European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS ON 'COMMUNITY HERBAL MONOGRAPH AND LIST ENTRY ON *ELEUTHEROCOCCUS SENTICOSUS* (RUPR. ET MAXIM.) MAXIM., RADIX' (EMEA/HMPC/244569/2006) and (EMEA/HMPC/83756/2007)

Table 1: Organisation(s) providing comments on the draft 'Community herbal monograph on Eleutherococcus senticosus (Rupr. et Maxim.) Maxim., radix' and 'Community list entry on Eleutherococcus senticosus (Rupr. et Maxim.) Maxim., radix' as released for consultation on 5 July 2007 until 15 October 2007.

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 51
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

Table 2: Discussion of comments

Paragraph no.	Comment and Rationale	Outcome
General comments to draft documents	An interested party: 'We appreciate the above-mentioned draft documents prepared by the Herbal Medicinal Products Committee (HMPC) as it provides harmonised and sound criteria which should facilitate the granting of marketing authorisation of products containing this plant in Europe.'	N/A
	Another interested party: 'We appreciate both the drafts prepared by Committee on Herbal Medicinal Products. Although we are of the opinion that due to the high number of clinical studies a well-established use for Eleutherococcus senticosus is well justified, in the light of the draft 'Reflection paper on adaptogenic concept' (EMEA/HMPC/102655/2007) we conclude a respective request as redundant. Nevertheless, in both the drafts we consider less restrictions regarding the type of preparations in the context of a long standing use only as necessary as well as to widen the dosage range according to the published literature [1 – 3]……. Although we are of the opinion that due to the high number of clinical studies a well-established use for Eleutherococcus senticosus is well justified, in the light of the draft 'Reflection paper on adaptogenic concept' (EMEA/HMPC/102655/2007) we conclude a respective request as redundant.'	Please refer to the individual sections below. See next comment.
	Another interested party: 'We in principle welcome the preparation of the above-mentioned Community list. However, we are of the opinion that this draft needs some improvement because some items cannot be deduced from scientific literature. A large number of preparations from Eleutherococcus senticosus is based on the monographs of Commission E and ESCOP as well as on pharmacological and clinical investigations. For this reason they should be classified as "well-established medicinal use"'.	The lack of a harmonised agreement within the scientific community on adaptogenic properties is a source of concern. Despite the fact, that number of clinical studies have been published, most of them are not of aedequate quality and don`t prove the efficacy of the drug in a well-defined clinical condition. The extensive studies on ER have contributed much to the beginning of an understanding of the adaptogenic response. Based on the available literature a traditional can be accepted. Please refer to the HMPC 'Reflection paper on the adaptogenic concept'

	SPECIFIC COMMENTS ON TEXT	
Paragraph no.	**Comment and Rationale**	**Outcome**
2. Qualitative and quantitative composition	"Comminuted herbal substance for tea preparation Liquid extract (1:1, ethanol 30-40% V/V) Dry extract (13-25:1, ethanol 40% V/V) Dry extract (17-30:1, ethanol 70% V/V) **Dry extract (13-25:1, methanol 30% V/V) ?** Tincture (1:5, ethanol 40% V/V) and other equivalent preparations." in order to cover the preparations in the market. Amongst herbal preparations, "**powdered herbal substance**" should be added	Powder included in the monograph. Although no evidence of 30 years of traditional use has been submitted, information has been provided that the powder has been marketed in at least one member state prior to January 1978.
	Comminuted herbal substance for tea preparation **powdered herbal substance** Liquid extract (1:1, ethanol 30-40% V/V) Dry extracts (ethanol 30% -70% V/V) Tincture (1:5, ethanol 40% V/V)	see above
	Herbal preparations A) Fluid 1:1; 30% (V/V) ethanol, B) Fluid 1:1, 40% (V/V) ethanol C) Dry extract; DER 13-25:1, 30% (V/V) methanol D) Dry extract; DER 13-25:1, 30% (V/V) ethanol E) Dry extract; DER 13-25:1, 40% (V/V) ethanol Other preparations equivalent to these liquid and dry extracts	Not accepted. The preparations covered by the monograph/list entry need to be clearly defined.
3. Pharma-ceutical form	*Herbal substance in solid dosage form for oral use*. **Would suggest deleting**	Accepted
4.1. Therapeutic indications	Eleutherococcus, an adaptogenic herbal substance, is used in case of decreased mental and physical capacities such as weakness, exhaustion, tiredness and loss of concentration as well as during convalescence (ESCOP monograph)	Not accepted. See above, general comments

Paragraph no.	Comment and Rationale	Outcome
4.2. Posology and method of administration	**Herbal preparations, daily dose** Herbal preparations daily dose 0.5 -4 g per day as comminuted herbal substance as herbal tea or similar preparation. Liquid extract: 2-3 ml *Dry extract (ethanol 30%-70% v/v) corresponding to 0.5-4.0 dried root* Tincture: 10-15 ml	Accepted
	The use of the powdered herbal substance is described in different documents. We would therefore like to add the following under "Herbal preparations – Daily dose": **"0.6-3.0g per day as powdered herbal substance"**	Powder included in the monograph with 0.75 - 3 g as daily dose. See above
	Posology *Adolescents over 12 years of age, adults, elderly* Daily dose: Children: fluid extract (1:1) 1-2 drops per year of age (ESCOP monograph) Adults: 1-2 ml of fluid extract (1:1) 1-3 times daily 65-195 mg of dry extract (13-25:1, 40% (V/V) ethanol) daily 50 mg dry extract; DER (13-25:1, 30% (V/V) ethanol) three times daily **Duration of use** Not to be taken for more than 2 months **Method of administration** Oral use	Not acceptable. No data on the use in children of different age groups submitted beyond simple statement in ESCOP monograph

Paragraph no.	Comment and Rationale	Outcome
4.3.Contra-indications	Known hypersensitivity to the active substance and to the preparations. It is not justified to include arterial hypertension because there is no information available in literature.	Not accepted. The German Commission E notes that people with high blood pressure should avoid Eleutherococcus preparations, but there is not any good clinical evidence to support this caution. In two of the studies, it was recommended that the extract should not be given to subjects having blood pressure in excess of 180/90 mm Hg (Dalinger, 1966b; Lapchik, 1967). No studies that might refute the concern have been submitted
4.4. Special warnings and precautions for use	None	Not accepted. No data submitted.
4.6. Pregnancy and lactation	Safety during pregnancy and lactation has not been established. **No** adverse effects have been reported from the use of Eleutherococcus preparations as a medicinal product during pregnancy and lactation. As a precautionary measure, the use during pregnancy and lactation is not recommended. This corresponds to the ESCOP monograph.	Original text has been maintained. No data have been submitted.
4.7. Effects on ability to drive and use machines	No studies on the effect on the ability to drive and use machines have been performed. However a sedating effect can be excluded, as insomnia is listed under undesirable effects of the drug, to avoid sleep disturbances the last dose of Eleutherococcus preparations should not be taken after 3pm.	Standard wording has been maintained. No study data submitted.
4.8. Undesirable effects	Insomnia, irritability, tachycardia and headaches may occur in unknown frequency	Standard wording has been maintained.
5.1. Pharmaco-dynamic properties	Wording from the ESCOP monograph has been proposed.	Not accepted. Data not relevant/required for traditional herbal medicinal products.

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5.2. Pharmaco-kinetic properties	Studies on pharmakokinetics of ^{3}H –labelled eleutheroside B in rats after i.p. injection indicated that elimination is mainly urinary (90% within 48 h). Organ distribution of 3H –labelled eleutheroside B in rats after i.p. injection showed maximum levels in liver and kidneys within 75 minutes, high levels were found also in the pancreas, medium levels in pituitary, adrenals and spleen.(ESCOP).	Not accepted. Data not relevant/required for traditional herbal medicinal products.
5.3. Preclinical safety data	Acute toxicity The acute LD_{50} of powdered eleutherococcus was 31.0 g/kg bw. For a fluid extract (33% ethanol, 1:1), the oral LD_{50} was greater than 20 ml/kg bw. in rats, the i.p. oral LD_{50} was 14.5 ml/kg bw. in mice. For an ethanolic extract 23 ml/kg bw. were found as oral LD_{50} , 8 ml/kg bw. as i.v. LD_{50}. Repeated dose toxicity An extract prepared with ethanol at 80°C in doses up to 400 mg/kg bw. for 33-47 days caused no signs of toxicity in rats. 5 ml/kg bw. given to rats for 320 days caused no toxicity. Genotoxicity, carcinogenicity, teratogenicity Available tests on genotoxicity (liquid extract with 60% ethanol) and on carcinogenicity (undefined extract) did not give any reason for concern. Teratogenic studies in rats, mink, rabbits and lambs using an ethanolic extract of eleutherococcus revealed no abnormalities in the offspring and no adverse effects in the parent animals	Not accepted. No studies on carcinogenicity and toxicity to reproduction have been submitted. The data available do not allow any conclusion.