EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Echinacea purpurea* (L.) Moench., herba recens

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC as amended (traditional use)

Final – revision for systematic review

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Echinacea purpurea* (L.) Moench., herba recens
Herbal preparation(s)	Expressed juice from fresh herb (DER 1.5-2.5:1); Dried juice corresponding to the expressed juice above
Pharmaceutical forms	Herbal preparations in liquid or solid dosage forms for oral use and in liquid or semi-solid dosage forms for cutaneous use
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1. Introduction

This Assessment report (and corresponding monograph) is *a priori* limited to *Echinacea purpurea* (L.) Moench., herba recens and preparations thereof. Therefore the medicinal products containing the roots of the same plant (or the combination of roots and herb) and other plant species are out of the scope of this document. Nevertheless some data on the research on products with roots and other *Echinacea* species are given for information.

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

- Herbal substance(s)

Echinacea purpurea (L.) Moench., herba recens

The monograph in the European Pharmacopoeia (reference 01/2008:1823) defines only the dry herbal substance "Purple coneflower herb" as: Dried, whole or cut flowering aerial parts of *Echinacea purpurea* (L.) Moench.

Content: minimum 0.1 per cent for the sum of caftaric acid ($C_{13}H_{12}O_9$; M_r 312.2) and cichoric acid ($C_{22}H_{18}O_{12}$; M_r 474.3) (dried drug).

The US Pharmacopeia contains the monograph "*Echinacea purpurea* Aerial Parts", which defines the drug as: "consists of the aerial parts of *Echinacea purpurea* (L.) Moench (Fam. *Asteraceae*). It is harvested during the flowering stage. It contains not less than 1.0 percent of chichoric acid, and not less than 0.01 percent of dodecatetraenoic acid isobutylamides ($C_{16}H_{25}NO$) on the dry basis" (Giancaspro 2004).

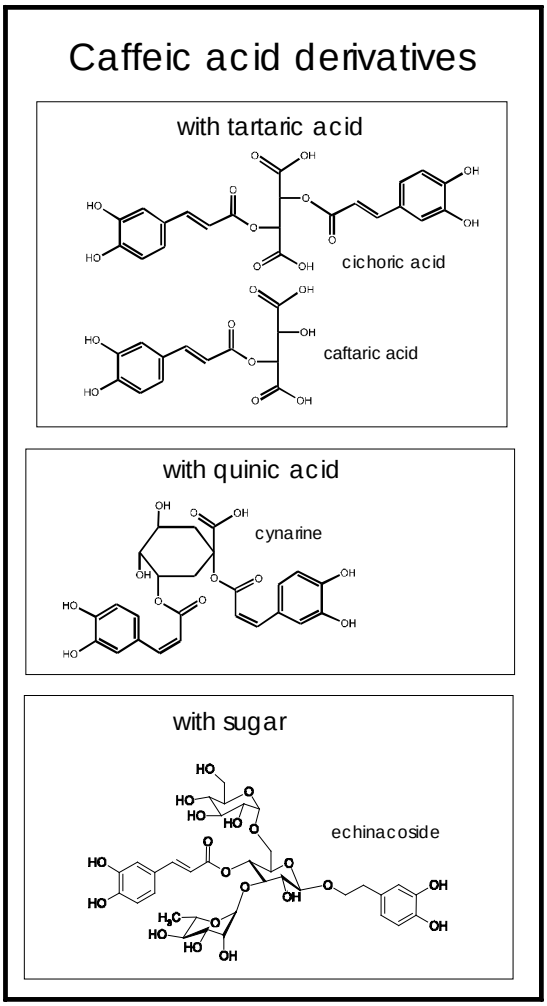
Fresh herbal drug is described in the monograph *Echinacea purpurea* in the German homoeopathic pharmacopoeia (2011).

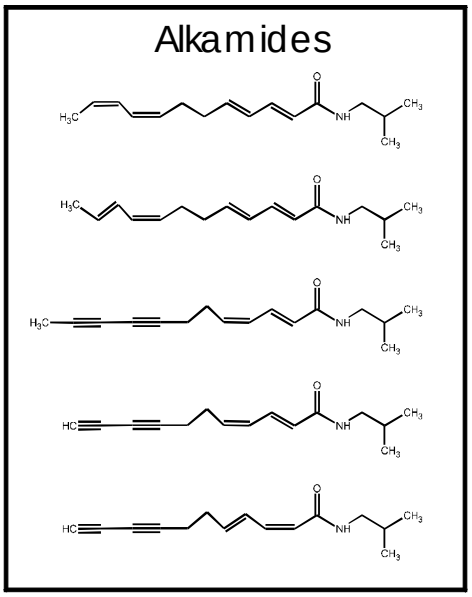
Constituents:

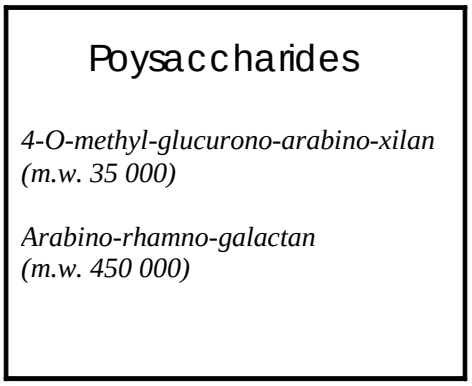
- **Caffeic acid derivatives:** Cichoric acid (2,3-O-dicaffeoyl-tartaric acid) is the major caffeic ester derivative found in the aerial parts of *Echinacea purpurea* with a concentration range of 1 to 5%, followed by caftaric acid (2-O-caffeoyl-tartaric acid) (Kreft 2005, Manček & Kreft 2005, Bauer *et al*. 1988b). Commercial products can contain as little as 0.13 mg/g of cichoric acid and 0.14 mg/g of caftaric acid (Gotti *et al*. 2002). Cichoric acid is also present in roots of *Echinacea purpurea* (0.6%-2.1%) (Bauer *et al*. 1988b). Other derivatives like 2-O-feruloyl-tartaric acid and 2-O-caffeoyl-3-coumaroyltartaric acid are present in small quantities in the aerial parts. Cynarine and echinacoside are characteristic of other *Echinacea* species and are practically not present in the aerial pars of *Echinacea purpurea* (Gotti *et al*. 2002, Bauer *et al*. 1988b, Pietta *et al*. 1998).
- **Alkamides** with the isomeric dodeca-2*E,*4*E*,8*Z*,10*E/Z*-tetraenoic acid isobutylamide as the main compound (Binns *et al*. 2002a). In the inflorescences of *Echinacea purpurea* germlings its content was 3.45 mg/g. The content of other alkamides was below 0.6 mg/g. The content of alkamides in the roots is much higher with 4 alkamides above 1 mg/g: undeca-2Z,4E-diene-8,10-diynoic acid isobutylamide; dodeca-2*E*,4Z-diene-8,10-diynoic acid isobutylamide; dodeca-2*E*,4*Z*-diene-8,10-diynoic acid 2-methylbutylamide and dodeca-2*E*,4*E*,8*Z*,10*E/Z*-tetraenoic acid isobutylamide.
- **Volatile oil** (0.08–0.32%) contains, among other compounds, borneol, bornyl acetate, pentadeca-8-(*Z*)-en-2-one, germacrene D, caryophyllene and caryophyllene epoxide.

- **Polysaccharides (PS)** such as PS I, a 4-O-methyl-glucuronoarabinoxylan with an average MW of 35,000 D, and PS II, an acidic arabinorhamnogalactan with a MW of 450,000 D, have been isolated from *Echinacea purpurea* herb. A xyloglucan (MW 79,500 D) has also been isolated from the herb and a pectin-like polysaccharide from the expressed juice. The content of polysaccharides in dry *Echinacea purpurea* herb is 2 to 7 % (Glavač *et al*. 2012).
- **Melanins** (Pasco *et al*. 2005, Pugh *et al*. 2005),
- **Lipopolysaccharides** and **lipoproteins** (Tamta *et al*. 2008, Pugh *et al*. 2013).

Several very different groups of constituents are suggested to be effective principles of *Echinacea purpurea*: caffeic acid derivatives, alkamides, polysaccharides (ESCOP 2003), melanins (Pasco *et al*. 2005, Pugh *et al*. 2005), lipopolysaccharides and lipoproteins (Tamta *et al*. 2008, Pugh *et al*. 2013).







- Herbal preparation(s)

Echinacea purpurea (L.) Moench., herba recens, succus, succus siccum

The juice is expressed from the fresh herbal drug as soon as possible. The expressed juice is preserved by pasteurisation or stabilised with a suitable quantity of ethanol.

European Pharmacopoeia monographs are being drafted for *Echinacea purpurea* herb juice (Pharmeuropa 2014).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable.

1.2. Search and assessment methodology

The two major electronic databases PubMed and Toxline were searched in 2006 with the search term "*Echinacea purpurea*". For revision of the monograph the same databases were searched in May 2013.

Results:

PubMed: 940 references obtained in 2013.

Toxline: 385 references obtained in 2013.

The abstracts of the references found were screened manually and all articles deemed relevant were accessed and included in the assessment report.

2. Data on medicinal use

2.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory Status (date, Member State)**
AUSTRIA			
1. dried pressed juice from fresh herb (22-65:1)	1.-6.supportive treatment and prophylaxis of recurrent infections of the airways	1 tablet contains 100 mg dried pressed juice *adolescents and adults*: 3-4 times daily 1 tablet *children 6-11 y*: 2-3 times daily 1 tablet	authorised 2004
2. pressed juice from fresh herb (1.5-2.5:1)		100 g solution contain 80 g pressed juice *adolescents and adults*: 3 times daily 2.5 ml solution	authorised 2002
3. dried pressed juice from fresh herb (31.5-53.6:1)		1 pastille contains 88.5 mg dried pressed juice *adolescents and adults*: 4 times daily 1 pastille *children 4-6 y*: 1-2 times daily 1 pastille *children 6-12 y*: 2-3 times daily 1 pastille	authorised 1998
4. dried pressed juice from fresh herb (31.5-53.6:1)		100 g solution contain 2.34 g dried pressed juice *adolescents and adults*: 3 times daily 5 ml *children 4-5 y*: 3 times daily 2.5 ml *children 6-12 y*: 2 times daily 5 ml	authorised 2000
5. dried pressed juice from fresh herb (22-65:1)		1 tablet contains 100 mg dried pressed juice *adolescents and adults*: 4 times daily 1 tablet	authorised 2004
6. pressed juice from fresh herb (1.7-2.5:1)		100 g solution contain 80 g pressed juice *adolescents and adults*: 3 times daily 2.5 ml	authorised 1994
		duration of use 1.-6.: Without break not longer than 8 weeks. If symptoms do not improve within 10 days, a doctor has to be consulted.	

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
BELGIUM			
1. pressed juice of *Echinacea purpurea*	symptomatic treatment of infections of the upper respiratory tract after a serious illness has been excluded	80 g pressed juice of *Echinacea purpurea* for 100 g of oral solution. *adults*: 2.5 ml followed by 1.25 ml every 2 hours, afterwards 2.5 ml 3 times daily, max dose: 15 ml/day *children younger than 2 y*: only on medical advice *children 2-12 y*: 1 dr/kg BW per day	authorised 2000
BULGARIA			
1. *Echinacea purpurea* herba succus recens (1.5-2.5:1)	herbal medicine for diseases due to common cold; helps to support in case of recurring infections of the respiratory tract	oral drops, solution 75.6 ml/100 ml *adolescence and adults*: 55 drops (equals 2.75 ml) 3-4 times a day *children 1-6 y*: 2.0-4.0 ml (13-27 drops 3 times a day or 10-20 drops 4 times a day) *children 6-12 y*: 6.0-8.0 ml a day (40-53 drops 3 times a day or 30-40 drops 4 times a day) Should not be used without interruption for longer than 8 weeks.	authorised 2002
2. *Echinacea purpurea* herba succus recens siccum (31.5-53.6:1)	supportive treatment of recurrent infections of respiratory tract	syrup, 2.34 g/100 g *adolescence and adults*: 5 ml 3 times a day *children 4-6 y*: 2.5 ml 3 times a day *children 6-12 y*: 5 ml 2 times a day Should not be used without interruption for longer than 2 weeks.	authorised 2007
3. *Echinacea purpurea* herba succus recens (1.7-2.5:1)	traditionally used as a mild acting medicine for the promotion of wound healing	ointment 16 g/100 g *adolescents and adults* should apply a strip of the ointment 1-2 cm in length 2-3 times daily and spread it thinly and uniformly over the skin and/or the wound dressing. Should not be used without interruption for more than 1 week.	registered 1999
4. *Echinacea purpurea* herba succus recens (1.7-2.5:1)	supportive treatment of recurrent infections of respiratory and urinary	oral drops, solution 80 g/100 g *adolescence and adults*: 2.5 ml 3 times a day *children 4-6 y*: 1.25 ml 3 times a day	authorised 1999

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	tracts	*children 6-12 y*: 2 ml 3 times a day. Should not be used without interruption for longer than 2 weeks.	
CROATIA			
1. dry expressed juice from *Echinacea purpurea*, herba recens (purple coneflower herb) (ratio of fresh herb:dry expressed juice = 30–60:1; ratio of juice:dry expressed juice = 18–25:1)	1.-2. herbal medicinal product for the short-term prevention and treatment of common cold	oral solution *adolescents and adults* : 4 ml solution 2 times daily	authorised 2010
2. dry expressed juice from *Echinacea purpurea*, herba recens (purple coneflower herb) (ratio of fresh herb:dry expressed juice = 31–60:1; ratio of juice:dry expressed juice = 18–25:1).		tablets *adolescents and adults*: 1 tablet 3-4 times daily *children 1-12 y*: (under assessment)	authorisation procedure in progress
CZECH REPUBLIC			
1. *Echinaceae purpureae* succus	1.-3. for short-term prevention and treatment of common cold	drops - oral use 2.5 ml contain 2.0 ml of *Echinaceae purpureae* herbae succus: 2.5 ml 3 times daily	authorised 1994
2. *Echinaceae purpureae* herbae succus siccus (30-60:1)		uncoated tablets - oral use 1 tablet contains 80 mg: 1 tablet 3-4 times daily	authorised 2008
3. *Echinaceae purpureae* herbae succus siccus (31.5-53.6:1)		syrup - oral use 5 ml contain 117 mg: 5 ml 3 times daily	authorised 2010
DENMARK			
1. *Echinaceae purpureae* pressed juice (2-2.9:1)	1.-4. relief of minor symptoms of cold	oral drops, solution *adults*: 2.5 ml, 3 times daily for maximum 8 weeks Should not be used in children below 12 years of age without contacting a doctor.	authorised 1998
2. *Echinaceae purpureae* pressed juice, dried (DER fresh plant 33-50:1)		compressed lozenge *adults*: 1 compressed lozenge (88.5 mg dried pressed juice), 3 times daily in maximum 8 weeks	authorised 1998

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		Should not be used in children below 12 years of age without contacting a doctor.	
3. *Echinaceae purpureae* 165 mg ethanolic extract, corresponding to 500 mg dried herb		oral drops, solution *adults*: 10-20 drops (½-1 ml), 2 times daily for maximum 8 weeks Should not be used in children below 12 years of age without contacting a doctor.	authorised 2002 (withdrawn in 2009)
4. extract of 1250 mg fresh plant, corresponding to 240 mg dried herb		oral drops, solution *adults*: 10-20 drops (1 ml ~25 drops), 2-5 times daily for maximum 8 weeks Should not be used in children below 12 years of age without contacting a doctor.	authorised 1999 (withdrawn in 2006)
GERMANY			
From AR 2008: expressed juice from *Echinaceae purpurea*	adjuvant in (frequently occuring) recurrent respiratory tract infections and/or urinary tract infections	85 herbal medicinal products containing *Echinacea purpurea* are on the market. They exist in various pharmaceutical forms for oral use: syrup, oral liquid (expressed juice), effervescent tablet, oral gum, soft capsule, tablet, film-coated tablet, coated tablet.	marketing authorisation marketing authorisation for traditional use (according to German Drug Law)
	herbal medicinal product traditionally used as mild acting adjuvant in wound healing	ointment 100 g contain 16 g of expressed juice	marketing authorisation for traditional use before 1978
Information in 2013: 1. dried expressed juice from *Echinaceae purpureae* herba recens (38-56:1)	for short-term prevention of common cold	coated tablet 1 tablet contains: 175 mg dried expressed juice *adolescents and adults*: 1 tablet 2-3 times daily	authorised 2010
2. dried expressed juice from *Echinaceae purpureae* herba recens (38-56:1)	adjuvant in (frequently occuring) recurrent respiratory tract infections and urinary tract infections	coated tablet 1 tablet contains: 175 mg dried expressed juice *adolescents and adults*: 1 tablet 2-3 times daily	authorised 2010
3. expressed juice from fresh *Echinaceae purpureae* herba (0.9-1.1:1)	adjuvant in (frequently occuring) recurrent respiratory tract infections	100 g liquid contains 80 g expressed juice *children 6-10 y*: 1st day: starting dose 25 drops, then every 2 hours 15 drops (max. 125 drops per day), the	authorised in 1993 for children over 6 years of age, based only on bibliographic

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	and urinary tract infections	following days: 4-5 times daily 25 drops *11-15 y*: 1st day: starting dose 35-40 drops, then every 2 hours 20-25 drops (max 200 drops per day), the following days: 4-5 times daily 35-40 drops *≥16 y*: 1st day: starting dose 50 drops, then every 2 hours 30 drops (max. 250 drops per day), the following days: 4-5 times daily 50 drops 1 ml=22 drops duration of use: 10 days (for children 4 days)	data, no clinical studies in children, no confidential data
4. dried expressed juice from fresh flowering *Echinaceae purpureae* herba (22-65:1)	adjuvant in (frequently occurring) recurrent respiratory tract infections and urinary tract infections	1 tablet contains 100 mg dried expressed juice *children 6-12 y*: 2-3-times daily 1 tablet *>12 y*: 3-4-times daily 1 tablet duration of use: 10 days	authorised in 1997 for children over 12 years of age The use in children over 6 years of age was accepted in 2005. Marketing authorisation was granted on confidential data.
5. dried expressed juice from fresh flowering *Echinaceae purpureae* herba (22-65:1)	adjuvant in (frequently occurring) recurrent respiratory tract infections and urinary tract infections	100 g liquid contains 3.75 g dried expressed juice *children 6-11 y*: 3-4 times daily 2 ml (=2 g) liquid *≥12 y*: 3-4 times daily 3 ml (=3 g) liquid (3 ml correspond to 2.1 ml expressed juice) duration of use: 10 days	authorised in 2000 for children over 12 years of age The use in children was accepted in 2004 based on confidential data. Marketing authorisation was granted on confidential data.
6. dried expressed juice from fresh flowering *Echinaceae purpureae* herba (22-65:1)	for short-term prevention of common cold	100 g juice contains 1.076 g dried expressed juice *children 1-4 y*: 2-3 times daily 5 ml *children 4-12 y*: 2-3 times daily 10 ml *>12 y*: 2 times daily 15 ml (15 ml correspond to 3.8 ml expressed juice) duration of use: 10 days	authorised in 2001 for children over 12 years of age authorised in 2008 for children over one year of age. Marketing authorisation was granted on confidential data.
7. dried expressed juice from fresh flowering *Echinaceae purpureae* herba (22-65:1)	adjuvant in (frequently occuring) recurrent respiratory tract infections	100 g juice contains 0.828 g dried expressed juice *children 1-3 y*: 3 times daily 5 ml (corresponding to 0.89 ml expressed juice) *children 4-6 y*: 3 times daily 7.5 ml (corresponding to 1.34 ml expressed juice) *children 7-11 y*: 3 times daily 10 ml (corresponding to	authorised in 2003 for children over 12 years of age authorised in 2010 for children over one year of age. Marketing authorisation was

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		1.78 ml expressed juice) ≥*12 y*: 3 times daily 15 ml (15 ml corresponding to 2.67 ml expressed juice) duration of use: not longer than 2 weeks	granted on confidential data.
8. expressed juice from fresh flowering *Echinaceae purpureae* herba (1.7-2.5:1)	for short-term prevention of common cold	100 g liquid contains 80 g expressed juice *children 4-6 y*: 3 times daily 1.25 ml *children 6-12 y*: 3 times daily 2 ml *>12 y*: 3 times daily 2.5 ml (2.5 ml corresponding to 2 ml expressed juice) duration of use: not longer than 2 weeks	authorised in 2003 for children over 4 years of age, based on bibliographic data Dorsch *et al*. 2002 (p 58 and 163) retrospective, confidential data with questionnaires of doctors to efficacy and safety of the use in 60,200 children from 0-12 years, were used as supporting data
9. expressed juice from fresh flowering *Echinaceae purpureae* herba (1:0.65-0.85)	adjuvant in (frequently occurring) recurrent respiratory tract infections and urinary tract infections	100 ml contain 100 ml expressed juice *children 4-10 y*: 2–3 times daily 2 ml *10-16 y*: 1 time daily 6 ml to 2 times daily 4 ml *>16 y*: 2 times daily 5 ml duration of use: not longer than 2 weeks	authorised in 2003 for children over 12 years of age later authorised for children over 4 years. Marketing authorisation was granted on confidential data.
10. dried expressed juice from fresh flowering *Echinaceae purpureae* herba (31.5-53.6:1)	adjuvant in (frequently occurring) recurrent respiratory tract infections and urinary tract infections	1 lozenge contains 88.5 mg dried expressed juice *children 6-12 y*: 2-3 times daily 1 lozenge *>12 y*: 4 times daily 1 lozenge duration of use: not longer than 2 weeks	authorised in 2004 for children over 6 years of age Marketing authorisation was granted on confidential data.
11. dried expressed juice from fresh flowering *Echinaceae purpureae* herba (31.5-53.6:1)	adjuvant in (frequently occurring) recurrent respiratory tract infections	100 g liquid contains 2.34 g dried expressed juice *children 4-6 y*: 3 times daily 2.5 ml liquid *children 6-12 y*: 2 times daily 5 ml liquid *>12 y*: 3 times daily 5 ml liquid (5 ml correspond to 2.5 ml expressed juice) duration of use: not longer than 2 weeks	authorised in 2004 for children over 4 years of age Marketing authorisation was granted on confidential data.
12. expressed juice from fresh flowering *Echinaceae purpureae*	adjuvant in (frequently occurring) recurrent	100 g liquid contains 80 g expressed juice *children 4-6 y*: 3 times daily 1.25 ml liquid	authorised in 2004 for children over 4 years of age

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory Status** **(date, Member State)**
herba (1.7-2.5:1)	respiratory tract infections and urinary tract infections	*children 6-12 y*: 3 times daily 2 ml liquid *>12 y*: 3 times daily 2.5 ml liquid (2.5 ml correspond to 2 ml expressed juice) duration of use: not longer than 2 weeks	Marketing authorisation was granted on confidential data.
13. dried expressed juice from *Echinaceae purpureae* herba (25-83:1)	adjuvant in (frequently occurring) recurrent respiratory tract infections and urinary tract infections	1 lozenge contains 60-120 mg dried expressed juice corresponding to 2 ml expressed juice *children 5-9 y*: 1-3 times daily 1 lozenge *≥10 y*: 3-4 times daily 1 lozenge duration of use: not longer than 8 weeks	authorised in 2004 for children over 12 years of age later authorised for children over 5 years Marketing authorisation was granted on confidential data.
14. expressed juice from fresh flowering *Echinaceae purpureae* herba (1.7-2.5:1)	cutaneous use as mild acting adjuvant in wound healing	100 g of ointment contains 16 g of expressed juice *≥12 y*: 2-3 times daily 1-2 cm ointment	registered for traditional use in 2005 (the product was already on the German market in 1976)
		Information on duration of use in the prevention of cold and posology for children From the 42 preparations only 11 preparations have a posology for children. The use in children was accepted on confidential data in the dossier.	
HUNGARY			
1. expressed juice from fresh flowering *Echinaceae purpureae* herba (1.7-2.5:1)	1.-3. short-term prevention and treatment of common cold (duration of use: 10 days, in accordance with HMPC monograph)	100 g liquid contain 80 g expressed juice *adolescents, adults and elderly*: 3 times daily 2.5 ml liquid (2.5 ml correspond to 2 ml expressed juice)	authorised 2010 (WEU) (from 1994 to 2010 registered as a healing product)
2. dried expressed juice from fresh *Echinaceae purpureae* herba (31.5-53.6:1)		5 ml of syrup contain 124 g dried expressed juice *adolescent* and adults: 5 ml three times daily	authorised 2001 (WEU)
3. dried expressed juice from fresh *Echinaceae purpureae* herba (31.5–53.6:1)		1 pastille contains 75.22 mg dried expressed juice corresponds to 1.7 ml expressed juice) *adolescent, adults and elderly*: 75.22 mg four times daily	authorised 2010 (WEU)
4. expressed juice from the fresh *Echinacea purpurea* (L.) herba (1.7-2.5:1)	traditional herbal medicinal product for treatment of small superficial wounds	1 g of ointment contains 160 mg of expressed juice *Adolescent and adults*: 2-3 times daily apply a thin layer on the affected area	registered 2010 (THMP)

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
LATVIA			
1. *Echinacea purpurea* herb dried expressed juice (31-60:1)	1.-2. short term prevention and treatment of common cold	1 tablet contains 80 mg of dried expressed juice *adolescents, adults, elderly*: 1 tablet 3-4 times per day contraindicated for children below 1 year not recommended for children 1-12 years duration of use: not to be used more than 10 days use of medicines can be restarted not earlier than after a 14 days pause	authorised 2003
2. *Echinacea purpurea* herb expressed juice		oral drops, solution: 0.8 ml/ml *adolescents, adults, elderly*: 2.5 ml 3 times per day contraindicated for children below 1 year not recommended for children 1-12 years duration of use: not to be used more than 10 days use of medicines can be restarted not earlier than after a 14 days pause	authorised 1996
LITHUANIA			
1. expressed juice from *Echinacea purpurea*, herba (fresh purple coneflower herb) (1.5-2.5:1)	1.–2. herbal medicinal product for the short-term prevention and treatment of common cold	1 ml of oral drops, solution contains 0.8 ml of expressed juice *adolescents, adults, elderly*: 2.5 ml of solution 3 times daily paediatric population: The use in children below 1 year of age is contraindicated. The use in children between 1 and 12 years of age is not recommended.	authorised 1995
2. expressed juice from *Echinacea purpurea*, herba (fresh purple coneflower herb) (1.5-2.5:1)		1 ml of oral drops, solution (20 drops) contains 0.756 ml of expressed juice *adolescents, adults, elderly*: 55 drops (2.75 ml) 3-4 times daily The use in children below 1 year of age is contraindicated. The use in children between 1 and 12 years of age is not recommended.	authorised 2002

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
NETHERLANDS			
1. dried juice of fresh aerial parts of *Echinacea purpurea* (20-28:1)	traditional medicinal product for relief of symptoms of influenza	one effervescent tablet contains 176 mg dried juice *adolescents* and adults: 1-2 tablets per day, solved in glass of water (200 ml) Solved tablets should be drunk immediately. Do not use this product longer than 10 days. If symptoms persist longer than 10 days, or in case of high fever, or if symptoms get worse, a doctor should be consulted.	registered (THMP) 2012
POLAND			
1. expressed juice (dried) from *Echinacea purpurea*, herba (31.5-53.6:1)	adjunctively in recurrent infections of airways	1 g of syrup contains 23.4 mg of expressed juice (dried) *adolescents and adults*: 5 ml 3 times daily *children 4-6 y*: 2.5 ml 2 times daily *children 6-12 y*: 5 ml 2 times daily duration of use: not more than 14 days	authorised 2004
2. expressed juice from *Echinacea purpurea*, herba (1.7-2.5:1)	adjunctively in recurrent infections of airways and descendent urinary tract	1 g of oral liquid contains 800 mg of expressed juice *adolescents and adults*: 2.5 ml 3 times daily *children 4-6 y*: 1.25 ml 3 times daily *children 6-12 y*: 2 ml 3 times daily duration of use: not more than 14 days	authorised 2004
3. expressed juice (dried) from *Echinacea purpurea*, herba (31.5-53.6:1)	adjunctively in recurrent infections of airways	1 pastille contains 88.5 mg of expressed juice (dried) *adolescents and adults*: 1 pastille 4 times daily *children 6-12 y*: 1 pastille 2 to 3 times daily duration of use: not more than 14 days	authorised 2004
4. extract (as soft extract) from *Echinacea purpurea*, herba (30-40:1), extraction solvent: ethanol 23-30% (V/V)	short-term prevention and treatment of symptoms of cold	1 film-coated tablet contains 100 mg of extract (as soft extract) *adolescents and adults*: 1 to 2 tablets 3 times daily duration of use: not more than 10 days	authorised 1994
5. extract (as soft extract) from *Echinacea purpurea*, herba (30-40:1), extraction solvent: ethanol 23-30% (V/V)	treatment of small superficial wounds	1 g of ointment contains 50 mg of extract (as soft extract) cutaneous use *adolescents and adults*: apply 2 to 3 times daily duration of use: up to 7 days	authorised 1994

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
6. expressed juice (dried) from *Echinacea purpurea*, herba (22-65:1)	for short-term prevention of cold, for treatment of first symptoms of cold	1 tablet contains 100 mg of expressed juice (dried) *adolescents and adults*: 1 tablet 3 to 4 times daily duration of use: not more than 10 days	authorised 1999
SLOVENIA			
1. juice from *Echinacea purpurea*, herba (1.5-2.5:1)	1.-4. for short-term prevention and treatment of common cold	1 ml of solution contains 0.8 ml of the juice *adolescents and adults*: 3 times a day 2.5 ml of solution *children 6-12 y* (only after consultation with a doctor): 3 times a day 1.5 ml of solution	authorised 1997
2. dried juice from *Echinacea purpurea,* herba (31–60:1)		1 tablet contains 80 mg of dried juice *adolescents and adults*: 3-4 times a day 1 tablet *children 4-6 y* (only after consultation with a doctor): 2 times a day 1 tablet *children 6-12 y* (only after consultation with a doctor): 3 times a day 1 tablet	authorised 2001
3. dried juice from *Echinacea purpurea*, herba (30–60:1)		1 ml of oral solution contains 46.5 mg of dried juice *adolescents and adults*: 2 times a day 4 ml of solution *children 4-12 y* (only after consultation with a doctor): 2 times a day 2 ml of solution	authorised 2008
4. dried juice from *Echinacea purpurea*, herba (18-25:1)		one tablet contains 170 mg of dried juice *Adolescents and adults*: 3-4 times a day 1 tablet not recommended for children below 12 years	authorised 2002
SPAIN			
1. fresh expressed juice from *Echinacea purpurea,* herba (1.7-2.5:1)	treatment of common cold	oral solution *adolescents and adults*: For the first 24 hours of treatment, an initial dose of 2.5 ml is recommended, followed by doses of 1.5 ml every 2 hours, up to a maximum daily dose of 15 ml. The maintenance dose corresponds to 7.5 ml per day (2.5 ml three times a day) duration of use: 7 to15 days	authorised 1997

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
SWEDEN			
1. *Echinacea purpurea*, herb, dried expressed juice	1.-4. for short-term prevention and relief of common cold	1 effervescent tablet contains 176 mg dried expressed juice *adolescents, adults, elderly*: first day: 1 tablet every other hour; after: 1 tablet 2-3 times daily	since 2003, reclassified to HMP 2009
2. *Echinacea purpurea*, herb, dried expressed juice		1 ml of oral solution contains 800 mg dried expressed juice *adolescents, adults, elderly*: 2.5 ml 3 times daily	since 2006, reclassified to HMP 2009
3. *Echinacea purpurea*, herb, dried expressed juice		1 ml of oral drops, solution contains 800 mg dried expressed juice *adolescents, adults, elderly*: 2.5 ml 3 times daily	since 1995, reclassified to HMP 2009
4. *Echinacea purpurea*, herb, dried expressed juice		1 orodisposible tablet contains 88.5 mg dried expressed juice *adolescents, adults, elderly*: 1 tablet 4-5 times daily	since 1995, reclassified to HMP 2009
5. expressed juice from *Echinacea purpurea*, herb (1.7-2.5:1)	traditional herbal medicinal product used for sores on the lips and other small, superficial wounds such as chapping in the corner of the mouth or on the fingertips The indications are based solely on experience and use during a long period of time	1 g ointment contains 160 mg expressed juice cutaneous *adolescents, adults, elderly*: apply 2-3 times daily on the affected area	since 1984, reclassified to THMP 2009
UNITED KINGDOM			
1. dried pressed juice from *Echinacea purpurea* fresh herb (31.5-53.6:1)	1.-5. A traditional herbal medicinal product used to relieve the symptoms of the common cold and influenza type infections based on traditional use only	5 ml of oral liquid contains 0.117 g of dried pressed juice equivalent to 3.7-6.3 g *Echinacea* *adolescents, adults, elderly*: one 5 ml teaspoonful to be taken 3 times a day Do not take this product for more than 10 days.	registered as THMP
2. pressed juice from *Echinacea purpurea* fresh herb (1.7-2.5:1)		2.5 ml (2.49 g) of oral solution contains 1.99 g of pressed juice (equivalent to 3.4-5 g *Echinacea purpurea*	registered as THMP

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		adolescents, adults, elderly: 2.5 ml of oral solution 3 times daily Do not take this product for more than 10 days.	
3. dried pressed juice from fresh flowering *Echinacea purpurea* herb (38-56:1)		1 coated tablet contains 175 mg of dried pressed juice *adolescents, adults, elderly*: one tablet 3 times a day Do not take this product for more than 10 days.	registered as THMP
4. dried pressed juice from fresh flowering *Echinacea purpurea* herb (20-28:1)		1 soft capsule contains 176 mg of dried pressed juice (equivalent to 3520-4928 mg of fresh flowering *Echinacea purpurea)* *adolescents, adults, elderly*: 1 or 2 soft capsules daily Do not take this product for more than 10 days.	registered as THMP
5. dried pressed juice from fresh flowering *Echinacea purpurea* herb (20-28:1)		1 effervescent tablet contains 176 mg of dried pressed juice (equivalent to 3520-4928 mg of fresh flowering *Echinacea purpurea)* *adolescents, adults, elderly*: 1 or 2 effervescent tablets daily Do not use the product for more than 10 days.	registered as THMP

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Information on relevant combination medicinal products marketed in the EU/EEA

Croatia

There are authorised medicinal products containing a combination of purple coneflower herb tincture (as dry extract) from *Echinacea purpurea*, herba recens, extraction solvent: ethanol 65% V/V (1:12) and purple coneflower root tincture (as dry extract) from *Echinacea purpurea*, radix recens (purple coneflower root) (extraction solvent: ethanol 65% V/V (1:11), 95:5, in the form of tablets, chewable tablets and oral drops, solution on the market.
Indications: treatment and prevention of common cold symptoms such as coughing, lacrimation, sore throat, headache and muscle pain. To improve resistance to the common cold, flu accompanied by fever and recurrent infections.

There is also an authorised medicinal product containing tincture from *Echinacea purpurea*, herba recens (purple coneflower herb), (extraction solvent: ethanol 65% V/V, DER 1:12); tincture from *Echinacea purpurea*, radix recens (purple coneflower root) (extraction solvent: ethanol 65% V/V, DER 1:11) and tincture from *Salvia officinalis* folium recens (sage leaf) (extraction solvent: ethanol 68% V/V, DER 1:17) in the form of oromucosal spray on the market.
Indication: symptomatic treatment of inflammation in the mouth and pharynx.

Finland

Echinacea purpurea herb is on the market only in a combination product containing 910 mg of *Echinaceae purpureae* herb. et rad. congelat. extr. spir. fl. (1:3) (extraction solvent: ethanol 48% V/V).
Indication: traditional herbal medicinal product for temporary relief and prevention of common cold; treatment of small superficial wounds.

Ireland

Echinacea purpurea herb preparations are only available in combination products which also contain *Echinacea purpurea* root preparations. All of the products are registered as traditional medicinal products for relief of common cold and flu-like symptoms. None of the products are indicated for use in under 12 years of age.

Netherlands

There is a registered traditional medicinal product containing a combination of dried ethanolic extracts of fresh flowering aerial parts of *Echinacea purpurea* (corresponding with 300-600 mg fresh plant material) and fresh *Echinacea purpurea* roots (corresponding with 17-29 mg fresh *Echinacea* roots), extraction solvent: ethanol 65% V/V on the market.
Indications: insufficient immunity, influenza and cold.

Poland

There are medicinal products on the market containing *Echinacea purpurea* herb preparations in combination with various herbal drugs/herbal drug preparations for treatment of common cold and other mild upper respiratory tract infections with accompanying cough:
Plantago lanceolata, folium or *Plantago lanceolata*, folium, *Grindelia robusta*, herba, *Rosa canina*, fructus, *Thymus vulgaris*, herba or *Aronia spp.*, fructus *Arctium spp.*, radix, *Matricaria recutita*, flos U*rtica dioica* and/or *Urtica urens* herba or *Allium sativum*, bulbus.

Slovenia

There are authorised medicinal products containing combination of purple coneflower herb dry extract from *Echinacea purpurea*, herba recens, extraction solvent: ethanol 65% V/V (DER 1:12) and purple coneflower root dry extract from *Echinacea purpurea*, radix recens extraction solvent: ethanol 65% V/V (DER 1:11), 95:5, in the form of tablets, chewable tablets and oral drops, solution on the market.
Indications: prevention and treatment of common cold.

There is also a registered traditional medicinal product containing a combination of a tincture from *Echinacea purpurea*, herba recens (purple coneflower herb), (extraction solvent: ethanol 65% V/V (1:12); a tincture from *Echinacea purpurea*, radix recens (purple coneflower root) (extraction solvent: ethanol 65% V/V *(*1:11) and a tincture from *Salvia officinalis* folium recens (sage leaf) (extraction solvent: ethanol 68% V/V (1:17) in the form of oromucosal spray on the market.
Indication: traditional herbal medicinal product used to relieve symptoms of oral cavity and throat inflammations.

United Kingdom
There are medicinal products containing combination of purple coneflower dry extract from *Echinacea purpurea*, herba recens, extraction solvent: ethanol 65% V/V and purple coneflower root dry extract from *Echinacea purpurea*, radix recens, extraction solvent: ethanol 65% V/V, 95:5, in the form of tablets, chewable tablets and oral drops, solution on the market. Indications: traditional herbal medicinal product used to relieve the symptoms of the common cold and influenza type infections.
There is also a registered traditional medicinal product containing a combination of a tincture from *Echinacea purpurea*, herba recens (purple coneflower herb), (extraction solvent: ethanol 65% V/V (1:12-13); a tincture from *Echinacea purpurea*, radix recens (purple coneflower root) (extraction solvent: ethanol 65% V/V *(*1:11-12) and a tincture from *Salvia officinalis* folium recens (sage leaf) (extraction solvent: ethanol 68% V/V (1:17-18) in the form of oromucosal spray on the market.
Indication: traditional herbal medicinal product used to relieve sore throats associated with coughs, colds and flu.

Information on other products marketed in the EU/EEA (where relevant)

Italy
Echinacea purpurea herb is included in the list of herbal substances and herbal preparations allowed in food supplements, published on the website of the Italian Ministry of Health, with the following indications: natural body defence. Urinary ways function. First airways function.

2.2. Information on traditional/current indications and specified substances/preparations

Medicinal uses of *Echinacea* species among American Indians were many and varied. *Echinacea angustifolia* was universally used as an antidote for snakebite and other venomous bites and stings and poisonous conditions. *Echinacea* has been used as a remedy for more ailments than any other plant (Foster 1996). *Echinacea purpurea* was first mentioned in 1787. It was used for treating ulcers on a horses' back caused by saddles. Subsequently, the plant was largely neglected until the first edition of the Eclectic Dispensatory in 1852. The European history of the introduction and use of *Echinacea purpurea* in many ways parallels its history in the U.S. By 1895 *Echinacea* products for homeopathic physicians had become available in Germany. Over the next 30 years the demand increased, while shortages were prevalent in Europe. Subsequently, in the late 1930s, commercial cultivation of *Echinacea purpurea* began in Germany, introducing *Echinacea* products to a wide European audience for the first time. The majority of pharmacological and clinical studies conducted since 1939 have involved *Echinacea purpurea* preparations made from the fresh expressed juice of the flowering plant . The pharmaceutical forms of the products included an ointment, a liquid form for external use, a liquid form for internal use, as well as ampoules for intravenous injection (Rote liste 1961).

Information about the use of the plant from traditional healers ranges from external application for wounds, burns and insect bites to the chewing of roots for toothache and throat infections, and internal application for pain, coughs, stomach cramps and snake bites. The interest of white settlers was also

drawn to this medicinal plant. The first *Echinacea* preparation, known as Meyers Blood Purifier, arrived on the market around 1880, with rheumatism, neuralgia and rattlesnake bites as indications (Hostetman 2003).

Medicinal use of juice and dried juice from *Echinacea purpurea* (L.) Moench., herb has been documented continuously in last decades in many pharmacognostical texts, handbooks and compendia (Table 2).

Table 2: Documented oral medicinal use of juice and dried juice from *Echinacea purpurea* (L.) Moench., herba

Herbal substance/preparation	Indication	Reference
purple coneflower herb consists of fresh, above-ground parts, harvested at flowering time, of *Echinacea purpurea* (L.) Moench, as well as its preparations in effective dosage	supportive therapy for colds and chronic infections of the respiratory tract and lower urinary tract	Kommission E 1989
powdered aerial part of *Echinaceae purpureae* herba, pressed juice and galenic preparations thereof	supportive therapy for colds and infections of the respiratory and urinary tract	WHO 1999
pressed juice; other equivalent preparations	adjuvant therapy and prophylaxis of recurrent infections of upper respiratory tract (common colds) and also urogenital tract	ESCOP 2003
Echinacea purpurea herb	preventing and treating the common cold, flu, and upper respiratory tract infections (URIs)	Blumenthal *et al*. 2000
Echinaceae purpureae herba, pressed juice	supportive treatment of recurrent infections of the respiratory tract and lower urinary tract	Blaschek *et al.* 2004 and 2008
Echinacea spp., incl. the aerial parts of *Echinacea purpurea*	prophylaxis of bacterial and viral infection treatment of upper respiratory infections such as the common cold	Martindale 2009

Table 3: Documented topical medicinal use of juice and dried juice from *Echinacea purpurea* (L.) Moench., herba

Herbal substance/preparation	Indication	Reference
purple coneflower herb consists of fresh, above-ground parts, harvested at flowering time, of *Echinacea purpurea*, as well as its preparations in effective dosage	poorly healing wounds and chronic ulcerations	Kommission E 1989

powdered aerial part of *Echinacea purpurea*, pressed juice and galenic preparations thereof	promotion of wound healing and treatment of inflammatory skin conditions	WHO 1999
Pressed juice of *Echinaceae purpureae* herba, pressed juice in semi-solid preparations	as an adjuvant for the treatment of superficial wounds	ESCOP 2003
Echinaceae purpureae herba	poorly healing superficial wounds	Wichtl 2009
Echinaceae purpureae herba, pressed juice	poorly healing superficial wounds	Blaschek *et al.* 2004 and 2008

Information on medicinal products in Member States

Oral use

The information exchange between the competent authorities of the EU Member States in 2007 showed that in Austria, Bulgaria, Germany, Hungary and Poland medicinal products, containing (dried) expressed *Echinacea* juice have been on the market as herbal medicinal products for adjuvant therapy and prophylaxis of recurrent infections of the upper respiratory tract (common cold) and also of the urogenital tract while in Belgium, Finland, Latvia, Romania, Slovenia, Sweden have been used for treatment of symptoms of the upper respiratory tract infections (common cold) only.
The use of *Echinacea* for treatment of urogenital infections is not supported by relevant clinical studies. *Echinacea* was traditionally known as an 'anti-infective' agent and was indicated in bacterial and viral infections, also for recurrent infections of lower urinary tract (Barnes *et al*. 2007).

On the basis of the survey between the competent authorities of the EU Member States in 2013 medicinal products containing expressed (DER 1.5-2.5:1) or dried (corresponding to the express juice DER 1.5-2.5:1) *Echinacea* juice in the EU have the following indications:

Austria: supportive treatment and prophylaxis of recurrent infections of the airways
Belgium: symptomatic treatment of infections of the upper respiratory tract after a serious illness has been excluded
Bulgaria: supportive treatment of recurrent infections of respiratory tract
Croatia, Czech Republic, Hungary, Latvia, Lithuania, Slovenia, Sweden: short-term prevention and treatment of common cold
Germany: short-term prevention and treatment of common cold; adjuvant in (frequently occurring) recurrent respiratory tract infections and urinary tract infections

Denmark: relief of minor symptoms of cold
Netherlands: traditional medicinal product for relief of symptoms of influenza
Poland: adjunctively in recurrent infections of airways; adjunctively in recurrent infections of airways and descendent urinary tract, short-term prevention and treatment of symptoms of cold
Spain: treatment of common cold
United Kingdom: a traditional herbal medicinal product used to relieve the symptoms of the common cold and influenza type infections based on traditional use only.

The indications of medicinal products, containing (dried) expressed *Echinacea* juice for oral use can be summarised in 'short-term prevention and treatment of symptoms of cold'.

In most EU Member states medicines, containing (dried) expressed *Echinacea* juice are authorised as herbal medicinal products with well-established use.

In two Member states (NL, UK) these medicines are considered traditional herbal medicinal products.

Topical use

There is a history of traditional use of ointment prepared from expressed juice of *Echinacea purpurea*, herba recens (1.7-2.5:1) for more than 30 years for treatment of small superficial wounds in Germany and Sweden:
Indication in Germany: herbal medicinal product traditionally used as mild acting adjuvant in wound healing.
Indication in Sweden: traditionally used for treatment of sores of the lips and on other small superficial wounds such as chapping in the corner of the mouth and fingertips.

In Bulgaria ointment from expressed juice of *Echinacea purpurea* herba, recens (DER 1.7-2.5:1) is registered as mild acting medicine for the promotion of wound healing and in Hungary as a traditional herbal medicinal product for treatment of small superficial wounds.

Wording 'traditional herbal medicinal product for treatment of small superficial wounds' integrates above mentioned indications.

2.3. Specified strength / posology / route of administration / duration of use for relevant preparations and indications

Oral use

Table 4: posology and duration of oral use recommended by monographs and reviews are

Herbal substance/preparation	Posology	Duration of use	Reference
powdered aerial part of *Echinacea purpurea*, pressed juice and galenic preparations thereof	6-9 ml per day; information on dosages for children is not available	no longer than 8 successive weeks	WHO 1999
expressed juice of *Echinacea purpurea* herb or other equivalent preparations	6-9 ml per day for adults; proportional dose for children	the duration of continuous treatment should not exceed 8 weeks	ESCOP 2003
expressed juice of *Echinacea purpurea* herb	6-9 ml per day	no longer than 8 weeks.	Kommission E 1989
Expressed juice of *Echinacea purpurea* herb	3 ml per day (1-4 years of age) 3-5 ml per day (4-10 years of age) 6-9 ml per day (10-16 years of age)	not defined	Dorsch *et al*. 2002

Information on medicinal products in Member States

Oral use

Daily dose 6-9 ml of expressed juice from fresh herb *Echinacea purpurea* (1.5-2.5:1) or equivalent dried expressed juice in various dosage forms for oral application, divided in 1-3 (up to 4) single doses, is recommended for adolescents, adults, elderly, in most cases.

The duration of use without interruption is limited mainly to 10 days, sometimes to 14 days.

Topical use

Kommission E (1989), ESCOP (2003) and WHO (1999) monographs recommend semi-solid preparations with a minimum of 15% of *Echinaceae purpureae* herb pressed juice.

In the assessment report 2008 there was information that 10 to 20 g of expressed juice per 100 g of preparation was used in products on the European market. Even if that could not be verified in 2013 there seems to be a tradition on usage of that range, e.g. in the Rote liste 1961 there is information on ointment with 10% of *Echinaceae purpureae* herb pressed juice. It is assumed that dried juice corresponding to the expressed juice above could be equally appropriate for traditional medicinal products for cutaneous use.

From the exchange of information between competent authorities in 2013 it can be seen that 16 g of expressed juice per 100 g of preparation is used in medicinal products on the European market.

Dosage: adolescents, adults and elderly: thin layer of ointment is applied 2-3 times daily on the affected area.

For detailed information on oral and cutaneous use see the Table 2 and 3 in chapter “2.1 Information on period of medicinal use in the European Union” and Table 5 in chapter “4.2.2. Clinical studies (case studies and clinical trials)”.

3. Non-Clinical Data

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

The mechanism by which the clinical effect (treatment and short term prevention of common cold) is achieved is not known. Antiviral and immunomodulatory effects were demonstrated in pharmacological studies, but their relevance for the clinical efficacy is not known. Therefore it was not possible to classify pharmacodynamic studies into primary and secondary pharmacodynamic.

3.1.1. Antiviral Effects

Pressed juice

In vitro

Orinda *et al*. (1973) reported about a virustatic effect of an *Echinacea purpurea* expressed juice (dry, DER 31.5-53.6:1). It was shown that the expressed juice in the presence of DEAE-Dextran mouse-L-929 cells were protected against the cytopathic effect of *Encephalomyocarditis virus* (EMC virus) and *Vesicular Stomatitis virus* (VSV). The virustatic effect was quantitatively measured by 2 methods (Wacker & Hilbig 1978): the Plaque reduction method in the cell culture and the colour method by Finter. The extract of *Echinacea purpurea* herb was fractionated by TLC and the virustatic activity of

the fractions was tested. The virustatic activity was distributed to all fractions of the entire TLC. The antiviral principle could not be inactivated by a two-hour treatment at 60 to 80°C.

Other herbal preparations, crude fractions

In vitro

Both a decoction and a 30% ethanolic extract of *Echinacea purpurea* herb (DER not provided) inhibited the intracellular propagation of ECHO9 HILL virus in a monkey kidney cell culture. A 50% virus inhibition was still observed with dilution rates between 1:6 to 1:15 (Skwarek *et al*. 1996).

Stems, leaves, and flowers of *Echinacea purpurea* were fractionated by various solvents and the fractions evaluated for antiviral activity (Vimalanathan *et al*. 2005). All of the aqueous fractions exhibited potent activity against herpes simplex virus and influenza virus. In addition, the ethanol- and ethyl acetate–soluble fractions from leaves and stem contained an uncharacterised but potent antiviral photosensitiser, which was absent from the flower extract. None of the fractions, however, had anti-rhinovirus activity.

Other or non-specified plant parts / species

Human H1N1-type IV, highly pathogenic avian IV (HPAIV) of the H5- and H7-types, as well as swine origin IV (S-OIV, H1N1), were all inactivated in cell culture assays by an *Echinacea purpurea* preparation (ECH) (65% V/V ethanol extract of freshly harvested *Echinacea purpurea* herb (DER 1:12) and roots (DER 1:11), 95:5) (Pleschka *et al*. 2009). A direct contact between the ECH and virus was required, prior to infection, in order to obtain maximum inhibition of virus replication. Hemagglutination assays showed that the extract inhibited the receptor binding activity of the virus, suggesting that the extract interferes with the viral entry into cells. In sequential passage studies under ECH treatment in cell culture with the H5N1 virus no ECH-resistant variants emerged, in contrast to oseltamivir, which produced resistant viruses upon passaging. Furthermore, the oseltamivir - resistant virus was just as susceptible to EF as the wild type virus.

Anti-rhinovirus efficacy of ECH was evaluated in a 3-dimensional organotypic model of normal human airway epithelium (Sharma *et al*. 2010). Individual replicate tissue samples, maintained as inserts in culture for 3 days or 3 weeks, were infected with rhinovirus type 1A (RV1A), *Echinacea* alone, a combination of the two, or medium only. None of the treatments affected the histological appearance or integrity of the tissues, all of which maintained a high level of cell viability and preservation of cilia. RV infection resulted in increased mucopolysaccharide inclusions in the goblet cells, but this feature was reversed by ECH treatment. This result was confirmed by measurements of mucin secretion, which was stimulated by RV but reversed by ECH, suggesting that mucus production during colds could be ameliorated by ECH. No evidence of virus replication was found, although the RV-infected tissues secreted substantial amounts of the pro-inflammatory cytokines IL-6 and IL-8 (CXCL8), and this response was reversed by ECH treatment.

Using mouse fibroblasts, it was demonstrated that incubation previous to virus infection for at least 4 hours with methanolic and aqueous extracts of *Echinacea purpurea* root resulted in resistance to *Influenza* A2, *Herpes,* and *Vesicular stomatitis* virus infection for 24 hours (Wacker & Hilbig 1978).

A high molecular weight fraction (M_r >10,000 D) containing polysaccharides and glycoproteins from purple coneflower root exhibited antiviral activity against *Herpes simplex* virus (HSV) and *Influenza* virus (Beuscher *et al*. 1995).

Extracts of 8 taxa of the genus *Echinacea* were found to have antiviral activity against HSV Type I *in vitro* when exposed to visible and UV-A light. n-Hexane extracts of roots containing alkenes and amides were more active in general than ethyl acetate extracts containing caffeic acids. The most

potent inhibitors of HSV were *Echinacea pallida* var. sanguinea crude (70 % ethanol) inflorescence extract (MIC=0.026 mg/ml), cichoric acid (MIC=0.045 mg/ml) and *Echinacea purpurea* n-hexane root extract (MIC=0.12 mg/ml) (Binns *et al*. 2002b).

Caffeic acid derivatives

In vitro

Cichoric acid from *Echinacea purpurea* expressed juice was found to reduce a yield of VSV in mouse L-929-cells. 125 µg/ml cichoric acid after 4 h incubation reduced the infectivity of VSV by more than 50% (Cheminat *et al*. 1988).

3.1.2. Antibacterial Effects

Alkamides

In vitro

For trideca-1,11-dien-3,5,7,9-tetrain and trideca-1-en-3,5,7,9,11-pentain, both main alkylamides from *Echinacea purpurea*, bacteriostatic effects were described. Total growth inhibition of *Escherichia coli* by the constituents was found in concentrations of 100 and/or 50 µg/ml, and of *Pseudomonas aeruginosa* in concentrations of 5.0 and/or 1,000 µg/ml, respectively (Schulte *et al*. 1967a, Schulte *et al*. 1967b). For both constituents the following inhibitory concentrations were determined: *Staphylococcus aureus* 0.005% and/or 0.01%; *Pseudomonas aeruginosa* 0.005% and/or 0.1% and *Escherichia coli* 0.0005% and/or 0.005% (Reisch *et al*. 1967).

3.1.3. Effects on wound healing

Pressed juice

In vivo

The healing of standardised, surgery made skin wounds on guinea pigs was accelerated by a *Echinacea* ointment (commercial product, plant species and herbal substance is not specified in the article; in the Rote Liste 1984 the concerned product contained *Echinaceae purpurea* herb pressed juice (DER 2.5:1) (Kinkel *et al*. 1984). The wound area at day 6 and 9 after surgery was significantly ($p<0.05$) smaller than those of the untreated control animals. In comparison with the control group, the clinical picture was significantly improved in the group treated with *Echinacea* ointment already on day 3 ($p<0.05$).

Echinacea-fibrin grafts stimulated the healing tendency in guinea pig. Compared with pure fibrin grafts, healing tendency of the wound areas increased and less marked leucocytic infiltration were observed in *Echinacea*-fibrin grafts (Tünnerhoff & Schwabe 1956).

Other herbal preparations

In vitro

10 and/or 30 µl of an extract from *Echinacea purpurea* fresh plants, manufactured with 90% ethanol, (final ethanol concentration 65%), with a dry residue of 10.5 mg/ml, significantly inhibited the concentration of collagen lattices populated with C3H10T1/2-fibroblasts *in vitro*. Ethanol of equal concentration did not have influence. Dependent on the time of the addition of the extract the elongation of fibroblasts and the cell processes leading to the cross-linking of the collagen were inhibited. If the extract was applied 1 h after the beginning of cross-linking, no more influence could be determined. The authors discussed the significance of these observations in relation to the process of wound healing (Zoutewelle *et al*. 1990).

3.1.4. Immunomodulatory effects

Pressed juice

In vitro

Treatment of leukocyte suspensions with lyophilised expressed juice of *Echinacea purpurea* (1.0 or 5.0 mg/ml) induced a dose-dependent and highly significant increase (79% to 95%, $p<0.001$) in the percentage of phagocytosing granulocytes. It also significantly stimulated (about 50%, $p<0.01$) the phagocytosis index. With the highest tested dose of 12.5 mg/ml both the number of phagocytosing granulocytes and the phagocytosis index decreased (Stotzem *et al*. 1992).

In vivo

Phagocytosis of isolated peritoneal macrophages from mice and macrophages of isolated perfused rat liver was significantly stimulated after i.p. and/or p.o. application of *Echinacea purpurea* expressed juice (Bauer 1988a, Bauer et al. 1989).

Other herbal preparations, crude fractions

In vitro

Tamta *et al*. (2008) determined the contribution of bacterial lipopolysaccharides and Braun-type bacterial lipoproteins to the overall immune-enhancing activity of *Echinacea purpurea* and *Echinacea angustifolia* bulk root and aerial material, obtained from six major growers/suppliers in North America. Substantial variation in activity (up to 200-fold) was observed in extracts of these materials when tested in two monocyte/macrophage cell lines. The majority of activity was negated by treatment with agents that target bacterial lipoproteins (lipoprotein lipase) and lipopolysaccharides (polymyxin B). Experiments comparing the activity of freeze-dried, freshly harvested *Echinacea* plants with those harvested and dried using various commercially relevant conditions, suggested that postharvesting procedures did not substantially contribute to the variation observed in the commercial material.

In another study by the same group (Pugh *et al*. 2013), the total bacterial load of *Echinacea purpurea* root and herb samples was determined with PCR-based quantification. It ranged from 6.4×10^6 to 3.3×10^8 bacteria/g of dry plant material. Differences in total bacterial load within *Echinacea* samples were strongly correlated with the activity (NF-κB activation in THP-1 cells) and content of bacterial lipopolysaccharides within extracts of this plant material.

The influence of different *Echinacea* preparations including *Echinacea purpurea* herb extract (250 µg/ml) on the regulation of human immune gene expression was studied on THP-1 cells by Randolph *et al*. (2003). Gene expression was studied by measuring the amount of respective mRNA with quantitative PCR. Expression of interleukin-1alpha, interleukin-1beta, TNF-alpha, intracellular adhesion molecule, interleukin-8 and interleukin-10 genes increased up to 10-fold in *Echinacea* treated THP-1 cells. The results of this study are consistent with the results of an older study, where the cytokine production of normal human peripheral blood macrophages at *in vitro* stimulation with commercial preparations (liquid (no details available) and dry (DER 50:1) juice of *Echinacea purpurea* herb) was measured with ELISA (Burger *et al*. 1997). *Echinacea* stimulated immune cells produced significantly higher amount of interleukin-1, TNF-alpha, interleukin-6 and interleukin-10.

In vivo

The carbon clearance test of an extract manufactured from *Echinacea purpurea* herb with ethanol (not further specified) showed on mice after p.o. application (dosage equals 1.7 mg extract/kg; 3 times daily for two days) an increased carbon elimination by the factor 1.4 in relation to control. The

chloroform-soluble fraction was stronger (factor 2.1); the water-soluble fraction was weaker (factor 1.3). A mother tincture of *Echinacea purpurea*, manufactured according the German Homoeopathic Pharmacopoeia, stimulated in a dosage of 0.17 ml/kg 3 times daily over 2 days (p.o.) the carbon clearance around the factor 2.1 (Bauer *et al*. 1989).

Polysaccharides

In vitro

Echinacea polysaccharides were isolated from aerial parts and roots of *Echinacea purpurea*. Further purification yielded a protein-free preparation called EPS (Stimpel *et al*. 1984) and two polysaccharides: PSI, 4-O-methylglucuronoarabinoxylan (35,000 D) and PSII, a 50,000 D acidic arabinorhamnogalactan (Proksch & Wagner 1987). *In vitro* these polysaccharides did not influence T and B cell proliferation or cytokine production but affected the phagocytosis, chemotaxis, and production of cytokines observed in granulocytes and macrophages (Stimpel *et al*. 1984, Wagner *et al*. 1985). These polysaccharides also enhanced the cytotoxic action of macrophages toward tumour P815 cells (Stimpel *et al*. 1984). Later work repeated and extended the earlier studies by using an acidic arabinogalactan (75,000 D) isolated from *Echinacea purpurea* grown in tissue culture (Wagner *et al*. 1988). This polysaccharide enhanced macrophage activation and intracellular killing of *Leishmania enriettii* (Luettig *et al*. 1989).

The concentrations of *Echinacea* polysaccharides required to obtain the *in vitro* effect on immune cells discussed above were extremely high. In studies using EPS (Stimpel *et al*. 1984) concentrations of 1 mg/ml were required to enhance macrophage cytotoxicity. In addition, this high concentration of EPS was required to enhance macrophage IL-1 production to levels 50% of those achieved using maximal concentrations of *Salmonella* lipopolysaccharide (LPS). Concentrations 0.25 mg/ml of the purified arabinogalactan isolated from cultures of suspension cells of *Echinacea purpurea* (Wagner *et al*. 1988) were required to enhance the cytokine production of macrophages to levels equal to (interferon-beta) or 20% (IL-1) of those achieved with maximal concentrations of *Escherichia coli* lipopolysaccharide (0.010 mg/ml).

In vivo

Animal studies using i.v. EPS (0.01 mg/ml) demonstrated enhanced phagocytosis (27%) (Wagner *et al*. 1985). Arabinogalactan injected i.v. into mice exhibited enhanced resistance against systemic infections with *Listeria monocytogenes* and *Candida albicans* in both normal (Roesler *et al*. 1991) and immunocompromised (Steinmüller *et al*. 1993) animals. Oral administration of a polysaccharide fraction from *Echinacea purpurea* aerial parts (125, 1000, 3000 mg/kg/day, which is much more than in the recommended human dosage) had no effect on lung macrophage function in normal rats (Goel *et al*. 2002).

Caffeic acid derivatives

In vitro

In a granulocyte assay, cichoric acid concentrations between 10 and 100 ng/ml caused strong stimulation of phagocytosis (Bauer *et al*. 1989).

In vivo

Cichoric acid in concentration 10^{-3} – 10^{-6} mg/ml enhanced carbon clearance in mice (Bauer *et al*. 1989).

Alkamides

In vitro

The upregulation of TNF-alpha mRNA by *Echinacea* alkylamides (1-5 µM) was found to be mediated by cannabinoid receptor CB2, increased cAMP (cyclic adenosine monophosphate), p38/MAPK (protein 38/ mitogen activated protein kinase) and JNK (Jun N-terminal kinase) signalling pathways, as well as NF-kappa (nuclear factor kappa B) and ATF-2/CREB-1 (activating transcription factor-2/ cAMP responsive element binding protein-1) activation (Gertsch *et al*. 2004).

In vivo

A purified non-polar fraction enriched in alkamides, isolated from *Echinacea purpurea* and *Echinacea angustifolia* roots, (10 ml/kg 3-times a day for 2 days of a solution that contained 1 mg of alkamid-fraction in 30 ml) enhanced phagocytosis in the carbon clearance test by 1.5 to 1.7 fold (Bauer *et al*. 1989).

A purified alkamide fraction administered orally to rats was found to enhance the phagocytic activity and phagocytic index of lung alveolar macrophages. In addition, alveolar macrophages collected from alkamide-treated rats produced more TNF-alpha and nitric oxide after stimulation with LPS *in vitro* than any other active component or the control (Goel *et al*. 2002).

Melanin

In vitro

Melanin as a tentative active constituent of *Echinacea purpurea* was shown to have immunostimulant activity (Pasco *et al*. 2005, Pugh *et al*. 2005). Ingestion of melanin by mice for four days *ex vivo* increased the production of interferon-gamma by spleen cells and IgA and interleukin-6 by Peyer's patch cells. The isolated melanin was an amorphous dark colour pigment (reddish brown and similar to pheomelanin), general insoluble in most solvents, bleaching by oxidizing agents (H_2O_2), and had pheomelanin-like solubility in alkali and phenol. Elemental analysis indicated about 50% carbon, 13% nitrogen, 7% hydrogen, 0.8% sulphur and 0.08% phosphorus. NF-kappa B/luciferase reporter gene based monocyte activation assay was used to screen for immunomodulatory activities of extracts. The EC_{50} value for *Echinacea* melanin was 1 µg/ml with maximal activation occurring at 10 µg/ml, while that of *Escherichia coli* LPS was 0.25 µg/ml. Monocyte activation by *Echinacea* melanin substantially increased the expression of cytokine mRNAs characteristic of this state. *Echinacea* melanin induced IL-1 mRNA expression to the same extent as maximally activating concentrations of LPS.

Other or non-specified plant parts/species

In vitro

The dry residue of an ethanolic extract of *Echinacea purpurea* root showed a maximum phagocytosis stimulation of 33% in the granulocyte smear test at the concentrations of 1-100 µg/ml. Higher dilutions did not show any effect. The ethanolic extract was separated into a polar (water) and non-polar (chloroform) fraction. The water-soluble fraction (10^{-3}%) caused a 42% phagocytosis stimulation and the chloroform fraction (10^{-3}%) 37% (Bauer *et al*. 1988a).

Effects of *Echinacea purpurea* (plant part not further specified) water-soluble extracts were on natural killer (NK) cells present in human peripheral blood mononuclear cells (PBMC). Flow cytometric methods were used to examine activation, cytotoxicity, NK-target binding, and killer cell frequency. Treatment of PBMC with *Echinacea* overnight resulted in the activation of CD69 expression and increase in mean fluorescence intensity in both the $CD16^+$ and $CD16^+CD56^+$ NK subsets. However, the frequency of

$CD16^+$ cells was decreased as well as the mean fluorescence intensity was down-regulated. NK cytotoxicity was increased 100% at the concentration of 0.1 µg/ml of *Echinacea* in a short time (4 h) assay. At the single cell level the frequency of $CD56^+$ NK-target conjugates increased and a plateau was reached after 30-60 min of incubation. Likewise, the frequency of $CD56^+$ killer cells in the conjugates was also significantly increased by *Echinacea*. There was a recruitment of non-conjugated $CD56^+$ cells into $CD16^+$ NK-target conjugates and activation of the NK-target non-killer conjugates into killer cells (Gan *et al*. 2003).

Echinacea herb and root powders (plant species not specified) were also found to significantly enhance the viability and/or proliferation of human peripheral blood mononuclear cells *in vitro* (Rininger *et al*. 2000).

In vivo

The dry residue of an ethanolic extract of *Echinacea purpurea* root was resolved in ethanol 90% (DER 1:10) and given to mice (p.o.; dosage equals 17 mg root/kg; 3 times daily for two days). In the carbon clearance test, the administration lead to a 3-fold increased phagocytosis in relation to the control group. The polar (water) fraction of this ethanolic extract lead to an 1.9-fold increased phagocytosis in relation to the control group (Bauer *et al*. 1988a).

The study of Currier & Miller (2000) was designed to assess the numbers/production of NK cells in the spleen and bone marrow of aging, normal mice, after dietary administration of 0.45 mg/day (dose/body weight being adjusted from assorted anecdotal and experimental studies in humans and a variety of rodents) of *Echinacea purpurea* root extract (14 days), or, after injection of thyroxin, a stimulant of NK cell function (10 days). The immunostimulating effect was studied on natural killer (NK) cells since these cells are active in spontaneous, non-specific immunity against neoplasms and virus-mediated infections. Aging mice were selected as a model animal, since at this stage of life, like humans, the above-mentioned afflictions increase in frequency. Immunoperoxidase labelling techniques, coupled with haematologic tetrachrome staining were used to identify NK cells in both the spleen (primary site of NK cell function) and the bone marrow (site of NK cell generation). Double immunofluorescence staining, employing propidium iodide, was used to assess NK cell lytic function. The results revealed that *Echinacea purpurea*, but not thyroxin, had the capacity to increase NK cell numbers in aging mice. This reflected on the increased new NK cell production in their bone marrow generation site, leading to an increase in the absolute numbers of NK cells in the spleen, their primary destiny. The *Echinacea purpurea*-mediated increase in NK cell numbers was indeed paralleled by an increase in their anti-tumour, lytic functional capacity.

3.1.5. Anti-inflammatory effects

Alkamides

In vitro

Alkamides from the roots of *Echinacea purpurea* were examined for anti-inflammatory activity in an *in vitro* model system (Clifford *et al*. 2002). Cyclooxygenase-I (COX-I) and cyclooxygenase-II (COX-II) inhibitory activities were assessed at pH 7 for alkamides isolated from *Echinacea purpurea* roots to compare inhibitory activities between the two cyclooxygenase isozymes. At 100 µg/ml, several *Echinacea purpurea* alkamides inhibited COX-I and COX-II enzymes in the range of 36-60% and 15-46%, respectively, as compared to controls.

Other herbal preparations, species

In vitro

5-lipoxygenase-inhibiting activity of extracts of five wild and three commercially used species of the genus *Echinacea* were investigated to characterise anti-inflammatory activity of *Echinacea* (Merali *et al*. 2003). The inhibition of the 5-lipoxygenase (5-LOX) enzyme of the arachadonic acid pathway was determined by HPLC detection of a direct metabolic product (LTB4) of 5-LOX derived from stimulated rat basophilic cells. Root extracts of the three commercial species of *Echinacea* (*Echinacea purpurea*, *Echinacea pallida* var. *angustifolia*, *Echinacea pallida* var. *pallida*) inhibited the 5-LOX enzyme.

3.1.6. Antioxidative effects

Pressed juice

In vivo

Dried pressed juice from *Echinacea purpurea* whole plants significantly ($p < 0.05$) elevated superoxide dismutase activity when given to a mice in a dose of 360 mg/kg every other day for 3 weeks (Mishima *et al*. 2004).

Other herbal preparations, plant species, constituents

In vitro

The radical scavenging activity of methanolic extracts from the roots of different *Echinacea* species and isolated phenolic compounds was evaluated *in vitro* with a spectrophotometric method based on the reduction of an alcoholic 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical solution at 517 nm in the presence of a hydrogen donating antioxidant (Pellati *et al*. 2004). Among the pure compounds, echinacoside had the highest capacity to quench DPPH radicals (EC_{50}=6.6 µM), followed by cichoric acid (8.6 µM) and cynarin (11.0 µM). Chlorogenic acid, caffeic acid and caftaric acid had lower activity (18.9 µM, 19.1 µM and 20.5 µM, respectively). The average EC_{50} values for *Echinacea purpurea*, *Echinacea pallida* and *Echinacea* angustifolia were 134, 167 and 231 µg/ml, respectively.

Caffeic acid derivates

In vitro

Caffeic acid derivates protected collagen from free radical-induced degradation in a dose dependent manner; the IC_{50} for cichoric acid was 16.5 µM (Facino *et al.* 1995).

3.1.7. Antifungal effects

Other or non-specified plant parts/species

In vitro

Isobutylamides and polyacetylenes from *Echinacea purpurea* have phototoxic antimicrobial activity against fungi, including clinically relevant pathogenic fungi. A hexane extract of *Echinacea purpurea* herb inhibited the growth of yeast strains of *Saccharomyces cerevisiae, Candida shehata, Candida kefyr, Candida albicans, Candida steatulytica* and *Candida tropicalis* under near UV irradiation (phototoxicity) and to a lower extent without irradiation in the conventional antifungal activity (Binns *et al*. 2000).

Alkamides

In vitro

For trideca-1,11-dien-3,5,7,9-tetrain and trideca-1-en-3,5,7,9,11-pentain, both main alkylamides from *Echinacea purpurea*, a fungistatic effect was described. The following inhibiting concentrations were determined: *Aspergillus niger* >0.01% and/or 0.1%; *Candida albicans* 0% and/or 0.2%, respectively (Reisch *et al*. 1967).

3.1.8. Safety Pharmacology

No studies are available.

3.1.9. Pharmacodynamic Interactions

No studies are available.

Theoretically it can be expected, that *Echinacea* preparations could interact with immunomodulatory therapy (immunostimulatory and immunoinhibitory). However, no clinical cases of drug interactions have been reported (Izzo & Ernst 2001, Izzo & Ernst 2009).

3.1.10. Conclusions

There are many non-clinical studies available with *Echinacea purpurea*, but there relevance is not clear. Since the mechanism by which the clinical effect is achieved (treatment and short term prevention of common cold) is not known, it was not possible to classify pharmacodynamic studies into primary and secondary pharmacodynamics. Demonstrated antiviral and immunomodulatory effects could be connected to the indication, but also antibacterial, antifungal and antiinflamatory action could contribute to the clinical effect. Nevertheless the relevance of most findings is low, since the studies were performed with different herbal preparations (different plant part, extracts), *in vitro/in vivo* correlation is questionable due to low bioavailability (polysaccharides and cichoric acid) and the doses used in the studies are usually higher than in clinical practice or they cannot be compared due to incomplete reports.

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

Pharmacokinetics of caffeic acid and related hydroxycinnamates (Bourne & Rice-Evans 1998, Westendorf & Czok 1978) and of alkamides were studied *in vivo* and *ex vivo* (in cell cultures).

Studies of transport of alkamides trough a cultured monolayer of colonic cells (Jager *et al*. 2002) were performed on human adenocarcinoma colonic cell line Caco-2 (ATCC) as a model to assess the epithelial transport of dodeca-2*E,*4*E,*8*Z,*10*E/Z*-tetraenoic acid isobutylamides. Thirty minutes after apical loading of 25 µg/ml, about 15% of these alkamides were detectable on the basolateral side.

Close monitoring of the transport during 6 hours revealed a nearly complete transport to the basolateral side after 4 hours and no significant metabolism was observable. Transport experiments performed at 4 °C showed only a slight decrease in transport, which is a strong hint that dodeca-2*E,*4*E,*8*Z,*10*E/Z* -tetraenoic acid isobutylamides cross biological membranes by passive diffusion. Nearly the same results were obtained after the preincubation of Caco-2 cells with lipopolysaccharides (LPS) or phorbol 12-myristate-13-acetate (PMA) to mimic an inflammatory status. These results

supported the assumption that the alkamides could be easily transported from the intestinum and hence may contribute to the *in vivo* effects of *Echinacea* preparations.

Permeability of alkylamides and caffeic acid conjugates through Caco-2 cell monolayer model was studied again in 2004 (Matthias *et al*. 2004). Caffeic acid conjugates (caftaric acid, echinacosides and cichoric acid) permeated poorly through the Caco-2 monolayers although their potential metabolite, cinnamic acid, diffused readily with apparent permeability of 10^{-4} cm/s. Alkylamides were found to diffuse with apparent permeability ranging from 3×10^{-6} to 3×10^{-4} cm/s. Compounds with apparent permeability > 1×10^{-6}, are considered to have almost complete intestinal absorption.

Absolute and relative bioavailabilities of dodeca-2*E,*4*E,*8*Z,*10*E/Z* -tetraenoic acid isobutylamides (tetraens), administered as pure compounds or in the form of an *Echinacea purpurea* root extract preparation was studied by Ardjomand-Woelkart *et al*. (2011). Tetraens were administered orally by gavage or intravenously in a dose of 0.75 mg/kg to rats. The extract was administered orally in a dose of 158.6 mg/kg which corresponds to the same amount of tetraenes. Mean tetraen dose-normalised plasma areas under the concentration-time curve (AUC_0-∞/dose) were 3.24 ± 0.32 min · ng/ml/µg and 0.95 ± 0.16 min · ng/ml/µg after i.v. and oral administrations, respectively, and 1.53 ± 0.18 min · ng/ml/µg after oral administration of the *Echinacea* root extract. The absolute oral bioavailability of tetraens was 29.2 ± 2.3%, which was increased to 47.1 ± 7.2% (1.6-fold) by administration of the *Echinacea* extract. Administration of an *Echinacea* extract increased blood exposure with no impact on C_{max}, but prolonged the elimination half-life to 123.3 ± 15.7 min in comparison to 35.8 ± 6.5 min after administration of the pure dodeca-*2E,*4*E*,8*Z*,10*E/Z*-tetraenoic acid isobutylamides.

Matthias *et al*. (2005b) have investigated the metabolism of the alkylamides by human liver microsomes. No significant degradation of alkylamides was evident in cytosolic fractions. Time- and NADPH-dependent degradation of alkylamides was observed in microsomal fractions suggesting they are metabolised by cytochrome P450 (P450) enzymes in human liver. Pure synthetic 2-ene alkylamides inhibited the degradation of 2,4-diene alkylamides.

The dose-dependent pharmacokinetics of caffeic acid were studied on rabbits (Uang & Hsu 1997). Three different doses (5, 10 and 25 mg/kg) were administered intravenously to six rabbits each. The concentration-time profiles for caffeic acid could be fitted by a two-compartment model for each dose. The results showed that total-body clearance and elimination rate constant from the central compartment (k10) after a 5 mg/kg dose were greater than those after the other two doses. Furthermore, the terminal elimination half-life (beta half-life) and mean residence time (MRT) after a 5 mg/kg dose were less than after the other doses. The AUC value increased linearly with dose within the range of 10-25 mg/kg. Most of the unchanged caffeic acid was excreted in the urine within 2 h. The percentage of unchanged caffeic acid excreted in the urine was 63, 60, and 55% after doses of 5, 10 and 25 mg/kg, respectively, which were not significantly different. However, significant differences in the renal clearances and renal excretion rate constants were observed with a 5 mg/kg dose compared to the other doses. On the other hand, nonrenal clearances and nonrenal excretion rate constants showed no dose-related differences. The differences observed in total-body clearance, k10, beta halflife, and MRT between a 5 mg/kg dose and the other doses can be explained on the basis of the differences in renal clearance and renal excretion rate constants.

3.2.1. Pharmacokinetic interactions

The interaction potential of *Echinacea purpurea* (the article states, that the herbal preparation was an extract, but the commercial preparation used was declared as juice in other literature (DER 1.7-2.5:1)) towards P-gp mediated drug transport was studied in human intestinal Caco-2 cells (Hansen & Nielsen

2009). Digoxin (30 nmol) was used as a substrate and verapamil as a control inhibitor. Ethanol, 0.8%, needed for herbal extraction and compatibility with the commercial products, inhibited the net digoxin flux by 18%. *Echinacea purpurea* influenced to a higher degree the B-A transport of digoxin than the A-B transport. A minor increase in net digoxin flux was observed at low concentrations of *Echinacea purpurea*, an effect anticipated to be allosteric in nature. At higher concentrations, from 0.4 to 6.36 mg dry weight/ml, a statistically significant linear dose-related decrease was observed in the net digoxin flux, indicating a dose dependent *Echinacea purpurea* inhibition of P-glycoprotein. Both V_{max} and K_m of the net digoxin flux, calculated to 23.7 nmol/cm^2/h and 385 µm, respectively, decreased in the presence of *Echinacea purpurea* in an uncompetitive fashion. Although the effects of *Echinacea purpurea* on systemic P-glycoprotein mediated drug transport are probably limited, an influence on drug bioavailability cannot be excluded.

In *in vitro* test *Echinacea purpurea* demonstrated mild inhibition of CYP3A4 activity with 7- benzyloxy-4-trifluoromethylcoumarin as the model substrate, but mild inducing effects in the presence of the model substrate resorufin benzyl ether. Little effect on CYP2D6 and moderate inhibition of CYP2C9 was seen with *Echinacea purpurea* (Yale & Glurich 2006).

Ethanolic extracts from fresh *Echinacea purpurea* roots were examined with regard to their ability to inhibit cytochrome P450 (2E1) mediated oxidation of p-nitrophenol *in vitro*. In addition, individual constituents of these extracts, including alkylamides and caffeic acid derivatives from *Echinacea purpurea*, were tested for inhibition using the same assay. Extract prepared with 95 % ethanol inhibited the P450 (2E1) by 29%, but extract prepared with 33% ethanol did not inhibit it at all. The alkylamides present in *Echinacea purpurea* showed significant inhibition at concentrations as low as 25 mM, whereas the caffeic acid derivatives had no effect (Raner *et al*. 2007).

Mrozikiewicz *et al*. (2010) have investigated potential influence of standardised *Echinacea purpurea* herb extract (DER not reported, not reported if the plant was fresh or dry, extraction solvent 60% ethanol) containing 3.7% polyphenolic compounds, on the mRNA expression level of major CYP450 enzymes using animal model. The level of mRNA expression in liver was analysed by real-time quantitative PCR using specific target primers for CYP450 genes. A significant increase of rat CYP2D1 and CYP1A1 expression level by 40% ($p=0.007$) and 80% ($p=0.01$), respectively was demonstrated. A weak inducing effect of the extract was observed for CYP1A2 by 16% ($p > 0.05$) compared with the control group. The levels of rat CYP3A1 and CYP3A2 mRNA were reduced by 41% ($p < 0.05$) and 25% ($p=0.001$), respectively. A weak inhibitory effect was observed for CYP2D2 by 15% ($p=0.008$) and CYP2C6 by 18% ($p=0.004$) after long application of the *Echinacea purpurea* herb ethanolic extract. CYP2D2 and CYP2C6 activities were also inhibited by extract but in a lesser degree than CYP3A1 activity. Moreover, very little or no inhibition was noted for CYP2E1 both after 3 and 10 days of treatment.

The *in vitro* CYP3A4 inhibition profiles of *Echinacea purpurea* (the article states that the herbal preparation was an extract but the preparation in the concerned product was declared as juice in other literature), was evaluated by three different substrates: 7-benzyloxy-trifluoromethylcoumarin (BFC), 7-benzyloxyquinoline (BQ) and testosterone (Hansen & Nielsen 2008). Testosterone metabolism showed a much lower CYP3A4 inhibition (IC_{50}=5394 µg/ml) compared to the fluorescent substrates BFC and BQ (IC_{50}=354 and 452 mg/ml, respectively). It is suggested that the substrate/assay-dependent effects may arise from a complex nature of *Echinacea purpurea* constituents, involving different CYP3A4 substrate binding sites.

Modarai *et al*. (2010) found, that inhibition of CYP3A4 is more than 50 fold lower with *Echinacea purpurea* herb juice (no further details available; IC_{50}=1.8 g/l), compared to *Echinacea purpurea* herba tincture (no further details available; IC_{50}=0.022 g/l) or to *Echinacea purpurea* herba et radix tincture

(65% V/V ethanol extract of fresh *Echinacea purpurea* herb (DER 1:12) and roots (DER 1:11), 95:5; IC_{50}=0.027 g/l). This was correlated to the content of the alkamides in these products.

Different preparations of *Echinacea angustifolia*, *Echinacea purpurea* and *Echinacea pallida* were investigated for their cytochrome P450 (CYP) interaction potential in rats (Ardjomand-Woelkart *et al*. 2012). Rats were assigned to the different study groups with various dosages, positive controls (ketoconazole, quinidine), or pure compounds (dodeca-2*E*,4*E*,8*Z*,10*E/Z* -tetraenoic acid isobutylamides; tetraenes). After pre-treatment with the different *Echinacea* preparations for 14 days, a cocktail of probe drugs for CYP enzymes (theophylline [CYP1A2], tolbutamide [CYP2C9], dextromethorphan [CYP2D6] and midazolam [CYP3A4]) was orally administered before blood sampling. Plasma levels of probe drugs and their metabolites were quantified before and 0.25, 0.5, 1, 2, 4, 6, 10 and 24h after a single dose of the probe cocktail. Some *Echinacea purpurea* preparations (details not given in this Congress Abstract) showed significant inhibitions in CYP1A2 activities. In addition, the tetraenes inhibited CYP1A2 with a geometric mean ratio (GMR) of 8.65 (7.72-9.68) for the AUC_{last} and 2.96 (2.59-3.39) for C_{max}. *Echinacea* preparations showed no inhibition in CYP3A4 and CYP2C9, and only a moderate or weak inhibition in CYP2D6 activities.

Oseltamivir is a prodrug that requires metabolic activation by the carboxylesterase. HPLC-DAD-ESI-MSD and fluorometric assays were used to determine if 50-pooled mixed gender human liver microsomes can mediate the formation of the active carboxylate metabolite and then if this reaction is affected by natural health products (Liu *et al*. 2010). Several products reduced the formation of the active drug. Extracts from *Echinacea* (*Echinacea purpurea*, 500 mg powder capsules, aerial parts of the plant, NRP 451) reduced the formation of the active drug by 10%. Ethanol (0.25%) reduced it by 40%. *In vitro* studies would suggest that there is the potential for some natural health products used by patients in response to pandemic A/H1N1 to reduce drug efficacy.

3.2.2. Conclusions

Many of the above reports show some (even statistical significant) inhibition of CYP activities by alkamides and extracts from *Echinacea purpurea*. The clinical relevance of this inhibition remains unclear. It appears that the expressed juice from *Echinacea purpurea* has much lower effect on CYP activities than *Echinacea purpurea* herba tincture or *Echinacea purpurea* herba et radix tincture.

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single-Dose Toxicity

Echinacea purpurea and in particular the expressed juice is toxicologically well examined. Acute intoxications are not reported and on the basis of the animal experimental data are not expected. After single p.o. or i.v. application of *Echinacea purpurea* expressed juice in dose of p.o. 15,000 mg/kg or i.v. 5,000 mg/kg on rats and p.o. 30,000 mg/kg or i.v. 10,000 mg/kg on mice the animals showed no abnormalities. Since no deaths were observed, the LD_{50} could only be determined by approximation method. The sections at the end of the experiments did not result in referring to organ changes (Mengs *et al*. 1991).

A mixture of polysaccharides from the herb of *Echinacea purpurea* and two polysaccharides, obtained from a cell culture medium of *Echinacea*, resulted after i.p. application on mice in LD_{50}-values of >2,500 mg/kg and/or >5,000 mg/kg. For the two pure polysaccharides (fucogalactoxyloglucan, acid arabino galactan) no toxicity was stated (Lenk 1989).

3.3.2. Repeat-Dose Toxicity

After 4 weeks of oral administration of *Echinacea purpurea* expressed juice in doses of 800, 2,400 or 8,000 mg/kg daily, male rats (2,400 and 8,000 mg/kg) showed a statistically significant fall in plasma alkaline phosphatase compared to control group of rats, while the females (2,400 and 8,000 mg/kg) showed a rise in prothrombin time compared to control. Since all the values were still within the range of physiological variation for the used strain of rats, and since there was no dose proportionality, no toxicological significance could be ascribed to these findings. All the other laboratory results, together with the body weights, food consumption, ophthalmoscopy, necropsy findings and histology failed to show any evidence of relevant differences between the groups receiving different doses of *Echinacea purpurea* juice and control (Mengs *et al*. 1991).

3.3.3. Genotoxicity

Lyophilised *Echinacea purpurea* expressed juice in concentrations from 8 to 5,000 µg/plate was examined. In the examined bacterial test systems on *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) with and without metabolic activation by the S9-fraction from liver of Arochlor-1254-treated rats no evidence of toxicity or mutagenicity was observed. In the mouse lymphoma assay with and without S9-fractions (up to 5,000 µg/ml), in the human lymphocyte assay (up to 5,000 µg/ml), and in the micronucleus assay (25,000 mg/kg) lyophilised *Echinacea purpurea* expressed juice showed no genotoxic effects or cell transformation effects (Mengs *et al*. 1991).

Neither significant dose-dependent sister chromatid exchange (SCE) inducing activity nor a clastogenic potency were observed in human lymphocyte culture, treated with neutral polysaccharide NFA 10 (concentrations up to 500 µg/ml), isolated from *Echinacea purpurea* tissue culture; neither in the short term nor in the long-term experiment (Schimmer *et al*. 1989).

Tsai *et al*. (2012) studied the mutagenic and antimutagenic effects of ethanol extracts obtained from freeze-dried *Echinacea purpurea* flowers containing: total phenols, caffeic acid derivatives, and cichoric acid 473.34 mg chlorogenic acid equivalents/g, 302.20 mg/g and 217.61 mg/g, respectively. The 50% ethanolic flower extract did not show toxicity and mutagenicity toward *Salmonella typhimurium* TA98 and TA100 with or without S9 mix. The ethanolic extract at 0.25-5 mg/plate exhibited a dose-dependent inhibitory effect against the mutagenicity of 2-aminoanthracene.

3.3.4. Carcinogenicity

So far no Guideline-conform investigations are present which would permit the evaluation of a cancer risk.

In a cell transformation test, expressed juice from *Echinacea purpurea* herb did not produce any morphological transformation of embryonic hamster cells (Mengs *et al*. 1991). *In vitro* model systems of this kind are gaining increasing credibility for the testing of carcinogenic potential, since there is good correlation between the results of such tests and of chronic whole-animal carcinogenicity studies. Because of the negative results of the experimental investigations for genotoxicity it is not necessary to carry out long-term carcinogenicity studies in mammals.

3.3.5. Reproductive and developmental Toxicity

No Guideline-conform preclinical data on reproductive and developmental toxicity of *Echinacea purpurea* is available.

A study on mice showed that the pregnancy-induced elevation in splenic lymphocytes was reduced by a diet containing *Echinacea purpurea* extract. Such diet also reduced the number of foetuses, although the diet started only after the pregnancy was established. None of the observed changes except for the pregnancy-induced elevation in immune function was significant (Chow *et al*. 2006).

Washed sperms were incubated with *Echinacea purpurea* (plant part and type of preparation not declared) or control medium. Parameters were measured on a Hamilton-Thorn analyser after 1, 4, 24, and 48 h at 37°C. High-concentration (8 mg/ml) *Echinacea* inhibited motility at 24 and 48 h and interfered with sperm enzymes (Ondrizek *et al*. 1999). These findings are difficult to interpret since there is a lack of detail regarding the preparation of *Echinacea purpurea* (in the article it is mentioned only that *Echinacea purpurea* is derived from the root of the purple coneflower) and their clinical relevance is questionable (Barnes *et al*. 2007).

3.3.6. Local tolerance

Data on local tolerance of *Echinacea purpurea* preparations are not available.

3.3.7. Immunotoxicity

There are no specialised immunotoxicity studies available for *Echinacea purpurea* preparations.

3.3.8. Conclusions

Substantial amount of toxicological investigations were performed, including genotoxicity. They indicate no safety concern for the use of *Echinacea* preparations at recommended doses and duration. Studies on reproductive toxicity and carcinogenicity are not available, therefore the use during pregnancy and lactation is not recommended.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on *Echinacea* preparations to support the proposed indications are very limited. Several pharmacological effects are reported, however since the mechanism by which the clinical effects are achieved is not known, the relevance of these findings cannot be assessed. The exact pharmacological mechanisms and active compounds for the effects still remain to be elucidated.

Pharmacokinetic data are very limited and are focused especially on alkamides. Results support the assumption that alkamides (in contrast with caffeic acid conjugates) can be easily transported from the intestine and hence may contribute to the *in vivo* effects of *Echinacea* preparations. Pharmacokinetic data concerning the cutaneous use do not exist.

Studies on metabolism suggest that alkamides of *Echinacea* are metabolised by cytochrome P450 and may effects the CYP450-mediated metabolism of other concurrently ingested pharmaceuticals. Comparative investigation showed that the expressed juice from *Echinacea purpurea* herb has much lower effect on CYP activities than *Echinacea purpureae* herba tincture. The clinical relevance of this activity remains unclear.

Toxicity of *Echinacea purpurea* herb is low. Available genotoxicity data on lyophilised *Echinacea purpurea* expressed juice showed no reason for concern about the safety of these herbal preparations. Appropriate preclinical data on reproductive toxicity and carcinogenicity are not available. Due to lack of data the use during pregnancy and lactation is not recommended.

4. Clinical Data

4.1. Clinical Pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s) / preparation(s) including data on relevant constituents

Stimulation of phagocytic activity and production of cytokines by oral application of a commercially available *Echinacea* preparation was studied in humans *in vivo* (Schwarz *et al*. 2002). Forty healthy male volunteers (ages 20-40 years) participated in the study. They received either a freshly expressed juice of *Echinacea purpurea* herb without roots (with 22% ethanol) or placebo juice using a double-blind placebo-controlled crossover design with two treatment periods of 14 days and a wash-out period of 4 weeks in between. Endpoints for immune stimulation were phagocytic activity of polymorphonuclear leukocytes and monocytes measured by flow-cytometry, production of tumour necrosis factor alpha (TNF-alpha) and interleukin-1 beta (IL-1 beta) by LPS-stimulated blood monocytes. *Echinacea purpurea* herb did neither enhance phagocytic activity of polymorphonuclear leukocytes nor that of monocytes when compared with placebo. The production of TNF-alpha and IL-1beta by immune cells isolated from volunteers treated with *Echinacea purpurea* herb did not increase. *Echinacea purpurea* herb decreased serum ferritin concentration (p=0.0005). All other laboratory and safety data remained unchanged. Authors concluded that other immunomodulatory effects may explain the benefits of *Echinacea* preparations in reducing duration and severity of upper-respiratory tract infections found in randomised, double-blind clinical trials (Schwarz *et al*. 2002).

In 2005 Schwarz *et al*. made further research on possible mechanism of action. They investigated whether or not oral *Echinacea purpurea* pressed juice (EPP) has any effect on important lymphocyte-subpopulations in a double-blind placebo controlled cross-over designed study (40 healthy volunteers) with two treatment periods of 14 days. After 1 week of treatment with verum the mean value of the total number of lymphocytes decreased slightly (6%, p=0:033) compared to the initial value. Treatment for 1 and 2 weeks with EPP had only minor effects on two of the 12 subtypes of lymphocytes. No significant changes were observed in the verum period for the following types of cells: T- and B-lymphocytes, $CD4^+$- and $CD8^+$-T-lymphocytes including the subgroups of ''naive'' and ''memory'' $CD4^+$-and $CD8^+$-T-lymphocytes as well as the natural killer cells. Using a modified version of the Wilcoxon–Mann–Whitney-U-test, which is claimed to be optimal for the evaluation of the results of studies with a cross-over design, a significant difference was found for the number of $CD8^+$-T-lymphocytes and natural killer cells corresponding to either a decrease during treatment with verum or an increase in the number of these cells in the placebo period. The small differences observed in the number of $CD8^+$-T lymphocytes and natural killer cells are only of questionable physiological relevance. Authors suggest that stimulation of certain parts of the lymphocyte system by *Echinacea* preparations observed in *in vitro* experiments or following parenteral application of the drug are caused by direct contact of the constituents with the cells of the immune system under investigation, a feature which markedly differs from the situation when *Echinacea* preparations are given orally (Schwarz *et al*. 2005).

Echinacea preparation (commercial product, tablets, *Echinacea purpurea* herb and root and *Echinacea angustifolia* root, no further details available) was given to healthy volunteers (n=6) and gene expression in their blood cells was examined). *In vivo*, many lymphokines were down regulated, but the expression of interferon-alpha steadily rose, consistent with an antiviral response (Randolph *et al*. 2003).

Ability of *Echinacea purpurea* to prevent or to relieve experimental infection with rhinovirus type 39 (RV-39) was evaluated in a randomised, double-blind, placebo-controlled clinical trial (Sperber *et al*. 2004). Forty-eight previously healthy adults received pressed juice of the above-ground plant parts of *Echinacea purpurea* placed in a 22% alcohol base (DER 1.5-2.7:1) or placebo, 2.5 ml 3 times per day, for 7 days before and 7 days after intranasal inoculation with RV-39. Symptoms were assessed to evaluate clinical illness. Viral culture and serologic studies were performed to evaluate the presence of rhinovirus infection. A total of 92% of *Echinacea* recipients and 95% of placebo recipients were infected. Colds developed in 58% of *Echinacea* recipients and 82% of placebo recipients (p=0.114, by Fisher's exact test). Administration of *Echinacea* before and after exposure to rhinovirus did not significantly decrease the rate or the severity of infection; however, the trend of beneficial effect of *Echinacea* was shown in nearly all measured parameters: mean score of sore throat was 1.04 in *Echinacea* group and 2.45 in placebo group, mean score of congestion was 1.87 in *Echinacea* group and 2.66 in placebo group, mean score of headache was 0.63 in *Echinacea* group and 0.92 in placebo group. Mean total symptom score was lower in *Echinacea* group than in placebo group on every individual day of the trial. Authors concluded that because of the small sample size, statistical hypothesis testing had relatively poor power to detect statistically significant differences in the frequency and severity of illness.

Similarly, effectiveness of *Echinacea* for prevention of experimental Rhinovirus colds was not statistically significant in an earlier study (Turner *et al*. 2000). Infection occurred in 44 and 57% and illness occurred in 36 and 43% of the *Echinacea*- and placebo-treated subjects, respectively.

Water-ethanol extracts of various parts of fresh herbs of *E. purpurea* (commercial product standardised to alkamides/cichoric acid/polysaccharides: 0.25/2.5/25 mg/ml) or placebo were administered to volunteers (n=150) at the onset of their cold for a period of 7 days, with 8 doses (5 ml/dose) on day 1 and 3 doses on subsequent days. Fasting blood samples were obtained before and during their colds. The decrease in total daily symptomatic score was more evident in the *Echinacea* group than in the placebo group (p<0.05). In the later part of the cold, the *Echinacea* treatment suppressed the cold-related increase in superoxide production by the neutrophils. These results suggested that the extract by eliciting free radical scavenging properties may have led to a faster resolution of the cold symptoms (Goel *et al*. 2005).

Polysaccharides purified from *Echinacea purpurea* tissue culture injected i.v. into patients undergoing chemotherapy for gastric cancer showed a lessening of leucopoenia (Melchart *et al*. 2002).

Assessors' conclusion

Activation of macrophages leading to enhanced phagocytosis and production of several cytokines found in vitro, failed to be confirmed in in vivo human studies for Echinacea puprurea herb juice. It was not confirmed that lymphocyte subpopulations were increased by oral application Echinacea purpurea pressed juice, either. It appears that stimulation of certain parts of the lymphocyte system by Echinacea preparations observed in in vitro experiments or following parenteral application of the drug are caused by direct contact of the constituents with the cells of the immune system under investigation, a feature which markedly differs from the situation when Echinacea preparations are given orally. Furthermore, the concentration/dose used in non-clinical studies was higher (although in most cases the exact comparison is difficult).

Administration of Echinacea purpurea herb juice before and after exposure to rhinovirus did not significantly decrease the rate or the severity of infection, but the trend of beneficial effect of Echinacea was shown in nearly all measured parameters.

Further studies are needed to clarify the mechanism(s) which are responsible for the beneficial effect of Echinacea preparations observed in clinical studies.

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

In a recent study (Goey *et al*. 2012) three cancer patients ingested 20 drops of a commercial extract of *Echinacea purpurea* (65% V/V ethanol extract of freshly harvested *Echinacea purpurea* herb (DER 1:12) and roots (DER 1:11), 95:5) three times daily for fourteen days. After the last ingestion in the morning of day 15, blood samples for pharmacokinetics of dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamides (DTAI) were drawn at t=0, 30, 60 and 120 min. For all three patients the plasma concentration–time curves showed a similar time course with a maximum plasma concentration of DTAI achieved at 30 min after ingestion. C_{max} was 0.04, 0.05 and 0.18 ng/ml for the three patients respectively.

Absorption of alkamides after oral application of *Echinacea purpurea* was studied (Dietz *et al*. 2001). One hour after oral application of 65 ml of *Echinacea purpurea* (plant part is not declared) concentrated tincture, containing 4.3 mg of dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamides, it was possible to detect 44 ng of this alkamide per ml of human blood. An HPLC quantification method has been developed. Since the volume of distribution of the substance in the body is at least 5 litres, it can be calculated that at least 5% of alkamide was absorbed one hour after oral application.

Matthias *et al*. (2005a) have examined serial plasma samples from 9 healthy volunteers who ingested tablets manufactured from ethanolic liquid extracts of *Echinacea angustifolia* root and *Echinacea purpurea* root immediately after a standard high fat breakfast. Caffeic acid conjugates could not be identified in any plasma sample at any time after tablet ingestion. Alkamides were rapidly absorbed and were measurable in plasma 20 min after tablet ingestion and remained detectable for up to 12 h. The maximal concentrations for the sum of alkamides in human plasma were reached within 2.3 h post ingestion and averaged 336 +/- 131 ng eq/ml plasma. No obvious differences were observed in the pharmacokinetics in 2 additional fasted subjects. This single dose study provides evidence that alkamides are orally available and that their pharmacokinetics are in agreement with the one dose three times daily regimen already recommended for *Echinacea*.

There is a huge (more than 1000 fold) difference between the C_{max} in a study of Goey *et al*. (2012) and study of Matthias *et al*. (2005a). The reasons for the difference might be in different concentration and different types of alkamides (double bond vs. triple bond) present in *Echinacea purpurea* and *Echinacea angustifolia.* The studies also differed in the analytical method for alkamides (one isoform vs. sum of alkamides) and design (multiple doses vs. single dose).

Alkamide content in plasma samples obtained from a randomised, open, single-dose, crossover study after oral administration of a 60% ethanolic extract from the roots of *Echinacea angustifolia* to 11 healthy subjects was analysed by liquid chromatography electrospray ionisation ion-trap mass spectrometry (Woelkart *et al*. 2005). The maximum concentration of dodeca-2*E*,4*E*,8*Z*,10*E*/*Z*-tetraenoic acid isobutylamides, the main alkamides in the roots of *Echinacea angustifolia*, appeared already after 30 min and was 10.88 ng/ml for the 2.5 ml dose.

Interactions

Kommission E (1989), ESCOP (2003) and WHO (1999) monographs state no pharmacodynamic or pharmacokinetic drug interactions of any preparations (juice or extract) of *Echinacea purpurea* herb or isolated constituents in humans. Theoretically it can be expected, that *Echinacea* preparations could

interact with immunomodulatory therapy (immunostimulatory and immunoinhibitory). However, no clinical cases of drug interactions have been reported (Izzo & Ernst 2001, Izzo & Ernst 2009).

There is one pharmacokinetic drug interaction study of a standardised *Echinacea purpurea* fresh whole plant ethanol liquid extract 8:1 (250 mg) softgel capsules, containing standardised amounts of alkamides 0.25 mg/ml, polysaccharides 25.5 mg/ml and cichoric acid 2.5 mg/ml. The influence of this *Echinacea purpurea* preparation with 500 mg (two 250 mg capsules) 3 times/day for 28 days on the pharmacokinetics of lopinavir (400 mg)/ ritonavir (100 mg) twice/day and on CYP 3A and p-glycoprotein activity by using the probe substrates midazolam (8 mg) and fexofenadine (120 mg) as single doses, respectively, has been investigated. Thirteen volunteers received 14 days *Echinacea purpurea* in combination with lopinavir/ritonavir or 14 days *Echinacea purpurea* alone. Neither lopinavir nor ritonavir pharmacokinetics were significantly altered by 14 days of *Echinacea purpurea* co-administration, most likely due to the presence of the potent CYP3A inhibitor, ritonavir. A modest, but statistically significant decrease in midazolam exposure (−27%; p=0.008) and an increase in midazolam apparent oral clearance (37%; p=0.02) were observed. The half-life of midazolam was reduced by 45% after *Echinacea purpurea* administration, which trended toward statistical significance (P=0.051). C_{max} and T_{max} were unchanged by *Echinacea* administration. These results suggest induction of the CYP3A-mediated metabolism of midazolam by *Echinacea purpurea*. So, *Echinacea purpurea* induced CYP3A activity may cause modest decreases in plasma concentrations of other CYP3A substrates. The pharmacokinetics of fexofenadine, the p-glycoprotein probe substrate, did not significantly differ before and after *Echinacea purpurea* administration (p > 0.05) (Penzak *et al*. 2010).

In the last decade some investigations on *Echinacea purpurea* root and combination on *Echinacea purpurea* root with herb were also performed.

Clinical trial using 12 healthy volunteers (6 women, 6 men) revealed that the effects of *Echinacea purpurea* root on CYP activity were minor. Nevertheless, authors conclude that further study into the interaction potential of this botanical is merited (Gurley *et al*. 2004).

The effect of *Echinacea* (*Echinacea purpurea* root) on CYP activity *in vivo* was assessed by use of the CYP probe drugs caffeine (CYP1A2), tolbutamide (CYP2C9), dextromethorphan (CYP2D6), and midazolam (hepatic and intestinal CYP3A). Twelve healthy subjects (6 men) completed this 2-period, open-label, fixed-schedule study. Caffeine, tolbutamide, dextromethorphan, and oral and intravenous midazolam were administered before and after a short course of *Echinacea* (400 mg 4 times a day for 8 days) to determine *in vivo* CYP activities. *Echinacea* administration significantly increased the systemic clearance of midazolam by 34%, from 32 +/- 7 l/h to 43 +/- 16 l/h (p =0.003; 90% CI, 116%-150%), and significantly reduced the midazolam area under the concentration-time curve by 23%, from 127 +/- 36 µg*h/l to 102 +/- 43 µg*h/l (p =0.024; 90% CI, 63%-88%). In contrast, the oral clearance of midazolam was not significantly altered (p =0.655; 90% CI, 75%-124%), 137 +/- 19 l/h compared with 146 +/- 71 l/h. The oral availability of midazolam after *Echinacea* dosing was significantly increased (p =0.028; 90% CI, 108%-153%), from 0.23 +/- 0.06 to 0.33 +/- 0.13. Hepatic availability (0.72 +/- 0.08 versus 0.61 +/- 0.16; p =0.006; 90% CI, 73%-90%) and intestinal availability (0.33 +/- 0.11 versus 0.61 +/- 0.38; p =0.015; 90% CI, 125%-203%) were significantly altered in opposite directions. *Echinacea* dosing significantly reduced the oral clearance of caffeine, from 6.6 +/- 3.8 l/h to 4.9 +/- 2.3 l/h (p =0.049; 90% CI, 58%-96%). The oral clearance of tolbutamide was reduced by 11%, from 0.81 +/- 0.18 l/h to 0.72 +/- 0.19 l/h, but this change was not considered to be clinically relevant because the 90% CIs were within the 80% to 125% range. The oral clearance of dextromethorphan in 11 CYP2D6 extensive metabolisers was not affected by *Echinacea* dosing (1289 +/- 414 l/h compared with 1281 +/- 483 l/h; p =0.732; 90% CI, 89%-108%). *Echinacea* (*Echinacea purpurea* root) reduced the oral clearance of substrates of CYP1A2 but not the oral clearance of substrates of CYP2C9 and CYP2D6. *Echinacea* selectively modulates the catalytic activity

of CYP3A at hepatic and intestinal sites. The type of drug interaction observed between *Echinacea* and other CYP3A substrates will be dependent on the relative extraction of drugs at hepatic and intestinal sites. Caution should be used when *Echinacea* is co-administered with drugs dependent on CYP3A or CYP1A2 for their elimination (Gorski *et al*. 2004).

The study of Gurley *et al*. (2008) evaluated the effects of an *Echinacea* extract (combination of *Echinacea purpurea*: aerial, root and seed parts; *Echinacea angustifolia*: root parts) on the pharmacokinetics of digoxin, a recognised P-glycoprotein substrate. Eighteen healthy volunteers were randomly assigned to receive *Echinacea* (267 mg three times daily) supplement for 14 days, followed by a 30-day washout period. Subjects were also randomised to receive rifampin (300 mg twice daily, 7 days) and clarithromycin (500 mg twice daily, 7 days) as positive controls for P-glycoprotein induction and inhibition, respectively. Digoxin (0.25 mg) was administered orally before and after each supplementation and control period. Serial digoxin plasma concentrations were obtained over 24 h and analysed by chemiluminescent immunoassay. Comparisons of area under the curve (AUC_{0-3}), AUC_{0-24}), elimination half-life, and maximum serum concentration were used to assess the effects. *Echinacea* supplementation did not affect digoxin pharmacokinetics.

Pharmacokinetic and pharmacodynamic interactions of *Echinacea* (1275 mg four times daily containing a mixture of 600 mg of *Echinacea angustifolia* roots and 675 mg of *Echinacea purpurea* root; standardised to contain 5.75 mg of total alkamides per tablet;) with warfarin in healthy subjects were investigated (Abdul *et al*. 2010). This was an open-label, randomised, cross-over, clinical trial in healthy male subjects (n= 12) of known CYP2C9 and VKORC1 genotype who received a single oral dose of warfarin alone or after 2 weeks of pre-treatment with herbal medicine at recommended doses. Pharmacodynamic (INR, platelet activity) and pharmacokinetic (warfarin enantiomer concentrations) end points were evaluated. The apparent clearance of (S)-warfarin (90% CI of ratio; 1.01, 1.18) was significantly higher during concomitant treatment with *Echinacea* but this did not lead to a clinically significant change in INR (90% CI of AUC of INR; 0.91, 1.31). *Echinacea* significantly reduced plasma concentrations of S-warfarin. However, it did not significantly affect warfarin pharmacodynamics, platelet aggregation or baseline clotting status in healthy subjects.

The potential of *Echinacea purpurea* root extract to interact with etravirine, a nonnucleoside reverse transcriptase inhibitor of HIV was investigated (Moltó *et al*. 2012). Fifteen HIV-infected patients receiving antiretroviral therapy with etravirine (400 mg once daily for at least 4 weeks) were included. *Echinacea purpurea* root extract-containing capsules were added to the antiretroviral treatment (500 mg every 8 h) for 14 days. Etravirine concentrations in plasma were determined by high-performance liquid chromatography immediately before and 1, 2, 4, 6, 8, 10, 12, and 24 h after a morning dose of etravirine on day 0 and etravirine plus *Echinacea purpurea* on day 14. *Echinacea* was well tolerated, and all participants completed the study. The geometric mean ratio (GMR) for etravirine coadministered with *Echinacea purpurea* relative to etravirine alone was 1.07 (90% CI, 0.81 to 1.42) for the maximum concentration, 1.04 (90% CI, 0.79 to 1.38) for the area under the concentration-time curve, and 1.04 (90% CI, 0.74 to 1.44) for the concentration at the end of the dosing interval. In conclusion, the coadministration of *Echinacea purpurea* with etravirine was safe and well tolerated in HIV-infected patients; the data suggested that no dose adjustment for etravirine is necessary.

In a very similar study, Moltó *et al*. (2011) investigated the potential of *Echinacea purpurea* root extract, to interact with the boosted protease inhibitor darunavir-ritonavir. The geometric mean ratio (GMR) for darunavir coadministered with *Echinacea purpurea* root extract relative to that for darunavir alone was 0.84 (90% CI, 0.63-1.12) for the concentration at the end of the dosing interval, 0.90 (90% CI, 0.74-1.10) for the area under the concentration-time curve from 0 to 12 h, and 0.98 (90% CI, 0.82-1.16) for the maximum concentration. In summary, coadministration of *Echinacea purpurea* with

darunavir-ritonavir was safe and well tolerated. Individual patients did show a decrease in darunavir concentrations, although this did not affect the overall darunavir pharmacokinetics. Authors discussed that the lack of an interaction between *Echinacea* and darunavir-ritonavir found in the study may be explained, because patients were also receiving low doses of ritonavir which is a potent CYP3A4 inhibitor. This inhibition of CYP3A4 by ritonavir could mask the influence of *Echinacea* on CYP3A4 activity. If so, a remaining question is whether this lack of significant interaction between boosted darunavir and *Echinacea* would be reproducible in patients receiving other antiretroviral agents which are CYP3A4 substrates but not necessarily coadministered with ritonavir, such as nonnucleoside reverse transcriptase inhibitors or maraviroc (Moltó *et al*. 2011).

In a systematic review (Hermann & Richter 2012) it was found, that *Echinacea* is neither a potent nor a moderate inhibitor or inducer of cytochrome P450 (CYP) enzymes or P-glycoprotein (ABCB1). Weak effects in terms of either induction or inhibition were found (presystemic/hepatic CYP3A4 inhibition/induction, CYP1A2 and CYP2C9 inhibition at high daily doses of *Echinacea*). The authors advise caution when CYP3A4 substrates with low oral biavailability due to pronounced intestinal CYP3A4 metabolism such as verapamil, cyclosporine, or tacrolimus or narrow therapeutic index drugs cleared by CYP3A4, CYP1A2 or CYP2C9, such as warfarin or theophylline are coadministered with *Echinacea* supplementation.

Assessors' conclusion

None of the above reports refers to interaction of Echinacea purpurea herb alone or on Echinacea purpurea expressed juice preparations. The reports on other Echinacea species and/or other plant parts mostly did not show clinically relevant interactions. Nevertheless, it appears that Echinacea may modulate the catalytic activity of CYP3A at hepatic and intestinal sites and inhibit CYP1A2 and CYP2C9 at high doses. Further pharmacokinetic testing is necessary before conclusive statements can be made about Echinacea puprurea herb juice interactions in concomitant use of Echinacea and CYP3A4, CYP1A2 and/or CYP2C9 substrates.

4.2. Clinical Efficacy

4.2.1. Dose response studies

There are no dose-finding studies available for products containing only *Echinacea purpurea* herba.

In a study of Brinkeborn *et al*. (1999) the treatment with 7-fold higher dosage was only slightly more effective than treatment with 36 mg of dry extract of *Echinacea purpurea* herba 95% and radix 5%.

4.2.2. Clinical studies (case studies and clinical trials)

Most of the clinical studies are related to the immunological effect and recurrent infections of the upper respiratory tract.

Table 5: The list of the placebo controlled clinical studies with oral use of expressed juice of *Echinacea purpurea* herb on the treatment of infections of the upper respiratory tract. These studies were used to assess the indications, posology and safety.

Authors, year	**Patients (age)**	**Indication**	**Formulation**	**Dose (mode of administration)**	**Control**	**Efficacy**	**Safety**	**Comment**
Yale & Liu 2004	128 (18-62 years)	**Treatment** of the common cold	Freeze-dried pressed juice from the aerial parts of *E. purpurea*	100 mg 3 times daily For no longer than 14 days	Placebo (lactose)	**Not significant**	Well tolerated	Lower dosing than in other trials
Hoheisel *et al*. 1997	120 (38±11 years)	**Treatment** of URI "first signs of cold" "justifiable initial signs of acute upper respiratory infection"	*E. purpurea* expressed juice (DER 1.7-2.5:1)	20 drops every 2 hours for the first day and thereafter three times daily. (in half glass of water) For 10 days	Placebo "identical in colour and ethanol concentration"	**Significant:** median time of improvement was 4 days (*Echinacea*) and 8 days (placebo)	No specific adverse events Tolerability of placebo and *Echinacea* was equal	
Schulten *et al*. 2001	80 (39 ± 12 years)	**Treatment** of URI (subjective sensation of having a cold and at least one of the symptoms)	*E. purpurea*, pressed juice from fresh flowering purple coneflower (DER 1.7-2.5:1) stabilised by ethanol	5 ml twice daily For 10 days	Placebo "indistinguishable in terms of appearance, taste, smell, colour and packaging"	**Significant:** In *Echinacea* group the median time of illness was 6 days and in placebo 9 days	Well tolerated	
Taylor *et al*. 2003	407 children (5.5 ± 2.7 years)	**Treatment** of URI	*E. purpurea* herba dried expressed juice (extract?), (31.5-54.6:1?) dissolved to give 1:1 extract.	3.75 ml of syrup twice daily for children 2 to 5 years and 5 ml twice daily for children 6 to 11 years	Placebo "was identical in appearance and similar in taste and smell"	**Not significant**	No difference in overall rate of adverse events, rash occurred in 7.1% in *Echinacea* and 2.7% in placebo	The content of herbal substance in the syrup is not clear, late onset of treatment
Weber *et al*. 2005	401 children (2-11 years)	Reduction of risk of subsequent URI	23.4 mg/ml *E. purpurea* herba dried expressed juice (DER 31.5-53.6:1)	As above (medication only during first URI)	Placebo	28% decreased risk of subsequent URI (**p=0.01**, CI 8%-44%).		Follow up of patients from Taylor *et al*. (2003)

Table 6: The list of other clinical studies with expressed juice or extract of *Echinacea purpurea* herb or combinations thereof. These studies contributed especially to the assessment of safety.

Authors, year	**Admin.**	**Patients (age)**	**Indication**	**Formulation**	**Dose**	**Control**	**Efficacy**	**Safety**	**Comment**
Turner *et al*. 2000	p.o.	117 adults	Prevention of **experimental rhinovirus** colds	**not clear** (contained 0.16% cichoric acid with almost no echinacosides or alkamides)	300 mg 3 times daily For 14 days	Placebo	**not significant, but important trend:** Infection occurred in 44 and 57% and illness occurred in 36 and 43% of the *Echinacea*- and placebo group	No side effects were observed	Unknown species
Sperber *et al*. 2004	p.o.	48 (18-64 years)	Prevention of **experimental rhinovirus** colds	*E. purpurea* herba expressed juice (DER 1.7-2.5:1)	2.5 ml 3 times daily	Placebo	**Not significant, but important trend:** colds in 58% of *Echinacea* and 82% of placebo	Not different from placebo	Poor statistical power
Grimm & Müller 1999	p.o.	108 (40±16 years)	Prevention of URI	*E. purpurea*, (: fresh expressed juice of whole flowering plants of *E. purpurea* without roots (DER 1.7-2.5:1); contains 22% alcohol)	4 ml twice daily	Placebo	**Not significant, but important trend:** The average number of colds and respiratory infections per patient was 0.78 in the *Echinacea* group, and 0.93 in the placebo group.	Side effects were observed in 20% of *Echinacea* group and in 13% of placebo group. The majority of adverse events was mild and transient.	
Baetgen 1984	**i.m.**	170 children (0-13 years)	Treatment of pertusis	Expressed juice from *Echinacea purpurea* herb	2 ml/day in children 1 ml/day in infants	Active (antibiotic)	**No statistical analysis.** Reduction of disease duration in 34% of patients in *Echinacea* group and in 10% in antibiotic group.	Well tolerated	Intramuscular use

Authors, year	Admin.	Patients (age)	Indication	Formulation	Dose	Control	Efficacy	Safety	Comment
Baetgen 1988	**i.m.**	1280 children (0-19 years)	Treatment of URI	Expressed juice from *Echinacea purpurea* herb	2 ml/day in children 1 ml/day in infants	Active (antibiotic)	**No statistical analysis** Reduction of disease in 46% of patients in *Echinacea* group, in 16% in antibiotic group and in 25% in patients receiving combination of *Echinacea* and antibiotic.	"The injections were remarkably well tolerated."	Intramuscular use
Barrett *et al*. 2002	p.o.	148 students	Treatment of URI	*E. purpurea* herb (25%) and root (25%) and *E. angustifolia* root (50%) provided	4 capsules (containing 247 mg of *Echinacea*) 6 times during the first 24 hours of the study, and then 4 capsules 3 times daily For no longer than 10 days	Placebo	**Not significant**	Not different to placebo	Combination with roots and with other species
Heinen-Kammerer *et al*. 2005	p.o.	995 adults	Treatment of chronic recurrent respiratory disease	*E. purpurea* expressed juice		Standard therapy	The risk of recurrent illness was 2.3 fold lower and the duration of relapse 1.4 days shorter in *Echinacea* group.		Non-randomised study

Authors, year	Admin.	Patients (age)	Indication	Formulation	Dose	Control	Efficacy	Safety	Comment
Lindenmuth & Lindenmuth 2000	p.o.	95 adults	Early symptoms of cold or flu	Herbal tea (*Echinacea* species?)	5 to 6 cups per day	Placebo	**Significant** difference between the *Echinacea* and placebo group for all 3 questions measured (efficacy, number of days the symptoms lasted, and number of days for change; $p < 0.001$)	No negative effects reported by any of the subjects in either group	Species not declared
Melchart *et al*. 2002	**i.v.**	50 adults	Counteraction of the undesired effects of chemotherapy	Fraction isolated from the *Echinacea purpurea* herb cell cultures	2 mg of polysaccha-rides per day	Matched historical controls	53% increase in median number of leukocytes, no effects on phagocytic activity of granulocytes or on lymphocyte subpopulations	68 adverse events including two deaths were observed, most likely due to chemotherapy and the general condition of the patients	Open prospective study with matched historical controls
Vonau *et al*. 2001		50 adults	Recurrent genital herpes	65% V/V ethanol extract of freshly harvested *Echinacea purpurea* herb (DER 1:12) and roots (DER 1:11), 95:5, as dried extract		Placebo (cross-over)	Not statistically significant		Combination with roots

Authors, year	Admin.	Patients (age)	Indication	Formulation	Dose	Control	Efficacy	Safety	Comment
Brinkeborn *et al*. 1999	p.o.	246 (41±14 years)	Treatment of URI "immediately after the onset of the first symptoms of common cold"	65% V/V ethanol extract of freshly harvested *Echinacea purpurea* herb (DER 1:12) and roots (DER 1:11), 95:5, as dried extract	3 times daily 2 tablets containing 6.78 mg of extract No longer than 7 days	Placebo "could almost not be distinguished by smell or taste"	**Significant:** index of 12 symptoms reduced for 63% in *Echinacea* and for 29% in placebo	Treatments were well tolerated. Frequency of adverse events was not different in verum and placebo.	Combination with roots
Goel *et al*. 2004	p.o.	128 (18–65 years)	Treatment of URI "first symptoms related to common cold…"	Water-ethanol extracts of **various parts** of fresh herbs of *E. purpurea* (alkamides/cichoric acid/polysaccharides: 0.25/2.5/25 mg/ml)	4 ml 10 times per day on first day and 4 ml 4 times per day for next 6 days	Placebo	**Significant:** total daily symptom scores were 23.1% lower in the *Echinacea* than in placebo	Not different to placebo	Combination with other parts of the plant
Jawad *et al*. 2012	p.o.	755 (mean age: 23.6±7.8 years)	Prevention of common cold episodes	Alcoholic (57.3% m/m) extract from freshly harvested *E. purpurea* (95% herb (DER 1:12) and 5% roots (DER 1:11)	3 times 0.9 ml per day for illness prevention 5 times 0.9 ml per day during acute stages of colds	Placebo	non-sign. reduced number of cold episodes, sign. reduced episode days, sign. reduced pain-killer medicated episodes, sign. reduced enveloped virus infections, sign. reduction of recurrent infections	Non-inferior to placebo	Combination with other parts of the plant

Authors, year	Admin.	Patients (age)	Indication	Formulation	Dose	Control	Efficacy	Safety	Comment
Götte & Roschke 2001	p.o.	1,192 (minimum age 2 years, mean age 5.3 years)	Treatment of the common cold	Pressed juice from the aerial parts of *E. purpurea*	Children 2 - 5 years: 2.5 ml daily, 6-12 years 5.0 ml twice daily and over 12 years 5.0 ml three times daily. Duration of treatment: 10 days.	No	84.8% of the parents assessed the efficacy as very good or good.	In 59.8% the tolerability was assessed by physician as very good and in another 37.6% as good. The parents observed a very good tolerability in 53.2% and a good tolerability in another 42.3%.	Combination with other parts of the plant, uncontrolled study

Controlled randomised trials on medicinal products for oral use containing herbal preparations made of *Echinacea purpurea* herba recens

Yale & Liu (2004) tested the efficacy of a standardised preparation of *Echinacea purpurea* in reducing symptom severity and duration of the common cold, in a randomised, double-blind, placebo-controlled trial. 128 patients received either 100 mg of freeze-dried pressed juice from the aerial parts of *Echinacea purpurea* or a lactose placebo, 3 times daily until cold symptoms were relieved but not longer than 14 days. Symptoms (sneezing, nasal discharge, nasal congestion, headache, sore or scratchy throat, hoarseness, muscle aches, and cough) were scored subjectively (no information on score) by the patient and recorded daily. Patients were enrolled within 24 h of cold symptom onset. No statistically significant difference was observed between treatment groups for either total symptom scores (p range, 0.29-0.90) or mean individual symptom scores (p range, 0.09-0.93). The time of resolution of symptoms was not statistically different (p=0.73).

Hoheisel *et al*. (1997) carried out a randomised double-blind placebo-controlled trial on 120 patients with initial symptoms of acute, uncomplicated upper airways infection. The peroral treatment with either *Echinacea purpurea* expressed juice (commercial product, according to German authorities DER of preparation in the concerned product is 1.7-2.5:1) or placebo lasted for up to 10 days. The dosage was 20 drops every 2 h for the first day and thereafter three times daily 20 drops. Only two patients were excluded for protocol violation and all completed the study. Patients recorded subjective symptoms daily on a diary card. At the end of the 10-days treatment period, each subject was asked by the physician, using an itemised questionnaire about the cold symptoms including fever, improvement and duration of symptoms and tolerability of the therapy. The primary variables were the number of patients who reported that they had had a “real” cold (fully expressed symptoms of disease) and the time of improvement in each treatment group. The time of improvement was significantly shorter ($p < 0.0001$) in the *Echinacea* group than in the placebo group. In the sub-group of patients with „real” cold, i.e. fully expressed disease, the median time taken to improvement was 4 days (*Echinacea* group) and 8 days (placebo group). Average termination of treatment due to improvement was after 6 days (*Echinacea* group) and after 10 days (placebo group). The patients started the therapy at beginning of first signs of disease (before the “real” cold developed. In the *Echinacea* group only 24 patients experienced a "real" cold compared to 36 in the placebo group. Therefore this is a mixture of prevention and treatment trial.

No specific adverse events were reported. The findings demonstrated that early initiation of treatment with the expressed juice of *Echinacea purpurea* could reduce the development of the disease and significantly shorten the duration of the common cold and reduce the length of the treatment period required.

Schulten *et al*. (2001) recruited a total of 80 adult male or female patients with first signs of a cold in a randomised double–blind placebo-controlled trial with *Echinacea purpurea*, (EC3lJO) pressed juice from fresh flowering purple coneflower (DER 1.7-2.5:1) stabilised by ethanol, 5 ml twice daily for 10 days. The number of days of illness with a complete picture of the common cold (defined by the modified Jackson score of at least 5 points and experience of rhinorrhea and/or a subjective sensation of having a cold) was the primary end-point. In the verum group the median time of illness was 6 days compared to 9 days in the placebo group, assigning zero time for patients without a complete picture (one-sided p=0.0112). EC31J0 was well tolerated and clinically effective in alleviating symptoms more rapidly than placebo in patients with a common cold.

Clinical trials in children are described in 4.3.

Non-controlled and non-randomised trials, trials on combinations, and trials with parenteral use

Brinkeborn *et al*. (1999) evaluated the efficacy and safety of different doses and preparations of *Echinacea purpurea* in the treatment of common cold in a randomised, double-blind, placebo controlled study. 246 of 559 recruited healthy, adult volunteers caught a common cold and took 3 times daily 2 tablets of different *Echinacea purpurea* preparations. Group I got a preparation of 95% herba and 5% radix, group II got the same preparation as group I but at 7 times higher concentration, group III got a special *Echinacea purpurea* radix preparation an group IV got placebo tablets. Duration of treatment was until the patients felt healthy again but not longer than 7 days. Primary endpoint was the relative reduction of the complaint index defined by 12 symptoms during common cold according to the doctor's record. The preparations of group I and II were significantly more effective than the special root extract or placebo. Treatment with 7-fold higher dosage of group II was only slightly more effective than dosage of group I. The index of 12 symptoms reduced for 63%, 64% and 45% in group I, II and III, respectively and only for 29% in group IV (placebo). All treatments were well tolerated. Among the *Echinacea* groups the frequency of adverse events was not significantly higher than in the placebo group.

Barrett *et al*. (2002) assessed the efficacy of dried, encapsulated, whole-plant *Echinacea* as early treatment for the common cold in a randomised, double-blind, placebo-controlled community-based trial at University of Wisconsin, on 148 students with common colds of recent onset. Each active capsule contained a dried mixture of *Echinacea angustifolia* root (50% [123 mg]), *Echinacea purpurea* root (25% [62 mg]), and *Echinacea purpurea* herb (25% [62 mg]). *Echinacea* capsules also contained thyme (49 mg) and peppermint (31 mg) to disguise taste and flavour, as well as citric acid (3 mg) as a preservative. The placebo capsules contained 333 mg of alfalfa. The patients took four capsules six times during the first 24 h of the study, and four capsules three times each day thereafter until symptoms resolved, for a maximum of 10 days. Severity and duration of self-reported symptoms of upper respiratory tract infection were recorded. No statistically significant differences were detected between the *Echinacea* and placebo groups for any of the measured outcomes. Trajectories of severity over time were nearly identical in the two groups. Mean cold duration was 6.01 days in both groups as a whole, 5.75 days in the placebo group, and 6.27 days in the *Echinacea* group (between-group difference, -0.52 day [95% CI, -1.09 to 0.22 days]). After controlling for severity and duration of symptoms before study entry, sex, date of enrolment, and use of nonprotocol medications, researchers found no statistically significant treatment effect (adjusted hazard ratio, 1.24 [CI, 0.86 to 1.78]). Multivariable regression models assessing severity scores over time failed to detect statistically significant differences between the *Echinacea* and placebo groups.

Goel *et al*. (2004) studied the efficacy of a well standardised formulation containing alkamides, cichoric acid, and polysaccharides at concentrations of 0.25, 2.5, and 25 mg/ml, respectively, in reducing the severity and duration of symptoms of a naturally acquired common cold. The preparation is prepared from various parts of freshly harvested *Echinacea purpurea* plants (water-ethanol extraction). In a randomised, double-blind, placebo-controlled trial, 282 subjects aged 18 to 65 years with a history of two or more colds in the previous year, but otherwise in good health, were recruited. The subjects were randomised to receive either *Echinacea* or placebo. They were instructed to start the *Echinacea* or placebo at the onset of the first symptom related to a cold, consuming 10 doses the first day and four doses per day on subsequent days for 7 days. Severity of symptoms (10-point scale: 0, minimum; 9, maximum) and dosing were recorded daily. A nurse examined the subjects on the mornings of days 3 and 8 of their cold. A total of 128 subjects contracted a common cold (59 *Echinacea*, 69 placebo). The total daily symptom scores were found to be 23.1% lower in the *Echinacea* group than in placebo in those who followed all elements of the study protocol ($p < 0.01$).

Throughout the treatment period, the response rate to treatments was greater in the *Echinacea* group. The average of every individual symptom (runny nose, sore throat, stuffy nose, fatigue, headache, chills) except in cough was significantly lower in *Echinacea* group compared to placebo. In cough the difference was not significant. No differences in white blood cell differential count were observed between the treatment groups.

Grimm & Müller (1999) randomly assigned 108 patients with a history of more than 3 colds or respiratory infections in the preceding year to receive 4 ml *Echinacea purpurea* expressed juice (EC3IJO, DER 1.7-2.5:1) (54 patients) or 4 ml placebo-juice (54 patients) twice a day in a double-blind, randomised, prospective study. The incidence and severity of colds and respiratory infections were determined during 8 weeks of follow-up, based on patient reported symptoms together with findings on physical examination. The severity of each infection was graded by the investigators. During the 8-week treatment period 35 (65%) of 54 patients in the *Echinacea* group and 40 (74%) of 54 patients in the placebo group had at least one cold or respiratory infection. The average number of colds and respiratory infections per patient was 0.78 in the *Echinacea* group, and 0.93 in the placebo group. Median duration of colds and respiratory infections was 4.5 days in the *Echinacea* group and 6.5 days in the placebo group. Although the incidence, duration and severity of colds and respiratory infections tended to be lower in the *Echinacea* group, none of the results reached statistical significance. Side effects (Table 7) were observed in 11 patients (20%) of the *Echinacea* group and in seven patients (13%) of the placebo group. The majority of adverse events was mild and transient and did not require discontinuation of the allocated treatment. In the *Echinacea* group there were 4 drop-outs because of nausea, constipation, awful taste of the study medication and patients' choice without any specific reaction.

Turner *et al*. (2000) assessed the effectiveness of *Echinacea* for the prevention of experimental rhinovirus colds in a randomised double–blind placebo-controlled trial. The preparation is not well described in the publication. It contained 0.16% cichoric acid with almost no echinacosides or alkamides. Infection occurred in 44 and 57% and illness occurred in 36 and 43% of the *Echinacea*- and placebo-treated subjects, respectively. The effect on either the occurrence of infection or the severity of illness was not significant.

Sperber *et al*. (2004) studied the ability of *Echinacea purpurea* to prevent experimental infection with rhinovirus type 39 (RV-39) in a randomised double–blind placebo-controlled trial. Forty-eight previously healthy adults received pressed juice (DER 1.7-2.5:1) of the above-ground plant parts of *Echinacea purpurea* placed in a 22% alcohol base or placebo, 2.5 ml 3 times per day, for 7 days before and 7 days after intranasal inoculation with RV-39. Nine symptoms were assessed three times daily for 14 days to evaluate clinical illness. Viral culture and serologic studies were performed to evaluate the presence of rhinovirus infection. A total of 92% of *Echinacea* recipients and 95% of placebo recipients were infected. Colds developed in 58% of *Echinacea* recipients and 82% of placebo recipients ($p=0.114$ by Fisher's exact test). Seven-day total symptom score was 30.3% higher in placebo group ($p=0.317$). The most significant difference was in sore throat, which was 135.6% higher in placebo group compared to *Echinacea* ($p=0.065$). The differences between the *Echinacea* and placebo were not significant; however, because of the small sample size, statistical hypothesis testing had relatively poor power to detect differences in the frequency and severity of illness.

Jawad *et al*. (2012) investigated the safety and efficacy of alcohol extract from freshly harvested *Echinacea purpurea* (95% herb and 5% root) in the prevention of common cold episodes in a large population over a 4-month period. Seven hundred fifty-five healthy subjects received either *Echinacea* or placebo. Participants were required to record adverse events and to rate cold-related issues in a diary throughout the investigation period. Nasal secretions were sampled at acute colds and screened

for viruses. A total of 293 adverse events occurred with *Echinacea* and 306 with placebo treatment. 10% of participants in *Echinacea* and 10% in placebo group experienced adverse events, which were at least possibly related to the study drug. *Echinacea* reduced the total number of cold episodes (non-significantly), cumulated episode days (significantly), and pain-killer medicated episodes (significantly). *Echinacea* inhibited virally confirmed colds and especially prevented enveloped virus infections (significantly). *Echinacea* also showed (significantly) reduction of recurrent infections, and preventive effects increased with therapy compliance and adherence to the protocol.

Ross (2010) performed an open uncontrolled multicentre study on the efficacy and safety of *Echinacea purpurea* herb and root (each 750mg tablet contained 1200 mg of tincture mass: 95% herb (DER 1:12) and 5% roots (DER 1:11), extraction solvent 65 % V/V ethanol) in adult athletes (n=80). It was showed that the prophylactic efficacy after 8 weeks of treatment was very good (n=42; 52.5%) or good (n=19; 23.8%). The therapeutic efficacy in case of cold symptoms was very good in 73.5% of cases. The tolerability was high (very good n=68; 85%) (Schoop *et al.* 2006).

Reviews

An overview and quantitative meta-analysis of the published *Echinacea* trials was performed by Melchart *et al*. (1994), Dorsch (1996), Barrett *et al*. (1999), Giles *et al*. (2000), Bauer (2002), Barrett (2003), Barnes *et al*. (2005), Linde *et al*. (2006), Barnes *et al*. (2007). Most of the authors reviewed not only studies with *Echinacea purpurea* expressed juice but also extracts of *Echinacea angustifolia*, *Echinacea pallida* and in combination with other plant extracts or homeopathic dilutions administered via different routes and with different dosage regimens.

In the review of Melchart *et al*. 1994, 26 controlled clinical trials were identified, but the methodological quality of most studies was rated low. The authors concluded that clinical trials indicated that *Echinacea* preparations could be efficacious immunomodulators but the evidence was still insufficient for clear therapeutic recommendations and further methodologically sound, randomised clinical trials should be conducted.

Barrett reviewed 9 treatment trials and 4 prevention trials of sufficient quality. Eight of the treatment trials reported positive results and 3 of the prevention trials reported marginal benefit (Barrett *et al*. 1999).

Giles *et al*. reviewed 41 references and concluded that *Echinacea* appears to be well tolerated with a low frequency of adverse effect, such as mild dyspepsia, headache and dizziness (Giles *et al*. 2000). Evaluated studies support *Echinacea* in the treatment of URI, but not to prevent infection.

Bauer reviewed new clinical studies (Bauer 2002). The author summarised that corresponding preparations can diminish the severity and the length of common colds significantly, and that they can also be used efficiently for the treatment of children. Bauer also concluded, that the stimulation of macrophages and induction of cytokines are major parts of the mode of action and the glycoproteins/polysaccharides and alkamides are part of the activity relevant constituents.

Barrett (2003) concluded in his second review that the treatment of acute upper respiratory infections with *Echinacea purpurea* is tentatively supported by the available literature. Reduction of symptoms with early treatment has been reported in several moderate quality randomised controlled trials. Benefits appear to be a modest, with a 10 to 40% reduction of symptoms as the most widely reported outcome. Benefit as a cold preventative appears marginal, at best, with an estimated 5 to 15% effect size.

The authors of Cochrane Review Linde *et al*. (2006) concluded: "*Echinacea* preparations tested in clinical trials differ greatly. There is some evidence that preparations based on the aerial parts of

Echinacea purpurea might be effective for the early treatment of colds in adults but results are not fully consistent. Beneficial effects of other *Echinacea* preparations, and for preventative purposes might exist but have not been shown in independently replicated, rigorous randomised trials."

A new Cochrane review was made by Karsch-Völk *et al*. (2014) on studies with different *Echinacea* species, plant parts and preparations. The authors concluded: "*Echinacea* products have not here been shown to provide benefits for treating colds, although, it is possible there is a weak benefit from some *Echinacea* products: the results of individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance." The differences in the conclusions of Cochrane review and this Assessment report can be due to different scope, different legal framework and different method. The two clinical studies, which are most important for efficacy assessment in this Assessment report (Hoheisel *et al*. 1997, Schulten *et al*. 2001), were excluded from Cochrane analysis of primary efficacy outcome, since the primary outcome was not the same as they have selected (median disease duration vs. mean disease duration) or not all the collected data were reported in the article. The conclusion on the results of safety in the review was: "The number of patients dropping out or reporting adverse effects did not differ significantly between treatment and control groups in prevention and treatment trials. However, in prevention trials there was a trend towards a larger number of patients dropping out due to adverse events in the treatment groups." These results on drop outs are however based on studies with different *Echinacea* species, plant parts and preparations. Prevention trials were mostly long term prevention studies.

A thorough review and meta-analysis was made by Shah *et al*. (2007) evaluating the effect of *Echinacea* on the incidence and duration of the common cold. Fourteen unique studies were included in the meta-analysis. Incidence of the common cold was reported as an odds ratio (OR) with 95% CI, and duration of the common cold was reported as the weighted mean difference (WMD) with 95% CI. Weighted averages and mean differences were calculated by a random-effects model (Der Simonian-Laird methodology). Heterogeneity was assessed by the Q statistic and review of L'Abbé plots, and publication bias was assessed through the Egger weighted regression statistic and visual inspection of funnel plots. *Echinacea* decreased the odds of developing the common cold by 58% (OR 0.42; 95% CI 0.25-0.71; Q statistic $p < 0.001$) and the duration of a cold by 1.25 days (WMD -1.25, -2.21 to -0.29; $p=0.01$). Similarly, significant reductions were maintained in subgroup analyses limited to two commercial product use (expressed juice of *E. purpurea* DER 1.7-2.5:1), concomitant supplement use, method of cold exposure, Jadad scores less than 3, or use of a fixed-effects model. The authors concluded that published evidence supports *Echinacea*'s benefit in decreasing the incidence and duration of the common cold (Shah *et al*. 2007).

4.3. Clinical studies in special populations (e.g. elderly and children)

Use in children

Out of the 19 clinical trials reviewed in Tables 1 and 2 and discussed in 4.2.2., 4 were performed in children. The youngest children were included in the two studies by Baetgen (Baetgen 1984, Beatgen 1988) where the minimal age was 1 month. The average age was 3.5 years in one study and 2.8 years and 3.1 years for boys and girls, respectively in the other study.

Taylor *et al*. (2003) studied the efficacy of *Echinacea purpurea* (dried expressed juice from the above ground parts of the plant harvested at flowering) in reducing the duration and/or severity of URI symptoms in children. The design of this study was randomised, double-blind, placebo-controlled trial of healthy children 2 to 11 years old (mean 5.5 years, standard deviation 2.7 years) recruited from a regional practice-based network and an alternative medical centre in 4-month periods from 2000 through 2002. Patients were randomised to receive either *Echinacea* or placebo for up to 3 URIs over a

4-month period. Study medication was begun at the onset of symptoms and continued throughout the URI, for a maximum of 10 days. Four point Likert scale was used for evaluation of results. Data were analysed on 707 URIs that occurred in 407 children, including 337 URIs treated with *Echinacea* and 370 with placebo. There were 79 children who completed their study period without having an URI. The median duration of URIs was 9 days (95% confidence interval, 8-10 days); no difference in duration between URIs treated with *Echinacea* or placebo was found (p=0.89). No difference in the overall estimate of severity of URI symptoms between the 2 treatment groups (median, 33 in both groups; p=0.69) was found. There were also no statistically significant differences between the 2 groups for peak severity of symptoms (p=0.68), number of days of peak symptoms (1.60 in the *Echinacea* group and 1.64 in the placebo group; p=0.97), number of days of fever (0.81 in the *Echinacea* group vs. 0.64 in the placebo group; p=0.09), or parental global assessment of severity of the URI (p=0.67). Overall, there was no difference in the rate of adverse events reported in the 2 treatment groups. However, rash occurred during 7.1% of the URIs treated with *Echinacea* and 2.7% of those treated with placebo (p=0.008). In this study adverse events were found in 45.1% of patients receiving *Echinacea* (and in 39.5% of patients receiving placebo). The most frequent adverse events were: stomach ache, diarrhoea, drowsiness, headache, "hyper" behaviour, rash and vomiting. Rash was the only side effect that was significantly more frequent in *Echinacea* group compared to placebo. The authors of the study concluded that *Echinacea purpurea*, as dosed in this study, was not effective in treating URI symptoms in patients 2 to 11 years old, and its use was associated with an increased risk of rash.

There were many critics on this study published in scientific literature (Kim *et al*. 2004, Firenzuoli & Gori 2004, Washam 2004, Le Tourneau 2004, Blumenthal 2004) and one answer of the authors (Taylor *et al*. 2004). The main critics were that the dosage of *Echinacea* extract in the product was not stated and the product was not standardised. Additional weakness of the study was that the placebo group used significantly more vitamins and mineral supplements. The patients started to take medication very late. The parents were asked to call coordinator of the study, when at least 2 symptoms of a URI developed, and they started to take medication after the coordinator confirmed that the child met criteria for having a URI. Barrett (2004) published a comment supporting the quality of Taylor's study.

Weber *et al*. (2005) made a follow up of the patients from the study of Taylor *et al*. (2003). The aim of this study was to determine whether *Echinacea purpurea* (23.4 mg/ml *E. purpurea* herba dried expressed juice (DER 31.5-53.6:1)) given to children for the treatment of acute upper respiratory tract infection (URI) was effective in reducing the risk of subsequent URI. A total of 524 children ages 2 to 11 years were enrolled in the study. Children were monitored for URIs over a 4-month observation period during the fall/winters of 2000-2001 and 2001-2002. At entry the children were randomised to receive *Echinacea* or placebo to treat acute URIs during the observation period. The occurrence of a second URI and the number of days between the end of the first URI and the start of the second URI was ascertained. Survival and Cox regression analyses were used to determine whether children who took *Echinacea* for their URIs were less likely to develop subsequent URIs. Among the 401 children with at least one URI treated with study medication, 69.2% of those receiving placebo developed a second URI versus 55.8% of those who received *Echinacea*. Use of *Echinacea* was associated with a 28% decreased risk of subsequent URI (p=0.01, 95% confidence interval 8%-44% decreased risk). *Echinacea purpurea* may be effective in reducing the occurrence of subsequent URIs in children.

Götte & Roschke (2001) made an observation in children with recurring infections of the upper respiratory tract to assess the tolerability and efficacy of (alcohol free pressed juice from the aerial parts of *Echinacea purpurea*). A good to very good tolerability and efficacy was found in children above the age of two years and in young adults. Three hundred thirty-eight paediatricians treated 1,327 children and young adults with recurring infections of the upper respiratory tract. Only children who

had been affected by at least two infections of the respiratory tract during the past twelve months were included in the observation. The children had to be at least 2 years of age and show recurring signs and symptoms of a respiratory tract infection. At conclusion of the treatment, the tolerability was assessed with the aid of the recorded adverse drug reactions and the global assessment by the physician and the parents of the patients. The considered symptoms were specified on the observation form (sneezing, running nose, blocked nose, sore throat, cough, headache, feeling of illness and chili). Furthermore, the physician and parents evaluated the duration of the respiratory tract infection in historical comparison to the duration of illness without treatment with the juice. A total of 1,322 children and young adults - males and females - were included in the assessment of efficacy. All patients who had taken the juice at least once were included. A total of 5 patients were excluded from the analysis of tolerability, because they had not shown up for the final examination and no data regarding the assessment of tolerability had been recorded for them. The evaluation of efficacy involved 1,192 children and young adults, 579 females and 609 males. In four cases, the data on sex were missing. On average, the juice was administered to the patients over a period of 11 days. The results obtained from this observation of use, with doses adjusted according to age, revealed a good to very good tolerability and efficacy. In more than 95% of cases, the physician and parents globally assessed the tolerability as good or very good. More than 60% of the treating physicians and parents reported that the duration of the respiratory tract infection was shorter in comparison to the duration of disease without treatment with the juice. The efficacy was rated by the physician as well as by the parents as very good or good in more than 80% of the cases. In comparison to treatment without the juice, the physician observed in this respiratory tract infection a shorter duration of disease in more than 60% and the course of disease was rated as less severe in more than 70% of all patients. The parents of the children and young adults made comparable assessments.

Baetgen (1984) compared the therapy i.m. injection of 1-2 ml of diluted *Echinacea purpurea* expressed juice alone or in combination with antibiotics on three successive days for the treatment of pertussis, in a retrospective study of 170 children. In about one third of cases (35%) the duration of pertussis could be reduced to five days by giving i.m. injections of *Echinacea* expressed juice. In 81% of cases the reduction of duration was to 10 days.

A combination of *Echinacea* and antibiotic is not equally effective. Out of this group of 77 patients only 9% improved within 5 days and 53% within 10 days of treatment. But the combination is superior to treatment with an antibiotic alone. Only 10% of the patients treated with antibiotics alone improved within 5 days and 46% within 10 days. Injections of *Echinacea* have been tolerated well; temperature rises up to 39°C on the day of treatment were only seen in isolated cases. Erythema and localised pain at the injection site were occasionally reported.

Baetgen (1988) obtained similar results in a comparative evaluation of 1,280 children suffering from bronchitis. In this retrospective evaluation it was demonstrated that 3 or 4 i.m. injections of *Echinacea purpurea* expressed juice can significantly shorten the duration of the infection in comparison with a group treated with antibiotics alone or with antibiotics plus *Echinacea purpurea* expressed juice. In *Echinacea* group 45.7% of patients improved in 5 days, in *Echinacea* + antibiotics and in antibiotics group the improvement was 25.5% and 16% respectively.

Information on 4 (unpublished) observational studies regarding the safety of the oral application of *Echinacea purpurea* herb preparations in different dosages for children below the age of 18 was submitted by German authority:

Four hundred fifteen children with a median age of 15 years, thereof 198 children below the age of 12 years, median age 8 years, suffering from acute respiratory tract infection received tablets containing 100 mg dried expressed juice of flowering herb of *Echinacea purpurea* (DER 22-65:1) for 2 weeks. Due

to the pharmaceutical form (tablets) the following posology for children (from 6-12 years of age) was used: 2-3 times 1 tablet and for adolescents (12-18 years of age) the adult posology. One exanthema, one nausea and one vomiting was observed, otherwise there were no reports concerning adverse events.

Three hundred and fifty-nine children thereof 357 in between 1-12 years (290 < 10 y; 67 > 11 y) suffering from acute respiratory tract infection received a liquid (100 ml containing 3.75 g dried expressed juice from fresh flowering herb of *Echinacea purpurea* (DER 22-65:1) for 2 weeks. 3 ml of the liquid correspond to 2.1 ml of fresh juice. Children from 6-11 years of age received 3-4 times 2 ml liquid daily (corresponding to 4.2-5.6 ml fresh juice). Reported adverse events were one bad taste and one generalised exanthema, which could be due to the infection as well.

One hundred forty children (0-1 year n=26; 1-4 years n=38; 4-12 years n=7 6) suffering from acute respiratory tract infection received daily doses as follows : 0-1 year - 1-2 times 2.5 ml; 1-4 years - 1-2 times 5 ml; 4-10 years - 2-3 times 5 ml and 10-12 years - 1 times 15 ml-2 x l0 ml of expressed juice of flowering herb of *Echinacea purpurea* (DER 1:0.65-0.85) for 2 weeks. 2 children dropped out due to the bad taste of the preparation. Adverse events were not reported.

Two hundred and seventy children (1-4 years n=140; 4-12 years n=130) suffering from acute respiratory tract infection received a liquid (100 g liquid contains 1.076 g dried expressed juice from fresh flowering *Echinacea purpurea* (DER 22-65:1; 10 ml liquid corresponds to 2.5 ml expressed juice). The posology was the following: 1-4 years - 2-3 times 5 ml liquid (average 14.4 ml liquid corresponding to 3.6 ml expressed juice); 4-12 years - 2-3 times 10 ml liquid (average 27.4 ml liquid corresponding to 6.85 ml expressed juice. The duration of treatment was 10 days. Eight children dropped out due to recovery, 10 drop outs were due to antibiotic treatment which was defined as elimination criterion, and one to bad taste. Adverse events reported one case of nausea and one bad taste.

Use in the elderly

In most clinical studies, the patients up to 65 years old were included (Hoheisel *et al*. 1997, Brinkeborn *et al*. 1999, Grimm & Müller 1999, Schulten *et al*. 2001, Turner *et al*. 2000, Barrett *et al*. 2002, Goel *et al*. 2004, Sperber *et al*. 2004, Yale *et al*. 2004).

No restrictions for elderly are known on the use of preparations from *Echinacea purpurea*.

Use in renal impairment

There are no reports on use of *Echinacea* in renal impairment.

4.4. Overall conclusions on clinical pharmacology and efficacy

Treatment

Based on positive results from randomised double blind placebo controlled clinical studies (Hoheisel *et al*. 1997, Schulten *et al*. 2001) which demonstrated that early initiation of treatment with the expressed juice of *Echinacea purpurea* for 10 days can significantly shorten the duration of the common cold and reduce the symptoms and the length of the treatment period required, and supported by other clinical studies, it can be concluded, that there is good clinical evidence on efficacy of expressed juice from *Echinacea purpurea*, herba recens for treatment of acute upper airways infection (common cold) in adults and adolescents.

Short term prevention

The efficacy of expressed juice from *Echinacea purpurea*, herba recens for short term prevention of upper respiratory disease can be seen from the study of Hoheisel *et al*. (1997) where the patients were instructed to take the medicine at the beginning of first signs of disease and where later the development of disease was examined by physicians. In the *Echinacea* group only 24 patients experienced a "real" cold compared to 36 in the placebo group.

Furthermore, the efficacy of prevention of common cold can be seen from the study of Weber *et al*. (2005) where short term use of *Echinacea purpurea* herb dried expressed juice decreased the risk of subsequent URI by 28% (p=0.01, CI 8%-44%).

Echinacea purpurea herb was also shown to prevent experimental infection with rhinovirus in clinical pharmacodynamic studies (see chapter 4.1.1).

Also meta-analysis made by Shah *et al*. (2007) concluded that *Echinacea* decreased the odds of developing the common cold by 58% (OR 0.42; 95% CI 0.25–0.71; Q statistic p<0.001) and the duration of a cold by 1.25 days (–2.21 to –0.29, p=0.01). Similarly, significant reductions were maintained in subgroup analyses limited to two commercial product (expressed juice of *E. purpurea* DER 1.7-2.5:1) use, concomitant supplement use, method of cold exposure, Jadad scores less than 3, or use of a fixed-effects model.

Published evidence supports *Echinacea*'s benefit in decreasing the incidence and duration of the common cold.

Preparations of *Echinaceae purpurea* (well-established use) were classified as “R05X Other cold preparations” according to the ATC code. This group comprises cold preparations with various ingredients, which cannot be classified in the other R05-groups and various remedies for symptomatic relief in cough and cold, e.g. inhalants with menthol, camphora, thymol etc. are also classified here. The mechanism of action is given with “not known”.

Based on literature data and clinical trials the following posology is recommended: 6-9 ml of expressed juice per day or equivalent amount of dried expressed juice, divided in 2 to 4 doses (adolescents, adults, elderly).

Since the efficacy of *Echinacea purpurea* herb juice is demonstrated in clinical trials where the medicine was administered for a maximum of 10 days, the duration of use is limited to this period.

The clinical trial by Taylor *et al*. (2003) failed to demonstrate reducing the duration and/or severity of URI symptoms in children. There are many drawbacks of the study but there is no other well-designed study with positive results. The clinical trials with i.m. application cannot support the well-established use of p.o. application.

There is no well-designed clinical study of *Echinacea purpurea* herb juice on long-term prevention of common cold with positive results.

So, the clinical evidence of efficacy for children, for long term prevention of common cold and for extracts is not sufficient for well-established use.

There is no clinical study on the efficacy of *Echinacea purpurea* herb juice ointment or other semi-solid or liquid preparations. Based on the long standing traditional use of *Echinacea purpurea* herb juice in liquid and semi-solid preparations, efficacy in treatment of small superficial wounds can be considered plausible.

Herbal remedies made from *Echinacea purpurea* in general appear to have a low potential to generate cytochrome P450 (CYP450) drug–herb interactions (presystemic/hepatic CYP3A4 inhibition/induction, CYP1A2 and CYP2C9 inhibition at high doses). The investigation on other *Echinacea* species and/or other plant parts mostly did not show clinically relevant interactions. There is no clinical study on interaction of *Echinacea purpurea* herb alone and on *Echinacea purpurea* herb expressed juice preparations, but preclinical investigation showed that inhibition of CYP3A4 is more than 50 fold lower with *Echinacea purpurea* herb juice compared to *Echinacea purpurea* herb tincture. Further pharmacokinetic testing is necessary before conclusive statements can be made about *Echinacea purpurea* herb juice interactions in concomitant use of *Echinacea* and CYP3A4, CYP1A2 and/or CYP2C9 substrates.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

In clinical studies preparations with *Echinacea purpurea* herb were very well tolerated. In most studies no specific side effects were observed or tolerability of placebo and *Echinacea* was equal.

In a multicentre uncontrolled study, a total of 1,231 patients with relapsing respiratory and urinary infections were treated for 4 to 6 weeks with *Echinacea purpurea* herb expressed juice. In 5% of patients adverse events were reported (Parnham 1996). The most frequently cited was an unpleasant taste of the study medication in 1.7% of patients, followed by nausea/vomiting (0.5%), recurrent infection (0.4%), sore throat (0.2%), abdominal pain (0.2%), diarrhoea (0.2%), difficulty in swallowing (0.2%), and other single reports (1.5%). The study was un-controlled, therefore it is not possible to assess, which events were due to placebo. The adverse events from long term use cannot be extrapolated to short term use. Nevertheless, the frequency of *Echinacea* related adverse events in short term use cannot be higher than frequencies found in this large scale study.

Table 7: Adverse reactions during 8 week use of *Echinacea* product in a study of Grimm & Müller (1999)

Adverse reactions	*Echinacea* Group (n=54)	Placebo Group (n=54)	p Value
Any	11 (20%)	7 (13%)	0.44
Central nervous system symptoms (tiredness, somnolence, dizziness, headache, tendency to aggressiveness)	4 (7%)	0 (0%)	0.12
Gastrointestinal symptoms (nausea or heartburn after intake, mild epigastric pain,constipation)	4 (7%)	4 (7%)	1.00
Increased urge for micturition	1 (2%)	1 (2%)	1.00
Sweating or paresthesia after intake	0 (0%)	2 (4%)	0.49
Eczema	1 (2%)	0 (0%)	1.00
Increased hair loss	1 (2%)	0 (0%)	1.00

None of the adverse reaction in *Echinacea* group was significantly different to placebo.

A systematic review, based on clinical studies, case reports and surveillance programmes of national medicines regulatory authorities and WHO (1999), concluded that *Echinacea* (species and plant part not defined) products have a good safety profile when taken in the short term, while data on long-term use is not available. If adverse events occur they tend to be transient and reversible, the most common being gastrointestinal or skin related. Gastrointestinal upsets and rashes occur most frequently. However, in rare cases, *Echinacea* can be associated with allergic reactions that may be severe (Huntley *et al*. 2005).

In a study with 407 children no difference in overall rate of adverse events was observed, the only different adverse effect between placebo and verum was rash (rash occurred in 7.1% of the *Echinacea* group and 2.7% of the placebo group) (Taylor *et al*. 2003).

There is no clinical trial on the topical use of *Echinacea purpurea* herb juice preparations in semi-solid or liquid dosage forms.

Assessors' conclusion

Adverse effects associated with clinical studies are infrequent, minor and similar to those noted for placebo. Rash was the only significantly different adverse effects between placebo and verum.

5.2. Patient exposure

Echinacea purpurea preparations have been marketed worldwide in large quantities.

More than 5,000 patients have been included in studies listed in Table 5 and Table 6. In many European and non-European countries medicinal products containing *Echinacea* are among the top selling/mostly used products.

Among a stratified random sample (n=15,985) of the adult members of the Kaiser Permanente Medical Care Program of Northern California it was the most used herb used by 14.7% (Schaffer *et al*. 2003). It was also the most used herb among Turkish students (n=1871), used by 38.6% (Ayranci *et al*. 2005). *Echinacea* is after *Salvia* and *Calendula* the third most used herb in Slovenia (Razinger-Mihovec 2007), and the fifth most used herb in Germany (Grünwald & Büttel 1996). In many countries products containing *Echinacea purpurea* herb are also available as food supplements.

5.3. Adverse events, serious adverse events and deaths

On the basis of the results of the investigations reviewed above, the preparations were well-tolerated without exception in the case of oral administration. In parenteral applications, localised symptoms and fevers occasionally occurred.

In rare cases hypersensitivity reactions e.g. skin reactions may occur (ESCOP 2003, Hänsel *et al.* 1993, Blumenthal *et al*. 2000, Mullins 1998). Individuals with allergic tendencies, particularly those with known allergy to other members of the *Asteraceae* family should be advised to avoid *Echinacea* (Barnes *et al*. 2007, Hänsel *et al.*1993).

In an analysis of the events of IgE-mediated hypersensitivity reactions in the Australian Adverse Drug Reactions Advisory Committee's database, 51 reports were found to be related to *Echinacea* use (species and plant part not defined). Twenty-six reactions including urticaria, angio-oedema, asthma and anaphylaxis were confirmed to be IgE-mediated reactions to *Echinacea*. More than half of the affected patients had a history of asthma, allergic rhinitis or atopic dermatitis. Four persons required hospitalisation due to their reactions and no deaths occurred. In 94% of patients, the symptoms appeared within 24 hours of *Echinacea* ingestion. 80% of the patients included were female and the medium age was 32 years (Mullins & Heddle 2002).

Assessors conclusion

Hypersensitive reactions to Echinacea purpurea herb and its preparations are possible. Known hypersensitivity to Echinacea or to plants of the Asteraceae (Compositae) family should be contraindicated. In case of allergic reaction, Echinacea should not be taken again.

Published case reports of adverse events

Kemp & Franco (2002) published a case report of leucopoenia associated with long-term use of *Echinacea*. A 51-year-old woman appeared healthy from all aspects with the exception that her white cell count had decreased from 5,800/µl the preceding year to 3,300/µl (normal range 4,000 to 11,000). For the past 8 weeks she had been taking 1350 mg of *Echinacea* per day. One month after discontinuation of therapy with *Echinacea*, her white cell count had increased to 3,700/µl. Next year she resumed taking *Echinacea* and after two months her white cell count was 2,880/µl. Two months after discontinuing *Echinacea*, her white cell count was 3,440/µl and 7 months later rose to 4,320/µl. The connection between the *Echinacea purpurea* therapy and the undesirable effect was estimated as certain.

Soon & Crawford (2001) reported on a case of a 41 years old man with 4 recurrent episodes of erythema nodosum. According to the authors, it was temporally and perhaps causally associated with the use of *Echinacea* herbal therapy, but *Echinacea* species, plant part and herbal preparation is not reported. Each episode was preceded by prodromi of myalgias, arthalgias, fever, headache and malaise, which resolved under prednisolone therapy. Comedication was loratadine as needed, St. John's wort for 6 month, and intermittent *Echinacea* (plant species, substance and preparation not reported) for 18 month. Other reasons were excluded. After dechallenge he was free of erythema nodosum despite persistence of intermittent flulike symptoms for over a year. A rechallenge with *Echinacea* was refused by the patient.

Logan & Ahmed (2003) reported, that a 36 year old woman had taken St. John's wort, *Echinacea* and Kava for 2 weeks when she developed a severe general muscle weakness, which resolved under supplementation of $NaHCO_3$ and KCl. Complaints of joint stiffness, fatigue, dry mouth and eyes surfaced 6 weeks later. The serum was negative for double stranded anti DNA, Smith and RNP antibodies. Sjögren's Syndrome was diagnosed and Plaquenil treatment begun. The abnormalities of renal tubular function resulting in hypokalemia and acidification with muscle weakness are reported because of a Sjögren's Syndrome. Problems resolved under therapy with prednisone and cyclophosphamide, which underlines the autoimmunogenesis. The authors discussed an association with *Echinacea* but they also acknowledged that this association may be purely incidental and a temporal association only. Plant species, type of preparation and application or dosage are not reported.

Schwarz *et al*. (2000) describes one case of encephalitis disseminata following the injection of *Echinacea angustifolia* containing homeopathic combination product. This product contains different plant species, different herbal substance and its route of application is different to the products covered in this Assessment report.

Liatsos *et al*. (2006) reported on a case (32 years old Caucasian male) of severe thrombotic thrombocytopenic purpura 20 days after the use of a water-alcoholic extract of *Echinacea pallida* for about one week.

Maskatia & Baker (2010) reported on a case of hypereosinophilia associated with *Echinacea* (no detailed description of the product) use. 58-year-old white male was referred for eosinophilia found on a routine complete blood count. The patient's only complaint at the time was of having a several week history of mild crampy abdominal pain, with occasional nausea and diarrhea. His past medical history included a long history of controlled asthma and allergic rhinitis, hyperlipidemia, resolved hepatitis B infection, cholelithiasis, an inguinal hernia, and a hiatal hernia. He denied any smoking, alcohol, or illegal drug use, and his family history was noncontributory. Physical exam was unremarkable. Medications included esomeprazole, sildenafil citrate, ezetimibe/simvastatin, aspirin, cetirizine, fluticasone nasal spray, olopatadine eyedrops, calcium supplements, and glucosamine. He had also

started taking *Echinacea* supplements several weeks prior around the time his abdominal pain started. He otherwise had an allergy to iodine. Labs revealed a white blood cell count of 24,900/µl with 74% eosinophils, for an absolute eosinophil count of 17,800/µl (normal <350 eosinophils/µl). The rest of the differential included 7% neutrophils, 11% lymphocytes, and 11% monocytes. His hemoglobin was 12.7 g/dl, with a platelet count of 208,000. Serum chemistries were normal except for slightly elevated creatinine, which normalised a few weeks later. Liver function tests and lactate dehydrogenase levels were also normal. Of note, he had a very elevated Immunoglobulin E (IgE) level of 1390 IU/ml (normal <114 IU/m). Bone marrow aspirate showed a mildly hypercellular bone marrow, marked eosinophil hyperplasia with mild atypia, and trilineage hematopoiesis with normal maturation. No evidence of myeloproliferative disease, lymphoma, or infection was noted. Flow cytometry revealed increased eosinophils, but no monoclonal B cell population, aberrant T cell antigen expression, or increased immunophenotypic blasts. Bone marrow cytogenetics were also normal. Tests for adrenal insufficiency and parasitic and connective tissue disorders were also negative, including evaluation for human immunodeficiency virus (HIV), systemic lupus erythematosus, scleroderma, Wegener granulomatosis, celiac disease, *Clostridium difficile*, *Bartonella*, *Toxocara*, *Coccidioides*, *Cryptococcus*, and *Brucella.* Stool ova and parasite studies and serologic testing for IgG antibodies against *Strongyloides* antigens were also negative. Since the cause of hypereosinophilia was not readily apparent at first, the patient was treated for hypereosinophilic syndrome, a disorder characterised by persistent eosinophilia with no evident cause, and signs or symptoms of organ involvement by eosinophilic infiltration. Both hydroxyurea and imatinib were tried, but the only effective therapy was prednisone. Any attempt to taper prednisone resulted in increasing eosinophil counts and worsening nausea and diarrhoea. Three years after treatment had started, the patient mentioned that he had stopped taking *Echinacea* supplements but had continued taking the rest of his medications. Two weeks after *Echinacea* discontinuation, his eosinophil counts and IgE levels were checked, and they had markedly improved to almost normal levels. Prednisone was quickly tapered off, and, at the patient's last visit, he continued to have normal eosinophil counts and IgE levels six months after discontinuation of the supplement.

Table 8: Spontaneous reports of suspected adverse drug reaction associated with *Echinacea* preparations submitted to the UK Committee on Safety on Medicines/Medicines and Healthcare products Regulatory Agency for the period 01/07/1963 to 01/06/2004 (Adverse Drug reactions On-line Information tracking) are the following (Barnes et al. 2005):

System organ class	Reaction name	Total
Blood and lymphatic system disorders	Aplastic anaemia (1), coagulopathy (1), idiopathic thrombocytic purpura	3
Cardiac disorders	Supraventricular tachycardia (1), ventricular arrhythmia NOS (1), palpitations (1)	3
Central and peripheral nervous system disorders	Including convulsions (5); dizziness (3); headache (6)	17
Endocrine disorders	Basedow`s disease (1)	1
Eye disorders	Blurred vision (1)	1
Gastrointestinal disorders	Faecal incontinence (1), irritable bowel syndrome (1), dysphagia (1), nausea (1), tongue oedema (1)	5
General disorders and administration site conditions	Rigors (1), drug interaction NOS (3), drug interaction potentiation (1), fatigue (1), malaise (1), feeling abnormal (1)	8
Hepatobiliary disorders	Sclerosing cholangitis (1)	1
Infections and infestations	Parotitis (1)	1
Investigations	Blood pressure increased (1), INR increased (2), liver function test abnormal (1), weight increased (1)	5
Metabolism and nutrition disorders	Hyponatremia (1)	1

Musculoskeletal and connective tissue disorders	Arthralgia (2), myalgia (1), muscle twitching (1)	4
Nervous system disorders	Central pontine myelinolysis (1), memory impairment (1), ataxia (1), abnormal co-ordination NOS (1), loss of consciousness (1), burning sensation NOS (1), dysarthia (1), pilepsy NOS (1)	8
Psychiatric disorders	Agitation (1), panic reaction (1), confusional state (2), insomnia (1), sleep disorder NOS (1)	6
Renal and urinary disorders	Pollakiuria (1), urinary incontinence (1), heamaturia (1)	3
Respiratory, thoracic and mediastinal disorders	Asthma NOS (1), dyspnoea (1), dry throat (1), pharyngolaryngeal pain (1)	4
Skin and subcutaneous tissue disorders	Face oedema (1), urticaris NOS (3), erythema multiforme (1), erythema (1), pruritus (1), rash NOS (1)	8
Vascular disorders	Flushing (1), Hypertension NOS (1)	2
Total number of reactions		64

INR=international normalised ratio; NOS=not otherwise stated

The World Health Organisation's Uppsala Monitoring Centre (WHO-UMC; Collaborationg Centre for International Drug Monitoring) had received to the end of the year 2004 a total of 259 reports, describing a total of 537 adverse reactions, for products containing a single species of *Echinacea*. The majority of these reports describe reactions associated with *Echinacea purpurea*, most commonly (reactions listed 10 times or more): abdominal pain (n=10), angioedema (10), dyspnoea (18), nausea (14), pruritus (17), rash (18), nausea (14), pruritus (17), rash (18); rash erythemtosus (23), utricaria (23) (Barnes *et al*. 2005).

Jeschke *et al*. (2009) published the results of a prospective pharmacovigilance study of *Asteraceae* extracts, including *Echinacea*. Out of 18,830 patients (58.0% female, 60.3% children), who received 42,378 *Asteraceae*-containing remedies. This included 2,672 patients receiving 4,605 *Echinacea*-containing prescriptions (30% phytotherapeutic, 60%<D4, 10%>D4). No serious ADRs were reported. In a subgroup analysis, considering also non severe ADRs in 6,961 prescriptions for *Asteraceae*, 11 non-serious adverse reactions were detected (all for homeopathic preparations and none for phytotherapeutic preparations). Most of the reactions were associated with skin problems, allergic reactions or gastrointestinal complaints. The severity of all reactions was assessed as mild or moderate. This survey supports that 'treatment with *Asteraceae*-containing remedies, which are used frequently in the primary care setting, is not associated with a high risk of ADRs'. This supports the observation that allergic reactions due to *Echinacea* products are rather rare and mostly not serious.

Analysis of spontaneously reported adverse reactions submitted to the Swedish Medical Products Agency **(Jacobsson *et al*. 2009**) in the course of nearly 20 years showed that among a total of 64,493 reports, only 778 reports concerned adverse reactions related to CAM products. 63 reports concerned *Echinacea purpurea*, among them mostly urticaria (11) and exanthema (13).

Table 9: Pharmacovigilance reports from Member States on hypersensitive reactions and autoimmune diseases (causality has not been evaluated):

Bulgaria 2014	No reports on hypersensitive reactions and autoimmune diseases in connection with *Echinacea purpurea*, herba
Croatia 2014	No reports on mentioned hypersensitive reactions and autoimmune diseases in connection with *Echinacea purpurea*, herba.
Czech Republic 2014	No ADR reports related to *Echinacea purpurea*, herb as an active substance in the Czech PHV database.

Denmark 2014	Reports on a combination product (65% V/V ethanol extract of freshly harvested *Echinacea purpurea* herb (DER 1:12) and roots (DER 1:11), 95:5) therapeutic response increased alanine aminotransferase increased blood lactate dehydrogenase increased fatigue blood pressure decreased rash generalised cough dyspnoea 2x deep vein thrombosis
Estonia 2014	Not received any adverse effect reports for *Echinacea purpurea*, herb
Finland 2014	No pharmacovigilance reports or identified any published reports in Finnish medical journals on hypersensitive reactions and autoimmune diseases in connection with *Echinacea purpurea*, herba.
Ireland 2014	12 case reports including 24 adverse reactions as follows: 3 x abdominal pain, 2 x headache, 2 x urticaria, 1 x amenorrhoea, arthralgia, attention deficit/hyperactivity disorder, bone disorder, chest pain, dizziness, fatigue, feeling drunk, goitre, hypoglycaemia, oedema, parkinsonism, pharyngitis, pregnancy on oral contraceptive, purpura, renal impairment, white blood cell disorder 6 of the above cases were with a combination product (65% V/V ethanol extract of freshly harvested *Echinacea purpurea* herb (DER 1:12) and roots (DER 1:11), 95:5), in remaining reports the name of the medicinal product or *Echinacea* species and plant part are not identified.
Italy 2014	7 case reports with only one product, containing *Echinacea*, administered: - acute hepatitis with severe jaundice - tongue and lower lips oedema, laryngeal constriction/oedema, taste disturbance, difficulty in breathing, tachycardia - dermatitis eczematosa on the hands and forearm, urticaria - gastrointestinal disturbances, diarrhoea - aggravation of anxiety and nervousity in a predisposed person - hyperactivity - dry cough after administration In the report of Istituto Superiore di Sanità on phytovigilance of natural products there are other 21 cases of adverse reactions for combination of products (containing Echinacea as well). There is another case reported in the National Pharmacovigilance on-line database, observed in a asmatic four years old child during concomitant use of salbutamol plus beclomethasone dipropionate and sodium montelukast: irritative cough, lips oedema, oromucosal pain, tongue oedema.
Germany 2006	127 case reports of adverse events in patients taking *Echinacea* (any species, any plant part and any herbal preparation, in most cases in combination with other drugs) were documented in Germany from 1984 to 2006. Many adverse events happened in intravenous application of *Echinacea* extract for treating hypersensitivity, allergic rhinitis In patients with no concomitant therapy besides the oral therapy with *Echinacea* the following adverse events were observed in the period 1991-1996: 6 x : diarrhoea, nausea 4 x : pain abdominal, rash 3 x: taste disturbance

Germany 2006 cont.	2 x: itching, rigors, trombocytopenia, urticaria acute, vomiting 1 x: aggravation of existing disorder, allergic reaction, allergy aggravated, asthmatic attack, cough, cramp abdominal, diarrhoea bloody, dry mouth, dyspepsia, dysphagia, ear ache, erythema, exanthema, face oedema, facial flushing, facial pain, facial swelling, fainting, fever, haematuria, headache, hepatitis A, hives, hypersensitivity, leucopenia, lip oedema, malaise, numbness localised, numbness oral, pemphigus, petechiae, pharingitis, pruritis, pustular rash, Quinckes oedema, sweating attack, swelling non-inflammatory, swelling of knees, swollen eyelid, temperature elevation, therapeutic response decreased, urticaria, vertigo
Norway 2014	No hypersensitivity reactions reported
Slovak Republic 2014	No reports on hypersensitive reactions and autoimmune diseases in connection with *Echinacea purpurea*, herba
Slovenia 2014	No reports on hypersensitive reactions and autoimmune diseases in connection with *Echinacea purpurea*, herba (1 report of diarrhoea)
Sweden 2014	Three serious ADR healthcare reports concerning possible autoimmune reactions have been retrieved from Eudravigilance. The cases are complex and it is difficult to conclude on causality with certainty. A link to development of autoimmune diseases appears unlikely, but cannot be completely excluded. All three reports concern prolonged off-label use (3, 4 and 6 months, respectively) of a product containing the expressed juice from *Echinacea purpurea*, herba. Two of the reports are hepatic reactions; one of which had a lethal outcome. The third reaction concerns myositis.
United Kingdom 2014	The MHRA have received 58 reports through the Yellow Card scheme of adverse reactions suspected to be associated with the use of products containing *Echinacea*. These include 14 reports relating to hypersensitivity reactions. These are consistent with the current description in the monograph and include a variety of symptoms including rash, urticaria, angioedema, anaphylactic shock, difficulty breathing and asthma. Of these 14 patients, 5 reported existing asthma. There have been no reports of Stevens-Johnson Syndrome or Quincke edema associated with the allergic reactions reported in the UK, though one case did report an erythema multiforme like rash. The current monograph lists a possible association between *Echinacea* and a number of autoimmune diseases. There have been no reports of encephalitis disseminata, erythema nodosum, immunothrombocytopenia, Evans Syndrome, Sjögren's syndrome with renal tubular dysfunction in the UK. There have also been no reports received through the Yellow Card scheme of leucopoenia suspected to be associated with the use of herbal medicines containing *Echinacea*.
Eudra vigilance database	hypersensitive reactions: - Stevens-Johnson Syndrome (4 cases) - angioedema of the skin (3 cases) - bronchospasm with obstruction (1 case) anaphylactic shock (2 cases of anaphylactic shock and 1 case of anaphylactic reaction) association with autoimmune diseases: - erythema (1 case) - erythema multiforme (1 case) - Sjögren's syndrome with renal tubular dysfunction (1 case)

Assessors' conclusion

The existing pharmacovigilance reports are mostly with undeclared or different plant species (Echinacea angustifolia), undeclared or different plant part (roots), undeclared or different herbal preparations (extract), different type of product (homeopathic or parenteral) or different duration of use (up to several months).

Hypersensitive reactions in the form of rash, urticaria, itching, swelling of the face are possible. Cases of severe hypersensitivity reactions, such as Stevens-Johnson Syndrome, angioedema of the skin, Quincke edema, bronchospasm with airway obstruction, asthma and anaphylactic shock have been reported with confirmed/probable/possible causality. The frequency is not known.

Hypersensitive reactions (local rash, contact dermatitis, eczema and angioedema of the lips) may occur also after dermal administration of liquid and semi-solid preparations of Echinacea purpurea herb pressed juice. The frequency is not known.

Association with autoimmune diseases (encephalitis disseminata, erythema nodosum, immunothrombocytopenia, Sjögren's syndrome with renal tubular dysfunction) has been reported.

The causality of adverse events in pharmacovigilance cases concerning autoimmune diseases is not known or inconclusive (insufficient data). The cases are complex, a link to development of autoimmune diseases appears unlikely. It must be considered that infectious agents and inflammatory processes present in common cold can themselves promote autoimmune diseases. However, association with autoimmune diseases cannot be excluded.

Since gastrointestinal adverse reactions in clinical trials were equally frequent in placebo and verum group, it can be assumed that gastrointestinal adverse events reported in pharmacovigilance reports are not Echinacea related.

5.4. Laboratory findings

No clinical studies with laboratory examinations were performed. A case of leucopenia was found in apparently healthy woman. Laboratory examination showed that her white cell count was 3,300/µl (normal range 4,000 to 11,000). The details of this case are described above in the chapter 5.3. (Kemp & Franco 2002).

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

Several prospective interventional clinical trials were performed with *Echinacea* in children (see Chapter 4.2.3). Here additional information on other type of surveys is presented.

Godwin *et al*. (2013) determined how common it is for parents to give natural health products (NHPs) to their children, which NHPs are being used, why they are being used, and parents' assessments of the benefits and side effects of NHPs. A total of 202 (53.4%) of the 378 eligible parents who were contacted completed the survey. This represented 333 children. Mean (SD) age of the children was 5.1 (3.3) years. Overall, 28.7% of parents reported using nonvitamin NHPs for their children. A total of 137 children (41.1%) had taken NHPs (including vitamins); 61.1% of the NHPs being used were vitamins. The remainder fell under teas (primarily chamomile and green teas), *Echinacea*, fish or omega-3 oils, and a large category of "other" products. These NHPs were most commonly used to improve general health, improve immunity, and prevent colds and infections. Approximately half of the parents (51.7%) believed their children had benefited from taking NHPs, and 4.4% believed their

children had experienced adverse side effects. Slightly less than half of the parents (45.0%) had informed their physicians that their children were taking NHPs.

There is no clinical trial or evidence of traditional use on the topical use of *Echinacea purpurea* herb juice preparations in semi-solid or liquid dosage forms in children below 12 years.

Assessors' conclusion

In spite of evidence of relatively safe use of Echinacea purpurea herb in children between 1 and 12 years of age Echinacea purpurea herb cannot be recommended for well-established use in children below 12 years since there is absence of well-designed study with positive results in paediatric population. Its traditional use in children cannot be recommended since such tradition is not adequately documented.

Atopic patients and those with asthma should be cautious since rare allergic reactions have been reported (Barnes et al. 2005, Barnes et al. 2007, Huntley et al. 2005).

5.5.2. Contraindications

In case of hypersensitivity to the active substance or to plants of the *Asteraceae* (*Compositae*) family the use is contraindicated. No other concerns requiring contraindication were indicated.

5.5.3. Special Warnings and precautions for use

Based on the presumption that *Echinacea purpurea* herb has immunomodulatory effects, some authors declared, that its use is contraindicated in progressive systemic diseases such as tuberculosis, diseases of the white blood cells system, collagenoses, multiple sclerosis, AIDS, HIV infections, and other immune diseases (Barnes *et al*. 2005, Barnes *et al*. 2007, ESCOP 2003, Hänsel *et al.* 1993).

At present there is a lack of reliable clinical evidence to support the immunomodulatory effects of *Echinacea*, but in the view of the seriousness of the conditions listed above it is appropriate to avoid use in these disorders until further information is available (Barnes *et al*. 2005, Barnes *et al*. 2007).

In accordance with the 'Guideline on the Summary of Product Characteristics' dated September 2009, the statement that *Echinacea purpurea* herb is not recommended in progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosupression and diseases of the white blood cell system appears in the section 'Warnings and precautions for use' of the monograph on *Echinaceae purpureae* herba (not as a contraindication).

5.5.4. Drug interactions and other forms of interaction

The first report on possible drug-herbal interaction between *Echinacea* (details of drug administration not stated) and etoposide was published recently (Bossaer & Odle 2012). A 61-year-old man newly diagnosed with nonsmall cell lung cancer began concurrent chemoradiation with cisplatin and etoposide. He was admitted to the hospital on day 8 of his first cycle and found to be thrombocytopenic. His platelet count eventually reached a nadir of 16 × 10(3)/l, requiring platelet transfusion support. Upon admission, it was discovered that he was taking vitamin B12, vitamin E, vitamin D, vitamin C, *Echinacea* and 'vitamin B17' (laetrile-apricots kernel), which were discontinued. He received his next cycle of chemotherapy without taking herbal products and vitamins and with the addition of pegfilgrastim. His platelet count decreased to a nadir of 44 × 10(3)/l, but he did not require platelet transfusions. Since the patient stopped taking *Echinacea* after cycle 1, subsequent therapy during cycle 2 served as a control to test hypothesis that *Echinacea* (documented in *in vitro* studies to as a cytochrome P450 3A4 inhibitor) interacted with etoposide. As the patient also stopped taking

laetrile and his other vitamins after cycle 1, a potential interaction between laetrile and etoposide or cisplatin cannot be fully excluded.

Authors of the report concluded that since the exact preparation of *Echinacea* and corresponding plant extract constituents, was unknown, the interaction remains equivocal. Cautions should be exercised in patients receiving chemotherapy including CYP3A4 substrates (antracyclines, etoposide, vinca alcaloids, taxanes) while taking *Echinacea* (Bossaer & Odle 2012).

Assessors' conclusion

In a pharmacological study it was found that Echinacea purpurea radix inhibits intestinal CYP3A4 and induces hepatic CYP3A4 (Gorski et al. 2004). Modarai et al. (2010) found, that inhibition of CYP3A4 is more than 50 fold lower with Echinacea purpurea herb juice (no further details available; IC_{50}=1.8 g/l), compared to Echinaceae purpureae herba tincture (no further details available; IC_{50}=0.022 g/l) or to Echinaceae purpureae herba et radix tincture (65% V/V ethanol extract of fresh Echinacea purpurea herb (DER 1:12) and roots (DER 1:11), 95:5; IC_{50}=0.027 g/l). Nevertheless, due to unknown formulation and dosages of Echinacea preparation in this case interaction with etoposide could be considered as a signal also for Echinacea purpurea herb preparations and their possible interaction with etoposide and other CYP3A4 substrates.

5.5.5. Fertility, pregnancy and lactation

No prospective interventional clinical trials have been performed with *Echinacea* in pregnant or lactating women.

Pregnancy outcome in women who used *Echinacea* during pregnancy was studied to evaluate the safety of *Echinacea* (Gallo *et al*. 2000). Since at least half of all pregnancies are unplanned, many women inadvertently use *Echinacea* in their first trimester. A total of 206 women were enrolled and prospectively followed up after contacting the Motherisk Program (in Toronto, Canada) regarding the gestational use of *Echinacea*. In this study group, 112 women (54%) used the herb in the first trimester, with 17 (8%) exposed in all 3 trimesters; *Echinacea* tablets /capsules (58%, 250-1000 mg/day) or tincture (38%, 5-30 drops/day) were used. Some of them used *Echinacea purpurea* and some *Echinacea angustifolia* (the number of women using each species is not reported in the article) and only 1 woman used *Echinacea palida*. The plant part (root or herb) is not reported. There were a total of 195 live births, including 3 sets of twins, 13 spontaneous abortions, and 1 therapeutic abortion in *Echinacea* group. Six major malformations were reported, including 1 chromosomal abnormality, and 4 of these malformations occurred with *Echinacea* exposure in the first trimester. This cohort was disease-matched to women exposed to nonteratogenic agents by maternal age, alcohol, and cigarette use. Rates of major and minor malformations between the groups were compared. In the control group, there were 206 women with 198 live births, 7 spontaneous abortions, and 1 therapeutic abortion. Seven major malformations were reported. There were no statistical differences between the study and control groups for any of the end points analysed. The authors concluded that gestational use of *Echinacea* during organogenesis is not associated with an increased risk for major malformations.

In a survey among 400 Norwegian women (Nordeng & Haven 2004) 36% used herbal drugs during pregnancy with an average of 1.7 products per woman. *Echinacea* was used by 23% of pregnant woman and was by far the mostly used herb. No information about the plant species, plant part or type of preparation or duration of intake/trimester is given in the article.

A review on safety of *Echinacea* during pregnancy and lactation was published (Perri *et al*. 2006). The authors searched 7 electronic databases and compiled data according to the grade of evidence found.

A good scientific evidence from a prospective cohort study was found: oral consumption of *Echinacea* during the first trimester did not increase the risk for major malformations (study performed by Gallo *et al*. 2000). Low-level evidence based on expert opinion shows that oral consumption of *Echinacea* in recommended doses is safe for use during pregnancy and lactation. The authors concluded that *Echinacea* is non-teratogenic when used during pregnancy. Caution advised using *Echinacea* during lactation until further high quality human studies can determine its safety.

Nordeng *et al*. (2011) investigated the use of herbal drugs by pregnant women in relation to concurrent use of conventional drugs, delivery, and pregnancy outcome. Six hundred women at Stavanger University Hospital Norway were interviewed using a structured questionnaire within five days after delivery. Medical birth charts were reviewed with respect to pregnancy outcome. 39.7% of the women reported the use of herbal drugs during pregnancy, most commonly ginger, iron-rich herbs, *Echinacea* (7.5%) and cranberry. No information about the *Echinacea* species, plant part or type of preparation or duration of intake/trimester is given in the article. Although 86.3% of the women reported to have used conventional drugs during pregnancy there were few potential interactions between herbal drugs and conventional drugs. Except for birth weight, there were no significant differences between users and non-users of herbal drugs in general in any of the pregnancy outcomes investigated. Mean birth weight was higher among the users of herbal drugs during pregnancy (3,663 g vs. 3,508 g). There was a significant association between the use of iron-rich herbs during pregnancy and high birth weight, and use of raspberry leaves and caesarean delivery.

The study of Cuzzolin *et al*. (2010) explored the use of herbal products among Italian pregnant women and the possible influence of herbal consumption on pregnancy outcome. It was conducted over a 10-month period (2 days a week, from January to October 2009) at the Maternity wards of Padua and Rovereto Hospital. Data were collected through a face-to-face interview on the basis of a prestructured questionnaire including socio-demographic characteristics of the enrolled subjects, specific questions on herbal use, information about pregnancy and newborn. In total, 392 interviews were considered. 109 out of 392 women (27.8%) reported to have been taking one or more herbal products during pregnancy, in the 36.7% of cases throughout all pregnancy. The most frequently herbs were chamomile, liquorice, fennel, aloe, valerian, *Echinacea* (9.2%), almond oil, propolis, and cranberry. No information about the *Echinacea* species, plant part or type of preparation or duration of intake/trimester is given in the article. Four out of 109 women (3.7%) reported side-effects: constipation after a tisane containing a mix of herbs, rash and itching after local application of aloe or almond oil. Users were more often affected by pregnancy-related morbidities and their neonates were more frequently small for their gestational age. A higher incidence of threatening miscarriages and preterm labours was observed among regular users of chamomile and liquorice.

Holst *et al*. (2011) performed a survey at the antenatal clinic at Norfolk and Norwich University Hospital between November 2007 and February 2008 among 578 expectant mothers at least 20-weeks pregnant. 57.8% of them used one or more herbal remedies. The most commonly used herbal preparations during pregnancy were ginger, cranberry, raspberry leaf, chamomile, peppermint and *Echinacea*. No information about the *Echinacea* species, plant part or type of preparation is given in the article.

No fertility data are available.

Assessors' conclusion

Echinacea is among the most commonly used medicinal herbs during the pregnancy with no documented reports on pregnancy-related morbidities or cases of malformation.

In a prospective cohort study it was found that oral consumption of Echinacea during the first trimester did not increase the risk for major malformations comparing with non-consumption (Gallo et al. 2000). The study has several limitations, particularly the small sample size, meaning that the study would have the statistical power only to detect common malformations, and self-report of exposure, since it is possible that misclassification have occurred. In addition participants used a range of different preparations of Echinacea at different dosage regimens, so the study does not provide adequate evidence for any specific preparation (Barnes et al. 2007).

Referring also to the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005) which requires at least 300 first trimester exposed prospectively collected pregnancies (a moderate amount) with known pregnancy outcomes (births or fetopathological examinations) to make conclusion about save use and recommendation for use during pregnancy, use of Echinacea in pregnancy cannot be recommended.

In the absence of sufficient data, the use in pregnancy and lactation should not be recommended unless advised by a doctor. The doctor should consider the balance between benefit and potential risk for the patient based on the presented data.

There are no data on dermal use of Echinacea during pregnancy or lactation. Products containing Echinacea should not be applied to the breast of breastfeeding women.

5.5.6. Overdose

No case of overdose has been reported.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effects on the ability to drive or operate machinery or impairment of mental ability have been performed.

5.5.8. Safety in other special situations

No safety concerns in other special situations were reported.

5.6. Overall conclusions on clinical safety

Based on clinical trials with *Echinacea purpurea* herb expressed juice preparations and pharmacovigilance reports it can be concluded, that medicinal products containing this herbal preparation are safe for intended use, taking into account recommended contraindications, warnings and precautions for use. In most clinical studies no side effects were observed or their frequency was equal or lower than in placebo. Only in one study, the frequency of one adverse effect (rash) was higher in *Echinacea* group (Taylor *et al*. 2003).

There is a relatively low number of pharmacovigilance reports on adverse effects of *Echinacea* products, especially comparing to extremely high frequency of use of these products. In some cases, it is not possible to distinguish the side effect of the drug from the complication of a disease (e.g. inflammatory processes can trigger autoimmune disease). On the other hand there is under-reporting

of adverse effects of herbal medicinal products in many European countries, and the actual frequency of adverse effects might be higher.

Hypersensitive reactions in the form of rash, urticaria, itching, swelling of the face are possible. There are reported cases of severe hypersensitivity reactions, such as Stevens-Johnson Syndrome, angioedema of the skin, Quincke edema, bronchospasm with obstruction, asthma and anaphylactic shock) with confirmed/probable/possible causality. The frequency is not known. Severe hypersensitivity reactions are possible especially in atopic patients. Atopic patients should consult their doctor before using *Echinacea*.

Known hypersensitivity to *Echinacea* or to plants of the *Asteraceae (Compositae)* family is to be contraindicated. In case of allergic reaction, *Echinacea* should not be taken again.

Association with autoimmune diseases (encephalitis disseminata, erythema nodosum, immunothrombocytopenia, Sjögren's syndrome with renal tubular dysfunction) cannot be excluded.

There is one case of leucopenia after long-term use (more than 8 weeks) described in the literature with confirmed causality. This case supports the recommendation of the short term use (10 days) of *Echinacea purpurea* herb preparations.

Based on the presumption that *Echinacea purpurea* herb has immunomodulatory effects, its use is not recommended in progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system.

In spite of evidence of relatively safe use in children between 1 and 12 years of age *Echinacea purpurea* herb cannot be recommended for well-established use in children below 12 years since there is absence of well-designed study with positive results in paediatric population.

Limited data (several hundreds of exposed pregnancies) indicated no adverse effects of oral use of *Echinacea* on pregnancy or on the health of the foetus/newborn child. These data are not sufficient since there is no study of adequate scientific quality with sufficient number of first trimester exposed prospectively collected pregnancies and no other relevant epidemiological data are available. In the absence of sufficient data, the use during pregnancy and lactation is not recommended unless advised by a doctor.
There are no data on dermal use of *Echinacea* during pregnancy or lactation. Products containing Echinacea should not be applied to the breast of breastfeeding women.

No fertility data are available.

6. Overall conclusions (benefit-risk assessment)

Based on positive results from randomised double blind placebo controlled clinical studies which demonstrated that early initiation of treatment with the expressed juice of *Echinacea purpurea* for 10 days can prevent, reduce the development of the disease and significantly shorten the duration of the common cold and reduce the symptoms and the length of the treatment period required, supported by other clinical studies, it can be concluded, that there is good clinical evidence on efficacy of expressed juice from fresh herb of *Echinacea purpurea* for the short term prevention and treatment of acute upper airways infection (common cold) in adults and adolescents.

Therefore, medicinal products with expressed juice from fresh herb of *Echinacea purpurea* fulfil the criteria for well-established use for the short-term prevention and treatment of common cold. The common cold was in most clinical trials diagnosed by the patients on the basis of first symptoms.

According to literature data and clinical trials the following posology is recommended: 6-9 ml of expressed juice (1.5-2.5:1) per day or equivalent amount of dried expressed juice, divided in 2 to 4 doses (adolescents, adults, elderly).

The clinical evidence of efficacy for children, for long term prevention of common cold, for cutaneous use and for extracts is not sufficient for well-established use. There is no evidence of traditional use in children and long term prevention of common cold for these preparations for 30 years.

There is evidence of traditional topical use of liquid and semi-solid dosage forms containing expressed juice from fresh herb of *Echinacea purpurea*, herba recens (1.7-2.5:1) for more than 30 years for treatment of small superficial wounds. It is assumed that dried juice corresponding to the expressed juice above could be equally appropriate for traditional medicinal products for cutaneous use. Based on pharmacological data the use in this indication is plausible and appropriate for traditional herbal medicinal products. Proposed dosage is: adolescents, adults, elderly: small amount (thin layer) of ointment is applied 2-3 times daily on the affected area.

Benefit – Risk – Assessment

The overall body of evidence which includes several clinical trials proves the efficacy of expressed juice from fresh herb of *Echinacea purpurea* in accordance with EMEA/HMPC/104613/2005.

There is acceptable safety profile: mainly mild allergic reactions (rash, urticarial, angioedema) are reported in literature and pharmacovigilance reports. Cases of serious hypersensitivity reactions have been reported, especially in atopic patients. Atopic patients should consult their doctor before using *Echinacea*.

The use of the product is contraindicated in cases of hypersensitivity to *Echinacea purpurea* and to other plants of the *Asteraceae* (*Compositae*) family.

The use in children under 12 years of age is not recommended because efficacy has not been sufficiently documented although specific risk in children over 1 year of age is not documented.

Based on the presumption that *Echinacea purpurea* herb may have immunomodulatory effects, its use is not recommended in progressive systemic disorders, autoimmune diseases, immunodeficiencies, immunosuppression and diseases of the white blood cell system.

Genotoxicity investigations are available for lyophilised *Echinacea purpurea* expressed juice and ethanol extracts and they showed no genotoxicity.

Well documented interactions of the herbal preparations containing preparations from *Echinacea purpurea* herb with other medicinal products are not reported in literature.

Limited data (hundreds of exposed pregnancies) indicated no adverse effects of oral use of *Echinacea* on pregnancy or on the health of the foetus/newborn child. No other relevant epidemiological data are available. In the absence of sufficient data, the use in pregnancy and lactation is not recommended unless advised by a doctor.

No fertility data are available.

Intoxication, due to *Echinacea* medicinal preparations, is not reported in literature or reference sources.

It can be concluded that the benefit/risk assessment for *Echinacea purpurea*, herba recens, succus and succus siccus preparations is positive for the short-term prevention and treatment of common cold under specified conditions.

There is the evidence of traditional cutaneous use of liquid and semi-solid medicinal products containing expressed juice from fresh herb of *Echinacea purpurea* for more than 30 years. Based on pharmacological data the use in this indication is plausible. Beside the risk of hypersensitive reactions (local rash, contact dermatitis, eczema and angioedema of the lips) no concerns are known.

The risk is at an acceptable level for traditional herbal medicinal products.

No new safety concerns appeared during this revision. We therefore recommend to keep the inclusion in the European Union list.

Annex

List of references