



**This document was valid from 6 March 2008 until 24 November 2014.**

London, 6 March 2008  
Doc Ref. EMEA/HMPC/475463/2007

**OVERVIEW OF COMMENTS RECEIVED ON  
'COMMUNITY HERBAL MONOGRAPH ON  
ECHINACEA PURPUREA L., HERBA RECENS'  
EMEA/HMPC/104945/2006**

**OVERVIEW OF COMMENTS RECEIVED ON  
'COMMUNITY HERBAL LIST ENTRY  
ECHINACEA PURPUREA L., HERBA RECENS'  
EMEA/HMPC/189629/2007**

Table 1: Organisation(s) providing comments on the above mentioned documents on *Echinacea purpurea* l., herba recens as released for consultation on 8 March 2007 until 16 June 2007.

	Name of organisation or individual
1	AESGP (Association of the European Self-Medication Industry)
2	Biohorma/Bioforcep
3	AFSSAPS (Agence française de sécurité sanitaire des produits de santé)
4	Europlant Phytopharm sp. Z o.o.
5	INSTYTUT ROŚLIN I PRZETWORÓW ZIELARSKICH
6	Polski Komitet Zielarski [Polish Herbal Committee]
7	Prof. Michael Heinrich, The School of Pharmacy, University of London
8	Irish Medicines Board
9	GA - Society for Medicinal Plant Research, Gesellschaft für Arzneipflanzenforschung e. V.

Table 2: Discussion of comments

Paragraph no.	Comment and Rationale	Outcome
<b>GENERAL COMMENTS TO DRAFT DOCUMENT</b>	<p>Compared to the 2003 ESCOP monograph, the HMPC draft is much more restrictive concerning chapters '4.2 Posology and method of administration', '4.3 Contraindications', '4.4 Special warnings and precautions for use', '4.5 Interactions with other medicinal products and other forms of interactions' and '4.8 Undesirable effects'. The reasons for such stringent restrictions are difficult to understand given the long-term and wide use of preparations containing Echinacea purpurea and the fact that no new safety concerns have emerged from case reports.</p> <p>Therefore, we do not agree with most of the new risk information in chapters 4.3 to 4.8 because it gives the impression that Echinacea purpurea containing preparations are dangerous and should be avoided by children and many adults.</p>	<p>The committee opinion is that the differences between the HMPC and ESCOP monographs are results of different assessment approaches, and contributions of many different Member States.</p> <p>The detailed responses are given further in the document with the specific comments.</p>
	<p>Compare to the available literature like the ESCOP and WHO monographs this draft is more restrictive e.g. in composition, in posology, contraindication, warnings etc. Arguments for those restrictions are not given. It is not clear why those statements are included, frequently repeated and certainly it does not reflect the long-term use of Echinacea and the fact that there is no new safety concerns have emerged from reports.</p>	<p>See above.</p>
	<p>Maybe it is possible that draft versions have a short introduction where some background information e.g. why the HMPC has chosen for a special preparation, dosage form, explanation of the used references etc is given</p>	<p>The background information is included in the assessment report, which will also be published.</p>
	<p>We would suggest to classify bibliographic references according to their mention in the HMPC monographs (e.g. cluster them by section) or to include them (e.g. first name of the author and year of publication) at the place were they are used in the draft. So it becomes clear which article is used for the statement and it is helpful to evaluate the draft.</p>	<p>The references are included in the text of assessment report.</p>
	<p>We appreciate that for an increasing number of draft monograph a list of references for the assessment of is available. We suggest to include the references (first name of the author and year of publication) at the place were they are used in the draft. So it becomes clear which article is used for the statement and it is helpful to evaluate the draft. In the final version those references can go out.</p>	<p>See above.</p>
	<p>In this and other new draft monographs, adolescents over the age of 12 years are introduced as a new group under heading 4.2 Posology. The reason for the introduction of this new group of age is not given and cannot be a result of the recommendation of use of the herbal product or of safety reasons.</p>	<p>This age group is defined in European legislation and should be used in all medicinal products.</p>
	<p>Equivalent preparations (see ESCOP 2003), esp. water-ethanolic ones are widely available and generally have a very similar therapeutic profile. It does not seem plausible to limit this monograph to 'expressed juice' and 'dried expressed juice' (Section 2)</p>	<p>See comment at: <b>2. Qualitative and quantitative composition</b> <b>ii) Herbal preparations.</b></p>

	<p>According to the list of reference some articles were available in the form of an abstract. An abstract is a brief summary of the article and contains the conclusion of the authors. Essential information e.g. used plant species type of extract, other biological or clinical effects is not seen and will not be included in the monograph.</p>	<p>Due to a high number of articles, we had to restrict the number of purchased full text articles. All important articles (clinical trials, ...) were available in full text.</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>
	<p>2. The use of Echinacea preparations in children has a long tradition (e.g. in Germany) and it seems problematic to exclude children aged ca. 6 – 12 from the use of these products, ESCOP (2003), for example, specifically states that in children it should be used proportionally to the adult dose according to body weight and age.</p>	<p>See comment at: <b>4.2. Posology and method of administration.</b></p>
	<p>3. Why should Echinacea preparations not be used for more than ten days? Again there is a contradiction to ESCOP (2003): the duration of treatment should not exceed eight weeks. No adverse reactions have been reported after long-term oral administration. If symptoms persist for such a long period, instead it may be advisable to consult a health care professional should.</p>	<p>See comment at: <b>4.2. Duration of use.</b></p>
	<p>4. Overall, good quality preparations of Echinacea are generally safe and I am not aware of clinical evidence for some of the side effects mentioned (triggering of autoimmune disease, leucopenia). Several of these are obviously based on theoretical considerations.</p>	<p>See comment at: <b>4.8. Undesirable effects.</b></p>
	<p>5. Echinacea preparations are often used once early symptoms of a common cold have been detected (semi-preventive) and this use seems to be completely excluded from the monograph</p>	<p>See comment at: <b>4.1. Indication.</b></p>

Due to the referenced literature it is not acceptable to exclude **extracts (tinctures) of *Echinacea purpurea*** (and equivalent preparations) under paragraph 2 “*Qualitative and quantitative composition*”.

It should be evaluated to include the **prophylaxis** under paragraph 4.1 “*Therapeutic indications*”. The supportive literature – including two metaanalyses - you will find in the appendix. Also we strongly recommend not to restrict the usage of *Echinacea purpurea* to the treatment of early symptoms. It has always been recommended to start at early symptoms. As with every medication the treatment should last until complete recovery.

Similarly, it should not be discouraged to use *Echinacea purpurea* in children from **1 to 12 years** or to restrict usage to **10 days**. It rather should be allowed for the prophylactic intake over 2 months, which was proven to be safe (Parnham, 1996).

We do not understand how the listing of “*Contraindication, Special Warnings and Undesirable effects*” has been compiled. *Echinacea purpurea* has a very long tradition in which it proved its good safety profile. Considering the vast use of this plant it is clear that isolated reports might appear but it is not justified to include these in the monograph, as long as there is no increased incidence. Moreover it must be noticed that most of these events occurred under various co-medication and a correlation with *Echinacea purpurea* intake was not possible.

We appreciate to include “**Hypersensitivity to plants of the Asteraceae family**” and “**autoimmune diseases**” or “**immune suppression**” under *Contraindication*, paragraph 4.3, since there is sound data which justifies this. On the other hand we do not support to include **allergic diathesis**, when already the “Hypersensitivity” is mentioned.

We hope that the HPMC Community appreciates our input and considers the recommendations we give. The monograph in the present form is not acceptable and does not represent the scientific state of the art of *Echinacea purpurea*. We feel constrained to give our input here to support an adequate assessment of the available body of data - from our view long lasting experience.

See response to individual topics in paragraphs 2, 4.1., and 4.3.

	<p><b>SPECIFIC COMMENTS ON TEXT</b></p> <p><b>WELL ESTABLISHED USE</b></p>	
<p><b>2. QUALITATIVE AND QUANTITATIVE COMPOSITION</b></p> <p><u>ii) Herbal preparations</u></p>	<p>Expressed or dried expressed juices are the only herbal preparations mentioned in the draft monograph. However, the reference list shows that 24 articles support the use of press juice and 24 references the use of an ethanol extract. In 45 of the citations other preparation (e.g. tea), other Echinacea species (alone or as a mixture) or isolated constituents were investigated. Moreover, many clinical studies used alcoholic extractions from <i>E. purpurea</i> and demonstrated efficacy in the treatment of the common cold (e.g. Brinkeborn et al. 1999 and Goel et al. 2004). In addition for extracts of <i>E. purpurea</i> a conclusive molecular mode of action via modulation of inflammatory factors was shown. While inflammatory parameters like IL-1 or TNF-<math>\alpha</math> play a crucial role in the development of symptomatic cold episodes, <i>E. purpurea</i> extracts were demonstrated to act immune-modulatory (Gertsch et al. 2004; Goel 2002; Bauer 1988; Bauer 1989). The bioavailability of ingredients derived from lipophilic extracts of <i>Echinacea purpurea</i> were proven (e.g. Matthias et al. 2005; Woelkart et al. 2005). Further it should be noticed that the cited <b>review</b> articles drew conclusions on different preparations from <i>E. purpurea</i> (Barnes et al 2005; Barrett 2003; Huntley et al. 2005; Linde et al. 2006; Melchart et al. 1994). Thus, based upon the references used for the monograph, it seems appropriate not to restrict herbal preparations to (dried) expressed juice. Based on the wording of the ESCOP 2003 monograph, we suggest the following addition:</p> <ul style="list-style-type: none"> <li>- <b>expressed juice</b> and other comparable preparations</li> <li>- <b>dried expressed juice and other comparable preparations</b></li> </ul>	<p>The literature on <i>E. purpurea</i> herb was collected without any preference for any preparation. During assessment it turned out, that we were not able to locate any clinical study on efficacy of the extract from <i>E. purpurea</i> <b>herb</b>. Clinical studies mentioned by the commenter were performed with the extracts of mixture of herb and root or “various parts of freshly harvested plants”.</p> <p>There are at least two reasons why we can not assess well established use of extract based on the clinical studies on juice:</p> <ol style="list-style-type: none"> <li>1. Extracts are phytochemically different to expressed juice.</li> <li>2. The posology for extracts on the market is much lower (expressed as equivalents of herbal substance) than for expressed juice.</li> </ol> <p>The absence of the extracts from the monograph does not in any way prevent the registration of medicinal products containing extracts.</p>
	<p>Well established use is restricted to expressed juice or dried expressed juice. A close look to the reference list showed that 24 articles support the use of press juice and a same amount, 24 of the references the use of an ethanol extract. In 45 of the citations other preparation, other Echinacea species (as a single substance or in combination with other herbal preparations) or isolated constituents were investigated. Moreover, many clinical studies used alcoholic extractions from <i>E. purpurea</i> and demonstrated efficacy in the treatment of the common cold [e.g. Brinkeborn et al. 1999 and Goel et al. 2004, Goel et al 2005]. In addition for extracts of <i>E. purpurea</i> a conclusive molecular mode of action via modulation of inflammatory factors and binding on CB-2 receptor was shown. While inflammatory parameters like IL-8 or TNF-<math>\alpha</math> play a crucial role in the development of symptomatic cold episodes, <i>E. purpurea</i> extracts were demonstrated to act immune-modulatory [Woelkart et al. 2006, Gertsch et al. 2004; Goel 2002; Bauer 1988; Bauer 1989]. The bioavailability of ingredients derived from lipophilic extracts of <i>Echinacea</i> were proven [e.g. Matthias et al. 2005; Woelkart et al. 2005]. Further it should be noticed that the cited <b>review</b> articles did not specifically address the efficacy</p>	<p>See above.</p>

	<p>of pressed-juice but drew conclusions on different preparations from <i>E. purpurea</i> [Barrett 2003; Huntley et al. 2005; Linde et al. 2006; Melchart et al. 1994].</p> <p>Thus based upon the references, already included for the assessment, it becomes clear that other preparation should be added.</p> <p>In conclusion, it is proposed to change the wording of item “ii) Herbal substance” as follows:</p> <ul style="list-style-type: none"> <li>- expressed juice and other comparable preparations.</li> <li>- <b>(dried) expressed juice and other comparable preparations.</b></li> </ul>	
	<p><b>1. Pressed Juice and Extracts/Tinctures</b></p> <p>A discrimination of the references in the monograph according to the investigated products shows that only 24 articles are based on <b>pressed juice</b> from <i>Echinacea purpurea</i>. Another 23 references are on <b>extracts/tinctures</b> from <i>Echinacea purpurea</i>, and in the remaining papers mixed specimen (extracts, pressed juice, tea, a.o) or isolated substances were investigated or the specimen was not described.</p> <p>With this reference background, which includes <b>extracts/tinctures as well as pressed juices</b> to the same extent, the part <i>qualitative and quantitative composition</i> should be extended and adapted to the formulation as found in the ESCOP monograph 2003 and the complete Commission E monograph:</p> <p><b>“Pressed juice or other equivalent preparations at comparable dosage”</b></p> <p>It should be considered, that several clinical studies have been conducted with alcoholic extracts/tinctures of <i>Echinacea purpurea</i> and they also have demonstrated efficacy in the treatment of the common cold. Even if 5 % roots have been used in addition to 95 % of herb, these data are relevant for herb preparations as well, since the known constituents of aerial parts and roots are similar, especially with respect to alkaloids and caffeic acid derivatives. 5 % roots does not significantly change the composition. Even in the pharmacopoeia usually plus/minus 5 % deviation is accepted.</p> <p><b>Brinckborn RM, Shah DV, Degenring FH. (1999) Echinaforce and other <i>Echinacea</i> fresh plant preparations in the treatment of the common cold. A randomized, placebo controlled, double-blind clinical trial. <i>Phytomedicine</i> 6(1): 1-6.</b></p> <p><b>Goel V, Chang C, Slama JV, Barton R, Bauer R, Gahler R, Basu TK. (2002) Alkylamides of <i>Echinacea purpurea</i> stimulate alveolar macrophage function in normal rats. <i>Int Immunopharmacol.</i> 2(2-3): 381-7.</b></p> <p><b>Goel V, Lovlin R, Barton R, Lyon MR, Bauer R, Lee TD, Basu TK. (2004) Efficacy of a standardized <i>Echinacea</i> preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial. <i>J Clin Pharm Ther.</i> 29(1): 75-83.</b></p> <p><b>Bauer R. (2002) New knowledge regarding the effect and effectiveness of <i>Echinacea purpurea</i> extracts. <i>Wien Med Wochenschr</i> 152(15-16): 407-11.</b></p> <p><b>Vonau B, Chard S, Mandalia S, Wilkinson D, Barton SE. (2001) Does the extract of the plant <i>Echinacea purpurea</i> influence the clinical course of recurrent genital herpes. <i>Int J STD AIDS.</i>; 12(3):154-8.</b></p>	<p>The inclusion of the references of extracts/tinctures illustrates, that the assessment report was prepared without prejudice on any type of preparations. The decision to exclude extracts/tinctures from the monograph came later as a consequence of assessing the whole body of evidence.</p> <p>The Rapporteur agrees, that the research on products with 5% of roots are not completely irrelevant for assessing the herb, but this research can not provide the level of evidence required for well established use. The content of alkaloids in roots and herb is substantially different (Osowski S, Rostock M, Bartsch HH, Massing U. (2000) Zur pharmazeutischen Vergleichbarkeit von therapeutisch verwendeten <i>Echinacea</i>-Präparaten. <i>Forsch Komplementärmed Klass Naturheilkd.</i> 7: 294-300 (DOI: 10.1159/000057177)).</p> <p>Pharmacokinetic and pharmacodynamic investigations are not sufficient (and not even necessary) for the demonstration of well established use.</p>

- For extracts of *Echinacea purpurea* a conclusive molecular mode of action has recently been presented which is referenced in the monograph. It describes the modulation of inflammatory cytokines like TNF- $\alpha$  and the binding onto Cannabinoid Receptor-2 (CB-2). The effects on TNF- $\alpha$  were confirmed *ex vivo* after treatment with Echinacea extract by Woelkart et al. 2006.

**Gertsch J, Schoop R, Kuenzle U, Suter A (2004) Echinacea alkylamides modulate TNF- $\alpha$  gene expression via cannabinoid receptor CB2 and multiple signal transduction pathways. FEBS Letters 577, 3, 563-9.**

**Wölkart, K., Xu, W., Pei, Y., Makriyannis, A., Picone, R.P., Bauer, R. (2005) The endocannabinoid system as a target for alkamides from *Echinacea angustifolia* roots. Planta Medica 71, 701 - 705**

**Woelkart K, Bauer R. (2007) The Role of Alkamides as an Active Principle of Echinacea. Planta Med. May 31; [Epub ahead of print]**

**Goel V, Chang C, Slama JV, Barton R, Bauer R, Gahler R, Basu TK. (2002) Alkylamides of *Echinacea purpurea* stimulate alveolar macrophage function in normal rats. Int Immunopharmacol. 2(2-3): 381-7.**

**Bauer R, Jurcic K, Puhlmann J, Wagner H (1988a) Immunologic in vivo and in vitro studies on *Echinacea* extracts. Arzneimittel-Forschung 38: 276-81.**

**Bauer R, Remiger P, Jurcic K, Wagner H (1989) Beeinflussung der Phagozytose-Aktivität durch *Echinacea*-Extrakte. Zeitschrift für Phytotherapie 10: 43-8.**

**Woelkart K, Marth E, Suter A, Schoop R, Raggam RB, Koidl C, Kleinhappl B, Bauer R (2006) Bioavailability and pharmacokinetics of *Echinacea purpurea* preparations and their interaction with the immune system. Int J Clin Pharmacol Ther 44(9):401-8.**

- Ingredients derived from lipophilic extracts of *Echinacea purpurea* were proven to be bioavailable:

**Jäger H, Meinel L, Dietz B, Lapke C, Bauer R, Merkle HP, Heilmann J: Transport of Alkamides from *Echinacea* Species through Caco-2 Monolayers. Planta Med. 2000; 68: 469-71.**

**Clifford LJ, Nair MG, Rana J, Dewitt DL. (2002) Bioactivity of alkamides isolated from *Echinacea purpurea* (L.) Moench. Phytomedicine 9(3): 249-53.**

**Dietz B, Heilmann J, Bauer R (2001) Absorption of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides after oral application of *Echinacea purpurea* tincture. Planta Med. 67: 863-4.**

**Matthias A, Blanchfield JT, Penman KG, Toth I, Lang CS, De Voss JJ, Lehmann RP. (2004) Permeability studies of alkylamides and caffeic acid conjugates from *Echinacea* using a Caco-2 cell monolayer model. J Clin Pharm Ther. 29(1): 7-13.**

**Matthias A, Addison RS, Penman KG, Dickinson RG, Bone KM, Lehmann RP. (2005a) Echinacea alkamide disposition and pharmacokinetics in humans after tablet ingestion. Life Sci. 2005 Sep 2;77(16):2018-29.**

**Woelkart K, Koidl C, Grisold A, Gangemi JD, Turner RB, Marth E, Bauer R. (2005)**

This fact was taken into account.

	<p><b>Bioavailability and pharmacokinetics of alkamides from the roots of <i>Echinacea angustifolia</i> in humans. J Clin Pharmacol.; 45(6):683-9.</b></p> <p>All of these papers were referenced in the compilation of the present HPMC monograph for the pressed juice, but are based on investigations of extracts of <i>Echinacea purpurea</i>. With the current reference list and the available body of literature it is not tenable to exclude extracts from <i>Echinacea purpurea</i> in the monograph. Further it should be noticed that the cited review-articles did not specifically address the efficacy of pressed-juice but rather drew conclusions on different preparations from <i>Echinacea purpurea</i>:</p> <p><b>Barrett B. (2003) Medicinal properties of <i>Echinacea</i>: a critical review. Phytomedicine 10(1): 66-86.</b></p> <p><b>Huntley A, Coon JT, Ernst E (2005) The safety of herbal medicinal products derived from <i>Echinacea</i> species. Drug Safety; 28(5):387-400.</b></p> <p><b>Linde K, Barrett B, Wölkart K, Bauer R, Melchart D. (2006) <i>Echinacea</i> for preventing and treating the common cold. The Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD000530.pub2.</b></p> <p><b>Melchart D, Linde K, Worku F, Bauer R, Wagner H. (1994) Immunomodulation with <i>Echinacea</i> – a systematic review of controlled clinical trials Phytomedicine 1: 245-54.</b></p> <p><b>Yale SH, Liu K. (2004) <i>Echinacea purpurea</i> therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. Arch Intern Med. 2004 Jun 14;164(11):1237-41.</b></p> <p>Many publications were obviously available to the rapporteurs only in abstract form, which did not contain the valuable information on the kind of preparation or the used plant-species. This however, is a prerequisite for discrimination of the preparations and might explain the erroneous conclusion to exclude extracts from the monograph.</p>	<p>A call for submission of scientific data was addressed to interested parties at the beginning of preparation of the assessment report, but only one organisation responded. Nevertheless, the literature provided by the Rapporteur enabled a full assessment.</p>
<p><b>4.1 Therapeutic indications</b></p>	<p>The draft mentioned “treatment of early symptoms of common cold”. This formulation is misleading. Originally, the claim to start medication at appearance of first symptoms came from studies that found a benefit under early start of medication (e.g Brinkeborn et al 1999, Goel et al. 2004 and 2005). This does not mean that medication is restricted only to the treatment of first symptoms but should encourage patients to start as early as possible with the medication. It is not recommended to cease the treatment before complete resolution of symptoms.</p> <p>The prophylactic use of <i>E. purpurea</i> preparations recommended after reviewing three systematic reviews and meta-analysis [Blumenthal et al. 2007]. A reduction in the amount the common cold episodes by 55% after induced common cold episode and by 58% after naturally occurring common cold episode was reported [Schoop et al. 2006, Shah et al. 2006]. These studies and others [Schöneberger 1992, Weber et al. 2006, Cohen et al. 2004] support the prophylactic use <i>Echinacea</i> preparations.</p> <p>In conclusion, it is proposed to change the “therapeutic indications” as follows:  <b>Herbal medicinal product for the prevention and treatment of common cold</b></p>	<p>The committee agrees with the first comment (first symptoms), but can only partially follow the second one (prevention).</p> <p>The commenter did not submit the full text or at least full bibliographic information of the mentioned articles.</p> <p>The studies available to EMEA were performed on the products not covered by this monograph or showed no activity.</p>



	<p>We do not support the well established use indication for <i>Echinacea purpurea</i> [L.] Moench, herba recens for “the treatment of early symptoms of common cold”.</p> <p>The clinical studies presented are of inadequate quality and the data provided is insufficient to support the proposed well-established use indication. <i>Echinacea purpurea herb</i> has not been scientifically proven to have recognised efficacy in accordance with Annex 1 of 2001/83/EC, as amended.</p> <p>Furthermore the Cochrane Review 2006 concluded that while <i>Echinacea purpurea</i> may be effective for the treatment of colds in adults the results are not fully consistent .</p> <p>We do however support a traditional-use indication for <i>Echinacaea purpurea herb</i> for the treatment of early symptoms of the common cold.</p>	<p>It is the view of the committee, that the overall body of evidence which includes several clinical trials proves the efficacy of <i>Echinacea purpurea herba recens</i> in accordance with EMEA/HMPC/104613/05.</p>
<p><b>4.2 Posology and method of administration</b></p>	<p>The HMPC Draft Monograph does not recommend <i>Echinacea purpurea</i> preparations in children below 12 years of age.</p> <p>There is long-term experience of use of <i>Echinacea</i> products in children from 2 to 12 years of age which attests for its safety and effectiveness.</p> <p>It seems that the HMPC draws such a conclusion based on the following article alone:</p> <p>The HMPC Draft references the study by <i>Taylor et al. (2003)</i>. This randomised double blind placebo-controlled trial in 407 healthy children 2 to 11 years old investigated the effects of treatment for up to 3 upper respiratory tract infections (URIs) with either Echinacin® juice or placebo over a 4-month period. Dosing instructions were 3.75 ml (equivalent to 1.875 ml pressed juice) two times per day for children 2 to 5 years and 5 ml (equivalent to 2.5 ml pressed juice) two times per day for children 6 to 11 years.</p> <p>Although the difference for most efficacy parameters between verum and placebo was not statistically significant, the results of this study do not support a <b>contraindication in children under 12 years of age</b>. There were no overall differences in the rate of adverse events between both groups apart from rash which occurred more often in the verum group. Rash is a known side effect of treatment with <i>Echinacea purpurea</i> preparations and is mentioned in chapter 4.8 of the HMPC draft.</p> <p>Regarding efficacy, shortcoming and weaknesses of the study have to be taken into account. Most of them have already been discussed in detail by the investigators in their publication. Furthermore a summary of possible limitations of the trial is also given in a review article published in <i>Herbalgram (D. Brown, 2004)</i>: (e.g. “due to the large variation in patient response to URIs, more patients are often needed in these trials to find a difference compared to placebo.”).</p> <p><i>Taylor</i> himself also commented on the collecting of data in paediatric trials which usually come from the parents (i.e. ‘second hand’). In addition, most of the scoring systems used (including this one) have not been validated in children.</p>	<p>The minimal requirement for demonstration of efficacy of well established products is a well designed clinical trial. This requirement was not fulfilled in the case of <i>E. purpurea herb</i>.</p> <p>The committee is aware of many drawbacks of the study by <i>Taylor et al. (2003)</i>, but our decision was not based on its negative results, but it was based on the absence of any other well-designed study with positive results.</p> <p>The monograph does not contraindicate the use in children under 12.</p> <p>The studies of <i>Weber et al. 2005</i> and <i>Götte&amp; Roschke 2001</i> were not available to the committee but will now be included in the assessment report.</p> <p>The first one does not support the indication mentioned in the monograph and the second one is without a control group.</p> <p>It is the opinion of the committee, that the two articles are not sufficient for the proposed change of the monograph.</p>

Furthermore, the amount of concomitant medications differs significantly between the two groups and this could have markedly influenced the outcome of this trial. Children with URI in the placebo group received much more vitamins and/or mineral supplementation (preparations which are known for stimulating effects on the immune system) compared to those of the Echinacea group. The latter in contrast had a significantly higher intake of antipyretics and analgesics, i.e. drugs which could have a negative impact on the positive treatment effects of Echinacea on URIs.

An interesting and important unexpected finding of this investigation is that children taking Echinacin<sup>®</sup> juice were significantly less likely to have another URI compared to children receiving placebo (52.3% vs. 64.4%,  $p=0.015$ ). Meanwhile a subgroup analysis of the Taylor data has been published focussing on this significant reduction of the rate of re-infections in children being treated with Echinacin<sup>®</sup> juice (*Weber et al., 2005*). This article should therefore be included in the HMPC reference list as these findings explicitly support the indication of “recurrent infections” approved for Echinacea products in several European countries.

Additional data from another investigation in children with acute infections of the respiratory tract are available (*Götte / Roschke, 2001*). In this observational study, 1,327 children older than 2 years old and having experienced at least two infections of the respiratory tract during the past twelve months (mean number of infections 6.7) were included. The medication (Echinacin<sup>®</sup> juice) was administered over an average period of 11 days. Children of 2 to 5 years of age were given 2.5 ml (equivalent to 1.25 ml pressed juice) three times daily, children of 6 to 12 years 5.0 ml (equivalent to 2.5 ml pressed juice) twice daily and adolescents of over 12 years of age received 5.0 ml three times daily. The efficacy of the treatment was based on the total score value (individual values were applied for each symptom of the cold). Additionally, physicians and parents were asked separately to compare the duration of the respiratory tract infection under therapy with Echinacin<sup>®</sup> juice against the duration of previous infections.

The total symptom score had dropped from 10.7 (at baseline) to 1.8 at final examination. Among the different symptoms classified, improvement in coughing and feeling of illness was the most evident. Additionally 84.8 % of the parents assessed the efficacy as very good or good. Nearly two thirds of both physicians and parents rated the duration of the respiratory infection as shorter and less severe compared to earlier infections.

Regarding tolerability only 1.4% of the participants recorded adverse drug reactions with the vast majority being affections of the gastrointestinal tract. Only one patient developed an itching skin reaction. In only two cases the treating physician classified the relationship with the use of the medication as “probable”.

In conclusion, it is proposed to change the posology for the “Paediatric population” as follows:

	<p><i>Children between 2 and 5 years of age: 1,25 ml expressed juice or comparable preparations three times a day</i></p> <p><i>Children between 6 and 11 years of age: 2,5 ml expressed juice or comparable preparations twice a day</i></p>	
	<p><u>Adult, elderly</u></p> <p>Leave out the adolescents (see general comments) and include other preparations:</p> <p><b>Expressed juice 6-9 ml per day of dried expressed juice equivalent to 8-18 g of the herbal substance or comparable preparations, divided in 2 to 4 doses.</b></p> <p><u>Paediatric population</u></p> <p>The use in children between 1 and 12 years of age is not recommended. This recommendation is not result of an appropriately evaluation of the references used for the assessment [doc. Ref: EMEA/HMPC/11536/2007]. There is long-term experience of use of Echinacea containing products in children from 2-12 years of age which attest for its safety and effectiveness.</p> <p>Intramuscularly injections of E. purpurea (1-2 ml pressed juice) have shown good efficacy and safety in the treatment of upper respiratory tract infections (URIs) in 261 children aged up to 13 years [Beatgen 1984] and in 789 children of one month up to 19 years [Beatgen 1988]. No adverse events aside redness at the injection site/place were reported.</p> <p>Observational studies in children from 1 to 13 years old showed that an ethanol extract of E. purpurea was well tolerated. No adverse events were reported. In a second study a case of tremor was reported, but there was no relation with the intake of E. purpurea [Shah 1995 and 1996].</p> <p>In a randomised double blind placebo-controlled trail in 407 children 2 to 11 years old the effects of treatment for up to 3 URIs with either Echinacin or placebo during a period of 4 months were investigated. Regarding efficacy, shortcomings and weakness of the study have to taken into account and are discussed. Although the differences for most efficacy parameters between verum and placebo were not statically significant the results do not support a contraindication for children up to 12 year old. There were no overall differences in the rate of adverse events between both groups apart from rash which occurred more often in the verum group. Rash is a known side effect of treatment with E. purpurea preparations and is mentioned under heading "4.8 Undesirable effects" [Taylor 2003].</p> <p>In an observational study including 1327 children of 2 years and older who have experienced at least two URTs during the past twelve months. E. purpurea press juice (children 2-5 year 3x 1.25 ml; 6-12 years 3x 2.5 ml; &gt;12 years 3x 5 ml) was administered over an average period of 11 days. Only 1.4% of the participant recorded adverse reactions with the vast majority affections of the gastrointestinal tract. One patient developed an itching skin reaction. In only two cases the treating physician classified the relation of events and use of the medication as probable [Götte</p>	<p>See the response to general comments and to 2. <b>Qualitative and quantitative composition.</b></p> <p>The clinical trials with i.m. application can not support the well established use of p.o. application. See also the response one row above.</p>

	<p>and Roschke 2001].</p> <p>In conclusion, it is proposed to change the posology for the ‘Paediatric population’ as follows</p> <p><b>Children from 2 to 5 years 1.25 ml expressed juice and other comparable preparations three times a day</b></p> <p><b>Children from 6 to 12 years 2.5 ml expressed juice and other comparable preparations three times a day</b></p>	
	<p><b>2. Use in children / age restriction (&lt; 12 years)</b></p> <p>Some of the cited articles were – although referenced - not appropriately evaluated to determine the recommendations and restrictions in children below 12 years:</p> <p>Intramuscular injections of <i>Echinacea purpurea</i> have shown good efficacy and safety in the treatment of acute respiratory tract infections in 261 children, aged between infancy and 13 years (Baetgen (1964 and 1984)). Aside of redness at the injection site no other adverse events were reported that related to the study medication.</p> <p>Another study from Baetgen (1988) included data from 798 children aged between one month and 19 years given intramuscular injections of <i>Echinacea purpurea</i>. No adverse events apart from the redness at injection site were reported.</p> <p>These studies with parenteral application may not be considered as relevant. However, a controlled clinical study with oral application was recently performed in children from 2 to 11 years (Taylor, 2004). Aside of incidence of rashes in the <i>Echinacea purpurea</i> group, the treatment was generally considered as safe. No significant increase of other adverse events occurred when comparing with placebo. A total of 146 adverse events were recorded for placebo and 152 in the verum group.</p> <p>In a 4-month observational study Weber et al. (2005) demonstrated that a treatment with Echinacin reduced the risk of a second infection in 401 children above 2 years. <i>Echinacea purpurea</i> treated children suffered from 337 and placebo-treated children from 370 cold episodes.</p> <p>Weber W, Taylor JA, Stoep AV, Weiss NS, Standish LJ, Calabrese C. <i>Echinacea purpurea</i> for prevention of upper respiratory tract infections in children. <i>J Altern Complement Med.</i> 2005 Dec;11(6):1021-6.</p> <p>There are documented reports (248’679 treatments) on graduated usage of <i>Echinacea purpurea</i> containing preparations in children from &lt;1 to 10 years and 10 to 16 years. Only two adverse events were reported which occurred under co-medication and a correlation to the observed product could not be concluded.</p> <p><b>Köhler G, Elosge M, Hasenfuss I, Wüstenberg P. Kinderdosierungen von Phytopharmaka, Zeitschrift für Phytotherapie, 1998; 19:318 – 22.</b></p> <p>Along with the good safety in children below 12 years, the present HPMC monograph cites the work from the Kooperation Phytopharmaka (Dorsch, 2002), which suggest the</p>	<p>The committee agrees, that the studies with parenteral application have limited relevance to the assessment of oral use.</p> <p>This study will be included in the new version of the monograph.</p> <p>For the opinion of HMPC on its relevancy and sufficiency for extension to paediatric use, see above.</p>

	<p>usage of <i>Echinacea purpurea</i> in children as follows:  0-1 year : not recommended  1-4 years : 1/3 to 1/2 of the adult dose  4-10 years : 3 –5 ml of the adult dose  10 – 16 years : adult dose  The usage of <i>Echinacea purpurea</i> in children with a dosage graduation is scheduled also by the Commission E monographs and by the Commission D for the application of homoeopathic tinctures. The graduation is described as follows:  1 –6 years : 1/2 of the adult dose  6 – 12 years : 2/3 of the adult dose  above 12 years : the adult dose  Due to the above-mentioned references the use of <i>Echinacea purpurea</i> in children above 4 years should not be discouraged.</p>	
<p><b>Duration of use</b></p>	<p><i>Echinacea</i> preparation has been administered during long periods e.g. 8 weeks [Pernam et al 1996], 4 month [Taylor et al 2003] or 12 months [Götte and Roschke 2001]. In none of those studies serious adverse events related to the administration of the medical preparation are reported. In other words there are no safety concerns and the ‘Do not use the medical product for more than 10 days’ is difficult to understand. We thus propose to leave out the sentence: “Do not use .... for more than 10 days”.</p>	<p>In the article by Götte &amp; Roschke 2001 it is written: “The juice was administered to the patients over a period of 10 days.”  In the article by Taylor et al. 2003 it is written: “Study medication was begun at the onset of symptoms and continued throughout the URI, for a maximum of 10 days”.  The article of Pernam et al. 1996 is not available to the Rapporteur and was not provided by the commenter. Perhaps the commenter is referring to the reference Parnham 1996, which is mentioned in the assessment report. This review concludes that <i>Echinacea</i> is relatively safe in long term use, but it does not give any evidence on efficacy in long term use.</p>
	<p><i>Echinacea</i> preparations have been administered for a long period e.g. 8 weeks [Parnham et al 1996, Schoop et al 2006], 4 month and more [Taylor et al 2003, Vonau et al 2001, Götte and Roschke 2001]. In none of those studies serious adverse events related with the administration of the medical preparation are reported. Or in other words there are no safety concerns and the ‘Do not use the medical product for more than 10 days’ is difficult to understand. It is proposed to leave out the first paragraph; “Start the therapy .... 10 days”.</p> <p>The other well-known duration of use (as for example defined by national health authorities and by ESCOP) should read as follows:  <b>The duration of continuous treatment should not exceed 8 weeks. No adverse reactions have been reported after long-term oral administration</b></p>	<p>See above.</p>

	<p>The monograph states that the expressed juice of <i>Echinacea purpurea</i> is recommended in adults and adolescent over the age of 12.</p> <p>It has to be noted that the immune system develops until sexual maturity, and that immunotoxic effects induced in juveniles could have consequences on the adult immune system.</p> <p>Due to the pharmacological activity of the expressed juice, a toxic potential to the immune system cannot be excluded. In humans, hypersensitivity reactions were observed and fatal cases were reported with <i>Echinacea</i> in Germany.</p> <p>Consequently, the need of immunotoxicity studies should be discussed according to the NfG CHMP/167235/2004 (Note for guidance on immunotoxicity studies for human pharmaceuticals).</p> <p>Finally, the lack of immunotoxicity studies in adult and juvenile animals should be added in section 5.3</p>	<p>In the monograph the Pharmacodynamic is given as:  “Pharmacotherapeutic group: ATC-code: L03AW05 immunomodulators of plant origin .....  <i>Echinacea purpurea</i> stimulates non-specific immune system (phagocytosis by macrophages, natural killer cells activity).</p> <p>In the “Note for Guidance on immunotoxicity studies for human pharmaceuticals” (EMEA/CHMP/167235/2004) the following statement is given: “Immunotoxicity is, for the purpose of this guideline, defined as <b>unintended</b> immunosuppression or enhancement”. Furthermore “Drug induced Hypersensitivity” is taken out very clearly.</p> <p>For the remarks in the comment it is not clear which age “sexuell maturity” means.</p> <p>Immunotoxicity studies of <i>Echinacea</i> are therefore not needed and their lack does not have to be mentioned in the monograph.</p>
	<p><b>3. Acute treatment and long-term use in prophylaxis</b></p> <p>The present monograph states “Do not use the medicinal product for more than 10 days.”</p> <p>Whereas it is justified to state, “if after 10 days the symptoms still persist, a physician or a pharmacist should be consulted”, the use of <i>Echinacea purpurea</i> should not be restricted to 10 days:</p> <p>The rapporteurs of the new HPMC monograph for instance are referring to the article from Melchart et al (2005): “<i>preparations containing extracts of Echinacea probably can be effective in the prevention and treatment of common colds.</i>” Thus the duration of intake should not be restricted to 10 days to allow for prophylactic intake.</p> <p>The prophylactic intake of <i>Echinacea purpurea</i> today is promoted by MD, PhD Bruce Barrett after reviewing three very recent systematic reviews and meta-analysis (Blumenthal M, Milot B, Oliff HS, 2007). In induced and naturally occurring common cold episodes <i>Echinacea</i> preparations decreased the odds of developing the common cold by 55% (Schoop et al. 2006) and by 58% (Shah et al. 2006) – demonstrating a prophylactic efficacy.</p> <p><b>Blumenthal M, Milot B, Oliff HS. (2007) Three systematic reviews on Echinacea clinical trials suggest efficacy with cold symptoms. HerbalGram (74) : 28 – 31.</b></p> <p><b>Linde K, Barrett B, Wölkart K, Bauer R, Melchart D. (2006) Echinacea for preventing and treating the common cold. The Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD000530.pub2.</b></p>	<p>Including the reference in the assessment report does not mean that the committee agrees with every statement in that article.</p> <p>It is very wrong to transfer the statement: “likelihood of experiencing a clinical cold was 55% higher with placebo than with <i>Echinacea</i>” into: “<i>Echinacea</i> preparations decreased the odds of developing the common cold by 55%”.</p> <p>The mentioned meta-analysis includes different species of <i>Echinacea</i> and it evaluates short term prophylaxis (14 days).</p>

	<p><b>Schoop R, Klein P, Suter A, Johnston SL. (2006) Echinacea in the prevention of induced rhinovirus colds: a meta-analysis. Clinical Therapeutics; 28(2):174 – 183.</b></p> <p><b>Shah SA, Sander S, White CM, Rinaldi M, Coleman CI. (2006) Evaluation of echinacea for the prevention and treatment of the common cold: A meta-analysis of randomized, controlled trials. [abstract and poster] Amer Coll Clin Pharmacol.</b></p> <p>Since meta-analyses and even more review-articles on meta-analyses provide scientific evidence on the highest level they should receive primary attention. It is therefore astonishing that the reviewed articles were not considered in the present monograph. Articles from Schoeneberger (1992) Weber (2006) and from Cohen (2004) back the use of <i>Echinacea purpurea</i> containing products for prophylaxis of the common cold further.</p> <p><b>Schoeneberger D. (1992) The influence of the immunostimulating effects of pressed juice from <i>Echinacea purpurea</i> on the course and severity of cold infections; 8:18 – 22.</b></p> <p><b>Cohen HA, Varsano I Kahan E, et al. (2004) Effectiveness of an herbal preparation containing echinacea, propolis and vitamin C in preventing respiratory tract infections in children: a randomized, double-blind, placebo-controlled, multicenter study. Arch Pediatr Adolesc Med.: 158:217 – 221.</b></p> <p><b>Weber W, Taylor JA, Stoep AV, Weiss NS, Standish LJ, Calabrese C. (2005) Echinacea purpurea for prevention of upper respiratory tract infections in children. J Altern Complement Med. 11(6):1021-6.</b></p> <p>Above-mentioned articles contribute relevant and profound data regarding the prophylactic efficacy. Incorporation of the prophylaxis as indication should be reevaluated. Moreover, a prophylactic treatment for more than 10 days seems justifiable due to the good safety profile of <i>Echinacea purpurea</i> (see below).</p>	<p>At least one good clinical trial is required for demonstration of well established use (see above).</p>
<p><b>4.3 Contraindications</b></p>	<p>As mentioned in chapter 4.2, we agree with the contraindication for children under 1 year old. The other well-known contraindications (as for example defined by national health authorities and by ESCOP) regarding oral use should read as follows:</p> <p><b><i>Hypersensitivity to plants of the Compositae family. As with all immunostimulants, it is not recommended in cases of progressive systemic disorders and autoimmune diseases such as tuberculosis, leucosis, collagenoses, multiple sclerosis, AIDS or HIV infections.</i></b></p> <p>The contraindications: “<i>In case of immunosuppression</i>” ( e.g. <i>oncological cytostatic therapy; history of organ or bone marrow transplant</i>) and <i>haematologic systemic diseases of the white blood cell system (e.g. agranulocytosis)</i> have been added by the HMPC without giving reasons and references to verify the scientific background.</p> <p>We assume that the contraindication “allergic diathesis” is based on the publication of <i>Mullins RJ and Heddle R: Adverse reactions associated with Echinacea: The Australian experience. Ann.Allergy Asthma Immunol 2002, 88, 42-51</i>, which reported a possibly increased risk of allergic reactions in atopic patients. However, we have to note that no specifications concerning</p>	<p>The committee agrees with some of the comments. The adequate changes were introduced to the monograph. The decision of the committee to include additional contraindication was not based only on published case reports, but also on data available at NCAs and experience of MLWP/HMPC members.</p>

	<p>the Echinacea preparations were available. Therefore, it cannot be ruled out that the products showed quality standards divergent from pharmaceutical products authorised in Europe. The information about possible risks of Echinacea in atopic patients would be more appropriate in the section “special warnings”. An additional incorporation of “<b>allergic diathesis</b>” in the section “contraindication” is unhelpful and exaggerated.</p>	
	<p><i>Hypersensitivity</i> When there is a know hypersensitivity to plants of the Compositae family use of Echinacea (member of this plant family) is not advised. With mentioning “the active substance” and “Asteracea family” the same information is given twice. We propose to the wording and change into: <b>Hypersensitivity to plants of the Compositae family</b></p>	<p>Mentioning “the active substance” is in accordance to the guidelines. The plant family name is given twice because one name is scientifically correct (Asteraceae) but the other is generally known.</p>
	<p><i>Autoimmune diseases</i> The contraindication for progressive systemic disorders and autoimmune disease is based on theory. E. purpurea is best known for its effects on the immune system. Stimulation of various immune cells such as macrophages, other monocytes and natural killer cells has been demonstrated repeatedly <i>in vitro</i>. However, translation of these immunostimulating effects into better human health is less well understood. It is postulated that immunosuppression can result from exposure to allergens, illness, toxins or stress. In that view treatment with Echinacea could strengthen a weakened immune system, restoring balance and health. However, immunomodulation is a more appropriate term for Echinacea’s effect, as the immune system that Echinacea is reported to stimulate is high complex multi-component system with no clear “up” or “down”. Beneficial immunomodulation would include the reduction of harmful host response, such as inappropriate irritation or inflammation. Several symptoms and autoimmune diseases have been described in single case reports. Assessment of those reports showed that they don’t support the contraindication for progressive systemic disorders and autoimmune diseases. Although several official documents include this contraindication, based upon the first <i>in vitro</i> experiments, we are of the opinion that this wording can go out. Although only of theoretical consideration, as it should do for all plants with immune stimulating activity, it might be advisable to include:</p> <p><b>As with all immunostimulants, it is not recommended in cases of progressive systemic disorders and autoimmune diseases such as tuberculosis, leucosis, collagenoses, multiple sclerosis, AIDS or HIV infections.</b></p> <p><i>Immunosuppression and haematologic systemic diseases</i> There is <b>no</b> reference nor in the list of references or published elsewhere given the scientific background for the contraindications “In case of immunosuppression .... agranulocytosis, leukamias)”. Therefore it is proposed to leave out this part of the wording.</p>	<p>See the response 2 rows above.</p>



	<p><i>Allergic diathesis</i></p> <p>Mullins and Heddle (2002) reported a possible increased risk of allergic reaction in atopic patients. No detailed information of the used Echinacea preparations is available. The information about the possible risk of Echinacea in those patients would be more appropriate under heading 4.4 “special warnings”. It is not helpful and leads to confusion if the information is given here too.</p>	
	<p><b>5. Contraindication “allergic diathesis”</b></p> <p>Inclusion of “allergic diathesis” as a Contraindication is not justified since only isolated reports of skin and subcutaneous tissue disorders (&lt; 1:10’000) like skin hypersensitivity reactions were reported and which - according to Mullins and Hedge (2002) - are mainly represented by atopic subjects. As “Hypersensitivity to plants of the Asteraceae family” already is included under Contraindications and as atopic persons are prompted to visit the physician before using Echinacea, the passage on allergic diathesis should be deleted.</p>	See above.
<p><b>4.4 Special warnings and precautions for use</b></p>	<p>We agree that patients with serious infections or high fever should consult their doctor. We propose to modify the following sentence and say:</p> <p><i>There is a possible risk of <b>allergic</b> reactions in atopic patients. Atopic patients should consult their doctor before using Echinacea (Mullins et al 2002).</i></p> <p>We do not agree with and ask for the reason for the sentence “Patients should be aware that because of the intake of products containing Echinacea species <b>autoimmune diseases can be triggered</b>”. We have identified only one publication of a single patient case report (<i>Lee et al 2004: Activation of autoimmunity following use of immunostimulatory herbal supplements. Arch Dermatol 140(6): 723</i>) which describes a flare of pemphigus temporarily associated with the intake of Echinacea. It is scientifically not acceptable to base this serious warning on this single case report alone! In addition, the opinion of the author himself, who admitted that an exacerbation of pemphigus is a natural course of this condition and that URI contributed to the flare, should be taken into account.</p>	<p>The decision of the committee, to include the warning about the anaphylactic reaction is based on data available at NCAs (incl. pharmacovigilance data) and experience of MLWP/HMPC members.</p> <p>The committee agrees with the proposed changes to the monograph. The sentence was deleted from the monograph.</p>
	<p>As mentioned in chapter 4.2, we cannot agree that children should be excluded from the use of Echinacea purpurea.</p>	See chapter 4.2.
	<p>Even more, we cannot accept the following sentence which reads “The use in children is not recommended because efficacy has not been sufficiently documented although specific risk <b>other than</b> those mentioned in section 4.3, 4.6. and <b>4.8</b> in children over 4 years of age are not documented.”</p> <p>This implies that the undesirable effects mentioned in 4.8 have also been described in children. This sentence is unacceptable in the absence of published evidence for e.g. encephalitis disseminata, erythema nodosum, immunothrombocytopenia, Evans’ and Sjögren syndrome in children.</p>	<p>The committee agrees to change the monograph as follows: “The use in children is not recommended because efficacy has not been sufficiently documented although specific risk in children over <b>1</b> year of age is not documented.”</p>

	<p><i>serious infections or high fever</i> We agree that patients with serious infections or high fever should consult their doctor. But Echinacea is not recommended for serious infection and high fever and those symptoms are not accepted as the (first) symptoms of a common cold. That patients with serious infections or high fever should consult should be “daily practice”. Therefore this special warning is not applicable for use of Echinacea and can leave out.</p> <p><i>atopic patients</i> Proposal to modify the sentence and to avoid repeating delete allergic diathesis under heading “contraindication”.</p> <p><b>There is a possible risk of allergic reactions in atopic patients. Atopic patients should consult their doctor before using Echinacea (Mullins et al 2002)</b></p> <p>autoimmune diseases Only one publication of a single patient case report describes a flare of pemphigus associated to the intake of Echinacea [Lee et al 2004]. Information of the used preparation is missing and other explanations for the reported effects are possible. According to the author an exacerbation of pemphigus is a natural course of this condition or the URI could contribute to the flare. To adopt a high-risk statement based upon one article is not acceptable and this paragraph should be left out. However autoimmune diseases are mentioned under heading 4.3 “contraindication”.</p> <p><i>children</i> As mentioned under 4.2 we cannot agree that children should be excluded from the use of Echinacea. More over, we cannot accept the sentence “the use ... are not documented”. This implies that the undesirable effects mentioned in 4.8 have been described in children too. But there are <b>no</b> published evidence for encephalitis disseminata, erythema nodosum, immunothrombocytopenia, Evans’ and Sjörger syndrome in children.</p>	<p>Agreed.</p> <p>Agreed.</p> <p>Agreed.</p> <p>See the response above.</p>
<p><b>4.5 Interactions</b></p>	<p>It is not clear whether the mention of interactions with methotrexate and cyclosporine come from published materials as no such article seems to be included in the references. We assume this has been added on a purely theoretical basis and without clinical background. This should be clarified.</p>	<p>The (unpublished) information came from the national authorities. Nevertheless, we deleted this interaction from the monograph.</p>
	<p>It is not clear whether the mentioned interaction with methotrexane and cyclosporine comes from. The list of references does not contain any articles to support this statement. This should be clarified where this statement comes from or leave it out.</p>	<p>See above.</p>

<p><b>4.6. Pregnancy and lactation</b></p>	<p>The published results of a prospective study (<i>Gallo et al 2000: Pregnancy outcome following gestational exposure to Echinacea: a prospective controlled study: Arch Intern Med. 160(20): 3141-3</i>) suggest that gestational use of Echinacea during organogenesis is not associated with an increased risk of major malformations. Perri (<i>Perri D, Dugoua JJ, Mills E, Koren G: Safety and efficacy of Echinacea during pregnancy and lactation. Can J Clin Pharmacol. 2006 Fall;13(3):e262-7. Epub 2006 Nov 3.</i>) comes to the same conclusion after review of the existing scientific literature on the matter.</p> <p>Nordeng H and Havnen GC published a survey with 400 Norwegian women, who used herbal drugs in pregnancy (<i>Pharmacoepidemiol Drug Safety 13 (6): 371-380; 2004</i>). No relevant new information was found in this study about the safety of Echinacea during pregnancy.</p> <p>Chow G, Johns T, Miller S C: (<i>Dietary Echinacea purpurea during murine pregnancy: effect on maternal hemopoiesis and fetal growth. Biol Neonate 2006; 89 (2): 133-138</i>) undertook a study in gestating mice which were fed daily with Echinacea purpurea from the onset until days 10, 11, 12, 13, and 14 of gestation. The data indicate that the significant, pregnancy-induced elevation in splenic lymphocytes and nucleated erythroid cells was all but eliminated in those females which consumed E. purpurea daily throughout their gestation. Moreover, consuming E. purpurea during pregnancy reduced the number of viable foetuses. From the data, the authors concluded that it would be prudent that pregnant women abstain from taking Echinacea products during the early/mid stages of pregnancy.</p> <p>We are of the opinion that this study presents some shortcomings, for example, the background rate of conception in the used mice model is usually very low (<math>\approx 50\%</math>). Therefore, it is inappropriate to extrapolate such results to humans.</p> <p>Therefore we suggest deleting the following sentence: <i>“To date, no other relevant epidemiological data are available. The potential risk for humans is unknown”</i> and rewording the following sentence as follows: <b>“In accordance with general medical practice, the product should not be used during pregnancy or lactation without medical advice.”</b></p>	<p>The references provided by the commenter will be added to the assessment report.</p> <p>Based on this information we do not see a need to modify wording in a monograph.</p> <p>The monograph contains the information for the physician and is not intended for the patient.</p> <p>We agree that the wording in a package leaflet can read as proposed by the commenter.</p>
	<p>It is not clear why the lines “Data concerning... for humans is unknown” are include. Using Echinacea during pregnancy had no adverse effect on the foetus and newborn child. Published results of prospective studies [Gallo et al 200; Norden et al 2004; Perri et al 2006] are included. It is proposed to leave out the two lines and replace the last line In the ... not recommended with:</p> <p><b>In accordance with general medical practice, the product should not be used during pregnancy or lactation without medical advice.</b></p>	<p>These lines are in accordance with the guideline on SmPC. Nevertheless, we deleted the second sentence from the monograph.</p> <p>See the respond above.</p>

<p><b>4.8 Undesirable effects</b></p>	<p>We agree that hypersensitivity reactions may occur. However, in Europe the current product information text approved by national Health Authorities is more adapted to the symptoms and their frequencies and is more helpful for the patient:</p> <p><i>In very rare cases hypersensitivity reactions may occur. Skin eruptions, itching, seldom swelling of the face, difficult breathing, dizziness and hypotension have been observed in connection with medicines containing preparations from Echinacea purpurea.</i></p> <p>As said before, we also agree with the sentence:</p> <p style="padding-left: 40px;"><i>Echinacea can trigger allergic reactions in <b>atopic</b> patients.</i></p> <p>However, we propose to delete this sentence under 4.8 and only mention it under 4.4 since, in our opinion, this is a special warning.</p>	<p>The new guideline on SmPC requires a strong data to state the frequency of undesirable effects. Such strong data is not available to the committee.</p> <p>Agreed.</p>
	<p>The following list of serious symptoms and diseases which have been described in single case reports cannot be accepted.</p> <ul style="list-style-type: none"> <li>- <u>Encephalitis disseminata</u>: We presume that this mention is based on the publication of Schwarz, Knauth and Schwab (<i>Schwarz S, Knauth M, Schwab S, Acute disseminated encephalomyelitis after parenteral therapy with herbal extracts: a report of two cases. J Neurol Neurosurg Psychiatry 2000; 69: 516-518</i>) although the publication does not figure amongst the references listed. The authors attribute one case to the <i>injection</i> of an Echinacea angustifolia-containing combination product. This case report is not relevant for the safety of oral Echinacea and therefore outside the scope of the draft monograph.</li> <li>- <u>Erythema nodosum</u>: Soon and Crawford (<i>Soon SL and Crawford RI, Recurrent erythema nodosum associated with echinacea herbal therapy. J Am Acad Dermatol 2001; 44(2):298-299</i>) report a case of recurrent erythema nodosum that, in their opinion, was temporally and might have been associated with the use of Echinacea herbal therapy. However other causes of erythema nodosum could not be definitely excluded. We therefore consider this single case as not relevant.</li> <li>- <u>Immunothrombocytopenia</u>: We presume that this mention is based on the publication of Liatsos G, Elefsiniotis I (<i>Liatsos G, Elefsiniotis I, Severe thrombotic thrombocytopenic purpura (TTP) induced or exacerbated by the immunostimulatory herb Echinacea. Am J Hematol 2006; Mar 81 (3): 224</i>) although it is not among the references listed. The authors attribute a case of TTP to the intake of a water-alcoholic extract of Echinacea pallida. They did not consider possible idiopathic, secondary or genetic causes for the arising of TTP and the fact that the intake of Echinacea pallida could have been only temporarily associated.</li> <li>- <u>Evans' syndrome</u>: We could not find a reference.</li> <li>- <u>Sjögren syndrome</u>: Logan JL and Ahmed J (<i>Logan JL and Ahmed J, Critical hypokalemic renal tubular acidosis due to Sjögren's syndrome: association with the purported immune stimulant echinacea. Clin Rheumatol 2003; 22: 158-159</i>) describe a patient with Sjögren</li> </ul>	<p>The decision of the committee, to include additional undesirable effects was not based only on the published case reports, but also on data available at NCAs (pharmacovigilance reports from Member States) and experience of MLWP/HMPC members.</p>

	<p>syndrome who took St. John's wort, Echinacea and Kava two weeks before becoming ill. The authors discuss a possible correlation with the intake of Echinacea but they also acknowledge that the association may be purely incidental and a temporal association only. It can be alleged that the patient already had slight symptoms of Sjögren syndrome before the beginning of the Echinacea therapy.</p> <p>- <b>Leucopenia:</b> Kemp DE and Franco KN (<i>Kemp DE and Franco KN, Possible leukopenia associated with long-term use of Echinacea. J Amer Board Family Pract 2002; 15/5: 418-419</i>) reported about a woman who had taken an Echinacea-containing product for a period of 8 weeks as a prophylaxis against a cold, and who developed a leucopenia (3300/<math>\mu</math>l). Concomitantly with Echinacea, she had been taking vitamins C, E and B complex, ginkgo biloba, calcium, and bupropion (Wellbutrin SR) for depression. One month after withdrawal of Echinacea and Ginkgo her white cell count had increased slightly. Approximately 1 year later – the patient had resumed taking bupropion and Echinacea for the previous 2 months – her white cell count was about 3000/<math>\mu</math>l. Two months after discontinuing Echinacea her white cell count was 3440/<math>\mu</math>l and 7 months later rose to 4320/<math>\mu</math>l. Due to the fact that the authors could not find another reason for the leucopenia, they assumed a relationship to the intake of the Echinacea.</p> <p>The patient showed also low levels of the white cell counts without Echinacea. Therefore, it seems possible, that the leucopenia was associated with the treatment of bupropion. Reports are existing concerning the occurrence of hematologic changes, such as anemia and pancytopenia (product information Wellbutrin, PDR USA). In summary, we are of the opinion that the case has to be assessed as not relevant for the safety of Echinacea.</p> <p>The presentation of these isolated case reports is a simple listing and not a scientific assessment. They should not alone result in the mention in the HMPC monograph unless they are substantiated by further evidence. With regard to the overall well-known excellent safety and tolerability profile of Echinacea purpurea medicinal products, it is most likely that the above-mentioned “undesirable effects” are coincidental and not causal to the intake of Echinacea.</p>	
	<p><i>Hypersensitivity</i> In line with text approved by national Health Authorities we propose the following wording:</p> <p><b>In very rare cases hypersensitivity reactions may occur.</b></p> <p><i>atopic patients</i> The sentence Echinacea can .... atopic patients” is in our opinion a special; warning and should be felt out here (It is already mentioned under heading 4.4).</p>	<p>See above.</p> <p>Agreed.</p>

	<p><i>autoimmune disease</i></p> <p>Several symptoms and diseases are listed which has been described in single case reports. The presentation of these isolated reports is a simple listing and not a scientific assessment. When this work done in the properly it is likely that none of those items would have been included. A case report should not mention in the HMPC monograph unless it is substantiated by further evidence. With regard to the overall well known safety and tolerability profile it is not likely that the listed undesirable effects are coincidental and not causal to the intake of Echinacea.</p>	See above.
	<p><b>4. Undesirable effects, safety and duration of therapy</b></p> <p>Currently there is no substantial reason why <i>Echinacea purpurea</i> should not be used over a period of 2 months as stated by the ESCOP monograph 2003.</p> <p>In isolated case reports leucopenia or suppression of the immune system were described, but clinical correlation to the intake of Echinacea was lacking. To extrapolate from isolated and inadequately reported cases to a restriction in medication is not justified.</p> <p>Concerns that long-term use of <i>Echinacea purpurea</i> might cause leucopenia are not justified: The mentioned article (Kemp, 2002) represents an isolated case report of a 51-year old woman taking various vitamin preparations together with Ginkgo biloba and calcium and bupropion (300mg/d). For bupropion the drug company literature describes leukopenia secondary to bupropion. Therefore leukopenia should not be correlated with the intake of Echinacea.</p> <p>In many studies laboratory and hematological parameters were investigated and decreases in leukocytes were not found even during 2-months intake of Echinacea purpurea (Schoop et al (2007), Kim (2002), Goel (2005))</p> <p>In contrast to the observed case report in Agnew et al. (2005) rather a weak increase than a decrease in WBC was found.</p> <p><b>Schoop R, Buechi S, Suter A. (2007) Open, multicenter study to evaluate the tolerability and efficacy of Echinaforce Forte tablets in athletes. <i>Advances in Therapy</i>; 23(5):823 - 33.</b></p> <p><b>Kim LS, Waters RF, Burkholder PM. (2002) Immunological activity of larch arabinogalactan and Echinacea: a preliminary, randomized, double-blind, placebocontrolled trial. <i>Alternative Medicine Review</i>; 2(7): 138 – 149.</b></p> <p><b>Goel V, Lovlin R, Chang C, Slama JV, Barton R, Gahler R, Bauer R, Goonewardene L, Basu TK. (2005) A proprietary extract from the Echinacea plant (<i>Echinacea purpurea</i>) enhances systemic immune response during a common cold. <i>Phytother Res.</i>; 19(8):689-94.</b></p> <p><b>Agnew LL, Guffogg SP, Matthias, Lehmann RP, BoneKM, Watson K. (2005) Echinacea intake induces an immune response through altered expression of leucocyte hsp70, increased white cell counts and improved erythrocyte antioxidant defences. <i>Journal of Clinical Pharmacy and Therapeutics</i>: 30 : 363 - 369</b></p> <p>A long-term placebo-controlled cross-over treatment for 6 months with <i>Echinacea</i></p>	<p>There is no clinical trial which would demonstrate any clinical efficacy of <i>Echinacea purpurea</i> herba recens in a period longer than 10 days.</p> <p>The indication “treatment of common cold” that is included in the monograph does “per se” not allow longer use.</p> <p>See also the respond to the comments in section on <b>Duration of use.</b></p> <p>See the respond to the comments in section <b>4.8. Undesirable effects</b> (few lines above).</p>

	<p><i>purpurea</i> extract also is available. A total of five adverse events were reported from 50 participants of which none was serious. Most of the reported events affected the gastrointestinal tract. There was no indication as to a causal link with the study medication.</p> <p>Another article on long-term administration of <i>Echinacea purpurea</i> is available from Parnham (1996). Parnham concluded that <i>Echinacea purpurea</i> is well tolerated on long-term oral administration and that symptoms of immune stimulation (fever or shivering) only are associated with parenteral and not with oral use. Adverse events on oral administration for up to 12 weeks are infrequent.</p> <p><b>Vonau B, Chard S, Mandalia S, Wilkinson D, Barton SE. (2001) Does the extract of the plant <i>Echinacea purpurea</i> influence the clinical course of recurrent genital herpes? Int J STD AIDS.; 12(3):154-8.</b></p> <p><b>Parnham MJ. (1996) Benefit-risk assessment of the squeezed sap of the purple coneflower (<i>Echinacea purpurea</i>) for long-term oral immunostimulation. Phytomedicine; 3(1):95-102.</b></p> <p>An article from Logan (2003) shall be discussed shortly in the following section as it represents a typical example of how the items in the special warning sections were compiled:</p> <p><b>Logan 2003:</b> A single case study of a 36-year old woman who took <i>Echinacea</i>, St. John's worth and kava-kava for 2 weeks before she was hospitalized with diagnosed hypokalaemic renal tubular acidosis (due to Sjögren's syndrome). However in the report no information regarding the <i>Echinacea</i> species (<i>Echinacea purpurea</i>, <i>E. angustifolia</i>, or <i>E pallida</i>, ...), dosages and routes of administration are given. Also no re-challenge tests were performed and no conclusive correlation to the intake of the <i>Echinacea</i> product is possible. It is therefore not justified to mention Sjögren's syndrome in the undesirable effect list, as there is no cumulative occurrence of such syndromes in correlation with <i>Echinacea purpurea</i> intake. Since safety data from clinical trials were collected under rather controlled conditions (dosage, species, quality, assessment of co-medication) and under the surveillance of a physician, such data should be regarded as well:</p> <p>In the article by Melchart et al. (2004) safety data from 16 controlled clinical trials were resumed and included data from about 1000 participants treated with <i>Echinacea</i>. Overall the incidences of adverse events in the <i>Echinacea</i> group did not differ when comparing with placebo. Furthermore Barret (2003) in his review stated "the low number of reports of suspected adverse reactions associated with <i>Echinacea</i> preparations set against estimates of the high frequency of use of <i>Echinacea</i> has been used as an argument for the safety of <i>Echinacea</i>".</p> <p>It shall also be noted that <i>Echinacea</i> by the FDA authority is recognised as GRAS (generally recognized as safe).</p>	
5.3	Reproduction toxicity studies (segment II and III studies) were not performed.	Agreed. This statement was added to the 5.3. section of the monograph.
	No toxic effect was reported with <i>Echinacea purpurea</i> expressed juice administered to animals in the acute toxicity studies (up to 30 000 mg/kg and 15 000 mg/kg in mice and rats, respectively), and in the 4-week rat toxicity study (up to 8 000 mg/kg/day). These results are amazing and questionable (notably on GLP compliance) considering the very high dose levels used and the	In the reference (Mengs U, Clare CB, Poiley JA. (1991) Toxicity of <i>Echinacea purpurea</i> - Acute, subacute and genotoxicity studies. <i>Arzneimittelforschung</i> 41(10): 1076-1081.) full details about methodology are listed,

	<p>pharmacological activity of Echinacea. The bibliographic data do not suggest a genotoxic potential for the expressed juice tested. However, the extrapolation of these results to the expressed juice used in therapeutics should be discussed considering the characteristics of expressed juice. In addition, a definitive conclusion on the genotoxic potential of the expressed juice tested cannot be drawn due to some missing data (concentration/doses used for the MLA-TK and micronucleus assays) and the questionable quality of the studies (see above). <b>This precludes the listing of Echinacea purpurea.</b></p>	<p>including the tested product and doses used. MLA-TK test was not used in this research.</p>
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Superseded



TRADITIONAL USE		
<p><b>2. Qualitative and quantitative composition</b></p> <p>ii) Herbal preparation(s)</p>	<p>The use is restricted to expressed juice or dried expressed juice. For external use other preparations have been used and, for example, Hellemont (1988), Barrett (2003) mentioned the use of ethanol extracts or tinctures. This use should be included.</p> <p>We suggest the following rephrasing:</p> <p>“ii) <i>Herbal preparations</i></p> <ul style="list-style-type: none"> <li>- <i>expressed juice</i></li> <li>- <i>dried expressed juice</i></li> <li>- <i>ethanol extract or tincture from fresh flowering aerial parts</i>”</li> </ul>	<p>The 30 years period of topical use of extracts/tinctures is not adequately documented (posology and concentration of ethanol is missing).</p>
	<p>Beside the external use <i>Echinacea purpurea</i> preparations have a long tradition for prophylaxis and the treatment of common cold and flu (see comments 4. Clinical particulars. 4.1 therapeutic indications). As consequence the application route has to be changed and the following wording is proposed:</p> <p><b>Herbal preparation in semi-solid or liquid dosage forms for oral or topical use.</b></p>	<p>See the respond below (in Therapeutic indications).</p>
	<p>1. Stabilised juice (1:1 in 20-30 % (V/V) ethanol) in liquid dosage form should be added to the list of herbal preparations.</p> <p>Rationale:</p> <p>Tradition of stabilised juices has in Poland very long tradition (more than 45 years) [Draft of the label wording of 1981 for <i>Succus Hyperici</i> with the invalid declaration of the label of 1956; Lutomski and Małek 1973; Ożarowski 1980].</p> <p>Stabilised juice (<i>Succi stabilisatae</i>) are obtained from fresh herbal crude drugs, usually after preliminary inactivation of the enzymes, differently from expressed juices.</p> <p>The inhibitor which is most often used is ethyl alcohol. Fresh crude drug, previously cleaned and comminuted, is subjected to stabilisation with 95% ethyl alcohol vapours in autoclaves under 0.2 MPa for 2–4 h. Stabilised juice is obtained from thus prepared crude drug by its maceration with the solvent prepared from alcoholic extract fluid (obtained after stabilisation), 95% ethanol and water, in a ratio ensuring that the content of ethyl alcohol in the finished product is about 30%(V/V). The maceration time is differentiated – depending on the chemical nature of the active substances and on the plant part constituting the crude drug (root, rhizome, herb). The crude drug is subjected to pressing and the extract fluid obtained is combined with the fluid from the elution process. The product obtained is subjected to the sedimentation process and the time of seasoning depends on the preparation. After filtration, the juice is dosed into bottles.</p> <p>Due to quite different manufacturing processes the name of stabilised juice is proposed to distinguish both qualities.</p>	<p>The interested parties did not provide the information about the posology of traditional use of stabilised juice.</p>

<p><b>3. Pharmaceutical Form</b></p>	<p>1. Stabilized juice in liquid dosage form, for oral use, should be added to the list of herbal preparations. The use should not be limited only to topical application.</p> <p>Rationale:</p> <p>Stabilised juice of <i>Echinacea purpurea</i> herba recens for oral use, is presented on polish pharmaceutical market since 1990 (Registration Certificate of <i>Succus Echinacea</i>).</p> <p>Stabilised juices are obtained from fresh herbal crude drugs, usually after preliminary inactivation of the enzymes, differently from the previous group of juices. They exist as a pharmaceutical form of herbal medicinal products in Poland from several dozen years. The technology of stabilized juice was described in 1973 by Lutomski in “Technology of Herbal Drug” PZWL Warszawa (Lutomski &amp; Małek 1973) and then in consecutive edition of “Farmacja stosowana” by Janicki et al. in 1996, 1998, 2000, 2001 and 2006.</p> <p>According to bibliographic data it can be assumed that since 1956 domestic industry supplies the following juices for use in therapy: Hyperici succus and the following since 1980: Plantaginis succus, Taraxaci succus and Urticae succus, Echinacea succus, Betulae succus and Bardanae succus (Lutomski, Małek 1973; Ozarowski 1980; Janicki, Fiebig 1996).</p>	<p>See the response below (in Therapeutic indications).</p>
<p><b>4.1 Therapeutic indications</b></p>	<p>The draft mentioned the treatment of wound only. But Echinacea preparations have a much broader tradition. Known is the prophylaxis and treatment of mild to moderately severe colds, influenza [Barrett 2003, Hellemons 1988, Hänsel et al 1994, Newall et al 1996]. Different commercial preparations are more than 30 years in Europe on the market [e.g. Rote liste 1953]. In conclusion, it is proposed to change “traditional use” as follows</p> <p><b>Traditional herbal medicinal product for prophylaxis and treatment of common cold and flu and for the treatment of superficial wounds.</b></p>	<p>Traditional use itself is not enough for inclusion of indication in the “Traditional use” part of the monograph. Plausibility of the therapeutic effect as well as a high level of safety that enables the use without medical supervision must be shown. When there is enough data for well established use, the same indication can not be listed in traditional use.</p>
	<p>We propose to include the traditional medicinal use of stabilised juice for oral treatment, of early symptoms of common cold, especially in patients prone to recurrent respiratory tract infections, based on long tradition of use and experiences on Polish market with a marketed herbal medicinal product (since 1990 – Registration Certificate of <i>Succus Echinacea</i>).</p> <p>Adolescents over the age of 12 years, adults, elderly</p> <p>Stabilised juice 7.5 -10 ml per day (&gt; 12 years of age) equivalent to 7-10 g of the herbal substance, divided in 3-4 doses.</p>	<p>See above.</p>
<p><b>4.2 Posology and method of administration</b></p>	<p>The HMPC draft does not recommend external application of <i>E. purpurea</i> preparations in children below 12 years of age. However, there is long-term experience of use of Echinacea products in children from 2 to 12 years old. So far, no safety concerns have been reported. We therefore recommend the following rewording of the sub-heading:</p>	<p>Not agreed. No data on exposure of children during the 30 years of tradition is available.</p>

	<p><i>Children over the age of 2 years, adults, elderly.</i></p> <p>In addition, ethanol extracts should be added in the second line which would then read:  “10 to 20 g / 100 g of <u>ethanol extract, tincture</u>, expressed juice or equivalent amount of dried expressed juice”</p>	
<b>Posology</b>	<p>Tincture: 3 time 30-60 drops of a tincture [Hänsel et al 1994, Hellemont 1988].  For press juice and comparable preparations the same recommendation as is proposed for well-established use.</p>	Not agreed (see respond in 2).
<b>Duration of use</b>	<p>It is not clear were the restriction to one-week comes from. The ESCOP monograph recommends not exceeding 8 weeks.</p>	<p>The restriction comes from the requirement, in European legislation, that Traditional herbal medicinal products should be suitable for use without any professional advice. It is the opinion of the committee, that any condition on the skin that lasts for more than one week must be examined by the physician. The safety of long-term topical use of <i>Echinacea</i> has not been established.</p>
	<p>We propose to the following wording:</p> <p><b>The duration of continuous treatment should not exceed 8 weeks. No adverse reactions have been reported after long-term oral administration. If the symptoms worsen during the use of the product or persist for more than 10 days, a doctor or a qualified health care practitioner should be consulted.</b></p>	Not agreed. See above.
<b>Method of administration</b>	<p>It is proposed to change the “Method of administration” as follows:</p> <p><b>For internal and topical use</b></p>	Not agreed. See respond in sections 2 and 4.1.
<b>4.3 Contraindications</b>	<p><i>Hypersensitivity</i></p> <p>When there is a know hypersensitivity to plants of the Compositae family use of Echinacea (member of this plant family) is not advised. With mentioning “the active substance” and “Asteracea family” the same information is given twice. We propose to the wording and change into: <b>Hypersensitivity to plants of the Compositae family</b></p>	See response in well established use.
	<p><i>Autoimmune diseases</i></p> <p>Several mother tinctures of Echinacea are registered as homeopathic medicinal products. An examples of those products can be found on the website Medical Evaluation Board of the Netherlands. Although there are small differences in preparing a mother tincture or traditional used tincture the drug extract ratio is approximately 1:10 with the same alcohol content. As consequence chemical composition of both tinctures are the same. For the evaluation of the safety the same literature is available and is, or will be used. There are no safety concerns for mother tinctures and words concerning autoimmune diseased are not required as contraindication on the package and patient leaflet. This and the fact that Echinacea has immune modulatory properties (see below) it is plausible that traditional used Echinacea has the same safety profile.</p>	Autoimmune diseases are not a contraindication in traditional use.

<b>4.8 Undesirable effects</b>	The second line “Echinacea can trigger allergic reactions in atopic patients” does not fit under this heading and should be removed as it is already mentioned under ‘contraindication’.	The committee deleted the sentence. The sentence is not mentioned under “Contraindications” either.
<b>LIST ENTRY</b>	(comments other than those mentioned above)	
<b>Common name in all EU official languages</b>	The common name in Dutch is as follows: NL (Nederlands): <b>rode zonnehoe, kruid</b>	Accepted.
	There is a mistake in Polish name of the herb Proper Polish name of the herb is: jeżówka purpurowa	See below.
	In some languages name of the herb is given, in some other name of the herbal preparation is given. Polish name of the herb: jeżówka purpurowa Polish name of the herbal preparation: sok z ziela jeżówki purpurowej	The final decision of the committee in July 2007 was that a name of the herbal substance should be given. We introduced the name: jeżówka purpurowa, świeże ziele.
“Duration of use or any restrictions on the duration of use”	For the stabilised juice (1:1 in 20-30 % (V/V) ethanol) in liquid dosage form: Use the medicinal product for 10 days in case of everyday application or for 20 days in case of every second day application. The treatment can be repeated after two weeks break.	See the comment on “ <b>Duration of use</b> ” in Traditional use monograph section.