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**COMMITTEE ON HERBAL MEDICINAL PRODUCTS
(HMPC)**

Eleutherococcus senticosus (Ruppr. et Maxim.) Maxim., radix

**ASSESSMENT REPORT FOR THE DEVELOPMENT OF A COMMUNITY MONOGRAPH
AND FOR INCLUSION OF HERBAL SUBSTANCE(S), PREPARATION(S) OR
COMBINATIONS THEREOF IN THE LIST**

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ASSESSMENT REPORT
FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS
THEREOF WITH TRADITIONAL USE

Eleutherococcus senticosus (Rupr. et Maxim.) Maxim., radix

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND
16H OF DIRECTIVE 2001/83/EC AS AMENDED

Herbal substance(s) (binomial scientific name of the plant, including plant part) ¹	<i>Eleutherococcus senticosus</i> (Rupr. et Maxim.) Maxim., radix
Herbal preparation(s)	Comminuted herbal substance Powdered herbal substance Liquid extract (1:1, ethanol 30-40 % v/v) Dry extract (13-25 : 1, ethanol 28-40 % v/v) Dry extract (17-30 : 1, ethanol 70 % v/v) Dry aqueous extract (15-17:1) Tincture (1:5, ethanol 40 % v/v)
Pharmaceutical forms	Comminuted herbal substance for the preparation of a herbal tea, other herbal preparations in solid or liquid dosage forms for oral use. The pharmaceutical form should be described by the European Pharmacopoeia full standard term.
Rapporteurs	D. Pakalns D. Kalke

¹ The material complies with the Ph. Eur. monograph (ref. 01/2008: 1419 corrected 6.0)

I. INTRODUCTION

1.1. Description of the traditional herbal substance(s), herbal preparation(s) or combinations thereof

This assessment report is based on the scientific literature on *Eleutherococcus* root (ER) that is specified in the list of references. The most relevant articles from that list, particularly the pharmacological and clinical data, are discussed in more detail here.

The correct binominal botanic name is *Eleutherococcus senticosus* (Rupr. et Maxim.) Maxim., syn. *Acanthopanax senticosus* (Rupr. et Maxim.) Harms (Poyarkova, 1950). *Eleutherococcus* was formerly known as *Acanthopanax senticosus* (Rupr. et Maxim.) Harms and this name is still widely used by Chinese scientists (Hu, 1980a, 1980b; Li, 2005; Frodin, 2006).

In this assessment report the names “*Eleutherococcus*” or latin “*Eleutherococcus senticosus*” are used although both synonyms may be found in the original articles.

Herbal substance(s)

Eleutherococcus root (ER) (*Eleutherococci radix*).²

Constituents:

Although over 35 compounds have been identified from the ER, the search for active substances is not finished yet. *Eleutherococcus senticosus* is characterised by the co-existence of pentacyclic and tetracyclic triterpenoidal saponins and their prosapogenins, lignans, coumarins, phenylcarbonic acids and xanthenes (Jeljakov, 1972; Sandberg, 1973; Ro, 1977; Wagner, 1980; Obermeier, 1980; Shih, 1981; Hahn, 1986; Anetai, 1987, Sonnenborn, 1993). The main constituents are phenyl propane compounds [eleutheroside B – 0.5 %, chlorogenic acid, coniferyl aldehyde and its glucoside (Slacanin, 1991), caffeic acid derivatives (Wagner, 1982); lignanes (eleutheroside E – 0.10 % (Ovodov, 1965, 1967; Lapchik, 1970), eleutheroside B₄ (Suprunov, 1971) – 0.023 % (Bladt, 1990; Li, 2001); coumarins – (isofraxidin (Wagner, 1982) and its O-glucoside (Nörr, 1993)); triterpensaponines – (2-protoprimulagenin A-glycoside – 0.125 % (Segiet-Kujawa, 1991; Evans, 2002)). Other constituents comprise steroids, carbohydrates and immunologically active polysaccharides (heteroglycans and eleutherans) (Xu, 1983; Fang, 1985; Wagner, 1984; Wagner, 1985a 1985b; Hikino, 1986; Shen, 1991).

Herbal preparation(s)

- Comminuted herbal substance
- Powdered herbal substance
- Liquid extract (1:1, ethanol 30-40 % v/v)
- Dry extract (13-25 : 1, ethanol 28-40 % v/v)
- Dry extract (17-30 : 1, ethanol 70 %, v/v)
- Dry aqueous extract (15-17:1)
- Tincture (1:5, ethanol 40 % v/v)

Combinations of herbal substance(s) and/or herbal preparation(s)

ER and extracts are used in combinations with other herbal substances/herbal preparations (e.g. *Rhodiola rosea* L., radix; *Leuzea carthamoides* (Willd.) D.C., radix; *Schizandra chinensis* (Turcz.) Baill., fructus etc.). Such combinations have not been assessed. This assessment report refers exclusively to ER and preparations thereof.

² The material complies with the Ph. Eur. monograph (ref. 01/2008: 1419 corrected 6.0)

2. TRADITIONAL MEDICINAL USE

2.1. Information on period of medicinal use in the Community regarding the specified indication

References are going back at least until 1960 (Brekhman, 1960a). In fact ER has been used in medicine for many decades. ER is in medicinal use in France (Pharm. Franc, 10), in Germany (Aicher, 1998), in Russia (Ross Ph XI, Mashkowsky, 1997), in UK (British Herbal Pharmacopoeia) and in China (Pharmacopoeia of the People's Republic of China, 2005, Tang, 1992) The first English name, created in the USA for *Eleutherococcus*, was "Eleuthero" (Lucas, 1973; Baranov, 1979). "Siberian Ginseng" has been used in the USA as a second name since 1971, but the name has been banned by the Ginseng Labelling Act of 2002. (Soejarto, 1978; Farnsworth, 1986; Israelsen, 1993). 15 names that are based on the abbreviated Latin generic name "Eleuthero" are currently used in various EU official languages; in 4 languages variants from name "Siberian Ginseng", in 4 languages – variants from "Russian root" or "Russian ginseng root", and in German and in Hungarian variants from "Taiga root" - "Taigawurzel" and "tajga gyökér" are used.

Since the first article was published by Brekhman in 1960, over 1,000 articles have appeared.

Preparations from *Eleutherococcus* root, including powdered root, have been in medicinal use in Germany prior to January 1978 when corresponding medicinal products were notified to the German agency.

ER is now widely offered in pharmacies, health food stores and as food supplements in the United States and in Europe, though not always as a product that conforms to pharmacopoeial requirements (Barna, 1985). Based on the information found in literature and information provided by Member States, a period of at least 30 years of medical use as requested by Directive 2004/24 EC for qualification as a traditional herbal medicinal product is documented for the preparations included in the monograph and in the list entry.

2.2. Type of tradition, where relevant

In Chinese traditional medicine as "Ci-wu-jia" (Hübötter, 1957; Foster, 1996; Stöger, 1996; Winston, 2007); traditional of the Far East (Schroeter, 1975).

Duke (1985) reported that the plant was used in the North-eastern city of Harbin, China, as a folk remedy for bronchitis, heart ailments, and rheumatism. Referring to representatives from the China National Native Produce Corporation, Duke also reported that regular use of the plant is thought to help to restore vigour, improve general health, restore memory, promote good appetite and to increase longevity, basically serving as a preventive medicine and general tonic.

Lin (2000) has reported that *Eleutherococcus* is a popular folk medicine used in patients with hepatitis and cancer in Taiwan.

Reviews of studies performed in the former Soviet Union: Grinewicz, 1966; Brekhman, 1968a; Dardymov, 1976a; Halstead, 1984; Farnsworth, 1985; European traditional uses: Wikman, 1980, 1981b; Sonnenborn, 1993; Wagner, 1994; Aicher, 1998; Blumenthal, 1998; WHO monograph, 2002; ESCOP monograph, 2003.

2.3. Bibliographic/expert evidence on the medicinal use

There are pharmacological and clinical studies and reviews published in medical, pharmacological Journals, starting 1957.

In 1962 an ER extract was approved by the former Soviet Union Pharmacological Committee for clinical use as a "stimulant". In 1966 ER was recommended for use in the Soviet space program (Belay, 1966). In 1968 Brekhman published the first book on the subject entitled "Eleutherococcus". After that, results of many tests which have been performed in Russia have been verified by researchers all over the world. (Fulder, 1980).

This assessment report is based on the summary of the most relevant scientific literature which includes more than 300 articles. Hundreds of other articles related to research work are summarized in various monographs and reviews (Brekhman, 1968a; Brekhman et al, 1968c, 1969c; Dardimov,

1976a; Halstead, 1984; Farnsworth, 1985; Collisson, 1991; Sonnenborn, 1993; Aicher, 1998; WHO monographs on selected medicinal plants, 2002; ESCOP monographs, 2003). These texts were also used in preparing this assessment report.

2.3.1. Evidence regarding the indication/traditional use

Herbal medicinal products with ER are traditionally used to improve general health.

The following indications have been reported for ER:

- As a tonic in case of decreased performance such as fatigue and sensation of weakness, exhaustion, tiredness and loss of concentration (Brekhman, 1968a; Halstead, 1984; Duke, 1985; Aicher, 1998; Blumenthal, 1998; Szolomicki, 2000; ESCOP monograph, 2003, Hartz, 2004);
- As a prophylactic and restorative tonic for enhancement of mental and physical position for functional asthenia, strengthening and normalizing, as well as convalescence (Golikov, 1963; Zotova, 1966; Batin, 1981; Berdyshev, 1977, 1981a, 1981b; Farnsworth, 1985; Asano, 1986b; Turbina, 1986; Novikov, 1987; Obolentseva, 1988; Karnaukh, 1990; Wagner, 1992; Winther, 1997; Blumenthal, 1998; ESCOP monograph, 2003; Goulet, 2005);
- As adaptogen, to increase body resistance to such stressful exposures as heat, cold, physical exhaustion, viruses, bacteria, chemicals, extreme working conditions, noise, pollution (Korobkov, 1962; Kolotlin, 1963; Baburin, 1966a, 1966b, 1976; Dardymov, 1966b; Berdyshev, 1970, 1977, 1995; Lucas, 1973; Brekhman, 1965a, 1965b, 1966, 1968a, 1976, 1977, 1980a, 1980b, 1982b; Brekhman, 1971a, 1971b; Schezin, 1977, 1981; Demin, 1977; Gagarin, 1977; Galanova, 1977; Kalashnikov, 1977, 1986; Bulanov, 1981; Lindendbraten, 1981; Shornikov, 1981a, 1981b; Wikman, 1981a, 1981b, 1981c; Marochko, 1982; Sosnova, 1984; Sosnova, 1986; Shadrin, 1986; Yaremenko, 1990; Collinsson, 1991; Williams, 1995; Dowling, 1996; Azizov, 1997; Glatthaar-Saalmülle, 2001; Webb, 2001; Arushanian, 2003; Arushanian, 2004).
- ER was commonly used in Russia in oncology hospital departments to increase the tolerance of the patients to the adverse effects of chemotherapy and radiation therapy (Gvamichava, 1966; Khatiashvili, 1964, 1966; Kupin, 1986a, 1986b).

The pharmacological effects of ER preparations have been investigated by many researchers. However, the mechanism of action and the active compound(s) have not yet been fully identified.

Many clinical studies have been published. However, most of the publications are not of appropriate quality and do not provide sufficient information. The data are not sufficient to prove the efficacy of ER preparations in a well-defined clinical condition. The lack of complete data may be in part explained by the fact that ER preparations were tested in 1960-1970 with the view to support members of Soviet Union army and sportsmen and some information has been disclosed for this reason. Nevertheless efficacy of adaptogens has been reported by many groups of investigators. The extensive studies on ER have contributed much to the beginning of an understanding of the adaptogenic response. Modern clinical studies on adaptogens that were started only in recent years may provide a better insight in future (Makarov, 2007).

Therefore herbal medicinal products made of ER, can be only considered as a plausible traditional herbal medicinal product and not a "well-established" one.

Based on the available literature and the information provided by Member States on traditional use, the following indication is recommended:

Traditional herbal medicinal product for symptoms of asthenia such as fatigue and weakness. The product is a traditional herbal medicinal product for use in specified indications exclusively based upon long-standing use.

2.3.2. Evidence regarding the specified strength

Not relevant.

2.3.3. Evidence regarding the specified posology

Adolescents over 12 years of age, adults, elderly

The dosages used in studies to determine prophylactic use of the ER fluid extract ranged from as little as 0.5 ml every other day to as much as 22 ml per day. In experiments with healthy persons, stress-mitigating effects have been reported by giving single doses from 2.0 up to 16.0 ml of the extract (p.o.). The usual dose employed ranged from 0.5 to 6.0 ml. given one to three times a day for a period of up to 35 days. Additional courses of ER extract therapy were sometimes employed up to a series of eight courses. At the end of each course there has been a rest period of two to three weeks, during this period no extract was administered.

It is reported that patients should start on a low dose, i.e. 500 mg of powdered root, or its equivalent, three times a day; if no effect has been noted after two weeks, the dose can be increased to 1 g (Collinson, 1991).

Other posologies that were reported in literature are: 2-3 g per day of comminuted ER for teas for up to three months, as well as aqueous alcoholic extracts for internal use. A repeated course is feasible. Internally: as a rule ethanol fluid extract of ER is given 20 to 40 drops two to three times daily before meals (daily dose to 80 drops). The cure lasts 25 to 30 days; then it is repeated with one to 2-week breaks two to three times. If necessary, cures can be carried out without interruption for several years. Infusion: 2-3 g in 150 ml of water; fluid extract 1:1 (g/ml): 2-3 ml; tincture 1:5 (g/ml): 10-15 ml (Brekhman, 1968a).

Dosage – from ESCOP (2003): Adults 1-2 ml of fluid extract (1 : 1, ethanol 40 % v/v) one to three times daily (Aicher, 1998; Farnsworth, 1985). 65-195 mg of dry extract (14-25 : 1, ethanol 40 % v/v) daily (Strokina, 1967).

Other preparations corresponding to 2-3 g of dried root daily (Aicher, 1998; Farnsworth, 1985). For oral administration.

Dosage for powdered herbal substance that are present on the German market for more than 30 years: single dose 0.25 - 1 g, daily dose 0.75-3 g;

Dosage and recommended dosage forms – from WHO and others: Powdered crude drug or extracts in capsules, tablets, teas, syrups, fluid extracts (Sonnenborn, 1993).

Daily dosage: 2-3 g powdered crude drug or equivalent preparations (Blumenthal, 1998).

Dry roots: 0.6-3 g daily (Newal., 1996).

0.2-1 g of dried root equivalent, three times a day (Mills, 1985).

Daily dose 2-3 g (as powdered drug, cut drug for tea infusions or aqueous-alcoholic extracts (Bradley, 1992).

Can be taken daily in the amount of 0.6 to 4 g of crude drug (herb) or an equivalent dose of an extract-based preparation. (Dew, 2002).

Posology in children:

Only a few studies have tested the effect of ER in children.

Effect of ER on respiratory viral infectious morbidity in children in organised collectives has been studied by Barkan (1980).

Sheparev (1986) investigated the effect of preventive administration of ER extract on the health of children under school age. The morbidity rate is reported to have decreased by 30-40 %.

Vereshchagin (1978) and Vereshchagin (1982) have studied the effect of adaptogens on antibiotic therapy in children aged 0-14 years suffering from dysentery and Proteus infections.

No clear information on posologies in children of different age groups can be taken from these studies. The use of ER is generally not recommended in children below the age of 12 years.

Elderly:

Since ER has been reported to increase the feeling of strength and wellbeing, Schmidt (1984) has speculated upon the danger that older, weakened, and convalescent patients might overstrain themselves, when taking herbal medicinal products with ER. However, clinical studies or case reports about such an effect of ER intake are not available and no restrictions are known on the use of preparations of ER.

Turkewicz (1966a, 1966b, 1969) analysed the results with ER or Eleutherococcus leaves extracts in the treatment of patients with psychosis in the elderly and atherosclerotic psychoses. Patients at the age between 65 and 90 years were given 5-15-20 drops daily 30 minutes before food, the treatment lasted 1 month, then it was repeated, after a 10 days break, 2 to three times. It is reported that the number of patients with psychopathological symptoms: asthenia, depression, tension, mental deficiency, had been reduced and that biochemical parameters were improved. Normalization of all biochemical parameters did coincide with improved clinical symptoms.

Davydov, (2000) reported that ER improves self-reported quality of life in elderly, without affecting their blood pressure control. Similar results were described in young healthy adults (Asano, 1986b).

The aim of studies by Cicero (2004) was to test the effect of a middle term ER administration on elderly, health related quality of life (HRQOL). 20 elderly hypertensive and digitalized volunteers (age ≥ 65 years) were randomized in a double-blind manner to ER dry extract 300 mg/day (n = 10) or placebo (n = 10) for 8 weeks. After 4 weeks of therapy, higher scores in social functioning (p = 0.02) scales were observed in patients randomized to ER; these differences did not persist until the end of the study at 8-weeks. No adverse event has been observed in both groups of patients. No significant difference in both blood pressure control and digitalemia was observed in both treatment groups. Persons given ER have received more active therapy than persons given placebo (20 p.c., p < 0.05). The authors conclude that ER safely improves some aspects of mental health and social functioning after 4 weeks of therapy, although these differences attenuate with continued use.

On the basis the literature and information provided by Member States the following posology is proposed:

Adolescents over 12 years of age, adults, elderly

Herbal preparations

Daily dose

0.5-4 g per day as comminuted herbal substance as herbal tea.

Powdered herbal substance: 0.75-3 g

Liquid extract: 2-3 ml

Dry extracts (ethanol 28-70% v/v) corresponding to 0.5-4 g dried root

Dry aqueous extract (15-17:1): 90 – 180 mg

Tincture: 10-15 ml

The daily dose can be taken in one to three doses.

The use is not recommended in children under 12 years of age.

2.3.4. Evidence regarding the route of administration

The oral administration is the only route of administration for ER preparations in the recommended traditional indication. HMPC decided to provide specific information on the preparation of the tea:

Tea preparation: 0.5 to 4 g of comminuted herbal substance for decoction in 150 ml of water.

Dosage frequency: 150 ml should be divided in one to three doses taken during the day.

2.3.5. Evidence regarding the duration of use

Some authors recommend that ER should not to be taken for more than 2 months. For chronic conditions such as fatigue, preparations have been used for three months. Most authors recommend that, if a course is repeated, the next course should start after a 10-14 days break.

In a more recent study, the effect did not persist after 4 weeks of use (Cicero, 2004). As traditional herbal medicinal products can only be accepted if they can be used without medical advice for diagnosis and as the symptoms, should they persist for more than 2 weeks, might be a signal for a serious disease that needs medical advice, the HMPC decided to limit the duration of use to 2 month and to refer the patient to medical advice in case of persistent symptoms.

Duration of use

Not to be taken for more than 2 months.

If the symptoms persist for more than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

2.4. Assessor's overall conclusion on the traditional medicinal use

Preparations from ER have been traditionally used as a tonic for the relief of symptoms in case of decreased performance such as fatigue and sensation of weakness, exhaustion, tiredness and loss of concentration, also as a prophylactic and restorative tonic for enhancement of mental and physical position, and as adaptogen to increase body resistance to such stressful exposures for many decades. Since the clinical documentation is not fully satisfactory and no controlled clinical studies in well defined clinical conditions are available, the use of ER preparations has to be regarded as traditional. The indication given in the monograph and in the list entry reflects the consistent traditional use in EU Member States and it is plausible on the basis of the available studies.

2.5. Bibliographic review of safety data of the traditional herbal medicinal substances

2.5.1. Patient exposure

No exact data on patient exposure are available. In clinical investigations of more than 20,000 patients and test persons no signs of acute toxicity have been observed (Fulder, 1980). On the basis of the wide-spread use in some Member States over a period of more than 30 years a significant exposure can be expected.

2.5.2 Adverse events

Information on adverse events is inconsistent.

In general, only minimal adverse events have been reported. Systematic studies that were designed to detect adverse events are absent. Case reports and general evidence point to the following effects: ER may cause insomnia in some people if taken too close to bedtime. In two studies involving atherosclerotic patients, some cases of insomnia, shifts in heart rhythm, tachycardia, extrasystoles, and hypertonia were reported (Golikov PP, 1966a 1966b). Another study involving 55 patients with rheumatic heart disease (Mikunis et al, 1966a 1966b), showed that 2 of the patients (at high dose levels of the extract) reported headaches, pericardial pain, palpitations, and elevated blood pressure. Another study (Koshkareva, 1966), involving 11 patients diagnosed as hypochondriacs, reported that the ER extract was well tolerated at dose levels of 2.5-3.0 ml three times daily for 60 days, but some patients often presented insomnia, irritability, melancholy and anxiety at dose levels of 4.5-6.0 ml.

2.5.3 Serious events and deaths

None known for ER preparations administrated orally.

2.5.4.1 Intrinsic (including elderly and children)/extrinsic factors

None known

2.5.4.2 Drug-drug interactions and other interactions

None reported

2.5.4.3 Use in pregnancy and lactation

Effects on fertility or effects during lactation have not been reported for humans (Sonnenborn, 1993). In a therapy accompanying investigation in 619 pregnant women with a high risk for a prenatal dystrophy no teratogenic or embryo-toxic effects (Bolkhovitina, 1981) were observed with a prophylactic interval therapy about 3 weeks three times daily by 20 to 30 drops of the fluid extract of ER. Bolkhovitina (1986) investigated the influence of ER on pregnancy termination for mother, on the fetus and on experimental clinical investigation.

However, safety during pregnancy and lactation has not been fully established. In accordance with general medical practice and in absence of sufficient data, ER should not be used during pregnancy and lactation without medical advice (ESCOMP, 2003).

2.5.4.4 Overdose

No case of overdose has been reported.

2.5.4.5 Drug abuse

None known

2.5.4.6 Withdrawal and rebound

None known

2.5.4.7 Effects on ability to drive or operate machinery

None known (ESCOMP, 2003) No studies have been performed.

2.5.4.8 Contraindications (hypersensitivity and allergic potential to be both covered)

Known hypersensitivity to the active substance or to Araliaceae (WHO monographs, 2002). Literature that points to the occurrence of a general hypersensitivity to Araliacea has not been found. Arterial hypertension (Blumenthal, 1998).

2.5.5 Non-clinical safety data

2.5.5.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

The toxicity of ER extracts is reported to be extremely low (Brekman, 1969b; Curtze, 1980; Owen, 1981; Vogt, 1981; Halstead, 1984; Farnsworth, 1985; Baldwin, 1986; Hirose, 1986; Sonnenborn, 1993). In clinical investigations of more than 20,000 patients and test persons no signs of acute toxicity have been observed (Fulder, 1980).

Single-Dose toxicity

The oral acute LD₅₀ of powdered ER in mice is reported to be in the range of about 30.0 g/kg (Brekman, 1968a; Farnsworth, 1985; Baldwin, 1986). The oral LD₅₀ value of the 33 % ethanolic extract was about 14.5 g/kg body weight in mice (Brekman, 1960b, 1961, 1968a; Farnsworth, 1985). Toxic effects at very high dosages (sedation, ataxia, tremor, or vomiting) are thought to be more readily due to the alcohol content of the extract than to a toxic effect of the ER compounds themselves

(Curtze, 1980). Medon (1981) reported that a single dose of 3 g freeze-dried root extract did not cause death in mice.

Repeat-Dose toxicity

Preparations of the ER are reported to be non-toxic when administered over a long period of time. In clinical investigations of more than 6,000 patients and test persons no signs for toxicity have been observed. ER is reported to be free from a cumulative toxicity (Steinmann, 2001). In 29 patients that have been taken fluid extract of ER for more than 5 years there no signs of toxic effects have been reported (Wikman,1986).

Genotoxicity

In *in vitro* experiments, using the AMES assay with *Salmonella typhimurium* strains TA 100 and TA 98 and in the micronucleus test in mice, no mutagenic potential of ER aqueous and ethanolic extracts has been found (Hirose, 1986). A "desmutagenic effect" has been observed in *Drosophila* (Sakharova et al, 1985, 1986).

Carcinogenicity

Studies of carcinogenicity that would allow a reliable assessment have not been performed. In rats no carcinogenic potential of ER was detected (Hirose, 1986). Anticancer effects were noted in experimental animals with transplanted tumours (Monakhov, 1965, 1967a, 1967b; Sakharova, 1985, 1986; Stukov, 1965, 1966, 1967).

Reproductive and Developmental Toxicity

No teratogenic or other effects have been observed in studies on pregnant animals (Brekhman, 1982a, 1982 b). Dardymov et al (1972d) reported the absence of teratogenic effects in offspring from male and female Wistar rats given 10.0 mg/kg of total eleutherosides from ER daily for 16 days.

Gordeichuk (1986, 1993) have studied preventive administration of ER extract during prenatal and pre-embryonic periods of development. The extract prevented embryotoxic effect of subsequent treatment of pregnant rats with ethanol and sodium salicylate. ER abolished embryotoxic and teratogenic effects of ethanol manifested against the background of experimental syndrome of iron deficit in pregnant females. Mechanism of its antiteratogenic action is supposed to be based on stimulation of cell detoxification mechanisms. ER decreased embryotoxic activity (P=0.01) and completely eliminated of different teratogenes in rats (Chebotar, 1981).

Curtze (1980) reported that teratogenicity studies on rats (13.5 ml of the fluid extract per kilogram body weight during the sixth to fifteenth day of pregnancy) did not reveal any negative effects on dams or foetuses.

Local Tolerance

Not applicable.

Contraindications /application restrictions

The German Commission E notes that people with high blood pressure should avoid ER preparations, but there is limited general evidence and very limited information from studies to support this contraindication. 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).

The literature refers on isolated and controversially discussed reports on possible contraindications: acute myocardial infarction, heart rhythm disturbances, paroxysmal hypertension and hypertension in the stage II and III, acute period of infection illnesses (in particular bacterial infections) and other states are characterized by raised excitability (Brekhman, 1980b; Baldwin et al, 1986; Baranov, 1982). Golikov PP (1966b) mentioned that insomnia, tachycardia, extrasystoles and hypertonicity were relative contraindications against employment of the preparation of ER.

2.5.6 Assessor's overall conclusions on safe use

The oral administration of ER preparations can be regarded as safe under the conditions of use that are described in the monograph/list entry. Preparations of ER have been used in humans for many decades without any indication of serious risks.

3. PHARMACOLOGICAL PROPERTIES

3.1. Overview of pharmacological effects of herbal substance(s), herbal preparation(s) and relevant constituents thereof on the basis of long-standing use and experience

3.1.1. The Adaptogenic concept.

Reference is made to the HMPC reflection paper on the adaptogenic concept (EMA/HMPC/102655/2007).

3.1.2. Pharmacological studies in connection with the term adaptogen

The concept of "adaptogens" is not well-known to Western medicine. When more than 50 years ago physicians of West Europe used this type of medicines terms such as a "roborants" (strengthening substances), "tonics" (which restore normal tone to tissue) and "alteratives" (which cause favourable changes in the processes of nutrition and repair) were used. In 1958 the term "resistogen" or "adaptogen" was introduced by Soviet scientists with the view to describe the actions of ER.

The heterogenicity of pharmacological studies relates to the general concept that ER is expected to increase unspecific resistance to various "stressors". ER is often described as having a "stimulating and tonic effect" on the body. Stimulating action refers to the ability of medicinal substances to increase the work capacity of the organism after a single dose of the preparation. The tonic effect of a substance refers to the results obtained after prolonged doses of the medicament. This effect is reported to be manifested by an increase in work capacity, not only during the time period that the substance is being used, but for a sustained period of time thereafter (Dardymov, 1966a, 1972a, 1982).

Only a few studies on pharmacology of purified compounds from ER have been carried out so far (Hahn, 1986; Ro, 1977; Fang, 1985; Wagner, 1985b; Zhu, 1982; Yun-Choi, 1987; Anisimov, 1972; Brekhman, 1969c; Yang, 1984). These studies do not deliver a clear indication with respect to substances that may be responsible for the clinical effects. The pharmacology of ER reflects the synergistic effects of its combined phytochemical constituents, especially those effects produced by the glycosides (eleutherosides) which are present.

3.1.2.1. In vitro experiments

Several *in vitro* studies have been reported for ER extracts.

ER extracts are reported to inhibit the growth of a variety of viruses, bacteria and fungi:

An ethanolic fluid extract inhibited the replication of human rhinovirus, respiratory syncytial virus and influenza A virus in cell cultures (Wacker, 1978; Wacker, 1983; Wacker, 1986; Glatthaar-Saalmüller, 2001). The EC₅₀ of the extract was a 1/120 dilution in the case of rhinovirus and influenza A virus and 1/2240 in the case of respiratory syncytial virus. The effect of the fluid extract was affected neither by heat stress nor by conversion to a dry extract preparation (Glatthaar-Saalmüller, 2001; from ESCOP, 2003).

According to Wildfeuer (1994), the fluid extract of ER increased the *in vitro* phagocytosis of *Candida albicans* by granulocytes and monocytes from healthy donors by 30-45 %. Preparations did not induce *in vitro* transformation of lymphocytes and had no effect in either direction on intracellular killing of bacteria or yeasts.

When ER liquid extract (100 µg, after removal of ethanol) and a suspension of vesicular stomatitis virus were simultaneously introduced into mouse fibroblast culture, the growth of virus was not inhibited (Wacker 1978). However, when the extract was introduced into the mouse fibroblast culture

before contact with the virus, the cells became resistant to the virus. The duration of this effect, however, was only about 6 hours.

Parenteral administration of a 33 % ethanolic extract of the ER for 15 days prior to induced infection (dose not specified) increased the resistance of mice and rabbits to listeriosis, an infection caused by *Listeria monocytogenes*, capable of producing meningitis in man and animals (Cherkashin, 1966,1968). However, administration of the extract simultaneously with the bacteria increased the severity of the infection (Cherkashin, 1966).

Wikman (1980) has reported experiments performed in 1963 and 1965 by Pichurina and Bronnikov who investigated the protective action of ER towards infections and other harmful influences. In one experiment rabbits were contaminated with a cultivation of dysentery microbes (*Shigella flexneri*, 10⁹ microbes per rabbit). One hour before the test, one group had been given 0.1 ml of ER extract per 20 g of body weight. The control group remained untreated. Seventy-two hours later 36 % of the animals in the control group were still alive whereas 74 % of the animals in the ER group survived.

The antiviral activity of an ER ethanolic fluid extract was evaluated in experimental influenza infection. The virus and the extract were simultaneously administered intranasally to mice. The titre of influenza virus in the lungs of the animals was recorded over 6 days. On the 5th and the 6th day after infection marked virus titres were measured in the lungs of control animals, whereas no virus titre was found in the animals treated with ER extract (Protasova, 1986, from ESCOP, 2003).

3.1.2.2. Immunomodulating activity

The stimulating effect of ER preparations is thought to involve the activation of T-lymphocytes by the eleutherosides. There may also be an indirect immunoenhancing effect mediated via the glycosides' more non-specific antistressor activity – as stress may decrease the activity of the immune system, particularly that of natural killer T-cells (Collisson, 1991; Li, 1991). ER is reported to act as an effective γ -interferon inducer, immunomodulator and anti-viral agent (Zykov, 1986; Kupin, 1986b; Wacker, 1978; Wacker, 1983; 1986; Barenboim, 1986).

A study on the immunomodulatory activity of the ethanol extract of ER administered orally to healthy volunteers for 4 weeks, reported an increase in the absolute number of immune competent cells, especially T lymphocytes. No side effects were observed within 6 months (Bohn, 1987, 1988).

In vitro the polysaccharides caused a five- to tenfold increase in interferon titre in S 801 and S 7811 leukemic cell cultures (Yangl 1984).

ER extract have been shown to exhibit cytoprotective effects *in vitro* and antagonistic effects against different toxins in experimental animals (Brekhman, 1969b; Anetai, 1987; Monakhov, 1965; Sakharova, 1985). In addition, antistress properties and an antifatigue effect of the drug have been described by Kaznachejev, 1977; Kirillov, 1977; Baranov, 1982; Farnsworth, 1985; Hahn, 1986; Fulder, 1980, 1981; Gvamichava, 1966; Dalinger, 1966a, 1966b. The actions of ER may be partially explained by its antioxidant (Mikaelyan, 1986), or by its immuno-modulatory activities (Fang, 1985; Wagner, 1985a, 1985b; Barenboim, 1984, 1986; Barkan, 1980; Kupin, 1986a, 1986b; Bohn, 1987 – from Sonnenborn, 1993).

Although it has been reported that ER performs anti-fatigue and anti-stress actions, these actions still need to be further investigated. The same applies to the action on the immune system, especially natural killer (NK) activity and the endocrine system (corticosterone level).

3.1.2.3. *In vivo* experiments.

Many studies have been published relating to the pharmacological testing of ER extracts prepared with ethanol/water in animals. Most of these studies involve experiments designed to demonstrate the "adaptogenic" or "normalizing" effect of ER to a variety of adverse conditions (stress, immobilization, chemical challenge, etc.), or to elucidate the mechanism for these effects (Farnsworth, 1985).

There are studies that demonstrate that ER extract counteract the effect of different noxious substances or agents. Positive results have been described in application of ER for reducing toxicity of biological toxins, physical factors, chemical compounds, including drugs, and ionizing radiation as well as for its ability to increase human's resistance (Maianskii, 1962; Voskresensky, 1977; Voskresensky, 1986; Yonezawa, 1989; Collisson, 1991).

However, one *in vivo* experiment that evaluated the effect of ER on stamina and longevity found no significant difference between mice given ER and control mice (Lewis, 1983).

It has been reported by Elkin (1970) that ER extract shortens the duration of the sleep induced in mice by hexobarbital, chloralhydrate, sodium barbital and ether.

Brekhman (1982b) reported that ER extract raises the sensitivity threshold of test animals to narcotics (ether, chloralhydrate or sodium barbital) and to ethanol. A median lethal dose of 35 % ethanol for mice was doubled as a result of single administration of ER, while the prophylactic use of ER for a period of 30 days caused a 2.5-fold increase of the DL₅₀ value. These results point to the effect that ER extract may enhance ethanol tolerance in test animals. In another experiment on rats Brekhman (1982b) confirmed this hypothesis.

It has been found that intraperitoneal injection of ER in irradiated (X-ray) mice, at a dosage of 3.5 ml/kg for seven days, exerts a moderate radioprotective action. (Collisson, 1991). Irradiated (X-ray) mice treated with ER extract are reported to survive five times longer than controls (Brekhman et al, 1970b, 1970c).

Kirillov, (1966) has reported that ER given daily to rats under various types of stress normalized the weights of the thyroid and adrenal glands (usually shrunken by stress) and eliminated any evidence of stress upon the functions of these glands. It has been proposed (Panossian et al, 2007) that nitric oxide and cortisol may be used as appropriate stress markers that can be employed in the evaluation of the anti-stress effects of stress-protectors and adaptogens.

The total eleutherosides had no effect on oxygen utilization by rat liver mitochondria with succinate, glutamate, or tetramethylphenyl substrates (Dardymov, 1972b), but did increase oxygen uptake in whole rat liver homogenates. The eleutherosides are reported to potentiate the effect of insulin on glucose consumption *in vitro*, using the rat diaphragm (Dardymov, 1972c).

Glucocorticoids are major mediators of the stress response and directly suppress the natural killer (NK) activity. Thus, the response for body the stress is complex, involving metabolic, inflammatory, neuroendocrine, and immunological aspects. It has been speculated that the extracts of ER may have stress-reducing actions and consequently, may act on the reduction of NK activity and blood corticosterone elevations induced by stress (Fujikawa et al, 2002).

In support of reports of the glucocorticoidlike effects *in vivo* for ER, Pearce (1982) reported that 30 % ethanol extract of ER did bind to the estrogen receptor in rat uterus, mineralocorticoid, and glucocorticoid receptors in rat kidney *in vitro*, but not to the androgen receptor in rat kidney. Bykhovtsova (1966) have reviewed the results of studies of the effect of ER on certain metabolic processes. Intraperitoneal administration of an aqueous extract of the ER to rats (3mg/kg body weight) caused a significant increase in corticosterone levels 3 hours after injection, whereas adrenocorticotrophic hormone levels remained unchanged (Winterhoff, 1993). Belonosov (1966) administered ER extract in a dosage of 4 ml daily to blood donors for a period of one month. As a summary of their experiences, the author came to the opinion that the anabolic activity may be due to the action of ER on carbohydrate and protein metabolism. Nitrogen metabolism in normal and stressed rats has been reported to be normalized by s.c. 1.0 mL/kg ER extract (Feoktistova, 1966; Revina, 1966; Sal'nik, 1966). Anisimov, (1972) tested the effect of compounds isolated from *Araliaceae* family plants on the biosynthesis of protein *in vitro*.

Lin (2000) evaluated the antioxidant activity of the ER crude extract and the hepatoprotective activities on CCl₄ or acetaminophen-induced toxicity in the rat liver. Results suggest that ER may exert some antioxidant effects.

The working capacity of mice was assessed by forcing them to climb along an endless cord until complete exhaustion. ER was administered one hour before the experiment. At a dose of 2.5 ml/kg the animals' running time was significantly increased to 72 minutes; controls could only endure 52 minutes, representing an increase of 38 %. At a dose of 5 ml/kg the time increased to 76 minutes (45 %). However, a further increase in dosage to 7.5 ml/kg did not further increase the animals' working capacity (Collisson, 1991).

Kimura (2004) compared the effects of water extracts of *Eleutherococcus senticosus* bark on the swimming time, natural killer and blood corticosterone level using forced swimming stressed mice.

It was concluded that eleutheroside E may contribute to the anti-fatigue action and to the inhibition of elevation of corticosterone induced by swimming stress.

The results of pharmacological investigations of *Eleutherococcus* have been summarized by Dardymov, (1993). The authors postulate multiple effects on the human body, which involve:

- energy-mobilizing impact, primarily through intensified utilization of glucose;
- stress-protective effect conditioned by change in regulating the central nervous system and hormonal regulation;
- the action on the effects of hormones and their mediators, including changes in the contents of cyclic nucleotides and prostaglandins.

3.1.2.4. Clinical studies.

The main activity that is expected from an adaptogen is to enable an organism to adapt to and cope with unfavourable conditions, such as physical and psychological stress, infections, environmental pollutants, radiation and extreme climatic conditions. Since the early 1960's ER was extensively used in the former Soviet Union by athletes, particularly of Soviet Olympic Team, (Brunner, 1990), cosmonauts, physical labour workers, as well as it was administered to divers, sailors, miners and it had also been used to prevent stress-related illnesses.

Numerous clinical studies, designed to measure the adaptogenic effects of ER, have been performed in Soviet Union during the 1960s and 1970s (reviewed in Farnsworth, 1985: Afanasiev, 1973; Baburin, 1966a, 1966b, 1970a, 1970b, , 1972; 1976a, 1976b Berdyshev, 1970, 1977; Blokhin, 1966a, 1966b; Brandis, 1962, 1966a, 1966b; Dalinger, 1966a, 1966b; Dardymov, 1966b; Egorov, 1966; Gagarin, 1977; Golikov 1963; Korobkov, 1962; Medvedev, 1963; Oleinychenko, 1966). In 35 clinical trials without controls, involving over 2,100 healthy subjects (4-1,000 per study), oral administration of a 33 % ethanol root extract (2.0-20.0 ml, daily for up to 60 days) has been reported to improved physical and mental work performance under stress conditions, and reduced auditory disorders and the incidence of illness (Farnsworth., 1985, Halstead,1984). A statistical evaluation of the results was not carried out; control groups were absent.

Effects on the psychophysical one and the cognitive efficiency were examined in a placebo-controlled study of 190 pilots, co-pilots and flight engineers in different partial groups (Gubchenko, 1986a). The test persons received 1 ml liquid extract or placebo solution (controls) over more than 10 days twice daily. The psychophysical measurements were performed before the treatment and during the 10 days of treatment in the Arctic (Collisson, 1991). In the study on 655 flight crew members (including pilots, navigators, and radio operators), adaptogens are reported to have improved the recovery following long flight schedules, allowing physiological state to be significantly restored within three hours compared to a one day recovery that was needed in typical, non-treated cases (Brekhman, 1976).

Kolomievsky (1986) studied reactions in 147 cardiologic patients with hypertension, coronary heart disease and atherosclerosis induced by 30 drops of ER fluid extract over 7-10 days. The author reports an improvement of different blood count parameters (among them Lymphocytes) as compared to 42 untreated controls. A statistical evaluation of the results was not carried out.

ER is reported to improve the adaptation of sailors in the tropics and influence positively body functions and the work capacity of sailors on a cruise (Berdyshev, 1970, 1977, 1981a, 1981b; Wikman, 1981b), to help adaptation to high altitudes (Kalashnikov, 1977) and in the Arctic (Gagarin, 1977; Brekhman, 1977; Kalashnikov, 1977, 1986). During long-term navigation in the tropics, where high temperature and humidity substantially restrict working capacity, seamen were given either extract of ER or a placebo. It was found that ER reduces mental disturbances, such as depression, excitability, insomnia etc. ER is reported to have improved asthenia and depression, calmed excitability and normalized sleep. Novikov (1987) studied the influence of ER on the body resistance in sailors and Elizarov, (1977) reported about the effect of ER on physical exercises and on lipid metabolism in crew members of a submarine.

Korobkov (1962) and Brekhman (1968a) carried out experiments on more than 1,500 sportsmen. No adverse effects were observed except for an occasional feeling of sleepiness after administration of

the extract. This condition has been associated with a hypoglycemic condition. During one series of tests in 1961 and 1962 by Shkurdoda and Korobkov, as reported by Brekhman in 1968, 30 male and female Olympic athletes took the extract in a dose of 2 ml 30 minutes before sleep and 4 ml one hour before training. The control group received a placebo. The group of Olympic athletes was given the extract, included sprinters, high-jumpers, decathlon contestants, 5 and 10 kilometer runners, and marathon runners. For all of them an increased endurance and the preparedness to repeat the exercises soon after completion have been reported. The control group was less active, and the restoration of pulse, arterial blood pressure, and regain of tonicity of muscles required a greater period of time.

Asano (1986) has investigated the effects of a preparation of *ER* on physical performance and resources in maximal and submaximal work. A single-blind, placebo-controlled clinical trial in six baseball players assessed the effects of a 33% ethanol root extract on maximal work capacity. Three maximal work-capacity tests using a bicycle ergometer were performed on 3 consecutive days prior to treatment, and two tests were carried out after treatment with either 2ml extract (containing 0.53mg syringin (eleutheroside B) and 0.12mg syringaresinol-4,4 ϕ -O-b-diglucoside (identified here as eleutheroside D)) or placebo orally twice daily for 8 days. After each work test, maximal oxygen uptake, oxygen pulse, total work time and exhaustion time were measured. A significant improvement in all four parameters was observed in subjects treated with the extract ($P < 0.01$), including a 23.3% increase in total work time as compared with only a 7.5% increase following placebo treatment.

Several experiments carried out in the Soviet Union during the 1970s appear to demonstrate that *ER* extract, given prophylactically, can reduce the overall disease incidence by up to 35%. (Galanova, 1977; Schezin, 1977; Kalashnikov, 1977; Sheparev, 1981). An in-depth analysis of clinical studies on *ER* has been presented by Farnsworth et al (1985), reviewing the data available up to 1985. The effects of a 33% ethanol extract of the roots were assessed in 35 clinical trials without controls in 2,200 patients at the age between 19 and 72 years (5-1,200 per study) with various disorders, such as arteriosclerosis (Golikov, 1966b; Shekhtman, 1966); acute cranio-cerebral trauma, Sandler, 1970a, 1970b, 1972a, 1972b), hypertensive and hypotensive patients (Lyubomudrov et al, 1970), neurotic patients and neurasthenia (Strokina, Mukho, 1966a, Strokina 1966bc, 1967); stressed drivers and factory workers (Galanova, 1977); chronic bronchitis and pneumoconiosis (Lyubomudrov 1971, 1972), and rheumatic heart disease (Mikunis, 1966a, 1966b). Andreev (1976) investigated the influence of *ER* extract on secretion, as well as on fermentative and motor functions in 18-25 years old patients with chronic gastritis.

ER is reported to enhance vision and hearing. Stschichenkov (1963) performed 60 trials to determine the influence of *ER* on adaptation in darkness and acuteness of vision; Tikhomirova (1977) analysed vision in seamen given adaptogens during long-term navigation. Sosnova (1969) determined the effect of *ER* on the colour discrimination function in persons with normal trichromatic vision.

In a more recent study, Sosnova (1984) investigated to effect of *ER* in women performing visual control during a regime involving working with semi-conductor devices. The women were suffering from visual fatigue, followed by a significant and sharp reduction in productivity. A 40-day intake of *ER* and *Schisandra* are reported to have a favourable effect on the colour discrimination capacity, to reduce fatigue, reduce the time needed for performing the main operations and to improve the quality of work and to result in a higher productivity.

In other experiment Sosnova (1986) has examined also a visual performance in a placebo-controlled study involving the group of healthy 232 volunteers (locomotive engineers and assistants aged 24 to 45 years). All persons had normal colour perception and visual acuity. Spectral sensitivity, colour contrast sensitivity and stability of colour perception were determined at baseline of experiment and on days 1, 5, 20 and 40 and then 2-2.5 month after the course to determine duration of the tonic effect. The treated group received 2 ml of fluid extract per day. The contrast sensitivity and the sensitivity for red, green and blue light was increased with a maximum after 5 days of treatment. After 40 days a 2.5 to 4.5 fold increase, as compared to the pre-treatment results, is reported. The effect persisted after 2.5 months. No improvement has been observed in the placebo group.

Arushanyan (2003) studied the effect of *ER* on short-term memory and visual perception in healthy humans. It was reported that acute administration of liquid extract significantly improves short-term memory in healthy humans.

Hartz (2004) conducted a 2-month, randomized, blinded, controlled trial of ER in patients with chronic fatigue. Ninety-six subjects were randomized to treatment groups, and 76 provided information at 2 months of follow-up. Fatigue among subjects assigned to either placebo or ER, was substantially reduced during the study, but differences between treatment groups were not statistically significant. It was concluded that overall efficacy was not demonstrated. However, the findings of possible efficacy in a subgroup of patients with moderate fatigue suggest that further research may be of value.

In a double-blind, placebo-controlled study, 93 patients were treated orally with 400 mg of ER dry extract or placebo daily for 6 months as a prophylactic treatment to recurrent episodes of *Herpes simplex type II* infections. Based on questionnaires (covering the 6 months before treatment and after 6 months of treatment), 75 % of patients in the ER group reported an improvement in the frequency, severity and duration of outbreaks compared to 34 % in the placebo group; the results were significant in favour of the verum group ($p = 0.0002$ to 0.0007) (Williams, 1995).

In most of the studies, results were generally reported to be positive: e.g. blood pressure was normalized, serum prothrombin and cholesterol levels were reduced, and overall wellbeing and physical work performance improved (Farnsworth, 1985). However, these trials lacked good methodology (for example, very few patients were involved, lacked proper controls and randomization, experiments were not double-blind etc.). The clinical data have a number of shortcomings such as deficiencies in the description of inclusion and exclusion criteria, description of the medication, diagnosis, study design, analysis etc. There is a wide range of clinical conditions that have been investigated and in some studies the number of patients was very small. None of the studies would be sufficient to substantiate efficacy of ER preparations in a clearly defined clinical condition, although, in total, the data available are sufficient to justify further research into the concept of adaptogens.

Assessors overall conclusions on studies in connection with the term adaptogen

Brekhman (1968a) has coined the term “adaptogen” to designate substances which in a non-specific way: increase protein biosynthesis; raise antibody titre at immunisation; elevate the body’s metabolic capacity by means of general endocrine stimulation; enhance mental work capacity; uplift physical work capacity along with performance and endurance; quench free radicals; improve senses such as eyesight, colour perception, hearing and vestibular functions; offer beneficial effects in cardiovascular and respiratory systems; promote longevity; heighten the body’s non-specific resistance to various stressors such as toxins, excess cooling, overheating, altered barometric pressure, ultraviolet, ionizing radiation. Adaptogens must present a non-specific effect (raising the power of resistance to toxins of a physical, chemical or biological nature); must be harmless and disturb the body functions as little as possible. Accordingly, adaptogens are expected to strengthen the non-specific powers of resistance to non-infectious stresses, raise the general performance capacity during stress situations, and thereby prevent diseases that could develop as a result of over-stressing the organism.

There are numerous studies intended to support the adaptogenic nature of ER extracts in both animal models and humans. Although many clinical studies have been published, most of them are not of appropriate quality and does not prove the efficacy of the ER in a well-defined clinical condition. This may be linked to the fact, that the main intention has been to prove the adaptogenic concept and not the effect in the prevention or treatment of a well-defined disease. Whereas the term "adaptogen" is widely used and generally accepted in some countries, it is completely unknown or badly understood in many others. The term is absent from standard (western) handbooks such as Goodman and Gilman's *The Pharmacological Basis of Therapeutics* or Harrison's *Principles of Internal Medicine*.

Despite the great number of studies, ER preparations do not reach the level of WEU/scientific evidence that would be sufficient to grant a marketing authorisation. However, the studies provide a solid basis for plausibility of the traditional use. Please refer to the HMPC reflection paper on the adaptogenic concept for an in depth discussion.

4. PHARMACOKINETIC PROPERTIES

No specific data are available on the pharmacokinetics of ER.

ANNEX INFORMATION ABOUT THE LEGAL STATUS OF PRODUCT CONTAINING *ELEUTHEROCOCCUS SENTICOSUS, RADIX*, IN MEMBER STATES

Germany

Well-established use	Traditional use
<p>a) Eleutherococcus radix dry extract (15-18:1); ethanol 36%(V/V) b) Eleutherococcus radix fluid extract (1:1); ethanol 34%(V/V) c) Eleutherococcus radix (17-25:1); ethanol 30% (V/V) d) Eleutherococcus radix powder e) Eleutherococcus radix extract (1:11,3); sweet wine f) Eleutherococcus radix (15-18:1); ethanol 28% (V/V) g) Eleutherococcus radix dry extract (15-17:1); aqueous</p> <p>Indications: As a tonic for invigoration in fatigue and impairment, in decreasing capability and power of concentration as well as in reconvalescence.</p> <p>Pharmaceutical form: ad a) soft capsule ad b) oral liquid ad c) coated tablet ad d) powder ad e) oral liquid ad f) hard capsule ad g) lozenge</p> <p>Posology: ad a) 2 x daily 1 soft capsule with 100 mg extract ad b) 3 x daily 5 ml liquid with 20g fluid extract ad c) 3 x daily 1 coated tablet with 42.mg extract ad d) 3 x daily 0,25 - 1 g powder ad e) 3 x daily 10 ml (1/2 cup) oral liquid with 100 g extract ad f) 1 x daily 1 hard capsule with 140 mg extract ad g) 2 x daily 1-2 lozenge with 45 mg extract</p> <p>On the market prior to 1978</p>	<p>a) Eleutherococcus radix extract (1:20); sweet wine, aromatic with absinthe herba b) Eleutherococcus dry extract (16-24:1); ethanol 35% (V/V) c) Eleutherococcus radix fluid (1:1); ethanol 30% (V/V)</p> <p>Indications: Herbal medicinal product traditionally used to improve general condition. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.</p> <p>Pharmaceutical form: ad a) oral liquid ad b) coated tablet ad c) oral liquid</p> <p>Posology: ad a) 3-4 x daily 1 cup (20 ml) with 20,6 mg extract ad b) 3 x daily 1 coated tablet with 10 mg dry extract ad c) 2 x daily 1 cup (5 ml) with 10 g fluid extract</p> <p>On the market prior to 1978</p>

Sweden

Herbal substance: Rysk root - *Eleutherococcus senticosus*, radix

Herbal preparations: 35 products including mono- and combination products were notified. Some of the combination products contained multivitamins and minerals

Pharmaceutical forms: Tablet, mixture, capsule

Indication: Traditionally used as a mild stimulant and tonic, to increase physical and mental stamina, strengthening and normalizing, adaptogen, tonic during convalescence, to increase body resistance to signs of stress such as general fatigue and temporary mild tension”

Posology: Daily dosage range (of 35 products): extract corresponding to 0.2- 2g root, divided in 1 – 3 doses. Not recommended for children < 8 yrs.

Belgium

Eleutherococcus radix as powdered root in hard capsules, 250 mg per capsule is authorised since 2005.

Posology: 2 capsules two times a day, up to 6 capsules per day.

There are number of food supplements on the market as capsules, tablets, ampoules, pearls, solution.

Denmark

well-established use

a) *Eleutherococcus senticosus* extractum radix (10:1)

0,6 gram/100 ml oral solution

b) *Eleutherococcus senticosus* extractum radix (10:1), corresponding to 1 gram dry root, tablets, coated

c) *Eleutherococcus senticosus* extractum radix , 7,2 mg corresponding to 120 mg dry root, tablets

d) *Eleutherococcus senticosus*, powdered root 250 mg/capsule

Posology:

ad a) Adults: 15 ml daily, eventually 30 ml in a short period when needed.

Not to be used daily for more than 2-3 months.

ad b) 1 tablet daily, eventually 2 tablets daily in a short period when needed. Not to be used for more than 2-3 months.

ad c) 4 tablets 3 times daily. Not to be used for more than 2-3 months.

ad d) 2 capsules in the morning and 2 capsules in the middle of the day. Dosage may be increased to 3x2 capsules. Not to be taken for more than 3 months.

ad a-d) Not to be used by children below 12 years.

Indications:

ad a) Herbal medicinal product against tiredness and in periods of convalescence.

ad b) Herbal medicinal product against tiredness and in periods of convalescence.

ad c) herbal medicinal product for the relief of symptoms of cold. Herbal medicinal product against tiredness and in periods of convalescence.

ad d) Herbal medicinal product against tiredness and in periods of convalescence.

There are combination products with *Rhodiola rosea* radix, *Andrographis paniculata* herba, *Schisandra chinensis* fruit.

There are number of products containing ER which may also be sold as food supplements.

Italy

No herbal or conventional medicinal products containing *Eleutherococcus* radix or its preparation as an active substance are currently authorized or registered in Italy.

In fact there are number of food supplements on the market.

As for the products containing **Eleutherococcus radix** food supplements, the following information has been found:

Pharmaceutical forms: tablets, capsules, liquid extract (hydroalcoholic solution), herb tea

Part of plant used: root, root (dry extract), root (powder), root (dry extract – powder – freeze dried), root (hydro-alcoholic solution), root (freeze-dried extract), root (bark), bark.

Indications:

Physiological tonic-adaptive effect, it may support body's adaptive response to psychological and physical stress.

Poland

On the market from 2001, generally over 30 years.

a) Eleutherococci radice extractum fluidum (1:2), ethanol 60° - oral drops

b) Eleutherococci radice extractum siccum (13-25:1) – coated tablets

Posology: a - 1 teaspoon daily

b) 1 tablet 3 times daily

Indications: States of tiredness, weakness, in convalescence. Supplementary in prophylaxis of atherosclerosis.

Iceland

Eleutherococcus has been on the market in Iceland as adaptogen for many years, sometimes under the name Siberian Ginseng. However, since the products are classified as food supplement but not as herbal medicinal products IMCA does not have any information about the products.

EU Member States without any products containing ER:

- The Netherlands
- Finland
- Czech Republic
- Ireland
- United Kingdom