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Evaluation of Medicines for Human Use

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***Sambucus nigra* L., flos**

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

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TABLE OF CONTENTS

I. REGULATORY STATUS OVERVIEW 3
II. ASSESSMENT REPORT FOR HERBAL SUBSTANCE WITH TRADITIONAL USE 11
II.1 Introduction 12
II.1.1 Description of the herbal substance 12
II.1.2 Information on period of medicinal use in the Community regarding the specified indication 12
II.2 Non-Clinical Data 12
II.2.1 Pharmacology 12
II.2.1.1 Overview of available data regarding elder flower and relevant constituents thereof 12
II.2.1.2 Pharmacodynamics 13
II.2.1.3 Assessor's overall conclusions on pharmacology 15
II.2.2 Pharmacokinetics 15
II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof 15
II.2.2.2 Assessor's overall conclusions on pharmacokinetics 15
II.2.3 Toxicology 15
II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof 15
II.2.3.2 Asessor's overall conclusions on toxicology 15
II.3 Clinical Data 16
II.3.1 Clinical Pharmacology 16
II.3.1.1 Pharmacodynamics 16
II.3.1.2 Pharmacokinetics 16
II.3.2 Clinical Efficacy 17
II.3.2.1 Asessor's overall conclusion on the traditional medicinal use 20
II.3.2.2 Dose response studies/Traditional use: posology from handbooks 20
II.3.2.3 Clinical studies (case studies and clinical trials) 21
II.3.2.4 Clinical studies in special populations (e.g. elderly and children) 21
II.3.2.5 Assessor's overall conclusions on clinical efficacy 21
II.3.3 Clinical Safety/Pharmacovigilance 21
II.3.3.1 Patient exposure 22
II.3.3.2 Adverse events 22
II.3.3.3 Serious adverse events and deaths 22
II.3.3.4 Laboratory findings 22
II.3.3.5 Safety in special populations and situations 22
II.3.3.6 Assessor's overall conclusions on safe use 23
II.4 Assessor's Overall Conclusions 24

I. REGULATORY STATUS OVERVIEW[1]

MA: Marketing Authorisation;

TRAD: Traditional Use Registration;

Other TRAD: Other national Traditional systems of registration;

Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments[2]
Austria	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Trad
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	Trad
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Marketed
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

[2] Not mandatory field

Member State	Regulatory Status				Comments[2]
Poland	☐ MA	☒TRAD	☐ Other TRAD	☐ Other Specify:	Trad
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only combinations
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Information about the legal status of products containing *Sambucus nigra* L., flos in Member States (and Associate Members and Observer States):

Austria

Common name in respective national language:Holunderblüte

Traditional Use

Preparations (kind of extract, extraction solvent, DER)

Holunderblütenextrakt "Andrae", liquid extract, DER 1:1, ethanol 70%

Since when are the Preparations on the market? - 11/1997

Pharmaceutical Form (Standard Terms) - Oral liquid

Posology (Route of administration in Standard Terms + daily dosage) - Oral, 5 ml 3 times daily

Indications - Common cold

Risks (adverse drug effects, literature)

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation?	☒ **Yes**	☐ **No**
Risks known?	☐ **Yes**	☒ **No**
Pharmacovigilance actions taken?	☐ **Yes**	☒ **No**
Herbal substance(s) / herbal preparation(s) on the market?	☒ **Yes**	☐ **No**
Risks known?	☐ **Yes**	☒ **No**
Food Supplement?	☐ **Yes**	☐ **No**

Additional comments (e.g. information on relevant combination products):

Additionally numerous combination products are authorized (herbal teas, indication: common cold; liquid extracts: indications common cold and as a secretolytic in fixed combinations).

Ireland

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation?	☐ **Yes**	☒ **No**
Risks known?	☐ **Yes**	☒ **No**
Pharmacovigilance actions taken?	☐ **Yes**	☒ **No**
Herbal substance(s) / herbal preparation(s) on the market?	☐ **Yes**	☒ **No**
Risks known?	☐ **Yes**	☒ **No**
Food Supplement?	☐ **Yes**	☐ **No**

Additional comments (e.g. information on relevant combination products):

No combination products approved as medicines in Ireland.

We have no adverse reactions associated with *Sambucus nigra*, either alone or in combination, on our national database.

Belgium

No authorisations/registrations granted in Belgium

Poland

Common name in respective national language:

Traditional Use

Preparations (kind of extract, extraction solvent, DER)

1) and 2)) Infusion prepared of two 2g sachets in 200ml boiling water in isolated vessel.

3) Infusion prepared of 3 – 4g (1-1½ spoon) of flowers in 200ml boiling water in isolated vessel.

4) Infusion prepared of two 1,5g sachets in 200ml boiling water in isolated vessel.

5) Infusion prepared of two 2g sachets or 3-4g of flowers in 200ml boiling water in isolated vessel.

6) Decoction prepared of 3 – 4g (1-1½ spoon) of flowers in 200ml water.

7) Infusion prepared of two 1,5 sachets or 2g sachets in 200ml boiling water in isolated vessel.

8) Infusion prepared of two 2,5g sachets in 200ml boiling water in isolated vessel.

Since when are the Preparations on the market?

1) -8)1970 (Polish Pharmacopoeia IV)

Pharmaceutical Form (Standard Terms)

1) and 2) Herbal tea, sachets 2g

3) Herbal tea

4) Herbal tea, sachets 1,5g

5) Herbal tea, sachets 2g

6) Herbal tea (decoction)

7) Herbal tea, sachets 1,5g

8) Herbal tea, sachets 2,5g

Posology (Route of administration in Standard Terms + daily dosage)

1)-5) 3 - 4 x daily drink 100 – 150ml of infusion

6) 3 - 4 x daily drink 100 – 150ml of decoction

7) and 8) 3 - 4 x daily drink 100 – 150ml of infusion

Indications

1) As diaphoretic in fever diseases.

2) -8) As diaphoretic in fever diseases and adjunctive diuretic.

Risks (adverse drug effects, literature)

Not known

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation?	☒ **Yes**	☐ **No**
Risks known?	☐ **Yes**	☒ **No**
Pharmacovigilance actions taken?	☐ **Yes**	☒ **No**
Herbal substance(s) / herbal preparation(s)on the market?	☐ **Yes**	☐ **No**
Risks known?	☐ **Yes**	☒ **No**
Food Supplement?	☐ **Yes**	☐ **No**

Additional comments (e.g. information on relevant combination products):

Average number of combination substances:

☐ 2-3 ☒ 3-5 ☐ >5

Combination products

Farfarae folium (25%), Sambuci flos (30%), Tiliae inflorecscentia (30%), Salicis cortex (15%).

Salicis cortex, Sambuci flos, Tiliae inflorescentia, Betulae folium, Chamomillae anthodium (5 components).

Gentianae radix, Primulae flos, Rumicis herba, Sambuci flos, Verbenae herba.

Other information on relevant combination products:

Syrup containing composed ectract: Extractum fluidum (1:1) ex: Farfarae folium (25%), Sambuci flos (30%), Tiliae inflorecscentia (30%), Salicis cortex (15%). Composition used as antipyretic, antiphlogistic, and diaphoretic in common cold, pharyngitis and bronchitis.

Herbal tea composed of: Salicis cortex, Sambuci flos, Tiliae inflorescentia, Betulae folium, Chamomillae anthodium (5 components) used against fever.

Two preparations in form of drops and coated tablets, containing extracts of: Gentianae radix, Primulae flos, Rumicis herba, Sambuci flos, Verbenae herba, used in sinusitis.

The main pharmacodynamic effect is usually attributed to bitter compounds and the use of Sambuci flos in composition is based more on tradition than on experience.

Germany

Only combinations on the market, both as well-established and traditional use products.

Common name in respective national language: Holunderblüten

Additional comments (e.g. information on relevant combination products):

There is one **standard marketing** authorisation with Sambuci flos as active substance since 1986 as an herbal tea on the German market.

Indication: colds

Furthermore are five standard marketing authorisations in combination with other active ingredients also as herbal teas on the market.

Indication: For the symptomatic treatment of fever occurring during coughs and colds, in conditions in which a sweating cure is designate.

(Fieberhafte Erkältungskrankheiten, bei denen eine Schwitzkur erwünscht ist.)

Traditional use

There are five medicinal products in combination with other active substances in the Pharmaceutical Form of oral liquid (three), film coated tablets (one) and herbal tea (one) on the market.

The film coated tablet contains three active substances Sambuci flos, Sambuci folium and Sambuci fructus with the indication

Traditional herbal medicinal product to liquefy mucus in the airways. (Traditionell angewendet zur Unterstützung der Schleimlösung im Bereich der Atemwege)

One herbal tea in combination with two other active ingredients with the indication:

Traditional herbal medicinal product to help in symptoms of coughs and colds
(Traditionell angewendet zur Besserung des Befindens bei Erkältungskrankheiten)

Well-established use

There are two medicinal products in combination with Sambuci flos, Enzianwurzel (Gentianae radix), Schlüsselblumenblüten (Primulae flos), Eisenkraut (Verbenae herba) and Gartensauerampferkraut (Rumicis herba) as active substances (as drug powder and fluidextract) in the Pharmaceutical Form of oral liquid and tablet since 1978 on the German market.

Indication: acute or chronic sinusitis (Bei akuten und chronischen Entzündungen der Nasennebenhöhlen)

Latvia

Products on the market.

Common name in Latvian: Melná plûskoka, ziedi

About traditional use in Latvia

Internally. For treatment of influenza, common cold, oedema - caused by impaired lung or heart functions. Increases body resistance to viral infections. In cases of influenza and common cold is recommended together with Peppermint leaves. In combination with Yarrow and Hyssop – for the treatment of catarrhal conditions of the nose with deafness and sinusitis.
In the folk-medicine.
Internally for treatment of bronchitis, fever, rheumatism, arthritis, nephrolithic condition, as diaphoretic and diuretic, resolvent and mildly laxative remedy.
Externally. As a gargle in cases of angina, hoarseness, irritable gum. Warm poultice is used as an anodyne remedy on the painful areas;
for topical application and gargle (often together with Camomila flowers) in cases of angina, mouth inflammation, pain of eyes and ears, gout, hemorrhoids, croup pain.

Czech Republic

Common name in respective national language:

Traditional Use

Preparations (kind of extract, extraction solvent, DER) Sambuci flos pulveratus

Since when are the Preparations on the market? since 2000

Pharmaceutical Form (Standard Terms) For oral use or for gargling, herbal tea in bags

Posology (Route of administration in Standard Terms + daily dosage)

Single dose 1 bag 1.5 g 3 – 5 times daily

Indications

Treatment of common cold associated with elevated temperature, inflammations of oral cavity and upper respiratory tract; mild diuretic effect

Risks (adverse drug effects, literature)

No information

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation?	☐ **Yes**	☐ **No**
Risks known?	☐ **Yes**	☒ **No**
Pharmacovigilance actions taken?	☐ **Yes**	☒ **No**
Herbal substance(s) / herbal preparation(s) on the market?	☒ **Yes**	☐ **No**
Risks known?	☐ **Yes**	☒ **No**
Food Supplement?	☐ **Yes**	☐ **No**

Additional comments (e.g. information on relevant combination products):

Note: Sambuci flos has been a subject of Czechoslovak/Czech Pharmacopoeia since 1947, recommended dosage in the last version of the Czech Pharmacopoeia: single dose 2 – 3 g, daily dose 10 – 15 g

Combination products:

1) herbal tea containing Foeniculi dulcis fructus (15 %), **Sambuci nigrae flos** (25 %), Tiliae flos (25 %), Plantaginis folium (20 %), Liquiritiae radix (15 %) – on the market since 1997 – for oral use – indications: for treatment of common cold associated with elevated temperature, inflammations of oral cavity and upper respiratory tract; diaphoretic effect
2) herbal tea containing Matricariae flos (24 %), Foeniculi fructus (22 %), Menthae piperitae herba (12 %), Althaeae radix (10 %), Rubi fruticosi folium 10 %), Plantaginis folium (7 %), Lupuli flos (6 %), Serpylli herba (5 **%), Sambuci nigrae flos** (2 %), Liquiritae radix (2 %) – on the market since 1969 – indication – mild spasmolytic and sedative aid in children age
3) herbal tea containing Salviae officinalis herba (15 %), Althaeae radix(15 %), Polygonii avicularis herba 15 %), Thymi herba (15 %), Urticae herba (15 %), **Sambuci nigrae flos** (5 %), Plantaginis folium (5 %), Foeniculi fructus (10 %), Liquiritiae radix (5 %) – on the market since 1971 – for oral use, for gargling, for inhalations – indications: adjuvant for treatment of catarrhs of upper respiratory tract
4) herbal tea containing Fucus (15 %), Frangulae cortex (15 %), **Sambuci nigrae flos** (15 %), Sennae folium (10 %), Foeniculi fructus (10 %),Petroselini radix (10 %), **Sambuci nigrae flos** (10 %), Betulae folium (10 %), Liquiritiae radix (5 %) – on market since 1972 - for oral use - indications: reduction diet, obesity complicated with constipation and fluids retention

<u>Slovenia</u>

Common name in respective national language: cvet črnega bezga

Well-Established Use

Preparations (kind of extract, extraction solvent, DER)

1) Dried herbs (combination product)
2) liquid extract (1:11); extraction solvent: 59 % (V/V) ethanol (combination product)

Since when are the Preparations on the market?

1) 19.11.2003

2) 19.11.2003

Pharmaceutical Form (Standard Terms)

1) Coated tablet

2) Oral drops, solution

Posology (Route of administration in Standard Terms + daily dosage)

ad 1) oral use: up to 6 tablets per day

ad 2) oral use: 50 drops (3,1 ml) three times per day

Indications

1) For symptomatic treatment of acute and chronic inflammation of paranasal sinuses.

2) For symptomatic treatment of acute and chronic inflammation of paranasal sinuses.

Risks (adverse drug effects, literature)

1) Very rare: hypersensitivity reaction and gastrointestinal disorders

a2) Very rare: hypersensitivity reaction and gastrointestinal disorders

Herbal substance(s) / herbal preparation(s) on the market with a marketing authorisation? ☒ Yes ☐ No

Additional comments (e.g. information on relevant combination products):

Sambucus nigra L., flos is one of the active ingredients in medicinal product Sinupret (coated tablet and oral drops, solution). Other active ingredients are Gentianae radix, Primulae flos cum calycibus, Rumicis herba, Verbenae officinalis herba.

1 coated tablet contains dried herbal drugs:
Gentianae radix – 6,0 mg
Primulae flos cum calycibus - 18,0 mg
Rumicis herba – 18,0 mg
Sambuci flos – 18,0 mg
Verbenae officinalis herba - 18,0 mg

100 g of solution contains 29 g liquid extract (1 : 11) of herbal drugs:
Gentianae radix - 0,2 g
Primulae flos cum calycibus - 0,6 g
Rumicis herba - 0,6 g
Sambuci flos - 0,6 g
Verbenae officinalis herba - 0,6 g

II. ASSESSMENT REPORT FOR HERBAL SUBSTANCE WITH TRADITIONAL USE

Sambucus nigra L., flos

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Sambucus nigra* L., flos
Herbal preparation(s)	A) Liquid extract 1:1 DER in 25 % V/V ethanol B) Tincture, DER 1:5 extraction solvent: 25 % V/V ethanol
Pharmaceutical form(s)	Herbal substance for tea preparation Herbal preparations in liquid dosage forms for oral use.
Rapporteur	Pharm. Gro Fossum
Assessor(s)	Prof. Karl Egil Malterud Pharm. Asefeh Moradi

II.1 INTRODUCTION

II.1.1 Description of the herbal substance

Elder flower (Sambuci flos) consists of the dried flowers of *Sambucus nigra* L. It contains not less than 0.80 per cent of flavonoids, calculated as isoquercitrin ($C_{21}H_{20}O_{12}$; M_r464.4) with reference to the dried drug (Ph.Eur. 2007).

II.1.2 Information on period of medicinal use in the Community regarding the specified indication

The use of elder flower has been continuously documented in handbooks, pharmacopoeias and scientific literature. Elder is a highly valued plant with a history dating back to ancient Greece. Elder flower is used both in flavouring agent in foodstuff and as a medicinal herb. Traditional medicinal use of elder flower connected to the relief of the symptoms of the early phase of the common cold has been documented in handbooks such as Madaus (1938), Hagers Handbuch (Hänsel et al., 1994), Bisset and Wichtl (2001) and British Herbal Compendium (Bradley 1992).

II.2 NON-CLINICAL DATA

II.2.1 Pharmacology

II.2.1.1 Overview of available data regarding elder flower and relevant constituents thereof

Compounds:

Flavonoids (up to 3%):	Chief components are quercetin, rutin, isoquercitrin, kaempferol, astragalin (WHO 2002), nicotiflorin (Hänsel et al. 1994; Willer 1997) and hyperoside (Willer 1997; Fleming 2000; WHO 2002)
Triterpenes:	Ca 1% α- and β- amyrin, occurring mainly as fatty acid esters; Triterpene acids: Ca 0.85% oleanolic and ursolic acids, 20β-hydroxyursolic acid (Bisset and Wichtl 2001)
Volatile oil (0.03-0.14%):	High share (65%) of free fatty acids, including among others palmitic acid (share 38%) (Fleming 2000) and linoleic acid. 7% alkanes (Barnes et al. 2002). Numerous other constituent types have been identified, including ethers and oxides, ketones, aldehydes, alcohols and esters (Toulemonde and Richard 1983).
Caffeic acid derivatives (3%):	Chlorogenic acid (Fleming 2000)
Sterols:	About 0,11%, mainly β-sitosterol, stigmasterol, campesterol (WHO 2002) and cholesterol (Hänsel et al. 1994; Willer 1997)
Minerals:	8-9% (Blumenthal et al. 2000), high in potassium (Steinegger and Hänsel 1988)
Other constituents:	Tannin, mucilage (Bradley 1992), plastocynin (protein), pectin and sugar (Barnes et al. 2002)

II.2.1.2 Pharmacodynamics

***In vitro* experiments**

The following information has been retrieved from the literature:

Effect on blood glucose

Researchers in Northern Ireland conducted an *in vitro* study to evaluate the effect on blood sugar. In a two-armed study, aqueous extract of elder flower significantly increased glucose uptake, glucose oxidation, and glucogenesis in rat abdominal muscle. Elder flower extract incubated with rat pancreatic cells also had a dose-dependent stimulatory effect on insulin secretion. It was concluded that elder flower contains water-soluble components capable of stimulating insulin secretion and enhancing muscle glucose uptake and metabolism. However, the chemical nature of potential antihyperglycemic components of elder flower remains to be established. (Gray et al. 2000).

Anti-inflammatory activity

The ability of aqueous extracts from elder flower to inhibit the proinflammatory activity of major virulence factors from the periodontal pathogens *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* has been investigated. The study indicated that elder flower extract inhibits macrophage release of pro-inflammatory cytokines induced by *P. gingivalis, A. actinomycetemcomitans*, and selected components of these pathogens. Moreover, the elder flower extract suppressed the activation of neutrophils, which have also been implicated as effectors of periodontal tissue destruction. These effects could be attributed to inhibition of activation of NF-κB and phosphatidylinositol 3-kinase (PI3K).

The active ingredients responsible for the anti-inflammatory action of elder flower aqueous extract are unknown. The ability of aqueous extract (SNAE) to inhibit P13K has been suggested to be mediated at least partially through quercetin. The presence in *S.nigra* of anthocyanins with antioxidant action may be responsible for the ability of SNAE to inhibit oxidative burst of neutrophils, and partially, the inhibitory effect of SNAE on NF-κB activation (Harokopakis et al. 2006). A study by Yeşilada et al. (1997) et al. showed that the methanolic extract of elder flower and its lipophilic fractions possess a medium to low inhibitory effect on the biosynthesis of interleukin-1α, interleukin-1β and tumor necrosis factor α.

Antibacterial activity

Izzo et al. (1995) investigated 68 plant extracts from 65 species (including elder flower ethanol extract) for antibacterial activity against eight gram-positive and eight gram-negative bacteria. Elder flower showed activity against *Bacillus subtilis, Staphylococcus aureus, Salmonella typhi, Klebsiella pneumoniae* and *Pseudomonas aeruginosa.* According to Izzo et al (1995), a search of the literature showed that antibacterial properties of elder flower could be attributed to chlorogenic and caffeic acids.

Combination product:

Herpes simplex

A formula of *Sambucus nigra* (flower extract) in combination with *Hypericum perforatum* and *Saponaria officinalis* (SHS-174) was found to inhibit the replication of HSV-1 *in vitro*. Flavonoids, saponins, phenolic acids, tannins and polysaccharides in SHA-174 were considered having antiviral properties. (Serkedjieva et al. 1990). Since this formulation contained a mixture of plant extracts, its effect can not be ascribed to a single plant.

***In vivo* experiments**

Anti-inflammatory activity

An 80% ethanol extract of elder flower had moderate anti-inflammatory activity in rats: it inhibited carrageenan-induced footpad oedema by 27%. The extract was administered intragastrically (100 mg/kg body weight) one hour prior to administration of carrageenan. The control drug, indometacin (5 mg/kg body weight) inhibited carrageenan-induced footpad oedema by 45 (Mascolo et al 1987). A study by Delaveau et al. (1980), showed that intraperitoneal administration of an unsaponifiable fraction of the flowers to mice moderately enhanced phagocytosis at a dose of 0.5 ml/animal. More recent studies on anti-inflammatory activity are not available. Another potentially anti-inflammatory compound found in elder flower is rutin (a glycosylatedform of quercetin) which protects against experimental arthritis in rats (Guardia et al. 2001).

Diuretic activity

According to Rebuelta et al. (1983), intragastric administration of an elder flower infusion (20 ml/kg body weight), or of a potassium- and flavonoid-rich extract of the elder flower extract, had a diuretic effect in rats. The diuretic effect was greater than that observed with theophylline (5 mg/kg body weight). Another study done by Beaux et al. (1999) showed that elder flower caused a significant diuresis from 2-24 hours compared with the control in rats given 50 mg/kg aqueous extracts via the i.p route.

Diaphoretic activity

Bisset and Wicthl (2001) are referring to a study concerning diaphoretic effects of elder flower.

Pharmacodynamic interactions with other medicinal products

Elder flowers may have diuretic effects (Rebuelta et al. 1983; Beaux et al 1999). People taking diuretics or drugs that interact with diuretics should use caution when taking products containing elder flower. The diuretic effects of elder flower have not been established in humans.

Furthermore, elder flower extract (2 ml/kg), administered orally to rats, caused a significant decrease of the sleep induction time of pentobarbitone and increased sleeping time when compared with rats administered pentobarbitone only. Elder flower had no significant effect on the analgesic activity of morphine at this dosage. These preliminary experiments indicate a possible interaction potential between the elder flower and the centrally acting drugs morphine and pentobarbitone (Jakovljevic et al. 2001).

II.2.1.3 Assessor's overall conclusions on pharmacology

The effects of elder flower related to common cold have not been confirmed in non-clinical studies. The data published by Rebuelta (1983) and Beaux (1999), indicate that elder flower may have diuretic effects in rats, but this has not been established in humans. However, avoiding excessive or prolonged use of any drink, including elder flower tea seems reasonable when taking diuretics. Insufficient data are available for drawing any conclusions about elder flowers potential effect on the centrally acting drugs morphine and phentobarbitone.

II.2.2 Pharmacokinetics

II.2.2.1 Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Pharmacokinetic interactions with other medicinal products

The flavonols rutin and quercetin, which are found in elder flower, have been reported to inhibit xanthine oxidase (Nagao et al. 1999), and may theoretically affect caffeine and theophylline levels.

II.2.2.2 Assessor's overall conclusions on pharmacokinetics

No are available on pharmacokinetics.

II.2.3 Toxicology

II.2.3.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Acute toxicity:

No information available.

Repeated dose toxicity:

According to Chibanguza et al. (1984), no significant toxicity was observed in rabbits administered 50 fold human dosage of a combination product containing elder flower (Sinupret; 0,6 g elder flower in 2,6 g drug). An ethanol water extract of elder flowers (6,5 ml extract three times a day) was given intragastrically over a period of 3 days. Parameters measured included rate of breathing, pulse rate, red blood count, Quick value (prothrombin time), and serum calcium, potassium, and sodium.

Genotoxicity:

There are no data on genotoxicity, carcinogenicity, reproductive and developmental toxicity available on elderflower.

II.2.3.2 Assessor's overall conclusions on toxicology

No signals of elder flower having harmful effects have been identified in the non-clinical literature. Since minimum required data on mutagenicity (Ames' test) is not available, an inclusion to the Community list of traditional herbal substances and preparations can not be recommended.

However, raw unripe fruits and other parts of *Sambucus nigra* that contains the cyanogenic glycoside sambunigrin can cause diarrhoea and/or vomiting (Duke et al. 2002). Nigrin b, a lectin isolated from the bark of *Sambucus nigra* L., has a structure and enzymatic activity resembling that of ricin, a toxin. Both ricin and nigrin b depurinate mammalian ribosomes, a characteristic property of RIP (ribosome-inactivating protein). However, lectins from *Sambucus. nigra* L. are much less toxic to cells than ricin (Batteli et al. 1997) Nigrin b is 10^5 and 5 x 10^3 times less toxic for animal cells cultures and mice than ricin (Gayoso et al. 2005).

II.3 CLINICAL DATA

II.3.1 Clinical Pharmacology

No data available

II.3.1.1 Pharmacodynamics

No data available.

Pharmacodynamic interactions:

No data available.

II.3.1.1.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No data available.

II.3.1.1.2 Assessor's overall conclusions on pharmacodynamics

Due to lack of data, no conclusions can be made.

II.3.1.2 Pharmacokinetics

No data available

Pharmacokinetic interactions:

No data available.

II.3.1.2.1 Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No data available in humans.

II.3.1.2.2 Assessor's overall conclusions on pharmacokinetics

Due to lack of data, no conclusions can be drawn.

II.3.2 Clinical Efficacy[3]

Elder flower is used mainly in European traditional medicine. Elder flower's current use as a diaphoretic for the treatment of feverish, catarrhal complaints in Europe and the United States stems from traditional Greek medicine (Madaus 1938, Blumenthal et al. 2000). The same indications for use in traditional Greek medicine have been mentioned by Chopra et al in Glossary of Indian Medicinal Plants from 1956.

The following indications have been reported for elder flower:

Elder flower has been traditionally used against catarrhal conditions (especially in the upper respiratory tract), such as the flu, colds and sinusitis (Madaus 1938; Hänsel et al. 1994; Braun 1997; Fleming 2000; Weiss and Fintelmann 2000; Bisset and Wichtl 2001; Barnes et al. 2002; WHO 2002; Valles et al. 2004; Guarrera 2005; Mills and Bone 2005). Use as expectorant (Grieve 1931; Chiej 1984; WHO 2002) and use in chest complaints (Grieve 1931; Chiej 1984) are also reported.

Mild diuretic effect is reported in some handbooks (Chiej 1984; Bradley 1992; Mills and Bone 2005; Valles et. al. 2004; Barnes et al. 2002; Chopra et al. 1956). Mild diuretic effect is also mentioned by the Czech Republic under indications reported from Member States. The traditional and medicinal purpose of the diuretic usage is not specified, so more information is needed in order to suggest a traditional indication on this background.

Elder flower has been reported to be used as a diaphoretic (Fleming 2000; WHO 2002; Weiss and Fintelman 2000; Valles et al. 2004; Grieve 1931; Chiej 1984; Bisset and Wichtl 2001; Madaus 1938; Chopra et al. 1956; Roth and Schmid. 1978; Hänsel et al. 1994). This diaphoretic effect is also given as an indication by several of the Member States (Poland, Czech Republic and Latvia).

A laxative effect is mentioned in WHO (2002), but elder flower seems to be considered a flavouring agent in laxatives (Bisset and Wichtl 2001, Roth and Schmid 1978).

Elder flower is also used in the preparation of gargles/mouthwash (Roth and Schmid 1978; Hänsel, et al. 1994; Fleming 2000; Bisset and Wichtl 2001). The medical purpose of the gargling is not specified. Oral use for gargling is mentioned by the Czech Republic as an indication: "Inflammations of oral cavity and upper respiratory tract".

Elder flower is widely used in combinations with other herbal substances according to the information given by Member states. The indications reported for combination products are mainly related to the common cold.

[3] In case of traditional use the long-standing use and experience should be assessed.

Other uses mentioned:

Asthma	(Madaus 1938)
Inflammation	(Grieve 1931; Chiej 1984; WHO 2002)
Arthritis	(Lewis and Lewis 2003)
Syphilis	(Lewis and Lewis 2003)
Immunostimulant	(Weiss and Fintelmann 2000; Evans et al. 2002)
Diabetes	(WHO 2002)
Dry skin	(WHO 2002)
Headaches	(WHO 2002)
Rheumatism	(Chopra et al. 1956; WHO 2002)

Evidence regarding the traditional use and posology from handbooks:

Lehrbuch der Biologischen Heilmittel (Madaus 1938)

Traditional use: As a diaphoretic during treatment of common cold. It is used against catarrhal conditions such as laryngitis, bronchitis, cough, whooping cough, beginning pneumonia etc.

Oral dose: *5-15 g dried flowers as infusion.*

Duration of use: No information

Hagers Handbuch der Pharmazeutischen Praxis, Drogen P-Z (Hänsel et al. 1994)

Traditional use: Common cold. As a diaphoretic during the treatment of the cold. Elder flower is also used in other feverish conditions as a tea, or as a gargle.

Oral dose: As a single dose:
Decoction/extract: 1,5 g in a teacup
Average daily dose: 10 - 15 g drug as an infusion. Tea; About 2 full teaspoons (3-4 g) elder flower with approximately 150 ml hot water; several times daily. Especially in the second half of the day; 1-2 cups fresh prepared tea as hot as possible may be taken.

Duration of use: No information

Standardzulassungen für Fertigarzneimittel: Holunderblüten (Braun 1997)

Traditional use: Diaphoretic. Treatment of feverish cold

Oral dose: Tea; About 2 full teaspoons (3-4 g) elder flower with hot water (150 ml). Especially in the second half of the day; 1-2 cups fresh prepared tea as hot as possible may be taken.

Duration of use: No Information

Hagers Handbuch Der Pharmzeutischen Praxis: Sambucus (Roth and Schmid 1978)

Traditional use: As a diaphoretic and for the treatment of the cold, and other feverish conditions.

Oral dose: Daily dose: Infusion: 5-15 g in 200 ml water

Duration of use: No information

Herbal Drugs and Phytopharmaceuticals (Bisset and Wichtl 2001)

Traditional use: As a diaphoretic in feverish chills, etc. In folk medicine, the drug is also used in the preparation of gargles.

Oral dose: 3 g Elder flower as a tea

Duration of use: No information

WHO monographs on selected medicinal plants, volume 2 (WHO 2002)

Traditional use: As a diaphoretic for treatment of fever and chills, and as an expectorant for treatment of mild inflammation of the upper respiratory tract. Also for symptomatic treatment of the common cold.

Oral dose: Crude drug 3-5 g as an infusion (preferably taken hot) three times daily, 25 % ethanol; 3-5 ml; tincture (1:5 in 25 % ethanol); 10-25 ml

Duration *of use*: No information

The Complete German Commission E Monographs (Blumenthal and Busse 1998)

Traditional use: Colds

Oral dose: Average daily dose: 10-15 g drug, 1,5-3 g fluid extract and 2,5-7,5 g tincture.

Mode of administration: Whole herb and other galenical preparations for teas, 1-2 cups of tea sipped several times daily, as hot as possible

Duration of use: No information

British Herbal Compendium (Bradley 1992).

Traditional use: Common cold, feverish conditions

Oral dose: 3-5 g dried flowers in infusion three times daily (preferably taken hot)
Liquid extract (1:1, 25% ethanol): 3-5 ml three times daily
Tincture (1:5, 25% ethanol): 10-25 ml three times daily

Duration of use: No information

PDR for Herbal Medicines (Fleming 2000)

Traditional use: The drug is used for colds and coughs. It is a sweat producing remedy for the treatment of feverish colds.

Oral dose: 10-15 g elder flowers in infusion in doses of 1-2 cups several times-especially in the afternoon and evening

Duration of use: No information

On this background, the following traditional indication is proposed:

Herbal medicinal product traditionally used for relief of early symptoms of common cold.

Assessor's comment on traditional usage and the recommended indication:

The information about the usage submitted from Member states and the information found in literature on traditional use is mainly related to the common cold. According to how common cold is defined, this traditional usage could be considered covered by the indication "relief of symptoms of the early phase of the common cold". According to Heikkinen and Järvinen (2003) the common cold is a conventional term for a mild upper respiratory illness, the hallmark symptoms of which are nasal stuffiness and discharge, sneezing, sore throat, and cough. The common cold is usually a self-limiting illness confined to the upper respiratory tract.

Likewise, the medicinal rationale of the diaphoretic effect could be related to the initial phase of a common cold. A sensation of chilliness is an early symptom of common cold, and is sometimes explained as an initial stage of fever, since vasoconstriction of skin blood vessels may cause a fall in skin temperature that is perceived as chilliness. Common cold in the adult is rarely accompanied by fever and some subjects have a transient fall in body temperature during the early stages of common cold (Eccles 2005). The phytotherapeutic traditional use of elder flower as a diaphoretic is suggested to be interpreted as treatment that has been regarded to be especially beneficial in an early phase of common cold. The traditional usage of diaphoretics is therefore suggested to be regarded as included when the indication comprises the early phase of the common cold.

II.3.2.1 Asessor's overall conclusion on the traditional medicinal use

Traditional medicinal use of elder flower used for relief of early symptoms of common cold has been found to fulfil the requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2004/24/EC.

II.3.2.2 Dose response studies/Traditional use: posology from handbooks

There are no dose response studies available.

Based on the listed posology from handbooks (see II.3.2) the following dosages have been recommended for this indication:

Herbal preparations
Dried flowers; herbal tea (2-5 gram): three times daily
A) Liquid extract, DER 1:1, extraction solvent: 25 % V/V ethanol: 3-5 ml 3 times daily
B) Tincture 1:5 DER in 25 % V/V ethanol: 10-25 ml three times daily

Duration of use:

Not to be taken for more than 1 week due to the nature of the proposed indications. If the symptoms persist for more than one week, a doctor or a qualified health care practitioner should be consulted.

II.3.2.3 Clinical studies (case studies and clinical trials)

No human clinical studies have been found in the literature on elder flower.

However, combination products containing elder flowers have been subjected to studies, e.g.:

Samochowiec et al. (2000) preformed a clinical evaluation of antiatherosclerotic efficacy of plant mixture (MZ) composed of *Flos Calendulae, Folium Melissae* and *Flos Sambuci*. The study was carried out on 100 patients with atherosclerotic abnormalities (moderate increase of arterial blood pressure and elevated lipid concentrations) for 16 weeks. Improvements (prolonged walk distance, decreased blood pressure and diminished platelet aggregation as well as concentration of lipids) was noted in patients receiving MZ compared to placebo. The antiatherosclerotic activity was attributed to flavonoids, essential oils, phytosterols, triterpenes, polyphenolic substances and saponins in the plant mixture (MZ).

In a meta analysis by Melzer et al. (2006) on the herbal formula BNO-101, containing Gentianae radix, Sambuci flos, Primulae flos, Rumicis herbae, and Verbenae Herbae, ratio 1:3:3:3:3, 4 trials were examined. The database comprised approximately 900 patients, mostly young adult males. Melzer et al. (2006) concluded that BNO-101, combined with standard antibacterial therapy, significantly reduced the acute symptoms and signs of sinusitis.

Several other studies with a combination product containing elder flowers (Sinupret) have been performed, but the results of the studies done on this combination products cannot be ascribed to elder flower as a single plant.

II.3.2.4 Clinical studies in special populations (e.g. elderly and children)

None reported

II.3.2.5 Assessor's overall conclusions on clinical efficacy

There are no clinical investigations available for elder flowers as a monopreparation.

II.3.3 Clinical Safety/Pharmacovigilance

There are no risks (adverse reactions) reported from the Member states.
According to De Smet et al. (1992) the United States Dietary Supplement Health and Education Act of 1994 have generally recognised elder flower as safe (GRAS). It is freely available as a "dietary supplement" under DSHEA legislation (Barnes et al. 2002; Mills and Bone 2005) . In addition to GRAS recognition, elder flower is considered as a safe herb in a report of the American Food and Drug Administration (FDA) from 1975 (De Smet et al. 1992). Commission E and Standardzulassungen in Germany considers elder flower as safe, with no contraindications, adverse effects and interactions (De Smet et al. 1992).

II.3.3.1 Patient exposure

Products containing *Sambucus nigra* L., flos are widely available. The products have various regulatory statuses. A considerable patient/consumer exposure must be anticipated as elder flower is also widely used as a flavouring agent in the food area.

II.3.3.2 Adverse events

Bibliographic review of safety data of the traditional herbal medicinal substances

The following electronic databases were searched on 10th of April 2007 with the search term "*Sambucus nigra*, *Sambuci flos* OR elder flower". Results:

PubMed: 385 references obtained.

Toxline: 71 references obtained.

Scifinder: 1156 references obtained (Since this database covers both chemical abstracts and Medline, some references may be cited twice).

The Cochrane Library: 4 references obtained

www.nona.no (Norwegian natural medicine register): 2 references obtained

Out of these references, no case reports on adverse reactions or other signals of safety concern in connection with *Sambucus nigra* L., flos were identified.

No health hazards or side effects are known in therapeutic dosages (Hänsel et al. 1994; Fleming 2000; Kraft and Hobbs 2004).

There were no serious adverse events reported with the combination product containing *Gentianae radix, Primulae flos, Rumicis herba, Sambuci flos* and *Verbenea herba*; ratio 1:3:3:3:3 (Melzer et al. 2006). However, in large doses, elder flower may produce nausea, diarrhoea, and polyuria (Mills and Bone 2005).

The Commission E and the BHC list no known contraindications (Bradley 1992; Blumenthal et al. 2000). However, hypersensitivity to the active substance should be a contraindication.

II.3.3.3 Serious adverse events and deaths

None reported.

II.3.3.4 Laboratory findings

None reported.

II.3.3.5 Safety in special populations and situations

Children (younger than 12 years):

The use is not recommended in children under 12 years of age due to lack of data.

II.3.3.5.1 Intrinsic (including elderly and children) /extrinsic factors

No information available.

II.3.3.5.2 Drug interactions

There are no drug interactions reported

Excessive or prolonged use may possibly result in hypokalaemia in view of the putative diuretic effect.

II.3.3.5.3 Use in pregnancy and lactation

According to Mills and Bone (2005), there is no increase in frequency of malformation or other harmful effects on the foetus from limited use of elder flower in women. Health Canada's Compliance Policy for Natural Health Products, has elder flower on the list of botanicals with a history of safe use in pregnant and breastfeeding women (Health Canada 2006). However, in view of the lack of toxicity data, the use of elder flower can not be recommended during pregnancy or breast-feeding (Barnes et al. 2002; MedlinePlus 2007).

II.3.3.5.4 Overdose

No case of overdose has been reported.

II.3.3.5.5 Drug abuse

None reported

II.3.3.5.6 Withdrawal and rebound

None reported

II.3.3.5.7 Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

II.3.3.5.8 Assessor's overall conclusions on safe use

Elder flower is generally recognised as safe. However, elder flower cannot be recommended during pregnancy or breast-feeding or in children under 12 years of age due to lack of adequate data.
Plant parts other than the flowers and ripe berries are reported to be poisonous and should not be ingested (Barnes et al. 2002). Admixture with other parts of the plant should be avoided.
In accordance with other monographs concerning common cold, the following warning should be included in the monograph: When dyspnoea, fever or purulent sputum occurs, a doctor or a qualified health care practitioner should be consulted.

II.4 ASSESSOR'S OVERALL CONCLUSIONS

Elder flower is widely used in combinations with other herbal substances according to the information given by Member states. The indications reported for combination products are mainly related to the common cold. There are no clinical investigations available for elder flowers in mono-preparations.

Traditional medicinal use of elder flower for relief of early symptoms of common cold has been found to fulfil the requirement of medicinal use for at least 30 years (15 years within the Community) according to Directive 2004/24/EC. Since the documentation of traditional use and efficacy of elder flower is scarce concerning other indications, no further indications are recommended.

Elder flower is generally recognised as safe. However, elder flower cannot be recommended during pregnancy or breast-feeding or in children under 12 years of age due to lack of adequate data.

As minimum required data on mutagenicity (Ames' test) are not available, an inclusion to the Community list of traditional herbal substances and preparations can not be recommended.

ANNEXES

III. LITERATURE REFERENCES