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Committee on Herbal Medicinal Products (HMPC)

Addendum to Assessment report on *Echinacea angustifolia*, radix

Rapporteur(s)	Samo Kreft, Barbara Razinger
Peer-reviewer	Marisa Delbò

HMPC decision on review of monograph *Echinacea angustifolia*, radix adopted on 27 March 2012	30 January 2018
Call for scientific data (start and end date)	From 01/03/2018 to 31/05/2018
Agreed by Working Party on European Union monographs and list (MLWP)	September 2018
Adoption by Committee on Herbal Medicinal Products (HMPC)	20 November 2018

Review of new data on *Echinacea angustifolia*, radix

Periodic review (from 2008 to 2018)

Scientific data (e.g. non-clinical and clinical safety data, clinical efficacy data)

☒ Pharmacovigilance data (e.g. data from EudraVigilance, VigiBase, national databases)

☒ Scientific/Medical/Toxicological databases PubMed (Using the Mesh term "*Echinacea angustifolia*" from 2008 to present, Search date: 30 june 2018, 53 hits), ToxNet (Using the search term "*Echinacea angustifolia*" 0 hits excluding PubMed records, Search date: 30 June 2018), Cochrane Database of Systematic Reviews (Using the search terms "*Echinacea*", Search date: 30 June 2018, 1 hit).

☐ Other

Regulatory practice

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

☒ Old market overview in AR (i.e. products fulfilling 30/15 years on the market)

☒ New market overview (including pharmacovigilance actions taken in member states)

☐ Referral

☐ Ph.Eur. monograph

☐ Other

Consistency (e.g. scientific decisions taken by HMPC)

☐ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☐ Other

Availability of new information (i.e. likely to lead to a relevant change of the monograph)

Scientific data	Yes	No
New non-clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New clinical safety data likely to lead to a relevant change of the monograph	☐	☒
New data introducing a possibility of a new list entry	☐	☒
New clinical data regarding the paediatric population or the use during pregnancy and lactation likely to lead to a relevant change of the monograph	☐	☒
New clinical studies introducing a possibility for new WEU indication/preparation	☐	☒
Other scientific data likely to lead to a relevant change of the monograph	☐	☒
Regulatory practice	Yes	No
New herbal substances/preparations with 30/15 years of TU	☐	☒
New herbal substances/preparations with 10 years of WEU	☐	☒
Other regulatory practices likely to lead to a relevant change of the monograph	☐	☒
Referrals likely to lead to a relevant change of the monograph	☐	☒
New / Updated Ph. Eur. monograph likely to lead to a relevant change of the monograph	☐	☒
Consistency	Yes	No
New or revised public statements or other HMPC decisions likely to lead to a relevant change of the monograph	☐	☒
Relevant inconsistencies with other monographs within the therapeutic area that require a change of the monograph	☐	☒
Other relevant inconsistencies that require a change of the monograph	☐	☒

Summary and conclusions on the review

During the review 53 new references not yet available during the first/previous assessment were identified.

0 references were provided by Interested Parties during the Call for data.

9 references were considered to be relevant for the assessment. 44 references were about cultivation and phytochemical analytics and were not considered relevant.

0 references justify a revision of the monograph.

No revision is considered required because:

Scientific data:

In the scientific literature there are only a few new studies on the plant species *E. angustifolia*. Most of the studies report on non-clinical pharmacological activities. Only few can be considered to be related to the indication of the monograph (primary pharmacodynamics), e.g.: anti-inflammatory (Aarland *et al*., 2017), immunomodulation (Depas *et al*., 2014; Matthias *et al*., 2008, Zhai *et al*., 2008) and gene expression in ovine leukocytes (Sgoron *et al*., 2012). Most studies are on secondary pharmacodynamics: hypoglycaemic (Aarland *et al*., 2017), antioxidant (Aarland *et al*., 2017), antiproliferative (Aarland *et al*., 2017), p-glycoprotein inhibition (Romit *et al*., 2008). The study on p-glycoprotein inhibition (Romit *et al*., 2008) is related to the possibility of herb-drug interaction, but it was performed on hexane extract, which is not included in the monograph and the authors concluded, that "the observed effects do not appear dramatic".

One study was on pharmacokinetics of alkamides from *E. angustifolia* in rats (Jedlinszki *et al.,* 2014).

Two studies were investigating clinical efficacy of *E. angustifolia*. Bertoglio *et al*., 2012 studied it use in gastrointestinal mucositis due to cancer therapies in paediatric patients, which is not related to the indication of the monograph. The study of Di Pierro *et al*., 2012 was partially related to the monograph, but it was a small pilot study (number of volunteers in the three groups were 14, 12 and 20) and cannot be used to support well-established use. It showed promising results but it was not significant.

Pharmacovigilance: there are no relevant new reports on undesirable effects of oral use of *E. angustifolia* root from the Eudravigilance database. In 2010 the Austria reported one case of arthralgia in a patient receiving homeopathic intramuscular preparation of *E. angustifolia* (plant part not reported).

Assessor's comment:

There are no new safety concerns from non-clinical or clinical data (including pharmacovigilance). The new clinical studies do not enable the establishment of a well-established use monograph.

Regulatory practice:

No new medicinal products with *E. angustifolia* radix as the single active substance have been reported from the MS. Two MSs which had the product on the market in 2008, do not have it on the market any more. The product in one MS is now a combination product. Latvia is the only remaining MS with a product containing *E. angustifolia* radix as the single active substance (see Table 1 below).

Table 1: Information about products on the market in the Member States

	in 2008 (information in the AR published in 2012)	**in 2018** (information from information exchange)
Spain:	herbal substance, powdered, (250 mg of herbal substance/capsule) Preparation on the market: since 1990	No product currently on the market
Sweden:	dry extract (DER 1.7-4.7:1) ethanol 70% (V/V); 100 mg of extract/capsule, equivalent to 170-470 mg of the herbal	Currently, there are no medicinal products containing *Echinacea angustifolia*, radix, as an active substance on the Swedish market. The Swedish product included in the first version of the

	substance. Preparation on the market: since 2005	assessment report was on the Swedish market between 2005-2008, i.e. the dry extract (DER 1.7-4.7:1) ethanol 70% (V/V); 100 mg of extract/capsule.
Latvia:	tincture (1:5) ethanol 70% (V/V). Preparation on the market: since 2002	Product name: Echinaceae angustifoliae tinctura Qualitative and quantitative composition: 1 ml solution contains 1 ml *echinacea* roots tincture (Echinaceae tinctura) 1:5 (extraction solvent: ethanol 70%) Pharmaceutical form: Oral drops, solution Indication: product for supportive treatment of common cold Posology: adults, adolescents and older people 45-90 drops (1-2 ml) 3 time a day. Preparation on the market: since 2002
Hungary:	33.30 g liquid extract of *Echinacea angustifolia*, radix (mother tincture according to HAB 2000); extraction solvent: ethanol 86% (m/m) DER=2:1 in 100 g solution, ethanol 50% V/V). Preparation on the market: since 1991. Pharmaceutical form: oral solution.	*Echinacea* drops: 1 g solution contains: 0.33 g *Echinacae* mother tincture [***Echinacea angustifolia* et/aut *Echinacea pallida***]. Prevention and adjuvant treatment of infectious diseases,and enhance immunoresistance. Posology: prevention: 20 drops daily treatment: 50 drops on the first day, for the following 2 days 10-20 drops in every 2 hours. Healing product

Assessor's comment:

There is no need to revise the EU herbal monograph due to new regulatory practice.

Consistency with other monographs

The monograph on *E. angustifolia*, radix (current version from 2012) is from the point of view of content consistent with the TU Monographs of other *Echinacea* preparations for oral use (*E. purpurea*, radix 017 and *E. pallida*, radix 2018). There are some editorial differences (see Table 2 below). The monograph on *E. purpurea*, herba has no TU indication for oral use.

Table 2:

	***E. angustifolia*, radix 2012**	***E. purpurea*, radix 2017**	***E. pallida*, radix 2018**
Indications	THMP for supportive treatment of common cold.	THMP for the relief of symptoms of common cold. THMP used for the relief of spots and pimples due to mild acne.	THMP for the relief of symptoms of common cold.
Contraindications	Hypersensitivity to the active substance(s) and to other plants of the	Hypersensitivity to the active substance and to other plants of the	Hypersensitivity to the active substance and to other plants of the

	Asteraceae (Compositae) family.	Asteraceae (Compositae) family.	Asteraceae (Compositae) family.
Special warnings and precautions for use	Not recommended in cases of progressive systemic diseases such as tuberculosis, diseases of the white blood cells system, collagenoses, multiple sclerosis, AIDS, HIV infections and other immune diseases. If the symptoms worsen or high fever occurs during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. There is a possible risk of allergic reactions in sensitive individuals. Those patients should consult their doctor before using Echinacea. There is a possible risk of anaphylactic reactions in atopic patients. Atopic patients should consult their doctor before using Echinacea. The use in children under 12 years of age has not been established due to lack of adequate data.	The use is not recommended in cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system. If the symptoms worsen or high fever occurs during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. There is a possible risk of allergic reactions in sensitive individuals. Those patients should consult their doctor before using Echinacea. There is a possible risk of anaphylactic reactions in atopic patients. Atopic patients should consult their doctor before using Echinacea. The use in children under 12 years of age has not been established due to lack of adequate data.	The use is not recommended in cases of progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system. If the symptoms worsen or high fever occurs during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted. There is a possible risk of allergic reactions in sensitive individuals. Those patients should consult their doctor before using Echinacea. There is a possible risk of anaphylactic reactions in atopic patients. Atopic patients should consult their doctor before using Echinacea. The use in children under 12 years of age has not been established due to lack of adequate data. For tinctures 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.
Interactions	None reported	None reported	None reported

Current *E. angustifolia* monograph is considered for the intended use consistent with the other Echinaceae monographs.

References

a) References relevant for the assessment:

Aarland RC, Bañuelos-Hernández AE, Fragoso-Serrano M, Sierra-Palacios ED, Díaz de León-Sánchez F, Pérez-Flores LJ, *et al*. Studies on phytochemical, antioxidant, anti-inflammatory, hypoglycaemic and antiproliferative activities of *Echinacea purpurea* and *Echinacea angustifolia* extracts. *Pharm Biol*. 2017; 55(1):649-656.

Bertoglio JC, Folatre I, Bombardelli E, Riva A, Morazzoni P, Ronchi M, *et al*. Management of gastrointestinal mucositis due to cancer therapies in pediatric patients: results of a case series with SAMITAL(®). *Future Oncol.* 2012 Nov; 8(11):1481-6. doi: 10.2217/fon.12.132.

Dapas B, Dall'Acqua S, Bulla R, Agostinis C, Perissutti B, Invernizzi S, *et al*. Immunomodulation mediated by a herbal syrup containing a standardized Echinacea root extract: a pilot study in healthy human subjects on cytokine gene expression. *Phytomedicine.* 2014 Sep 25; 21(11):1406-10. doi: 10.1016/j.phymed.2014.04.034. Epub, 2014.

Di Pierro F, Rapacioli G, Ferrara T, Togni S. Use of a standardized extract from *Echinacea angustifolia* (Polinacea) for the prevention of respiratory tract infections. *Altern Med Rev*. 2012; 17(1):36-41.

Jedlinszki N, Rédei D, Haller J, Freund TF, Hohmann J, Zupkó I. Possible role of fat tissue in the pharmacokinetics of Dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides after oral administration of Echinacea angustifolia extract in rats. *Nat Prod Commun*. 2014; 9(6):843-5.

Matthias A, Banbury L, Bone KM, Leach DN, Lehmann RP. Echinacea alkylamides modulate induced immune responses in T-cells. *Fitoterapia.* 2008 Jan; 79(1):53-8. Epub 2007 Aug 11.

Romiti N, Pellati F, Nieri P, Benvenuti S, Adinolfi B, Chieli E. P-Glycoprotein inhibitory activity of lipophilic constituents of Echinacea pallida roots in a human proximal tubular cell line. *Planta Med.* 2008 Feb; 74(3):264-6. doi: 10.1055/s-2008-1034308.

Sgorlon S, Colitti M, Asquini E, Ferrarini A, Pallavicini A, Stefanon B. Administration of botanicals with the diet regulates gene expression in peripheral blood cells of Sarda sheep during ACTH challenge. Domest Anim *Endocrinol.* 2012 Oct; 43(3):213-26. doi: 10.1016/j.domaniend.2012.03.001. Epub 2012.

Zhai Z, Solco A, Wu L, Wurtele ES, Kohut ML, Murphy PA, *et al*. Echinacea increases arginase activity and has anti-inflammatory properties in RAW 264.7 macrophage cells, indicative of alternative macrophage activation. *J Ethnopharmacol.* 2009 Feb 25; 122(1):76-85. doi: 10.1016/j.jep.2008.11.028. Epub, 2008.

Rapporteur's proposal on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

HMPC decision on revision

☐ Revision needed, i.e. new data/findings of relevance for the content of the monograph

☒ No revision needed, i.e. no new data/findings of relevance for the content of the monograph

The HMPC agreed by majority not to revise the monograph, assessment report and list of references on *Echinaceae angustifoliae* radix.

While preferable alignment with other *Echinacea* monographs regarding the wording of the indication and the warning section was supported, a majority did not see a current urgent need for these changes that could be introduced at later stage when new scientific/market data are available.

The following members did not agree with the decision of the HMPC and were of the position that there are findings of relevance for the content of the monograph and a revision is needed: H. Foth, I. Chinou, J Wiesner, L Anderson, H. Pinto Ferreira.