2008.

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

**Table 2: Comments**

<b>Paragraph No.</b>	<b>Comment and Rationale</b>	<b>Outcome</b>
<b>GENERAL COMMENTS</b>	An interested party would like to comment on this HMPC draft Community herbal monograph. From our point of view, data on clinical experience justify an indication in the area of “well-established medicinal use”.	<p>Proposal of the introduction of the well-established use monograph could be based only on non-controlled, non-randomized clinical trials performed with use of dry extract of <i>Solidago virgaurea</i> (5.0-7.1:1). In these studies no statistical data were presented for clinical trials: Laszig R., Smiszek R, Stammwitz U, Henneicke-von Zepelin H-H, Akcetin Z. Klinische Anwendungsbeobachtungen zur Wirksamkeit und Sicherheit bei Monographie-konformem Einsatz eines Goldruten-extrakt-Präparates, <i>Drogenreport</i> 1999; 12:38-40; Schmitt M. Echte Goldrute normalisiert die Reizblase. Effective und nebenwirkungsarme Behandlung abakterieller Cystiden. <i>TW Urologie Nephrologie</i> 1996; 8:133-135.</p> <p>Therefore, there is no justification for inclusion of well-established use of <i>Solidago virgaurea</i> into the monograph.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
<p><b>2. Qualitative and quantitative composition</b></p>	<p><u>Well-established use</u></p> <p><b>With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended</b></p> <p>i) Herbal preparations</p> <ul style="list-style-type: none"> <li>- Liquid extract prepared with ethanol/water 16-25% v/v</li> <li>- Tincture (1:5) prepared with ethanol/water 45% v/v</li> <li>- Liquid fresh plant extract (1:1,5-2,5) prepared with ethanol/water 60% v/v</li> </ul> <p>Dry extract (5-7:1) prepared with ethanol/water 30-60% v/v</p>	<p>Proposal of the introduction of the well-established use monograph is based only on non-controlled, non-randomized clinical trials performed with use of dry extract of <i>Solidago virgaurea</i>.</p> <p>In these studies no statistical data were presented: Laszig R., Smiszek R., Stammwitz U, Henneicke-von Zepelin H-H, Akcetin Z. <i>Klinische Anwendungsbeobachtungen zur Wirksamkeit und Sicherheit bei Monographie-konformem Einsatz eines Goldruten-extrakt-Präparates, Drogenreport</i> 1999 12:38-40; Schmitt M. <i>Echte Goldrute normalisiert die Reizblase. Effective und nebenwirkungsarme Behandlung abakterieller Cystiden. TW Urologie Nephrologie</i> 1996; 8:133-135.</p> <p>The clinical studies with use of ethanolic extract were performed on limited number of patients (1<sup>st</sup> Study on healthy volunteers), and have never been published! (Klinisch-Experimentelle Studie Nr 23223. P 1. 1992. Bioforce AG). Klinisch-Experimentelle Studie Nr 23223. P 2. 1992. Bioforce AG).</p> <p>The quality of research data can not provide the adequate level of evidence required for well-established use. Therefore, there is no justification for inclusion of well-established use of <i>Solidago virgaurea</i> into the monograph.</p>
	<p>In clinical examinations with golden rod herb dry extracts prepared with 30% (V/V) ethanol (Bader 2006, available at HMPC) have been examined and – in a pharmacodynamic double-blind study – a tincture prepared with 45 % (V/V) ethanol (ESCOP 2003). Typical preparations from golden rod used against disorders of the urinary tract contain extracts with 16-25% (V/V) ethanol as a solvent and tinctures with 45% (V/V) ethanol.</p>	<p>Cited monographs of Bader (2006) and ESCOP (2003) are not presenting original data from clinical trials. Therefore they are not suitable to justify the clinical efficacy of the extracts.</p> <p>All interested parties have two opportunities to submit full text articles that they consider to be relevant for the assessment: at the beginning of assessment (calls for submission of scientific data) and during the consultation period.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
	<p>A combination of golden rod and other anti-inflammatory herbs, such as <i>Fraxinus excelsior</i> and <i>Populus tremula</i> (60% ethanolic extracts) was active in pharmacological tests and efficacious in a large number of clinical studies (Gundermann and Müller 2007). The use of golden rod extract should therefore be regarded as a well-established use also in rheumatic disorders. A community monograph for the combination of golden rod with <i>Fraxinus excelsior</i> and <i>Populus tremula</i> is suggested.</p> <p>Golden rod is also used in rheumatic disorders in combination with other anti-inflammatory herbs, such as <i>Fraxinus excelsior</i> and <i>Populus tremula</i>. This combination (60% ethanolic extract) was found active in many pharmacological test models, and also efficacious in 13 double-blind, 5 single-blind, 2 comparative and 19 open, non-comparative studies (Gundermann and Müller 2007).</p> <p>The pharmacological studies on the extract combination demonstrate that golden rod extract contributes to the overall effect. The use of golden rod extract can therefore be considered well-established not only in urinary tract disorders but also in rheumatic disorders.</p> <p>We also suggest that a Community Monograph on the combination <i>Solidago virgaurea</i>, <i>Fraxinus excelsior</i> and <i>Populus tremula</i> be developed.</p>	<p>The proposal of inclusion of the new community monograph for the combination of golden rod with <i>Fraxinus excelsior</i> and <i>Populus tremula</i> will be examined by the Committee.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
<p><b>2. Qualitative and quantitative composition</b></p>	<p><u>Well-established use</u> With regard to the marketing authorisation application of Article 10(a) of Directive 2001/83/EC as amended</p> <ul style="list-style-type: none"> <li>i) Herbal preparations <ul style="list-style-type: none"> <li>- Liquid extract prepared with ethanol/water 16-25% v/v</li> <li>- Tincture (1:5) prepared with ethanol/water 45% v/v</li> <li>- Liquid fresh plant extract (1:1,5-2,5) prepared with ethanol/water 60% v/v</li> <li>- Dry extract (5-7:1) prepared with ethanol/water 30-60% v/v</li> </ul> </li> </ul> <p><u>Traditional use</u> With regard to the registration application of Article 16d(1) of Directive 2001/83/EC as amended</p> <ul style="list-style-type: none"> <li>ii) Herbal substance Dried flowering aerial parts of <i>Solidago virgaurea</i> L.</li> <li>iii) Herbal preparations <ul style="list-style-type: none"> <li>- Liquid extract (1:1) prepared with ethanol/water 25% v/v</li> <li>- Tincture (1:5) prepared with ethanol/water 45% v/v</li> <li>- Liquid fresh plant extract (1:1,5-2,5) prepared with ethanol/water 60% v/v</li> <li>- Dry extract (5-7:1) prepared with ethanol/water 30-60% v/v</li> </ul> </li> </ul> <p>Comminuted herbal substance</p> <p><u>Rationale:</u> Dry extracts of golden rod herb prepared with 30% ethanol was clinically tested (Bader 2006) and a tincture prepared with 45% ethanol was the subject of a pharmacodynamic double-blind study (Anon 2003). Extracts of golden rod with 16-25% ethanol or 45% ethanol tinctures are commonly used against disorders of the urinary tract.</p>	<p>Proposal of the introduction of the <i>well-establish use Monograph</i> is based only on non-controlled, non-randomized clinical trials performed with use of dry extract of <i>Solidago virgaurea</i>.</p> <p>In these studies no statistical data were presented: Laszig R., Smiszek R, Stammwitz U, Henneicke-von Zepelin H-H, Akcetin Z. Klinische Anwendungsbeobachtungen zur Wirksamkeit und Sicherheit bei Monographie-konformem Einsatz eines Goldruten-extrakt-Präparates, <i>Drogenreport</i> 1999; 12:38-40; Schmitt M. Echte Goldrute normalisiert die Reizblase. Effective und nebenwirkungsarme Behandlung abakterieller Cystiden. <i>TW Urologie Nephrologie</i> 1996; 8:133-135.</p> <p>The last two clinical studies with use of ethanolic extract were performed on limited number of patients (1<sup>st</sup> Study on healthy volunteers), and were never published. (Klinisch-Experimentelle Studie Nr 23223. P 1. 1992. Bioforce AG). Klinisch-Experimentelle Studie Nr 23223. P 2. 1992. Bioforce AG).</p> <p>The quality of research data can not provide the adequate level of evidence required for well established use. Therefore, there is no justification for well-established use for <i>Solidago virgaurea</i> for inclusion into the monograph.</p> <p>Cited monographs of Bader (2006) and Anon (2003) do not present original data from clinical trials. Therefore can not justify the clinical efficacy of the extracts.</p> <p>The clinical trials of the fixed combination of <i>Populus tremula</i>, <i>Solidago virgaurea</i> and <i>Fraxinus excelsior</i> have shown in patients with different subtypes of rheumatic diseases the anti-inflammatory and analgesic efficacy comparable to NSAID treatment (Chrubasik and Pollak 2003; Ernst 2004; Jorcken and Okpanyi 1996; Klein-Galczinsky 1999).</p> <p>The proposal of inclusion of the new community monograph for the combination of golden rod with <i>Fraxinus excelsior</i> and <i>Populus tremula</i> will be examined by the Committee.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
<b>3. PHARMA- CEUTICAL FORM</b>	<p><u>Well-established use</u> Herbal preparations in liquid and solid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.</p> <p><u>Traditional use</u> Herbal substance or herbal preparation in solid or liquid dosage forms or as a herbal tea for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.</p> <p><u>Rationale:</u> This definition corresponds to the definition of the German Commission E monograph and cover products for which there is a long standing experience. The definition is also in line with the recommendations of the ESCOP monograph (Anon 2003).</p>	<p>The quality of research data is not sufficient to justify the adequate level of evidence required for a well-established use monograph.</p> <p><u>Traditional use</u> Rapporteur fully supports the opinion.</p>
<b>4.1. Therapeutic indication</b>	<p>We suggest to add the following indication under “well-established medicinal use”: Irrigation of the urinary tract, especially in cases of inflammation and renal gravel, and as an adjuvant in the treatment of bacterial infections of the urinary tract.</p> <p>This indication corresponds to the ESCOP monograph and is supported by two studies quoted in the ESCOP monograph. They can be seen as clinical experience and fulfil the criteria of the well-established medicinal use (Schmitt 1996, Laszig et al. 1999; already included in the HMPC list of references).</p>	<p>In view of lack of controlled clinical trials in patients with symptoms proposed as:...cases of inflammation and renal gravel.... the description of such serious clinical symptoms can not be included to the monograph for traditional use.</p> <p>See above</p> <p>The mentioned articles of Schmitt 1996, Laszig et al. 1999 do not present statistical data. The quality of research data cannot provide the adequate level of evidence required for well-established use monograph.</p>
	<p><u>Well-established use</u> Irrigation of the urinary tract, especially in cases of inflammation and renal gravel, and as an adjuvant in the</p>	<p><u>Well-established use</u> The quality of research data cannot provide the adequate level of evidence required for well established use monograph.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
	<p>treatment of bacterial infections of the urinary tract. Treatment of rheumatic disorders.</p> <p><u>Traditional use</u> Traditional herbal medicinal product to increase the amount of urine, to achieve flushing of the urinary tract as adjuvant in minor urinary complaints. Treatment of rheumatic disorders. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.</p>	<p>In view of lack of controlled clinical trials in patients with symptoms proposed as:...cases of inflammation and renal gravel.... the description of such serious clinical symptoms cannot be included to the monograph.</p> <p><u>Traditional use</u> Rapporteur fully supports opinion.</p> <p>The quality of research data cannot provide the adequate level of evidence required for well established use monograph.</p> <p>Cited monographs of Bader (2006) and Anon (2003) do not present original data from clinical trials. Therefore they cannot justify the clinical efficacy of the extracts.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
<p><b>4. CLINICAL PARTICULARS</b></p> <p><b>4.1 Therapeutic indications</b></p>	<p><u>Rationale:</u> The well-established use in the treatment of disorders of the urinary tract corresponds to the indication mentioned in ESCOP and Hager monograph (Anon 2003; Bader 2006). This is also in line with the ESCOP monograph which cites use as an aquaretic in inflammatory disorders of the urinary tract, and in prevention against the formation of gravel and stones (Schilcher and Kammerer 2003). This is also supported by two clinical studies (quoted in the ESCOP monograph) which fulfil the criteria of well-established medicinal use (Schmitt 1996, Laszig et al. 1999; already included in the HMPC list of references).</p> <p>The use in case of rheumatic inflammatory disorders of the joints is also known and recommended (Schilcher and Kammerer 2003) and mentioned, as traditional use, in the Hager monograph (Bader 2006). Such use is also stated in the Madaus monograph from 1938, where not only the anti-inflammatory effect is mentioned, but also a tea preparation (combination) for the treatment of rheumatic disorders is suggested (Madaus 1938).</p> <p>Golden rod extracts (60% ethanol) in combination with Fraxinus and Populus have been repeatedly tested in a number of clinical trials against rheumatic disorders (Gundermann and Müller 2007). Golden rod has been proved to make its own and distinct contribution to the overall efficacy; therefore, the indication of golden rod herb extract as well-established in the treatment of rheumatic disorders is justified.</p>	<p>No statistical data were presented for mentioned clinical trials: Laszig R., Smiszek R, Stammwitz U, Henneicke-von Zepelin H-H, Akcetin Z. Klinische Anwendungsbeobachtungen zur Wirksamkeit und Sicherheit bei Monographie-konformem Einsatz eines Goldruten-extrakt-Präparates, <i>Drogenreport</i> 1999, 12:38-40; Schmitt M. Echte Goldrute normalisiert die Reizblase. Effective und nebenwirkungsarme Behandlung abakterieller Cystiden. <i>TW Urologie Nephrologie</i> 1996; 8:133-135.</p> <p>It is the opinion of the Committee that these articles are not sufficient for the proposed change to the monograph.</p> <p><u>Well-established use</u> See above</p>



Paragraph no. line no.	Comment and Rationale	Outcome
<p><b>4.2 Posology and method of administration</b></p>	<p><b>Posology</b>  <i>Adolescents over 12 years of age, adults</i>            Single dose            - 3-5 g dried herb in 150 ml of water for preparations of an herbal tea, 2-4 times daily            - Equivalent preparations  <i>Children of 1-12 years of age</i>            Single dose            - 1-2 g dried herb in 150 ml of water for preparations of an herbal tea, 2-4 times daily            - Liquid extract: 0.5 – 2 ml, 3 times daily            - Tincture: 0.5 – 2 ml, 3 times daily            - Dry extract: 350 – 450 mg, 3 times daily</p> <p><b>Duration of use</b>            No restriction.            Medical attention should be sought if symptoms persist during the use of the medicinal product.</p> <p><b>Method of administration</b>            Oral use.            For extracts, ensure appropriate fluid intake</p> <p><b>Posology</b>  <i>Adolescents over 12 years of age, adults</i>            Single dose            - 3-5 g dried herb for preparations of an herbal tea, 2-4 times daily            - Liquid extract: 0.5 – 2 ml, 3 times daily            - Tincture: 0.5 – 2 ml, 3 times daily            - Dry extract: 350 – 450 mg, 3 times daily  <del>The use in children under 4 years of age is not recommended (see 4.4 special warnings and precautions for use).</del></p>	<p><u>Well-established use</u>            See above</p> <p>The quality of research data cannot provide the adequate level of evidence required for well-established use monograph.</p> <p><u>Traditional use</u>            The increase of the upper range of the single dose of dried herb from 4 to 5 g can be accepted. However, the single dose of the dried herb according to ESCOP Monograph (2003) and PDR (2000) is: 2 – 4 g.</p> <p>Single dose of dried herb in Bader publication is 3-5 g (for this information reference source is: Standardzulassungen für Fertigarzneimittel (1986) Goldenrutenkraut, Govi Verlag, Pharmazeutischer Verlag, Frankfurt/Main, Deutscher Apotheker Verlag, Stuttgart.            Moreover, the daily dose of 6 – 12 g is recommended (BAz Nr. 50 vom 13.03.1990), the same range of daily dose is proposed by PDR (2000).</p> <p>As no data on safety of use in children are available, products containing <i>Solidago virgaurea</i> L. cannot be recommended for use in children below the age of 12 years.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
	<p><b>Duration of use</b> The herbal substance is traditionally used over a period of 2 up to 4 weeks. If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.</p> <p>Medical attention should be sought if symptoms persist during the use of the medicinal product.</p> <p><b>Method of administration</b> Oral use. For extracts, ensure appropriate fluid intake.</p>	<p>The sentence: <i>Medical attention should be sought.....</i> is a repetition of the previous one: <i>If the symptoms persist during the use....</i>, therefore it does not need to be added.</p>
	<p>Medical attention should be sought if symptoms persist during the use of the medicinal product.</p> <p><b>Method of administration</b> Oral use. For extracts, ensure appropriate fluid intake.</p> <p><u>Rationale:</u> The information added in the ‘well-established use’ column is derived from the ESCOP (Anon 2003) and the Hager monographs (Bader 2006). The dose for adults is copied from the ‘German standard registration’, which states “3-5g per single dose”.</p> <p>The ESCOP monograph indicates a higher dose for children than for adults, which has been taken into account in this suggestion by adapting the dose to the range recommended for traditional use.</p> <p>The limitation of the dose for children and the warnings against the use of golden rod preparations in children is not supported by the monographs and the clinical experience, although the conditions (prevention of kidney stone formation and rheumatic disorders) are of no major relevance for children.</p>	<p>The sentence: <i>Medical attention should be sought.....</i> is a repetition of the previous one: <i>If the symptoms persist during the use....</i>, therefore it does not need to be added.</p> <p><u>Well-established use</u> See above</p> <p>As no data on safety of use in children are available, products containing <i>Solidago virgaurea</i> L. cannot be recommended for use in children below the age of 12 years.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
<p><b>4.2 Posology and method of administration</b></p>	<p><u>Traditional use</u></p> <p><b>Posology</b>  <i>Adolescents over 12 years of age, adults</i>  Single dose</p> <ul style="list-style-type: none"> <li>- 3-5 g dried herb for preparations of an herbal tea, 2-4 times daily</li> <li>- Liquid extract: 0.5 – 2 ml, 3 times daily</li> <li>- Tincture: 0.5 – 2 ml, 3 times daily</li> <li>- Dry extract: 350 – 450 mg, 3 times daily</li> </ul> <p><del>The use in children under 4 years of age is not recommended (see 4.4 special warnings and precautions for use).</del></p> <p><b>Duration of use</b>  The herbal substance is traditionally used over a period of 2 up to 4 weeks.  If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.  Medical attention should be sought if symptoms persist during the use of the medicinal product.</p> <p><b>Method of administration</b>  Oral use.  For extracts, ensure appropriate fluid intake.</p>	<p><u>Traditional use</u></p> <p>The increase of the upper range of the single dose of dried herb from 4 to <b>5</b> g can be accepted. However, the single dose of the dried herbal substance (Please, check consistency throughout the text) according to ESCOP Monograph (2003) and PDR (2000) is: 2 – 4 g.</p> <p>Single dose of dried herb in Bader Monograph is 3-5 g (for this information reference source is: Standardzulassungen für Fertigarzneimittel (1986) Goldenrutenkraut, Govi Verlag, Pharmazeutischer Verlag, Frankfurt/Main, Deutscher Apotheker Verlag, Stuttgart).</p> <p>Moreover, the daily dose of 6 – 12 g is recommended (BAz Nr. 50 vom 13.03.1990), the same range of daily dose is proposed by PDR (2000).</p> <p>As no data on safety of use in children are available, products containing <i>Solidago virgaurea</i> L. cannot be recommended for use in children below the age of 12 years.</p> <p>The sentence: <i>Medical attention should be sought.....</i> is a repetition of the previous one: <i>If the symptoms persist during the use....</i>, therefore it does not need to be added.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
<p><b>4.3 Contra- indications</b></p>	<p><u>Well-established use</u> Hypersensitivity to the active substance or to other plants of the Asteraceae family. European golden rod should not be used in patients with oedema due to impaired heart or kidney function.</p> <p><u>Rationale:</u> The contraindications in the left column are taken from the ESCOP and Hager monographs (Anon 2003, Bader 2006).</p> <p><u>Traditional use</u> Hypersensitivity to the active substance or to <i>other plants of the Asteraceae family</i>. Conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal diseases or obstructions of the urinary tract).</p>	<p><u>Well-established use</u> See above</p> <p><u>Traditional use</u> Agreed.</p>
<p><b>4.4 Special warnings and precautions for use</b></p>	<p><u>Well-established use</u> None required.</p> <p><u>Rationale:</u> Neither the ESCOP nor the Hager monographs report any warnings or precautions for use (Anon 2003, Bader 2006)</p> <p><u>Traditional use</u> The use is not recommended in children under 12 years of age because of the lack of available experience. If complaints of symptoms such as fever, dysuria, spasm or blood in the urine occur during the use of <i>the</i> medicinal product, a doctor or a qualified health care practitioner should be consulted. For tinctures and extracts containing ethanol, the appropriate labelling for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use", must be included.</p>	<p><u>Well-established use</u> See above</p> <p><u>Traditional use</u> Agreed</p>

Paragraph no. line no.	Comment and Rationale	Outcome
<p><b>4.5 Interactions with other medicinal products and other forms of interaction</b></p>	<p><u>Well-established use</u> None reported. <u>Rationale:</u> Neither the ESCOP nor the Hager monographs report any interactions (Anon 2003, Bader 2006)</p> <p><u>Traditional use</u> Concomitant treatment with synthetic diuretics is not recommended.</p>	<p><u>Well-established use</u> See above</p> <p><u>Traditional use</u> As the exact mechanism of diuretic action of <i>Solidago virgaurea</i> is not known, concomitant use of synthetic diuretics may induce fluid and electrolyte imbalance. The statement appears now as a warning in section 4.4.</p>
<p><b>4.6 Pregnancy and lactation</b></p>	<p><u>Well-established use</u> Safety during pregnancy and lactation has not been established. No adverse effects have been reported from the use of Herba Solidaginis (golden rod herb) as a medicinal product during pregnancy and lactation. In the absence of sufficient data, the use during pregnancy is not recommended. <u>Rationale:</u> This statement is in line with the ESCOP monograph (Anon 2003) Textbooks describe no known harmful effects in pregnant women in limited cases available and compatibility but specify compatibility with breastfeeding (Mills and Bone 2005).</p> <p><u>Traditional use</u> Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.</p>	<p><u>Well-established use</u> See above</p> <p><u>Traditional use</u> Full agreement of the rapporteur. Despite the opinion of compatibility with breastfeeding (Mills and Bone 2005), safety of use was not confirmed.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
<p><b>4.7 Effects on ability to drive and use machines</b></p>	<p><u>Well-established use</u> None known.</p> <p><u>Rationale:</u> As stated in the ESCOP monograph (Anon 2003)</p> <p><u>Traditional use</u> No studies on the effect on the ability to drive and use machines have been performed.</p>	<p><u>Well-established use</u> As above</p> <p><u>Traditional use</u> Agreed</p>
<p><b>4.8 Undesirable effects</b></p>	<p><u>Well-established use</u> None reported.</p> <p><u>Rationale:</u> Observational studies in 2232 patients (2-4 weeks treatment) showed an excellent tolerability with only one suspected case report of heartburn (Annon 2003). Hager mentions 12 drop-outs associated with abdominal complaints and ‘allergic reactions’ in an observational study of 3927 patients, whereas in another observational study in 1487 patients, there was only one report of heartburn as a non-syndrome related adverse event (Bader 2006). Therefore, we propose using the text of the ESCOP monograph (Anon 2003).The reference to hypersensitivity reactions is clearly linked to the references - also cited in the ESCOP monograph (Anon 2003; Schätzle et al. 1998). To date, this seems to be a single case (Myers and Wohlmuth 2005), which does not point to an outstanding allergenic potential. Experience drawn from animals showed that goldenrod was a weak sensitizer (Zeller et al. 1985).</p> <p><u>Traditional use</u> Hypersensitivity reactions and gastrointestinal complaints may occur. The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or a qualified health care practitioner should be consulted.</p>	<p><u>Well-established use</u> See above</p> <p><u>Traditional use</u> Agreed</p> <p>Even small number of registered abdominal complaints during treatment indicates the necessity of including such undesirable effects into the monograph.</p> <p>The hypersensitivity for <i>Asteracaeae</i> family is commonly known and is included in the monograph.</p>

Paragraph no. line no.	Comment and Rationale	Outcome
4.8 Undesirable effects	In accordance with the ESCOP monograph we suggest “none reported”, because there is no evidence available on hypersensitivity reactions and gastrointestinal complaints.	In the opinion of the Committee the exclusion of the proposed symptoms of the gastrointestinal complaints is not justified. The possibility of hypersensitivity reactions for Asteraceae spp. should be presented in the monograph. Patients suffering from allergic contact dermatitis due to <i>Compositae</i> species are requested to avoid contacts with <i>Solidago virgaurea</i> (De Jong et al. 1998; Lundh et al. 2006; Stingeni et al. 1999). The sensitizing capacity depends on the occurrence of sesquiterpene lactones (Schätzle et al. 1998; Zeller et al. 1985).
4.9 Overdose	<p><u>Well-established use</u> No case of overdose has been reported.</p> <p><u>Rationale:</u> As stated in the ESCOP monograph (Anon 2003)</p> <p><u>Traditional use</u> No case of overdose has been reported.</p>	<p><u>Well-established use</u> See above</p> <p><u>Traditional use</u> Agreed</p>
5. PHARMACOLOGICAL PROPERTIES 5.1 Pharmacodynamic properties	<p><u>Well-established use</u> <i>In vitro</i> and <i>in vivo</i>, preparations from Herba Solidaginis (golden rod herb) have been shown to possess antimicrobial, spasmolytic, anti-inflammatory and diuretic effects, and to prevent stone formation in the urinary tract. Extracts from Solidaginis herba, respectively its combination with <i>Fraxinus excelsior</i> and <i>Populus tremula</i> extract have been shown to be clinically efficacious in urinary tract disorders and rheumatic disorders, respectively.</p> <p><u>Rationale:</u> Various extracts and preparations of golden rod herb have shown a number of effects (cf. Schmitt 1996, Laszif et al.</p>	<p><u>Well-established use</u> See above</p>

Paragraph no. line no.	Comment and Rationale	Outcome
	<p>1999, clinical references mentioned under section 4.1). The following effects are mentioned in the additional references (i.e. not already included in the HMPC list of references or in the ESCOP monograph 2003):</p> <ul style="list-style-type: none"> <li>- anti-microbial effects <i>in vivo</i></li> <li>- spasmolytic effects <i>in vivo</i> and <i>in vitro</i></li> <li>- anti-inflammatory effects <i>in vitro</i> and <i>in vivo</i></li> <li>- diuretic and anti-lithiasis effects <i>in vivo</i></li> </ul> <p>The aquaretic and anti-inflammatory effects of a tincture from golden rod herb have been evidenced in a placebo controlled trial. Effects of dry extracts on the symptoms of irritable bladder syndrome were confirmed in observational studies (Anon 2003; Bader 2006). This confirms the well-established use of golden rod herb on disorders of the urinary tract.</p> <p><u>Traditional use</u> Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended.</p>	<p><u>Traditional use</u> Agreed</p>
<p><b>5.2 Pharmacokinetic properties</b></p>	<p><u>Well-established use</u> No data available.</p> <p><u>Rationale:</u> Kinetic data are only available for leiocarposide, a marker compound of golden rod extract (Anon 2003, Bader 2006). These data are, however, not applicable to the oral use of <i>Solidaginis herba</i> preparations.</p> <p><u>Traditional use</u> Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended.</p>	<p><u>Well-established use</u> See above</p> <p><u>Traditional use</u> Agreed</p>



Paragraph no. line no.	Comment and Rationale	Outcome
5.3.Pre-clinical safety data	<p><u>Well-established use</u></p> <p>Acute toxicity in mice was determined with 600 mg/kg body weight on i.p. administration of an ethanolic extract.</p> <p><u>Traditional use</u></p> <p>Not required as per article 16c(1)(a)(iii) of Directive 2001/83/ES as amended, <del>unless necessary for the safe use of the product.</del></p> <p><del>Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.</del></p> <p><u>Rationale:</u></p> <p>Directive 2001/83/EC does not require pre-clinical safety data. Safety of traditionally used products is sufficiently characterised by long-standing experience. The restriction “unless necessary for the safe use of the product” does not apply in case of <i>Solidago</i>, as there is no evidence of unsafe use.</p> <p>The oral LD<sub>50</sub> of the marker compound leiocarposide was 1.55 g/kg body weight in rats. Acute toxicity in mice was determined with 600 mg/kg body weight on i.p. administration of an ethanolic extract.</p>	<p>Not endorsed.</p> <p>In the mentioned paper of Sharma et al. 1978 (cited after Mills &amp; Bone) there are no data concerning toxicity of <i>Solidago virgaurea</i>. Moreover, LD<sub>50</sub> values for many plants presented in this article were given after experiments with rats (not with mice).</p> <p>Standard wording is used.</p>