European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT ON

SOLIDAGO VIRGAUREA L., HERBA

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ASSESSMENT REPORT

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

***Solidago virgaurea* L., herba**

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Herbal substance Flowering aerial parts of *Solidago virgaurea* L.
Herbal preparation(s)	A) Comminuted herbal substance B) Liquid extract (1:1), prepared with ethanol/water 25% v/v C) Tincture (1:5 w/v)), prepared with ethanol/water 45% v/v D) Dry extract (5-7:1) prepared with ethanol/water 30 – 60% v/v
Pharmaceutical forms	Herbal preparation in solid or liquid dosage forms or herbal tea for oral use.
Rapporteur	Dr Ewa Widy Tyszkiewicz

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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:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
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:	
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:	
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
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:	
Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
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:	
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

[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	Products	Status
Austria	**Traditional use**: The herbal substance is only available in combination products. Main combination substances are other herbs with diuretic properties. Average 2-3 substances are present in combinations. The combination product Phytodolor® (Populi cortex, Fraxini cortex, Solidaginis herba) is authorized in indication of rheumatic complains.	Traditional use
Bulgaria	No authorized herbal medicinal products containing *Solidago virgaurea* are on the market.	
Czech Republic	**Traditional use**: I. Comminuted herbal substance. Present on the market as authorized product since 1998. The herbal substance is only available in combination products. Pharmaceutical form: herbal tea. According to Czech Pharmacopoeia (Česky Lékopis, 2005): single dose 2.0 g, daily dose 10.0 to 20.0 g. Czech name of the herbal substance: nať zlatobýlu obecného Posology: for oral use; 1 tea spoon/250 ml boiling water several times daily. Indications: as an adjuvant therapy in inflammations of the urinary tract, prevention of cysto- and nephrolithiasis. Contraindications: contraindicated in cardiac and renal insufficiency. Risk of allergic reactions. II. Combination products. Average number of combination substances: 3-5 and >5. 1) Herbal tea – Filipendulae ulmariae herba, Salicis cortex, Violae tricoloris herba, Harpagophyti radix, Equiseti herba, **Solidaginis herba**, Callunae herba - on the market since 1999; for oral use; indications - as an adjuvant for inflammatory and degenerative diseases of locomotors apparatus (rheumatism, arthrosis, arthritis and gout), adjuvant therapy in flu like symptoms 2) Herbal tea – Epilobii herba, Bucco folium, **Solidaginis herba**, Calendulae flos cum calyce - on the market since 1999; for oral use; indication- for adjuvant therapy in case of micturition difficulties (e.g. associated with diagnosed benign prostate hyperplasia, prostatitis, inflammations of the urinary tract; special warning: not recommended for patients with chronic renal diseases, regular medical supervision is required! 3) Herbal tea – Uvae ursi folium, Equiseti herba, Myrtilli herba, Matricariae flos, Sambuci nigrae flos, **Solidaginis herba**, Thymi herba; - on the market since 1989, for oral use; indications - as an adjuvant therapy in acute and chronic infections and inflammations of the urinary tract.	Traditional use

Member state	Products	Status
Denmark	Herbal substance present on the market as an authorized product. **Well established use**: 1) Solidaforce® (MAH Bioforce). 1 ml ethanolic extract of Solidago virgaureae herba 320-468 mg, corresponding to 114 mg of dry herb. Pharmaceutical form: oral drops. Posology: 30-40 drops 3-4 times daily. Present on the market before 2000. 2) Solidamin 10® Indication: Herbal medicinal product for slightly increasing the diuresis, especially at irritation in the urinary tract. ATC code: C03 **Traditional use:** 1) A combination product: Salus tea nr. 23. Present on the market between 1993-2007 as a herbal medicinal product. Pharmaceutical form: herbal tea Adverse effects: Known hypersensitivity to *Compositae* flowers Pharmacovigilance actions were not taken on medicinal products containing the herbal substance.	Well established use Traditional use
Finland	No authorized herbal medicinal products containing *Solidago virgaurea* are on the market.	
Germany	**Well established use** There are 13 herbal medicinal products on the market: **1, 5, 12**) dry extract from Solidaginis virgaureae herba (5-7:1), extraction solvent: ethanol 30% m/m; **2, 4**) dry extract from Solidaginis virgaureae herba (5-7:1), extraction solvent: ethanol 60% V/V; **3, 13**) dry extract from Solidaginis virgaureae herba (5-7.1:1), extraction solvent: ethanol 30% m/m **6)** dry extract from Solidaginis virgaureae herba (5-6:1), extraction solvent: water **7**) powder from Solidaginis virgaureae herba **8, 11**)dry extract from Solidaginis virgaureae herba (5-6.1:1), extraction solvent: ethanol 50% m/m **9**) dry extract from Solidaginis virgaureae herba (6-7:1), extraction solvent: ethanol 60% V/V **10**) liquid extract from Solidaginis virgaureae herba (1:0.9-1.1), extraction solvent: ethanol 35% V/V Preparations 1, 2, 3, 11, 6, 7, 8, 9, 10, 11) are on the market at least since 1976; preparations 5, 13) since 1996; preparation 12 since 2000 Pharmaceutical forms: Preparations 1,7, 12 are film coated tablets. Preparations 2, 9 are tablets; preparations 3,4,5,6 are hard capsules; preparations 8, 10, 11 are oral liquid and preparation 13 is soft capsule	Well established use

Member state	Products	Status
Germany	Posology: All preparations are for oral use and all for use in adults and adolescents over 12 years. 1, 12) three times daily 1 film-coated tablet containing 342 mg dry extract 2) four-five times daily 1 tablet containing 342 mg dry extract 3, 5) three-four times daily 1 hard capsule containing 428.8 mg dry extract 4) three times daily 1 hard capsule containing 360 mg dry extract 6) three times daily 2-3 hard capsules containing 250 mg dry extract each 7) three times daily 4 film-coated tablets containing 500 mg powder each three times daily 5 ml oral liquid (100 g oral liquid = 93 ml contain 9 g dry extract) 9) two-three times daily 3 tablets containing 116.4 mg dry extract each 10) three-five times daily 50 drops (ca. 2 g) oral liquid containing 100% liquid extract 11) three times daily 5 ml oral liquid (100 g oral liquid = 92.8 ml contain 9 g dry extract) 13) three-four times daily 1 soft capsule containing 428.8 mg dry extract Indication: As a purging in inflammatory diseases of the urinary tract collection system, urolithiasis and renal gravel, preventive treatment in urolithiasis and renal gravel. Adverse effects: Preparations 1 – 13) Gastrointestinal complaints (pain, cramps, nausea) Allergic reactions (itching, exanthema, swelling of the tongue, oral and pharyngeal mucosa Case reports in our data bank, Schätzle M *et al*. Allergic contact dermatitis from goldenrod (Herba Solidaginis) after systemic administration. Contact dermatitis 1998, 39: 272. Pharmacovigilance actions were not taken on medicinal products containing the herbal substance. Well established use combination product: (1) contains Betulae folium and Orthosyphonis folium besides Solidago virgaureae herba. **Traditional use** Herbal medicinal authorised product: **1**) liquid extract from fresh Solidaginis virgaureae herba (1:1.9-3.2), extraction solvent: ethanol 57.3% m/m present on the market since 1976. Pharmaceutical form: oral liquid Posology: for oral use in adults and adolescents over 12 years 5 x daily 40 drops (1 ml = 32 drops) containing 100% extract Indications: Traditional herbal medicinal producst to support the elimination function of the kidney. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use.	Well established use Traditional use

Ireland	No authorized herbal medicinal products containing *Solidago virgaurea* are on the market.	
Latvia	No authorized herbal medicinal products containing *Solidago virgaurea* are on the market.	
Poland	**Traditional use** Present on the market as 3 authorized products since 1995. Preparations: Comminuted herbal substance Solidaginis herba prepared as herbal tea. Infusion made of 3 - 4 g of dried herb in 100 ml of boiling water, 3 times daily. Indications: Traditionally to increase the amount of urine, as adjuvant in treatment of minor urinary complaints. Adverse effects: not known Pharmacovigilance actions were not taken on medicinal products containing the herbal substance. Combination products: Most of products on Polish market are herbal teas (16 products) with Solidaginis virgaureae herba being one of components. There are also oral liquids (7 composed products); capsules containing pulverised herbs (1 product); pastae (2 composed products); one herbal granulate; drops (2 composed products); one product in form of tablets.	**Traditional use**
Slovenia	No authorized herbal medicinal products containing *Solidago virgaurea* are on the market.	
Spain	**Traditional use.** Comminuted herbal substance. Present on the market as registered product before 1980. Solidaginis herba prepared as herbal tea. Infusion made of 6 - 10 g of dried herb, one cup 3 -4 times daily. Indications: diuretic Pharmacovigilance actions were not taken on medicinal products containing the herbal substance. **Combination products**: Combination products of diuretic herbal substances for use as a Herbal tea Average number of combination substances: 3-5 and >5 in the product.	**Traditional use**

Sweden	**Traditional use** Herbal medicinal authorised product present on the market since 1978 1) Ethanol extract (1:8, 66 %) 910 mg. 1 ml contains 910 mg extract corresponding to 0.4 g fresh herb (or 0.1 g dried herb). Pharmaceutical form: oral drops, solution. Posology: Adults and adolescents: 1 ml in ½ glass of water, 3-5 times daily. Not recommended to children. Indications: Traditionally used for symptomatic relief of lower urinary tract disorders of the type that may benefit from an increased flow through the urinary tract, for example urinary tract irritation or light pain caused by passing urinary stones or kidney gravel Contraindications: Should not be used as a diuretic by oedema due to heart or kidney insufficiency. Allergy to *Compositae*. Precautions should be taken with a lot of water. If the symptoms persist more than 3 days or if symptoms such as blood in the urine, fever or low backpain occur the underlying condition should be investigated in order to exclude urinary tract infection or other serious condition. Pharmacovigilance actions were not taken on medicinal products containing the herbal substance. The product is approved as a natural remedy.	**Traditional use**
United Kingdom	No authorized herbal medicinal products containing *Solidago virgaurea* are on the market.	

II. ASSESSMENT REPORT FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH WELL-ESTABLISHED USE AND/OR TRADITIONAL USE

II.1 INTRODUCTION

Solidago virgaurea L. (synonyms: *Amphiraphis leiocarpa*, *Amphiraphis pubescens, Dectis decurrens, Doria virgaurea,* European golden rod) belongs to the family of *Asteraceae* (*Compositae*). The herbal substance consists of the dried, flowering parts of the plant (*Solidaginis virgaureae herba*, British Herbal Pharmacopoeia 1976; ESCOP Monographs 2003; Bader 1994; 1999; 2006; Goldenrod. http://www.Herbalgram.org; Hoppe 1975; PDR for Herbal Medicines 2000; Pharmeuropa 2001; http://www.pharmakobotanik.de/systematik/6droge-f/solida-v.htm; Pharmacopée Francaise 1989; Verga D'Oro 2001).

Solidago has been used for treatment of different diseases in Europe since medieval times (Arnold from Villanova (1240-1311), *Lonicerus* 1564; Hieronimus Bock 1565 and *Tabernaemontanus* (1530-1590). Its diuretic activity is mentioned in "*Thesaurus pharmacologicus*" Schroeder's, 1669 (Bader 1999); in Madaus "Lehrbuch der Biologischen Heilmittel" (1938) and in Mayer Monograph of Solidago *Virga aurea* L. (Mayer and Mayer 1950).

II.2 CHEMICAL COMPOSITION

European goldenrod contains miscellaneous flavonoids (1.5%) (quercetin, kaempferol and their glycosides, astragalin and rutoside) and antocyanidins, derivatives of cyanidin. Other constituents include triterpene saponins of the oleanane type (up to 2%), the bisdesmosidic phenol glycosides leiocarposide (0.08-0.48%) and virgaureoside A, diterpenoid lactones of the cis-clerodane type, phenolic acids (caffeic acid, chlorogenic acid (0.2-0.4%), ferulic acid, synapic and vanillin acids) and small amount of essential oil (cadinene, α and β pinene, myrcene, limonene, sabinene and germacren D) (Bader 1999; Bornschein 1987; ESCOP Monograph 2003; Fötsch and Pfeifer 1989; Fötsch *et al*. 1989; Gerlach 1972; Goswami *et al*. 1984; Hiller *et al*. 1975; Hiller and Gil Rjong 1980; Hiller and Fötsch 1986; Hiller *et al*. 1991; Inose *et al*. 1991, 1992; Jiang *et al*. 2006; Kalemba 1998; Knütter and Pohloudek-Fabini1969; Lück 2001 edoc.hu-berlin.de/dissertationen/lueck-lorna-2001-08-03/HTML/lueck-bib.html; Poetsch 1999; Prosser at al. 2002; Radoias *et al* 2004; Schilcher 1964, 1965). The polyphenolic compounds and terpenoids from *Solidago virgaurea* L. are presented in Table 1 according to Wittig and Veit (1999).

Table 1. Chemical composition of *Solidago virgaurea* L (according to Wittig and Veit 1999)	
Salicylic acid	Kalemba 1992
p-Hydroxybenzoic acid	Kalemba 1992
Protocatechuic acid	Kalemba 1992
p-Coumaric acid	Kalemba 1992
Gentisic acid	Kalemba 1992
Ferulic acid	Kalemba 1992
Synapic acid	Kalemba 1992
Vanillic acid	Kalemba 1992
Caffeic acid	Björkman and Holmgren 1960; Borkowski and Skrzypczakowa 1962; Kalemba 1992
Chlorogenic acid	Björkman and Holmgren 1960; Kalemba 1992; Borkowski and Skrzypczakowa 1962
Synapic acid	Kalemba 1992
Isorhamnetin	Wittig and Veit (1999)
Isorhamnetin 3-*O*-galactoside	Wittig and Veit (1999)
Isorhamnetin 3-*O*-glucoside	Wittig and Veit (1999)
Isorhamnetin 3-*O*-rhamno-glucoside	Wittig and Veit (1999)
Kaempferol	Wittig and Veit (1999)
Kaempferol 3-*O*-arabinoside	Wittig and Veit (1999)
Kaempferol-3-*O*-glucoside (Astragalin)	Skrzypczakowa 1962; Hiller *et al*. 1979 Wittig and Veit (1999)
Kaempferol-3-*O*-rutinoside	Hiller *et al*. 1979; Kalemba *et al*. 1992
Kaempferol-3-*O*-galactoside	Wittig and Veit (1999)
Kaempferol-3-*O*- rhamno-glucoside (Nicotiflorin)	Wittig and Veit (1999)
Kaempferol-3-*O*- rhamnoside (Afzelin)	Wittig and Veit (1999)
Kaempferol-3-*O*-robino-bioside	Wittig and Veit (1999)
Quercetin	Skrzypczakowa 1962; Wittig and Veit (1999)
Quercetin-D-glucoside	Hiller *et al*. 1979
Quercetin-3-*O*-arabino-pyranoside	Wittig and Veit (1999)
Quercetin-3-*O*-galactoside (Hyperoside)	Wittig and Veit (1999)
Quercetin-3-*O*-glucoside (Isoquercitrin)	Wittig and Veit (1999)
Quercetin-3-*O*-rhamno-glucoside (Rutin)	Thiem and al. 2001; Wittig and Veit (1999)
Quercetin-3-*O*-rhamnoside (Quercitrin)	Skrzypczakowa 1962; Wittig and Veit (1999)
Quercetin-3-*O*-roibinoside	Wittig and Veit (1999)
Rhamnetin-3-*O*-rhamno-glucoside	Wittig and Veit (1999)

Limonene	Fujita 1991Kalemba 1998
β-Caryophyllene	Kalemba 1998
β-Elemene	Fujita 1991
δ-Elemene	Fujita 1991
α-Humulene	Kalemba 1998
Germacrene B	Fujita 1991
Germacrene-D	Fujita 1991
δ-Cadinene	Fujita 1991
α-Muurolene	Kalemba 1998
Oleanolic acid	Tamas and Rosea 1988
Bayogenin	Tamas and Rosea 1988
Leiocarposide	Hiller *et al*. 1979; Bader *et al*. 1990a; 1998; Fötsch *et al*. 1988.
α-Pinene	Fujita 1991; Tucker and Maciarello 1999; Kalemba 1998
β-Pinene	Kalemba 1998
Sabibene	Kalemba 1998
β-Myrcene	Fujita 1991; Tucker and Maciarello 1999; Kalemba 1998
Virgaureasaponin 3	Bader *et al*. 1991; 1995
Virgaureoside A	Hiller *et al*. 1985
Solidagosaponins 21	Miyase *et al*. 1994
Solidagosaponins 22	Miyase *et al*. 1994 ,
Solidagosaponins 23	Miyase *et al*. 1994
Solidagosaponins 24	Miyase *et al*. 1994 ,
Solidagosaponins 25	Miyase *et al*. 1994
Solidagosaponins 26	Miyase *et al*. 1994
Solidagosaponins 27	Miyase *et al*. 1994
Solidagosaponins 28	Miyase *et al*. 1994
Solidagosaponins 29	Miyase *et al*. 1994
Solidagosaponins 30	Miyase *et al*. 1994

II.3 PHARMACOLOGY

The pharmacological and clinical effects of *Solidago virgaurea* has been described in several reviews (Bader 1999; Hiller and Bader 1996; Laszig *et al*. 1999, Melzig 2004, Schilcher 1987; Schilcher 1999, Schmitt 1996; Weiss 1980; Yarnell 2002).

A synergic action of several components of the *Solidago virgaurea* L. is proposed. Therefore, the herbal substance or herbal preparations from Solidago must be considered as the active ingredient.

II.3.1 NON-CLINICAL DATA

II.3.1.1 Pharmacodynamics

II.3.1.1.1 Anti-inflammatory activity

Anti-inflammatory activity of saponins from *Solidago virgaurea* L. was tested in experimental oedema model in rats. Pletysmographic estimation showed significant reduction of the volume of the oedema after iv administration of 1.25mg – 2.5 mg/kg of triterpene saponin complex (Jacker *et al*. 1981).

Terpene fraction or its derivatives were shown to present antiulcer activity. Such activity was described for a labdane diterpene from *Solidago chilensis* in HCl/ethanol induced gastric lesions in mice (Schmeda-Hirschmann *et al*. 2002).

In experiment on rats the combined preparation of *Solidago virgaurea*, *Fraxinus excelsior* and *Populus tremula* (Phytodolor®) was tested for an anti-inflammatory, analgetic and antipyretic activity. Activity was similar to that of reference substances salicyl alcohol and indomethacin. Each of the individual extracts exhibited significant efficacy (Okpanyi *et al*. 1989).

Extracts of *Solidago virgaurea* (aqueous/alcoholic) were tested for anti-inflammatory activity in carrageenen induced oedema and in adjuvant induced arthritis in rats. Both extracts of *Solidago* as well as extracts of *Populus tremula* and *Fraxinus excelsior* (composition of Phytodolor® preparation) significantly reduced the carrageenen oedema and reduced the volume of the arthritic paw (El-Ghazaly *et al*. 1992).

Anti-inflammatory activity was also demonstrated with samples from Phytodolor® in *in vitro* experiments, where significant inhibition of expression of TNF-α and COX-2 activity was observed (Schaser *et al*. 2006).

Anti-inflammatory influence of *Solidago virgaurea* extract from fixed composition Phytodolor® on the activity of myeloperoxidase (MPO) liberated by activated granulocytes was estimated in *in vitro* experiments. Solidago extract did not inhibit myeloperoxidase activity at concentrations up to 1% (Von Kruedener *et al*. 1995; 1996).

Saponins, flavonoids and caffeic acid esters from *Solidago virgaurea* inhibited the activity of leukocyte elastase, a protease involved in the progression of inflammation. The ester saponins increased permeability of cells and stimulated the synthesis and release of glucocorticoids in the adrenal glands (Melzig *et al*. 2000).

Anti-inflammatory activity of leiocarposide was tested in rats with carrageenen oedema test (Table 2, Metzner *et al*. 1984).

Table 2. Anti-inflammatory activity of leiocarposide and phenylbutazone in rats (Metzner *et al*. 1984).

Compound tested	**Dose mg/kg N=8**	**Oedema inhibition (%)**				
		1 h	2 h	3 h	4 h	5 h
Leiocarposide	100	0	0	5	6	20
Leiocarposide	200	10	3	10	14	27*
Phenylbutazone	50	15	53	55*	66*	54*

The pharmacological activity and toxicology of phytotherapeutic Ariven® composed of aqueous extract of *Solidago virgaureae*, *extr. Oleandris*, sparteine sulfate, pyridine-3-carbonic acid, pyridine-3-carbonic acid amide, vitamin B_1 and vitamin B_6. was estimated in several experiments testing antioedemic effects. The Solidago extract significantly inhibited the inflammatory skin reaction induced by X-ray radiation model in guinea pigs and examined with Trypan Blue method (Wagener 1966).

II.3.1.1.2 Antioxidant activity

Chlorogenic and caffeic acids have been reported to scavenge reactive species of oxygen and nitrogen (Kono *et al*. 1997).

Mixture of the ethanolic extracts (35% aqueous ethanol) from dried *Solidago virgaurea*, *Potentilla anserina*, *Radix Rubiae tinctorum*, *Equisetum arvense*, *Oleum Juniperi* and *Petroselini sativi fructus* was used *in vitro* to estimate glucose consumption by rabbit brain slices. Swelling of brain slices *in vitro* was significantly diminished with an increase of glucose consumption and the aerobic formation of lactic acid (Dittmann 1973).

Antioxidant activity of ethanolic extract of *Solidago virgaurea* (0.52 mg/ml of rutin, 0.64 mg/ml of flavonoids and ethanol 45.6% v/v) was tested *in vitro* as a component of the phytotherapeutic drug Phytodolor®. The activity of xanthine oxidase (XOD), diaphorase (NAD-dia-juglone), lipooxygenase (LOX) and the light activators, riboflavin and rose Bengal was studied. The results showed inhibition of production of reactive oxygen species in above mentioned reactions by *Solidago virgaurea* L. extract (Meyer and Elstner 1990; Meyer *et al*.; 1995).
Similar effects of Phytodolor® were described in another series of experiments (Germann *et al*. 2005).

II.3.1.1.3 Analgesic activity

Analgesic activity of leiocarposide was shown in experiments performed on mice in hot plate and withdrawal of a hind foot upon irradiation (the inhibition of a polysynaptic reflex) tests. This activity was compared with aminophenazone effects (Table 3, Metzner *et al*. 1984).

Table 3. Analgesic activity of leiocarposide and aminophenazone in mice (Metzner et al. 1984).

Test	**Compound tested**	**Dose mg/kg N=10**	**Analgesic effects (%)**		
			0.5 h	1 h	2 h
Inhibition of polysynaptic reflex	Leiocarposide	200	70	30	10
	Aminophenazone	100	60	40	40
Hot plate	Leiocarposide	200	100	90	20
	Aminophenazone	50	100	90	80

The analgesic potential of *Solidago virgaurea* was tested *in vitro* for affinity to three neuropeptide receptors involved in the mediation of acute pain in mammals: bradykinin, expressed in Chinese hamster ovary cells, neurokinin 1 expressed in astrocytoma cells and calcitonin gene related peptide. The Solidago methanolic extract of the seeds of the plant produced significant inhibition of radio-ligand binding for bradykinin receptors (Sampson *et al*. 2000).

II.3.1.1.4 Spasmolytic activity

In experiment performed *in vitro* on isolated smooth muscles of intestines of guinea pig *Solidago virgaurea* ethanolic extract induced spasmolytic activity in the range of 14.73% of papaverin (Westendorf and Vahlensieck, 1981).

Presence of flavonoids (quercetin and kaempferol) in *Solidago virgaurea* preparations may contribute to explain vascular smooth muscle relaxation. It can be concluded that vasodilatatory action depends on the inhibition of protein kinase C, inhibition of cyclic nucleotide phosphodiesterase or decrease of Ca^{2+} uptake (Rácz *et al*. 1980; Duarte *et al*. 1993).

In other experiments performed *in vitro* in acetylcholine pretreated urinary bladder of the rat the phytotherapeutic product (Urol®) combined of *Extr Rad. Rubiae tinct. Spir, Extr. Sem Ammeos visnagae spir., Extr. Herb. Solidago virgaureae spir., Extr. Rad. Taraxaci* and aescin exhibited spasmolytic activity. This effect was mainly due to the ingredient *Extr. Solidago virgaureae* (Westendorf and Wahlensieck 1983).

Aqueous extract of leaves of *Solidago virgaurea* (aqueous extraction, evaporation of eluate to a spissum extract and dilution with water) inhibited muscarinic M_2 and M_3 receptor-mediated contraction of rat and human bladder muscle strips. Low extract concentrations (0.01%) appeared to

result from non-competitive muscarinic receptor antagonism, whereas higher (0.1%) concentrations might have non-specific inhibitory effect. Relationship between *in vitro* concentrations and therapeutic doses remained unclear due to unknown bioavailability of the active ingredients of the extract (Borchert *et al*. 2004).

II.3.1.1.5 Antibacterial activity

Antibacterial activity of monovalent preparations (six extracts) and mixtures (ten preparations) of *Solidago virgaurea* were tested *in vitro* against urogenital bacterial pathogens (*Staphylococcus aureus, Staphylococcus epidermidis*). Tested mixtures (*Solidago virgaurea* combined with *Cortex Rhus aromaticae*, *Fol. Uvae ursi* and *Hb. Taraxaci*) showed significantly stronger antibacterial activity than monovalent preparations. The results indicate that *Solidago virgaurea* extracts exhibited antibacterial effect against *Staphylococcus aureus* and *Staphylococcus epidermidis*. Moreover these extracts of *Solidago virgaurea* demonstrated activity against a larger range of microbes than extracts of *Solidago gigantea* and *Solidago canadensis* (Brantner 1999).

Antimicrobial activity of ethanolic and methanolic extracts of *Solidago virgaurea* L. were tested *in vitro* by use of freeze-dried biomass from 4-week old callus cultures of the plant. The minimal bactericidal concentrations of the ethanolic and methanolic extracts of *Solidago virgaurea* estimated with the agar diffusion assay method showed a moderate activity and are presented in Table 4. (Thiem and Goślińska 2002).

Table 4. Antimicrobial activity (MBC) of extracts from plant and callus of *Solidago virgaurea* L. from *in vitro* cultures (Thiem and Goślińska 2002).

Microorganism	**Plant**		**Callus tissue**
	EtOH MBC	**MeOH MBC**	**MeOH MBC**
Bacillus subtilis	1.8	3.9	31.2
Bacillus pumilis	15.6	31.2	62.5
Proteus mirabilis	3.9	7.8	62.5
Proteus vulgaris	31.2	62.5	-
Micrococcus luteus	7.8	15.6	31.2
Pseudomonas aeruginosa	31.2	62.5	-
Staphylococcus aureus	62.5	12.5	62.5
Staphylococcus epidermidis	31.2	31.2	12.5
Escherichia coli	31.2	62.5	-
Aspergillus niger	62.5	62.5	-

MBC – minimal bactericidal concentration (mg/ml); - no activity

Inhibition of dihydrofolate reductase activity, an enzyme modulating cytostatic and antibacterial activity was found in *in vitro* experiments with water-soluble components of Phytodolor® phytotherapeutic composed of *Fraxinus excelsior*, *Populus tremula* and *Solidago virgaurea*. The *Solidago virgaurea* ethanolic extract (rutin 0.52 mg/ml, flavonoids 0.64 mg/ml, ethanol 45.6% v/v, Steigerwald Arzneimittelwerk) induced inhibition of the activity of dihydrofolate reductase

(I_{50}=0.013% v/v). However, the overall effect of the combination was more pronounced. The single component as the combined extracts exhibited activity in the range of effective NSAID's (Strehl *et al*. 1995).

II.3.1.1.6 Antifungal activity

In the course of screening for new antifungal agents Bader *et al*. (1987) showed that deacylated triterpenoid saponins of *Solidago virgaurea*, isolated after mild alkaline hydrolysis of the mixture of genuine ester saponins, showed higher activity against several *Candida* species (*Candida albicans, Candida tropicalis, Candida krusei, Candida parapsilosis, Candida pseudotropicalis, Candida guilliermondi, Candida glabrata* and *Cryptococcus neoformans*), than the mixture of ester saponins. These deacylated saponins (bisdesmosidic glycosides of polygalacic acid) virgaureasaponins 1, 2 and 3 (Bader *et al*. 1992) demonstrated higher antifungal activity than that of the corresponding prosapogenins (monodesmosides) (Bader *et al* 1990b).

In other experiments Pepeljnjak *et al*. (1998) showed antimycotic activity of *Solidago virgaurea* ethanolic extract against dermatophytes, especially against *Trichophyton mentagrophytes, Microsporum gypseum* and *Microsporum canis*. Antifungal activity against *Candida albicans* was very low.

II.3.1.1.7 Anticancer activity

Significant tumour inhibitory action of Virgaurea saponin E (1 mg/kg/day) was found *in vivo* in mice in allogenic sarcoma-180 model and in syngenic sarcoma model (Bader *et al*. 1996; 1998b). In another series of experiments the antitumour effects of polysaccharides were demonstrated.

In an SCID mouse model antineoplastic activity of *Solidago virgaurea* on prostatic tumour cells was tested and cytotoxic activity on various tumour cell lines was demonstrated (human prostate, breast, melanoma and small lung carcinoma). The active fraction of the extract corresponding to a molecular weight of ≅ 40,000 (G-100) was administered *i.p*. or s.c. every 3 days for 25 days in experimental tumour model in mice. The growth of the tumours was inhibited at 5 mg/kg (Gross *et al*. 2002).

II.3.1.1.8 Immunobiological activity

Immunomodulatory (induction of macrophages and activation of NK-cells) and antitumour activity of triterpene saponins (Virgaurea saponin E_1) were shown in *in vitro* experiments (Plohman et al. 1997, 1999).

Further chromatographic separation demonstrated the presence of five benzylbenzoates from the hexane soluble fraction of the methanolic extract of the aerial parts of *Solidago virgaurea var. gigantea*. By using *in vitro* mouse peritoneal macrophages two compounds (2-methoxybenzyl-2-hydroxybenzoate and benzyl-2-hydroxy-6-methoxybenzoate) exhibited stimulation macrophage

function (range of 1-100 µg/ml), suggesting potential use in the treatment of infectious diseases and tumours (Choi *et al*. 2005).

II.3.1.1.9 Diuretic activity

The diuretic properties of *Solidago spp.* are in prevalence based on studies performed on the European goldenrod (*S. virgaurea* L.). Leiocarposide (2'-hydroxybenzyl-2,4-dihydroxy-3-methoxybenzoate 2'.4-diglucoside) was isolated for the first time from *Solidago virgaurea var. Leiocarpa* (Benth/Gray) (Hiller *et al*. 1979) and was found in *Solidago virgaurea L* (Chodera *et al*. 1985a, 1985b; Budzianowski 1999). Leiocarposide is completely absent in *Solidago canadensis* L. and *Solidago gigantea* Ait. Acute toxicity (LD_{50}) of leiocarposide in rats was 1.55 g/kg. The compound was shown to exhibit diuretic activity in rats, only 75% lower than furosemide (Table 5, Chodera *et al*. 1985a). The action of leiocarposide was 30% higher after *i.p*. than *per os* administration. The diuretic action was delayed and started after 5 hours after administration and lasted up to 24 hours (Table 6, Chodera *et al*. 1985b).

The leiocarpic acid (3,6-dihydroxy-2-methoxybenzoic acid), part of the leiocarposide molecule, showed no diuretic activity at the dose 25 mg/kg *i.p*. (Budzianowski 1999).

Table 5. Diuretic activity of leiocarposide and furosemide in rats (Chodera *et al*. 1985a, b).

Groups	**N**	**Urine volume/rat/day (ml)**	**% Increase of urine volume after 24 h**
Control	10	7.8 ± 0.5	-
Furosemide 6 mg/kg *i.p.*	10	17.3 ± 0.5*	125
Leiocarposide 25 mg/kg *i.p.*.	10	13.3 ±*	70

*p<0.05 vs. control

Table 6.Diuretic activity of leiocarposide after intraperitoneal (*i.p*.) and oral (*per os)* administration (Chodera *et al*. 1985 b).

Groups (N=10)	**Urine volume/rat/day (ml)**				**% Increase of urine volume after 24 h**
	5 h	**6 h**	**12 h**	**24 h**	
Control ***per os***	1.0±0.1	1.7±0.1	2.7±0.2	4.7±0.3	
i.p	0.5±0.1	1.5±0.1	2.7±0.3	4.5±0.4	
Leiocarposide 25 mg/kg ***per os***	1.3±0.1	2.4±0.2	3.0±0.2	8.4±0.3*	80
i.p.	0.9±0.1	1.1±0.1	3.6±0.2	9.4±0.5*	110

*p<0.05

Table 7. Elimination of sodium, potassium and calcium ions in urine of the control, leiocarposide and furosemide treated rats (Chodera *et al* 1985b).

	N	Na^+ mMol/l	K^+ mMol/l	Ca^+ mMol/l
Control	10	32.41 ± 3.04	2.93 ± 0.21	0.51 ± 0.09
Leiocarposide 25 mg/kg *i.p.*	10	25.34 ± 3.12	1.76 ± 0.14	0.31 ± 0.06
Furosemide *i.p.*	10	54,43 ± 5.15*	1.74 ± 0.12	0.31 ± 0.06

The flavonoid fraction of *Solidago virgaurea* L. administered to rats showed an increase of diuresis (88% after 24^h). Decrease of an overnight excretion of potassium and sodium and increase of excretion of calcium ions was observed (Table 8, Chodera *et al*. 1991).

Table 8. Diuretic and saluretic activity of the flavonoid fractions of *Solidago virgaurea* (Chodera *et al*. 1991).

	N	Na^+ mmol/dm^3	K^+ mmol/dm^3	Ca^+ mmol/dm^3	Increase of diuresis after 24^h
Control NaCl, 5 ml *per os*	10	31.83±1.91	87.82±6.12	1.35±0.22	
Solidago Virgaureae* flavonoid fraction 25 mg/kg *per os	10	17.82±1.33*	68.04±4.31*	4.08±0.29*	88

Interestingly, it was also demonstrated, that leiocarposide diuretic activity was reduced by the presence of flavonoids and saponins. In contrary, some researchers suggest that diuretic activity of goldenrod is exerted by the mixture of flavonoids and saponins, but the others demonstrated in animal studies relative inactivity of flavonoid mixture (Schilcher *et al*. 1989).

In experimentally induced renal calculi model in rats it was shown, that after 6 weeks of administration of leiocarposide (25 mg/kg) the growth of the renal calculi was significantly decreased (Chodera *et al*. 1988).

Significant increase of diuresis in rats together with an increased elimination of sodium, potassium and chloride ions was observed after oral administration of infusion of *Solidago virgaurea* (0.3% of flavonoids, 4.64 ml/kg and 10.0 ml/kg). The lower dose was more efficient (Schilcher and Rau 1988).

Acylated triterpenoid saponins (especially virgaureasaponin B) present in *Solidago virgaurea* could transiently change the cell membrane permeability and induced alterations in ionic homeostasis with enhanced permeability between the intracellular and extracellular compartments. These effects could be the result of the structural similarity of acyl groups with fatty acids as constituents of the biological membranes (Melzig *et al*. 2001).

Comparison of diuretic activity of different fractions of *Solidago virgaurea* extracts (methanol/water, 70:30) on Sprague Dawley rats (N=12–16 per experimental group) showed significant diuretic and saluretic activity of some fractions of the extract.

The hydroxycinnamic acid fraction (100 mg/kg p.os) significantly increased sodium and potassium excretion in urine. This activity did not differ from furosemide efficacy 10 mg/kg/. There was no influence on calcium ion excretion, both in hydroxycinnamic acid and furosemide groups.

The flavonoid fraction (100 mg/kg) did not elevate urine volume or ion secretion. The significant increase of urine volume and saluretic activity for sodium and potassium ions was demonstrated for the saponin fraction (25 mg/kg – 100 mg/kg). These effects were comparable to those of furosemide (10 mg/kg *per os*) (Kaspers *et al*. 1998).

Active flavonoides of *Solidago virgaurea* (especially quercetin) inhibit NEP and angiotensin-converting enzyme (ACE) activity (Schilcher and Rau 1988; Melzig *et al*. 2001a; Melzig and Major 2000; Table 9, Major 2001 http://edoc.hu-berlin.de/dissertationen/major-hedda).

Table 9. Influence of the methanol extracts of *Solidago virgaurea* and their fractions on activity of neutral endopeptidase (NEP) (Major 2001, http://edoc.hu-berlin.de/dissertationen/major-hedda)

Tested compounds	**Concentration µg/ml**	**NEP Inhibition %**
Saponin mixture	200 100	- -
Flavonoids and phenolic acids	200 100	26 26
Flavonoids mixture with rutin	750 500 200	28 17 -
***Solidago virgaurea* extract (80%MeOH)**	750 500	38 29
***Solidago virgaurea* extract (96%MeOH)**	750 500	41 33

The mechanism of beneficial renal and cardiovascular activity of *Solidago virgaurea* can depend on modulation of neutral endopeptidase activity (NEP). By blocking the hydrolysis of the vasoactive peptides, Solidago treatment can regulate water and sodium balance and cardiovascular homeostasis by increasing water and sodium excretion and arterial and venous vasodilatation (Melzig and Major 2000).

II.3.2 Assessor's overall conclusions on pharmacology

Non-clinical data show diuretic, anti-inflammatory, antioxidant, analgesic and spasmolytic, antibacterial, antifungal, anticancer and immunomodulatory activity of *Solidago virgaurea*. However, as no single ingredient is responsible for these effects, the whole herbal preparation of *Solidago* inflorescences must be considered as the active ingredient.

II.3.3 Pharmacokinetics

A selection of several herbal medicinal products was analysed for their modulatory influence on expression of cytochrome P-450 enzymes CYP1A2, CYP3A4 and the transporter protein MDR1. The experiments were performed *in vitro* on cultures of LS180 cells. The *Solidago virgaurea* product Solidanin® (Bioforce, Roggwill, Switzerland) was resolved in DMSO and then diluted to final concentration of 100 μg/ml. Solidanin® solution did not influence CYP1A2 and MDR1 expression, however it induced 1.9±0.2 fold CYP3A4 genes. The activation of the nuclear receptor PXR is believed to be responsible for modulation CYP3A4 expression (Brandin *et al*. 2007).

II.3.3.1 Assessor's overall conclusions on pharmacokinetics

There are no specific data on pharmacokinetics of *Solidago virgaurea*. However, some interactions are possible due to influence on CYP3A4 genes expression.

II.3.4 Toxicology

II.3.4.1 Cytotoxicity

Constituents of the aerial parts of the plant *Solidago virgaurea var. gigantea* used as stomachic and diuretic in Korea were identified by chemical and spectroscopic methods. Six terpenoids and four phenolics were isolated from the hexane-soluble fraction of the total MeOH extract. Compounds: *ent*-germacra-4(15),5,10,(14)-trien-1β-ol, β-dictyopterol and 3,5-di-*O*-caffeoylquinic acid showed *in vitro* cytotoxicity against cultured lines of human tumour cells (A549-non small cell lung adenocarcinoma, SK-OV-3-ovarian, SK-MEL-2 – skin melanoma, XF498 – CNS and HCT15 –colon. The ED_{50} values ranged from 1.52-18.57 μg/ml (Table 10, Choi *et al*. 2004).

Table 10. Cytotoxic effects of *Solidago virgaurea* constituents (Choi *et al*. 2004).

EC_{50} values (concentration (μM) that caused 50% inhibition of cell growth *in vitro*.					
Compound	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
***ent*-germacra-4(15),5,10,(14)-trien-1β-ol**	14.21	17.06	12.30	14.34	14.17
β-dictyopterol	18.57	17.97	5.91	1.52	9.11
3,5-di-*O*-caffeoylquinic acid	>30	>30.0	>30.0	>30.0	>30.0

Other investigations on the constituents *Solidago virgaurea var. gigantea* revealed isolation of three cytotoxic compounds: erythrodiol-3-acetate, α-tocopherol-quinone and trans-phytol from the hexane soluble fraction (Sung *et al*. 1999).

II.3.4.2 Acute Toxicity

No data available. Acute toxicity of the leiocarposide in rats was reported: LD_{50} (oral) as 1.55 g/kg b.w. (Chodera 1985a).

II.3.4.3 Repeated dose toxicity

No data available.

II.3.4.4 Genotoxicity, Carcinogenicity

No information on genotoxicity and carcinogenicity is available.

II.3.4.5 Reproduction Toxicity

No data are available on reproductive or developmental toxicity.

II.3.4.5 Assessor's overall conclusions on toxicology

No relevant data are available on toxicology of *Solidago virgaurea* except of acute toxicity of leiocarposide. Because of the lack of data concerning mutagenicity and genotoxicity, the inclusion of *Solidago virgaurea* L. to the Community List cannot be considered.

II.4 CLINICAL STUDIES

II.4.1 Clinical Pharmacology

II. 4. 1. 1 Clinical studies with *Solidago virgaurea* products (Table 11)

In an open post marketing crossover study with placebo in 22 healthy patients (age 17 – 61 years), an ethanolic extract made from fresh plant *Solidago virgaurea* L. was tested. The patients received 100 (5x20) drops/day of the ethanolic extract (64 % V/V, Goldruten Tropfen®) for 2 days. In Solidago treated groups the significant increase of daily volume of urine (27%) was observed ($p<0.01$) (Klinisch-Experimentelle Studie Nr 23223. P 1. 1992).

In an open multicentre postmarketing study the ethanolic extract of *Solidago virgaurea* L. made from fresh plant (64 Vol%, Goldruten Tropfen®) was tested in 53 patients (45 female, 8 male, age: 6 – 83 years) with symptoms of urinary tract inflammation: dysuria, pollakisuria, tenesmus. The treatments lasted 1 year, but time of the treatment of individual patient differed, depending on the physician´s decision. The patients with renal stones, renal carcinoma, gonorrhoea, syphilis, AIDS and marked prostate hyperplasia were excluded, as patients with bacterial counts in urine over 10^4. Adult patients

received 100 drops (5x20) of Solidago extract. Patients younger than 12 years received 55 drops/day. After treatment in 65.4% treated patients the significant clinical improvement was observed with significant reduction of dysuria, pollakisuria and tenesmus (Klinisch-Experimentelle Studie Nr. 23223.P2. 1992).

The efficacy of the dry extract of *Solidago virgaurea* (5.4:1, Stromic®) was tested in an open multicentre study performed by 289 physicians in 745 female patients (age: 12-94 years) with dysuria of different origin. After 14 days of treatment with Solidago extract (three times 380 mg/day) in 69.2% patients micturition frequency was decreased as the other symptoms of cystitis (Schmitt 1996).
In the postmarketing study performed on 1487 patients with several urinary tract diseases (irritable bladder, urinary tract infections, renal calculi/gravel) the efficacy of an extract from *Solidago virgaurea* (5.0-7.1:1, ethanol 30% m/m) was estimated. Patients were treated in average for 4 weeks (Cystinol Long Kapseln®, 3x424.8 mg/day). Global improvement (in CGI scale) was evaluated by physicians and in 79% of patients reached significance (Laszig *et al*. 1999).
In an open multicentre (308 physicians) study performed on 1487 patients with chronic recurrent irritable bladder condition the subgroup of 512 patients (age: 13 – 96 years, 77% female) was treated for five weeks. The patients received *Solidago virgaurea* L. dry extract (5.0-7.1:1, 424.8 mg, 3x/day). In result, 96% of the patients treated showed improvement registered in CGI scale, and in 80.1% of patient´s estimation of effectiveness was good or very good. Side effects were not registered (Melzig *et al*. 2001b; Pfannkuch and Stammwitz 2002).

The case report of patients treated with *Solidago virgaurea* dry extract for 4 weeks after extracorporeal shock wave lithotripsy resulted with spasmolytic effects, and lack of additional spasmolytic treatment needed (Laszig *et al*. 1999).

II.4.1.2 Clinical studies with composition products

An open outpatient study was performed in 20 patients with renal calculi/gravel (age: 7 – 60 years) to test therapeutical efficacy of phytomedicine Fitolizyna® (Solidago extract as one of the components) for 2 weeks – 3 months (1 teaspoon of paste, three times daily). Significant diuretic effect was noted in all tested patients with very good tolerance of treatment (Krzeski 1960).
In patients with different subtypes of rheumatic diseases the anti-inflammatory and analgesic efficacy of the fixed combination of *Populus tremula*, *Solidago virgaurea* and *Fraxinus excelsior* (Phytodolor®) have shown a similar efficacy compared to NSAID treatment (Chrubasik and Pollak 2003; Ernst 2004; Jorken and Okpanyi 1996; Klein-Galczinsky 1999)
However, the relevant participation of *Solidago virgaurea* in clinical efficacy of composition products is not known.

Table 11. Presentation of the non–randomized open clinical studies with *Solidago virgaurea* products.

Reference	Quality of the study	Indication Baseline conditions	Preparation Daily dose Mode of administration Duration of treatment	Patients Number (N) Age	Statistics	Adverse events Toxicity	Final results Efficacy	Comment
Klinisch-Experimentelle Studie Nr 23223.P 1. 1992	Open, postmarketing, crossover, non-randomized with placebo group	Healthy volunteers	**Test phase:** Goldruten Tropfen® ethanolic extract of *Solidago virgaureae* fresh (64 Vol%). **Daily dose**: 20 drops x 5/day **Duration** : 2 days	N = 22 Age: 17 – 61 years Male: 8 Female: 14	Student t-Test	No data Good tolerance of treatment.	Increased urine volume during treatment of Goldruten Tropfen• compared to placebo effects (1.3 dl – 27%), $p<0.01$ Time between 20.00^{h} p.m. and 1-st miction episode related do urine volume was significantly shortened compared to placebo effects	Significant diuretic activity in healthy volunteers

Reference	Quality of the study	Indication Baseline conditions	Preparation Daily dose Mode of administration Duration of treatment	Patients Number (N) Age	Statistics	Adverse events Toxicity	Final results Efficacy	Comment
Klinisch-Experimentelle Studie Nr 23223.P 2. 1992	Open, prospective, multicenter study (16 physicians), postmarketing, non-randomized with placebo group	**Inclusion criteria**: Inflammation of urinary tract. Symptoms: dysuria, pollakisuria, tenesmus, gorączka, bacteriuria. **Exclusion criteria:** Bladder stones, bladder carcinoma, gonorrhea, syphilis, marked prostate hyperplasia, bacteriuria $\geq 10^4$	Goldruten Tropfen® ethanolic extract of *Solidago virgaureae* fresh (64 Vol%) **Daily dose**: 20 drops x 5/day **Duration**: 1 year	N = 53 8 patients excluded from trial **Age:** 6 – 83 (45.5 ± 20.1) Years Children <12 years: 3 Male: 8 Female: 45	No statistical data. For calculations SAS (Statistical Analysis System) Datasets, Version 6.04) was used.	Mild side effects in 2% of patients. Gastro-esophageal reflux symptoms. General good tolerance of treatment	Clinically relevant improvement according to the opinion of physicians reduction of: dysuria in 86.0%, pollakisuria in 86.4%, tenesmus in 72.7% was found in 75.5% of patients: (in 64.2% good, and in 11.3% moderate efects). Significant reduction of ascending infections of urinary tract in 90.0% of patients.	Significant diuretic and antiin-flammatory activity in patients with inflammation of urinary tract.

Reference	Quality of the study	Indication Baseline conditions	Preparation Daily dose Mode of administration Duration of treatment	Patients Number (N) Age	Statistics	Adverse events Toxicity	Final results Efficacy	Comment
Schmitt 1996	Open, prospective, multicenter study (289 physicians), postmarketing, non-randomized	Dysuria of different origin: hyperactive bladder with urine incontinence **Inclusion criteria:** pollakisuria: >5x/day **Exclusion criteria:** pollakisuria: ≤5x/day, bacteriuria, genital organs infections, heart and kidney insufficiency, others diuretics use, allergy to the *Solidago spp*.	Stromic® (dry extract of *Solidago virgaurea*, 5.4:1) **Daily dose**: 380 mg x 3/day **Duration**: 14 days	N = 745 **Age:** 12 – 94 years Mean: 47 years Female : 745	No data	In 12 patients (0.3%) side effects were noted: gastrointestinal disorders and allergic reactions.	After 14 days of treatment in 69.2% of patients micturition frequency was significantly decreased. According to opinion of physicians in 98.5% of patients effects of treatment were "very good or good". According to personal opinion of patients such results were observed in 97.5% of treated persons.	Successful reduction of symptoms of irritable bladder. Lack of statistical data.

Reference	Quality of the study	Indication Baseline conditions	Preparation Daily dose Mode of administration Duration of treatment	Patients Number (N) Age	Statistics	Adverse events Toxicity	Final results Efficacy	Comment
Laszig *et al*. 1999	Open, prospective, postmarketing, multicenter study (289 physicians), postmarketing, non-randomized CGI arbitrary scale	**Subgroups:** **1 group:** Infections of urinary tract **2 group:** Irritable bladder **3 group:** Urolithiasis Renal calculi, Renal and bladder gravel	Cystinol Long Kapseln® (dry extract, 5.0-7.1 : 1, ethanol 30% m/m) **Daily dose**: 424.8 mg x 3/day **Duration**: 4 weeks	N = 1487 **1 group** N = 555 **2 group** N = 512 **3 group** N = 427 **Age:** mean = 54 years	No data	No data	**1 group** Improvement was noted in 71% of patients. **2 group** Improvement was observed in 71% of patients. **3 group** Significant improvement was observed after 4 weeks of treatment in 79% of treated patients (evaluation by physicians by use of CGI scale) In 99% of patient opinion results were estimated as good/very good.	Significant therapeutic efficacy in infections of urinary tract, irritable bladder and in urolithiasis. Lack of statistical data.

Reference	Quality of the study	Indication Baseline conditions	Preparation Daily dose Mode of administration Duration of treatment	Patients Number (N) Age	Statistics	Adverse events Toxicity	Final results Efficacy	Comment
Pfannkuch and Stammwitz 2002	Open, prospective, postmarketing, multicenter study. (308 physicians), non-randomized CGI arbitrary scale Used by physicians and patients	**Subgroups:** Urolithiasis renal calculi, renal and bladder gravel, irritable bladder. infections of urinary tract. **1 group:** Irritable bladder with urine incontinence **2 group:** Urolithiasis renal calculi, renal and bladder gravel, **3 group** Infections of urinary tract	Cystinol Long Kapseln® (dry extract, 5.0-7.1 : 1, ethanol 30% m/m) **Daily dose**: 424.8 mg three times/day **Duration**: 5 weeks	N = 1487 Female : 77% **1 group (Active)** N = 512 Female N = 463 Male N = 49 **2 group** **3 group** N = 427 **Age:** 13 – 96 years	Wilcoxon-Test	Side effects observed in 0.07% of patients. General good tolerance of treatment.	In result of 5 weeks therapy 96% of the 512 patients treated showed improvement after 35 days, registered in CGI scale ($p<0.0001$). 95% of patients estimated results as ” very good”.	Successful reduction of symptoms of irritable bladder. Descriptive statistics included.

II.4.2.1 Clinical studies in special populations (e.g. elderly and children)

No relevant data available. No special studies for children and elderly were performed. The number of children included into studies is to small for further assessment. Products containing *Solidago virgaurea* L. cannot be recommended for use in children below the age of 12 years.

II.4.2.2 Assessor's overall conclusions on clinical efficacy

Solidago virgaurea products were used in 5 non-controlled, non-randomized open trials. The number of participants varied between the trials from 22 to 1487. On the basis of published results of these clinical trials, the quality of the available studies cannot be evaluated. The protocols with sample calculation are missing. Statistical methods are not shown in all protocols, characteristics of the patients are incomplete, in most trials inclusion and exclusion criteria are not given and no comparators (control groups) included. There is no information about dropping out cases. No specific questionnaires on the quality of life are given. The relevance of non-clinical studies has not been confirmed by clinical trials.

Overall, in the presence of missing information, assessing and interpreting treatment effects of *Solidago virgaurea* can be limited only to traditional use.

II.4.3 Adverse events

Hypersensitivity reactions and mild gastrointestinal disorders (in 0.07%-0.3% patients tested) were the only adverse reactions registered in connection with *Solidago virgaurea* L. intake.

Patients suffering from allergic contact dermatitis due to *Compositae* species are requested to avoid contacts with *Solidago virgaurea* (De Jong *et al*. 1998; Lundh *et al*. 2006; Myers and Wohlmuth 2005; Schätzle *et al*. 1998, Stingeni *et al*. 1999, Zeller *et al*. 1985).

II.4.4 Interactions

No data available.

II.4.5 Assessor's overall conclusions on clinical safety

No case reports on adverse reactions or other signals of safety concern in connection with *Solidago virgaurea* L., inflorescences were identified, except in patients allergic to *Compositae* species. As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended.

II.4.6 Use in pregnancy and lactation

No data available.

II.4.7 Overdose

No data available.

II.4.8 Effects on ability to drive or operate machinery

No data available.

II.4.9 Contraindications

Known hypersensitivity or allergy to *Compositae* (*Asteraceae*) or *Solidago spp*.

II.4.10 Overall conclusions on safety

As there is no information on reproductive and developmental toxicity the use during pregnancy and lactation cannot be recommended.

The traditional medicinal use of *Solidago virgaurea* L. has been documented within the Community. No specific clinical data of *Solidago virgaurea* L. adverse effects have been identified under normal conditions of use. Two post-marketing studies demonstrated good tolerability in 97 – 98% of patients (N=745 and 1487) treated for 2-4 weeks. Only one case of a minor adverse effect was noted (heartburn) (Schmitt 1996; Laszig *et al*. 1999).

As no data on use in children are available, products containing *Solidago virgaurea* L. cannot be recommended for use in children below the age of 12 years.

II.5 ASSESSOR'S OVERALL CONCLUSIONS

- The traditional use of *Solidago virgaurea* L. is well documented. However, because of absence of sufficient clinical data, the quality of the available studies cannot be evaluated. The results of clinical trials cannot support a well-established indication of use.
- Several non-clinical experiments indicate on diuretic, spasmolytic, anti-inflammatory, analgesic and antibacterial effects of the *Solidago virgaurea*. However, the relevance of non-clinical studies has not been confirmed by clinical trials.
- Although this phytotherapeutic treatment in urinary tract diseases is extremely popular, there is no detailed reasonable scientific explanation on effects and the exact mechanism of diuretic action.
- No isolated compound which has been isolated from *Solidago virgaurea* is recognized as responsible for its diuretic action, thus the complex mixture of constituents contributed to this effect.
- Indication of an increase of volume of urine, especially in cases of inflammation and renal calculi/gravel is well documented, both in monographs and textbooks, as in data regarding longstanding use.

- The therapeutic dose is 3.0-5.0 g dried herbal substance for preparation of an infusion, equivalent to 0.5-2.0 ml of liquid extract or to 0.5-2.0 ml of tincture, 2-4 times daily.
- There is almost no information on the toxicity, genotoxicity, carcinogenicity and reproductive and developmental toxicology. Therefore the use in pregnancy and lactation is not recommended.
- The use in children under 12 years of age is not recommended, as no data are available on safety of treatment.
- Products containing *Solidago virgaurea* L. are available in many Member States of the EU. Thus, the requirement of medicinal use for at least 30 years (15 years within the Community), Directive 2004/24/EC is fulfilled.
- Because of lack of data concerning mutagenicity, the inclusion of *Solidago virgaurea* L., herba to the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be considered.