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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb., herba

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

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Whole or cut dried aerial parts collected before or during flowering time of *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb.
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use
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Note: This draft assessment report is published to support the release for public consultation of the draft European Union herbal monograph on *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb., herba. It should be noted that this document is a working document, not yet edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

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

- Herbal substance(s)

Monographs in the European Pharmacopoeia or any national pharmacopoeia are not available.

There is a monograph "Epilobii herba" available in the Czech Pharmaceutical Codex 1993 (Český farmaceutický kodex 1993). It includes the dried flowering herb of *Epilobium parviflorum* SCHREB., *Epilobium montanum* L., *Epilobium collinum* C.C.GMEL. and *Epilobium roseum* Schreb. The herbal substance contains not less than 8.0% of tannins. According to the test for foreign matter and adulteration the two species *Chamerion angustifolium* (L.)HOLUB and *Epilobium hirsutum* (L.) must be absent.

According to Hänsel *et al.* (1993), Wichtl & Tadros (1982) and Wichtl (1984, 2009) the herbal substance consists of the whole or cut dried aerial parts of *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb. collected before or during flowering time. In the 1980s according to Flora Europaea the genus was structured into sectio Chamaenerion and sectio Epilobium. Today the plant name *Chamaenerion* (or sometimes *Chamerion*) *angustifolium* is regarded as a synonym for *Epilobium angustifolium* (Sennikov 2011).

Constituents (Hänsel *et al*. 1993, Lachinger 2004, Wichtl 2009, Granica *et al*. 2014):

Tannins and related compounds (4-14%): e.g. oenothein B, oenothein A, tri-, tetra-, and penta-O-galloylglucose

Flavonoids (1-2%): e.g. kaempferol, kaempferol 8-O-methyl-ether, kaempferol-3-O-rhamnoside, kaempferol 3-O-arabinoside, kaempferol-3-O-gluruconide, kaempferol-3-O-(6''-p-coumaroyl)-glucoside, quercetin, quercetin-3-O-rhamnoside, quercetin-3-O-glucoside, quercetin-3-O-galactoside, quercetin-3-O-arabinoside, quercetin-3-O-glucuronide, quercetin-3-O-(6''-galloyl)-galactoside, myricetin, myricetin-3-O-rhamnoside, myricetin-3-O-glucoside, myricetin-3-O-galactoside, myricetin-3-O-arabinoside, myricetin-3-O-glucuronide (according to Lachinger 2004 and Hiermann *et al*. 1991 only detected in *E. angustifolium*)

Phenolic acids and their derivatives: e.g. ellagic acid, valoneic acid dilactone, chlorogenic acid, neochlorogenic acid, coumarolyquinic acids, feruloylquinic acids, gallic acid, cinnamic acid, protocatechuic acid, caffeic acid, ferulic acid

Steroids (ca.0.4%) and triterpenes (ca. 1.5%): e.g. cholesterol, campesterol, stigmasterol, β-sitosterol, ursolic acid, corosolic acid, oleanolic acid

Other constituents: e.g. linoleic acid, palmitic acid, stearic acid, eicosenoic acid, behenic acid, arachidic acid

- Herbal preparation(s)

Comminuted herbal substance

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

The request for information exchange concerning preparations from Epilobium, herba revealed that the herbal tea is widely distributed in the food sector in Poland, also in combination products. However, such combinations are not subject of this assessment report.

1.2. Search and assessment methodology

The assessment is based on the sources mentioned in the list of references. Publications in other languages than English or German (at least abstract in English or German available) were precluded from assessment.

Search engines used: Google; key words: "Weidenröschen", "Koptischer Tee", "willow herb", "Ivan tea", "Kapor tea"

Scientific databases: Scifinder, Scopus; search date 29.10.2014; key words: "epilobium", "epilobium angustifolium", "chamaenerion angustifolium", chamerion angustifolium", "epilobium parviflorum", "willow herb", "myricetin-3-O-glucuronide", "oenothein"

Medical databases: Pubmed, Cochrane library; search date 29.10.2014; key words: "epilobium", "epilobium angustifolium", "chamaenerion angustifolium", chamerion angustifolium", "epilobium parviflorum", "willow herb", "myricetin-3-O-glucuronide", "oenothein"

Toxicological databases: Toxnet; search date 29.10.2014; key words: "epilobium", "epilobium angustifolium", "chamaenerion angustifolium", chamerion angustifolium", "epilobium parviflorum", "willow herb", "myricetin-3-O-glucuronide", "oenothein"

Pharmacovigilance resources: Not applicable.

Data from EU and non-EU regulatory authorities: Not applicable.

Other resources: Library of the University of Vienna (Pharmacy and Nutritional Sciences library)

2. Data on medicinal use

2.1. Information about products on the market

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

Information on medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
Epilobii herba*	For symptomatic treatment of mild micturition disorders related to benign prostatic hyperplasia,	Herbal tea for oral use, 1 teaspoon/250 ml of boiling water/15 minutes, 3 times daily	Registered as an herbal medicinal product (from 1997-2010 in CZ) Notified food

	irritable bladder		supplement (from 2010 until now in CZ)
Epilobium parviflorum herba	Relief of symptoms of benign prostatic hypertrophy or inflammation such as nocturia, frequent daytime micturition, lact of complete emptying	Tablets for oral use, 1 tablet 3 times daily	Registered as an herbal medicinal product (from 1999 to 22/08/2013 in HU)

*According to the monograph Epilobii herba included in the Czech Pharmaceutical Codex 1993

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

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

Austria:

In Austria three combination products (herbal tea) containing Epilobium angustifolium L. are known to be registered under a simplified procedure according to special national provisions (§11a Austrian Medicines Act). Data is available for two of them. One was marketed from 1997 to 2010; the other one is marketed since 1993:

Herbal tea

100 g herbal tea containing 30 g Epilobii angustifolii herba, 30 g Urticae radix, 20 g Uvae ursi folium, 20 g Herniariae herba.

Indication: inflammation of the bladder, irritable bladder and for prevention of prostate related disorders

Posology: 1 heaped teaspoon/150 ml of boiling water, 2 times daily, if necessary several times daily.

On the market: from 1997 to 2010

Herbal tea

100 g herbal tea containing 20 g Orthosiphonis folium, 20 g Uvae ursi folium, 20 g Epilobii angustifolii herba, 20 g Herniariae herba, 10 g Solidaginis herba, 10 g Ericae herba,

Indication: for flushing of the urinary tract and for adjuvant treatment of symptoms related to inflammation of the bladder and irritative bladder.

Posology: 2 teaspoons/150 ml of boiling water, 3-4 times daily

On the market since 1993

Czech Republic:

Epilobin Planta herbal tea

1 tea bag containing 750 mg Epilobii herba, 375 mg Bucco folium, 225 mg Solidaginis virgaureae herba, 150 mg Calendulae flos cum calyce
Indication: For symptomatic treatment of mild micturition disorders related to benign prostatic

hyperplasia
Posology: 1 tea bag/300 ml of boiling water, 2-3 times daily
On the market since: 1999 (registration was granted in the old legislative frame in 1999, switched to current TUR within the transition period in 2011)

Hungary

Herbal tea

1 tea bag containing 0.175 g Epilobii herba, 0.175 g Equiseti herba, 0.175 g Matricariae flos, 0.175 g Urticae folium.

Indication: Relief of urinary symptoms of benign prostatic hypertrophy

Posology: 2 tea bags 3 times daily

On the market since: 11/04/2005

Oral drops

1 ml liquid extract containing 80.00 mg Epilobii herba, 80.00 mg Urticae folium, 53.40 mg Urticae radix, 40.00 mg Solidaginis herba, 13.40 mg Foeniculi dulcis fructus; DER 1:5, extraction solvent: ethanol

Indication: Relief of urinary symptoms of benign prostatic hypertrophy and inflammation at the initial stage of disease

Posology: 30 drops 3 times daily

On the market since: 25/07/2002

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

The request for information exchange concerning preparations from Epilobium, herba revealed that the herbal tea is widely distributed in the food sector in Poland, also in combination products. However, no further product-specific details are given. In Austria and Germany the herbal substance "Herba Epilobii" was widely distributed for use according to folk medicine (Treben 1978, 1980, 1982; Wichtl & Tadros 1982, Saukel 1982, Schilcher 1982, Hiermann 1984). According to an Austrian wholesaler for herbal substances in Austria at least up to 1000-1500 kg per year of the herbal substance (ca. 70% E. parviflorum and 30% E. angustifolium) were sold also via pharmacies especially at the beginning of the 1980s (Kottas-Heldenberg 2014). Additionally, another Austrian wholesaler for herbal substances reported an amount of 400 kg of "Herba Epilobii" that was sold via pharmacies in 1984 (Zimmermann 2014).

2.1.2. Information on products on the market outside the EU/EEA

No information available.

2.2. Information on documented medicinal use and historical data from literature

Comminuted herbal substance as herbal tea for oral use

The genus Epilobium (Onagraceae) consists of approximately 200 species distributed worldwide (Granica *et al.* 2014), twenty-seven different species can be found in Europe (Saukel 1982). The roots

and herb of some of these species have been used traditionally as medicinal plants in and outside Europe. The roots and also the aerial parts of *Epilobium angustifolium* and other species were used externally by Native Americans to treat skin infections and rectal bleeding (Hänsel *et al.* 1993, Granica *et al*. 2014). Infusions from the aerial parts of Epilobium, especially *Epilobium angustifolium*, were recommended by American herbalists in the 19th and 20th century as a very effective agent to treat gastrointestinal diseases such as dysentery and diarrhoea of different aetiologies as well as other bowel and intestinal disorders associated with infection, irritation and inflammation (Granica *et al*. 2014). In Russia, the aerial parts of *Epilobium angustifolium* were consumed untreated or fermented as infusion, called "Ivan tea", "Kapor tea" or "Russian tea", to treat stomach ulceration, gastritis and sleeping disorders (List & Hörhammer 1972,1973; Granica *et al*. 2014). In Europe, the genus *Epilobium* was known as a medicinal plant from the 16th century for the treatment of wounds, to stop bleeding and for the treatment of female disorders. At that time the herbal substance was known as "Weiderich" or "Herba Lysimachiae" (Fuchs 1543, reprint 2001). In the 20th century, especially in Austria, Germany and Poland, the use of *Epilobium parviflorum* as an herbal tea in the treatment of benign prostatic hyperplasia, prostatitis as well as bladder and kidney disorders became very popular after the publication of experiences of Maria Treben (1978, 1980, 1982, 1986). Her knowledge on and experiences with several herbal remedies, among them also Epilobium, were first published in German language as a brochure in 1978 and as a book in 1980. Since then it has been translated in 27 languages and until today more than 8 million copies were sold. Due to the high popularity of the book an increasing demand for "Herba Epilobii" for the treatment of benign prostatic hyperplasia as well as bladder or kidney disorders was recognized in pharmacies, especially in Austria and Germany (Wichtl & Tadros 1982, Schilcher 1984). Also the scientific community became interested in the genus Epilobium and first botanical and phytochemical investigations were published (e.g. Saukel 1982, Saukel 1983, Hiermann 1983, Wichtl & Tadros 1982, Wichtl 1984). Even though Maria Treben recommended only the use of "small flowered" willow herb, such as *E. parviflorum*, *E. montanum*, *E. obscurum*, *E. lanceolatum*, *E. collinum*, *E. palustre*, *E. fleischeri* and *E. anagallidifolium* and considered *E. angustifolium* not to be effective, also *E. angustifolium* was marketed (via pharmacies and drug stores) since the 1980s. (Wichtl & Tadros 1982, Wichtl 1984, Wichtl 2009, Schilcher 1982, Schilcher 1984, Saukel 1982, Hiermann 1984, Lachinger 2004, Gerlach 2007). According to an Austrian wholesaler for herbal substances at least up to 1000-1500 kg per year of the herbal substance "Epilobii herba" (ca. 70% *E. parviflorum* and 30% *E. angustifolium*) were sold especially at the beginning of the 1980s in Austria (Kottas-Heldenberg 2014). In contrast, according to Schilcher (1982, 1984) and Hiermann (1984) the major part of the herbal substance on the market was derived from *E. angustifolium*. Such data suggest that both species were used as herbal substance. Additionally, another Austrian wholesaler for herbal substances reported an amount of 400 kg of "Herba Epilobii" that was sold via pharmacies in 1984 (Zimmermann 2014). Furthermore, until today *E. angustifolium* and/or *E. parviflorum* are also mentioned as traditional medicinal plants in several textbooks for phytotherapy (e.g. Jänicke *et al.* 2003, van Wyk *et al*. 2004, Frohne 2006, Schilcher *et al.* 2010) for the treatment of symptoms related to benign prostatic hyperplasia. Moreover, the Czech Pharmaceutical Codex (Český farmaceutický kodex 1993) includes a monograph "Epilobii herba" classifying the herbal substance as astringent and diuretic. Due to these findings it can be assumed that the comminuted herbal substances of *E. angustifolium* and *E. parviflorum* were used as an herbal tea for oral use at least since 1982 in considerable amounts in the treatment of benign prostatic hyperplasia as well as bladder and kidney disorders within the European Union. Thus the requirements for the period of medicinal use according to Directive 2001/83/EC as amended with respect to "traditional use" are regarded fulfilled.

The recommended posology is, according to Treben (1980), 1 heaped teaspoon per 250 ml of boiling water. One cup of tea should be taken in the morning on an empty stomach, 1 cup in the evening half

an hour before a meal. According to Wichtl (1984, 2009) the single dose is 1.5 – 2.0 g. Consequently the daily dose is 3-4 g. According to the Czech Pharmaceutical Codex (Český farmaceutický kodex 1993) the therapeutic dose is a single oral dose as an infusion using 2.0 g of the herbal substance.

Table 2: Overview of historical data

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
Comminuted herbal substance (*E. angustifolium*; *E. parviflorum* and other small flowered *Epilobium* species)	Treatment of benign prostatic hyperplasia	Comminuted herbal substance as herbal tea for oral use 1 heaped teaspoon per 250 ml of boiling water, 2 cups per day (1 cup in the morning on an empty stomach, 1 cup in the evening half an hour before a meal)	Treben (1978, 1980, 1982, 1986), , Hänsel *et al*. (1993), Wichtl & Tadros (1982), Wichtl (1984), Schilcher (1982, 1984), Lachinger (2004), Gerlach (2007), Granica *et al.* (2014)
Comminuted herbal substance (*E. parviflorum* and other small flowered *Epilobium* species)	Treatment of bladder and kidney disorders	Comminuted herbal substance as herbal tea for oral use 1 heaped teaspoon per 250 ml of boiling water, 2 cups per day (1 cup in the morning on an empty stomach, 1 cup in the evening half an hour before a meal)	Treben (1978, 1982, 1986)
Comminuted herbal substance (*E. parviflorum, Epilobium montanum, E. collinum, E. roseum*)	Diuretic, adstringent	Comminuted herbal substance as herbal tea for oral use, single dose: 2.0 of the herbal substance	Czech Pharmaceutical Codex (1993)

2.3. Overall conclusions on medicinal use

As discussed in 2.2 since the end of the 1970s/the beginning of the 1980s the medicinal use of the aerial parts of *Epilobium angustifolium* and *Epilobium parviflorum* has become very popular in folk medicine in several European countries for the treatment of benign prostatic hyperplasia as well as bladder or kidney disorders. Herbal medicinal products containing the single active substance Epilobium parviflorum, herba, were or are still on the market in CZ and HU (see table 3). Furthermore, combination products were or are still on the market in AT, CZ, and HU. Whereas the medicinal use for the treatment of symptoms of benign prostatic hyperplasia is well documented and known also in the scientific community, data are too scarce concerning the use in bladder and kidney disorders. Thus the requirements for the period of medicinal use according to Directive 2001/83/EC as amended with respect to "traditional use" are only regarded fulfilled for the indication benign prostatic hyperplasia.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Comminuted herbal substance (*E. angustifolium*, *E. parviflorum*) as herbal tea for oral use	Benign prostatic hyperplasia	1.5-2.0 g of the comminuted herbal substance in 250 ml of water as an herbal infusion 2 times daily.	Since 1982) Wichtl & Tadros (1982), Wichtl (1984), Schilcher (1982, 1984)

Based on available literature references the following posology is proposed:

Herbal tea: 1.5-2.0 g of the comminuted herbal substance in 250 ml of water as an herbal infusion 2 times daily

Based on the available literature references and with respect to the legal requirements for traditional herbal medicinal products the following indication is proposed:

Traditional herbal medicinal product for the relief of lower urinary tract symptoms related to benign prostatic hyperplasia, after serious conditions have been excluded by a medical doctor.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Anti-proliferative activity and potential effect on prostate cells growth as well as anti-inflammatory activities are considered as primary pharmacodynamic effects in the treatment of symptoms related to benign prostatic hyperplasia.

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Strength Dosage Route of administration	Experimental model *In vivo/* *In vitro*	Reference Year of publication	Main non-clinical conclusions
Comparable/similar preparations to preparations of the monograph				
Aqueous extracts of *E. angustifolium*, *E. parviflorum*, *E. hirsutum*	Cells were exposed to 20, 50, and 70 µg/ml of lyophylized aqueous extract (DER 4-5:1, extraction at 40°C)	*In vitro*, hormone dependent prostate cancer cells (LNCaP)	Stolarczyk *et al*. 2013a	Significant increase in the level of apoptotic cells via activation of the mitochondrial pathway
Aqueous extracts of *E. angustifolium*, *E. parviflorum*, *E. hirsutum*	Cells were exposed to 20, 50, and 70 µg/ml of lyophylized aqueous extract (DER 4-5:1, extraction at 40°C)	*In vitro*, hormone dependent prostate cancer cells (LNCaP)	Stolarczyk *et al.* 2013b	Inhibition of proliferation of LNCaP with IC_{50} values of 32.2 – 44.6 µg/ml, statistically significant reduction of PSA and inhibition of

Herbal preparation tested	Strength Dosage Route of administration	Experimental model *In vivo/* *In vitro*	Reference Year of publication	Main non-clinical conclusions
				arginase activity;
Aqueous extracts of *E. angustifolium, E. parviflorum*, *E. hirsutum*	Ratio herbal substance:extraction solvent: 1:10	*In vitro,* anti-inflammatory activity (inhibition of hyaluronidase , lipoxygenase; influence on elastase and myeloperoxidase release)	Kiss *et al*. 2011	Inhibition of hyaluronidase and lipoxygenase with IC_{50} of 5 µg/ml and 25 µg/ml (extracts) elastase release: IC_{50} >50 µg/ml; myeloperoxidase release: IC_{50} 26 µg/ml (*E. hirsutum*), >50µg/ml (*E. parviflorum*), 34 µg/ml (*E. angustifolium*)
Aqueous and other extracts of *E. angustifolium*	Ratio herbal substance: extraction solvent: 1:10; concentrations of 25, 50, and 100 µg/ml were tested	*In vitro,* neutral endopeptidase (NEP) in prostate cancer cells (PC-3)	Kiss *et al.* 2006a	Induction of NEP in prostate cancer cells, weak but significant inhibition of cell proliferation
Aqueous extract of *E. angustifolium*	Ratio herbal substance: extraction solvent: 1:10; concentrations of 25, 50, and 100 µg/ml were tested	*In vitro*, neutral endopeptidase (NEP) in prostate cancer cells (high expression SK-N-H vs. low expression PC-3)	Kiss *et al.* 2006b	Induction of NEP in prostate cancer cells, SK-N-H cells were much more suceptible
Aqueous extract of *Epilobium parviflorum*	Ratio herbal substance: extraction solvent: 1:10; concentration of 250 µg/ml of extract was tested; positive control: indomethacin	*In vitro*, COX-1 and COX-2 assay;	Steenkamp *et al.* 2006	Inhibition of COX-1 (ca. 60%) and COX-2 (<10%) catalysed prostaglandin biosynthesis
Aqueous extracts of *E. parviflorum*	Fractionated extraction (ligroin, $CHCl_3$, MeOH, H_2O)	*In vitro*, 5α-reductase	Lesuisse *et al.*1996	90% inhibition of 5α-reductase at 10µl
Aqueous extracts of *E. angustifolium*	Ratio herbal substance: extraction solvent; 1:15; Dosage: 40mg/kg/day for 20 days Route of administration: p.o.	*In vivo*; Anti-androgen assay on intact male Wistar rats and testosterone stimulated castrated male Wistar rats	Hiermann & Bucar 1997	Impact on growth of accessory sexual organs was observed: significant inhibitory effect on weight of seminal vesicles (antiandrogen effect) in intact animals; increase of weight of prostate, seminal vesicles and musculus laevator ani (pro-androgen effect)
Aqueous extracts of *E. angustifolium* and *E.*	Ratio of herbal substance: extraction	*In vivo*, carrageenan	Hiermann *et al*. 1986	Extract of *E. angustifolium*

Herbal preparation tested	Strength Dosage Route of administration	Experimental model *In vivo/* *In vitro*	Reference Year of publication	Main non-clinical conclusions
parviflorum	solvent: 1:50 and 1:30; Rat paw oedema: Dosage: 1 ml (corresponding to 33mg/ml dry herb per 100 g body weight) Route of administration: p.o Perfused rabbit ear: Dosage: concentrations of extracts in the perfusion solution were 1.25, 2.5, and 5.0 mg/ml (calculated as equivalents to the herbal substance)	induced rat paw oedema (female Sprague-Dawley rats), perfused rabbit ear (release of PG)		reduced PG-release and was strongly anti-inflammatory in the paw oedema model (comparable to indomethacin 2 mg/kg/p.o); Extract of *E. parviflorum* was less potent in reducing PG release and was inactive in the paw oedema model
Other preparations				
Aqueous-acetone extract of *Epilobium parviflorum*	Extraction solvent Aqueous acetone (80% V/V)	*In vitro*; COX-inhibition-assay	Hevesi *et al.* 2009	Decreased PGE_2-release (IC_{50} 1.4±0.1µg/ml) comparable to the positive control indomethacin
Ethanolic extract of *Epilobium angustifolium*	Cells were exposed to 19, 190, and 1900 µg of dry extract per ml medium	*In vitro*, human prostatic epithelial cells (PZ-HPV-7), MTT-assay	Vitalone *et al*. 2001	Anti-proliferative effect was observed at the highest concentration after 24 and 48h
Ethanolic extract of *Epilobium parviflorum*	Ratio herbal substance: extraction solvent: 1:10; concentration of 250 µg/ml of extract was tested	*In vitro*, COX-1- and COX-2-inhibition assay; positive control: indomethacin	Steenkamp *et al.* 2006	Inhibition of COX-1 (ca. 98%) and COX-2 (ca. 60%) catalysed prostaglandin biosynthesis
Single substances				
Oenothein B	IL-18 activation assay: Cells were exposed to 0, 10, 20, and 40 µg/ml of oenothein B K562 assay: Cells were exposed to 20 µg/ml of oenothein B	*In vitro*, lymphocytes (human, bovine)	Ramstead *et al.* 2012	Stimulation of innate lymphocytes, NK cells; enhancement of the production of IFNγ
Oenothein B	Cells were exposed to solutions of 10, 20, and 40 µM	*In vitro*, hormone dependent prostate cancer cells (LNCaP)	Stolarczyk *et al*. 2013b	Inhibition of proliferation of LNCaP with an IC_{50} value of 7.8 µM, statistically significant reduction of PSA and inhibition of arginase activity

Herbal preparation tested	Strength Dosage Route of administration	Experimental model *In vivo/* *In vitro*	Reference Year of publication	Main non-clinical conclusions
Oenothein B		*In vitro*, anti-inflammatory activity; human neutrophils (inhibition of hyaluronidase, lipoxygenase, influence on elastase and myeloperoxidase release)	Kiss *et al*. 2011	Inhibition of hyaluronidase and lipoxygenase with IC_{50} of 1.1µM; elastase release: no inhibition; myeloperoxidase release: IC_{50} 7.7µM
Oenothein B	Cells were exposed to solutions of 10, 20, and 40 µM	*In vitro*, neutral endopeptidase (NEP) in prostate cancer cells (PC-3)	Kiss *et al.* 2006a	Induction of NEP in prostate cancer cells, weak but significant inhibition of cell proliferation
Oenothein B	PC-3 cells were exposed to solutions of 10, 20, and 40 µM, and SK-N-H cells to solutions of 5, 10, and 20 µM	*In vitro*, neutral endopeptidase (NEP) in prostate cancer cells (high expression SK-N-H vs. low expression PC-3)	Kiss *et al.* 2006b	Induction of NEP in prostate cancer cells, SK-N-SK cells were much more suceptible
Oenothein B		*In vitro*, neutral endopeptidase (NEP), angiotensin converting enzyme (ACE),	Kiss *et al.* 2004	Inhibition of both metallopeptidases ACE: IC_{50} 250 µM NEP: IC_{50} 20 µM
Oenothein A		*In vitro*, aromatase, 5α-reductase	Ducrey *et al.* 1997	70% inhibition of aromatase at 50µM; 5α-Reductase: IC_{50} 1.24 µM
Oenothein B		*In vitro*, aromatase, 5α-reductase	Ducrey *et al.* 1997	33% inhibition of Aromatase at 50µM; 5α-Reductase: IC_{50} 0.44µM
Oenothein B		*In vitro*, 5α-reductase	Lesuisse *et al.*1996	Inhibition of 5α-reductase: IC_{50} 0.22 µM
Urolithins A, B, and C (metabolites of oenothein B)	Cells were exposed to solutions of 10, 20, and 40 µM	*In vitro*, hormone dependent prostate cancer cells (LNCaP)	Stolarczyk *et al*. 2013b	Inhibition of proliferation of LNCaP with IC_{50} values of 35.2 – 40 µM, statistically significant reduction of PSA and inhibition of arginase activity
Myricetin-3-O-beta-D-glucuronide	Rat paw oedema: Dosage: 0.04, 0.2 and 1.0 mg/kg body weight	*In vivo*, carrageenan-induced oedema in the	Hiermann *et al*. 1991	Strong antiinflammatory effect (0.2 mg/kg/b.w.) and

Herbal preparation tested	Strength Dosage Route of administration	Experimental model *In vivo/* *In vitro*	Reference Year of publication	Main non-clinical conclusions
	Route of administration: p.o Perfused rabbit ear: Concentrations of 0.1 and 1.0 µg/ml in the perfusate	rat hind paw and perfused rabbit ear		inhibitory effect on prostaglandin biosynthesis
Quercetion-3-glucuronide, quercetin3-O-(6''-galloyl)-galactoside	PC-3 cells were exposed to solutions of 100 µM, and SK-N-H cells to solutions of 25, 50, and 100 µM	*In vitro*, neutral endopeptidase (NEP) in prostate cancer cells (high expression SK-N-H vs. low expression PC-3)	Kiss *et al.* 2006b	Induction of NEP in prostate cancer cells, SK-N-SK cells were much more suceptible

3.1.2. Secondary pharmacodynamics

Antidiarrhoeal activity, analgesic activity, antioxidant activity (often also related to antiinflammatory processes) as well as antibacterial and antifungal activity are considered as secondary pharmacodynamic effects.

Antioxidant activity (*in vitro*)

Hevesi *et al* (2009)

The antioxidant and antiinflammatory effect of an aqueous-acetone (80% v/v) extract of *E. parviflorum* was investigated in the study. In the 2,2-diphenyl-1-picrylhydrazyl-assay (DPPH-assay) the extract possessed a stronger antioxidant activity than the reference substances Trolox or ascorbic acid. In the thiobarbituric acid-assay (TBA-assay) the extract showed a concentration-dependent inhibition of lipid peroxidation at concentrations over 0.20 mg/ml (IC_{50} 2.37±0.12 mg/ml).

Steenkamp *et al.* (2006)

Aqueous and methanolic extracts of *E. parviflorum* were examined for radical scavenging capacity by electron spin resonance spectrometry. Concentrations of 4 mg/ml of extract showed scavenging activities above 80%, comparable to 80 mg/l and 160 mg/l of Vitamin C.

Kiss *et al*. (2011)

Aqueous extracts of *E. angustifolium*, *E. parviflorum*, and *E. hirsutum* were investigated for antioxidant activity by evaluation of ROS (reactive oxygen species) production in formyl-met-leu-phenylalanine- and 4β-phorbol-12-β-myristate-α13-acetate-induced human neutrophils and for radical scavenging activity in the xanthine-xanthine oxidase assay. The tested extracts significantly reduced the production of ROS in the activated neutrophils with IC_{50} values of 5-30µg/ml, showing no significant differences between the species. For the radical scavenging activity IC_{50} values between 2.2 and 33 µg/ml were determined. Oenothein B showed a radical scavenging activity with IC_{50} < 1µM.

Shikov *et al.* (2006)

Different water-soluble extracts of *E. angustifolium* were screened in 5 assays [iron(III) to iron (II)reducing activity, iron(II) chelation activity, 2,2-diphenyl-1-picrylhydrazyl-radical scavenging (DPPH-assay), ascorbate-iron(III)-catalyzed phospholipid peroxidation, non-site-specific as well as site specific hydroxyl radical mediated 2-deoxy-D-ribose degradation] for antioxidant activity. In all test-systems considerable antioxidant properties were detected.

Antimicrobial activity (*in vitro*)

Kosalec *et al.* 2013

Extracts of flowers and leaves of *E. angustifolium* were tested for antimicrobial activity against gram-positive as well as gram-negative bacteria and yeasts. MIC values from 4.6 to 18.2 mg/ml were determined. There was no difference detected between flower- and leave-extracts.

Bartfay *et al.* 2012

Extracts of *E. angustifolium* (no further details) were tested for antibacterial activity against *Staphylococcus aureus*, *Micrococcus luteus*, *Escherichia coli* and *Pseudomonas aeruginosa*. The tested concentrations were not given but the extract showed bacterial growth inhibition in all tested strains, comparable to or more effective than 250 µg/ml vancomycin and tetracycline.

Battinelli *et al.* 2001

Extracts of *E. angustifolium*, *E. hirsutum*, *E. rosmarinifolium*, *E. palustre* and *E. tetragonum* were screened for antimicrobial activity in gram-positive as well as gram-negative bacteria, yeasts and fungi. Minimum inhibitory concentration (MIC) values and minimum cytocidal concentration (MCC) values were determined between 10 and 650 µg/ml for the different extracts depending on the respective microorganism.

Antidiarrhoeal activity (*in vivo*)

Vitali *et al*. (2006)

Ethanolic extracts (65% V/V) prepared from the whole fresh plants of *E. hirsutum*, *E. palustre*, *E. rosmarinifolium*, *E. spicatum* and *E. tetragonum* were tested in 4 different animal models for effects on the gastrointestinal tract (charcoal meal in mice, castor oil-induced diarrhoea in mice, intestinal fluid accumulation in mice, activity of rabbit jejunum). Epilobium extracts showed antidiarrhoeal activity (statistically significant from 25 mg/kg b.w. i.p), a decrease of intestinal transit (statistically significant from 50 mg/kg b.w. i.p), but no fluid intraluminal accumulation. Furthermore, spontaneous and acetylcholine-induced contractions of the rabbit jejunum were inhibited.

Analgesic activity (*in vivo*)

Tita *et al*. (2001)

An ethanolic tincture of *E. angustifolium* was evaporated to dryness (under vaccum at 45°C). The resulting dry extract was resuspended in 3% propylene glycol-water mixture and tested for analgesic activity in the hot plate test and writhing test. Concentrations of 0, 47.5, 95, 190, and 380 mg/kg bw were applied s.c. to Swiss ICR (CD1) male mice (about 30 g). The authors reported analgesic effects in the writhing test, comparable to the reference lysine acetylsalicylate (300 mg/kg s.c.).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

In an attempt to elucidate molecular mechanisms of *E. angustifolium* in benign prostate hyperplasia, Kujawski *et al.* (2009; 2010) investigated the effects of the extract on the expression of several cytochrome P450 genes known to participate in the metabolism of steroid hormones. Both repression and induction of mRNA expression were observed, but possible functional consequences of these findings remain hypothetical. In a more recent study (Kujawski *et al.* 2014), the authors suggest that *E. angustifolium* extract may cause interactions with synthetic drugs used in the treatment of proliferative changes in hormone-dependent reproductive organs, but potential consequences are purely hypothetical.

3.1.5. Conclusions

Most of the studies briefly described in table 4 were *in vitro* tests, thus allowing only limited conclusions on the real contribution of the observed effects to the plausibility of the therapeutic indication as no data on the bioavailability of the extracts or isolated compounds are available. However, the study by Stolarczyk *et al.* (2013b) could be considered important as also metabolites of oenothein B (urolithins) were investigated. According to Seeram *et al.* (2006) certain ellagitannins were shown to be metabolized by human gut microbiota to urolithins which are well absorbed after oral administration and can reach blood concentrations of 0.5-18.6 µM. Furthermore, according to Seeram *et al.* (2007) urolithins are able to accumulate in mice prostate gland. Although it has to be considered that to date similar experiments on bioavailability were not conducted with oenotheins A and B it seems possible that data obtained with the substances described by Stolarczyk *et al*. (2013b) might support the plausibility of the traditional use. Investigations on the activity and/or expression levels of phase I and phase II drug-metabolizing enzymes were conducted in rats. The results show certain changes, both repression and induction, in expression levels but do not allow firm conclusions on interaction potential with synthetic drugs also in humans.

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

Pharmacokinetic interactions

Karakurt *et al.* 2013

The study investigated *in vivo* effects of an aqueous extract of *Epilobium hirsutum* on CYP2E1, CYP1A1, NADPH quinone oxidoreductase 1 (NQO1) and glutathione peroxidase (GPx) activities, and protein and mRNA expression in liver tissue. Male Wistar albino rats were treated with 37.5 mg/kg b.w. (i.p) of the dried extract for nine consecutive days. Enzyme activity, protein and mRNA expression analysis revealed that CYP1A1 and CYP2E1 levels were decreased while those of NQO1 and GPx increased after treatment. The authors concluded that the metabolism of drugs might be altered due to changes in the expression and activity of these proteins by *Epilobium hirsutum*. The changes observed also implicate protection against possible reactive metabolites of drugs and chemicals.

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

3.3.1. Single dose toxicity

Tita *et al*. (2001)

The LD_{50} in Swiss ICR (CD1) mice of an *E. angustifolium* ethanolic tincture evaporated to dryness was determined to be 1.4 g/kg s.c.

3.3.2. Repeat dose toxicity

Roman *et al.* (2010)

1.5 ml of an Ethanolic extract (no further characterisation given) did not show signs of toxicity after 10 days of treatment in male albino wistar rats.

3.3.3. Genotoxicity

No data available.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data available.

3.3.8. Conclusions

Data on toxicity are very scarce but from the few available information no concern arises regarding the use of *E. angustifolium* and *E. parviflorum* as a herbal tea. As no data on genotoxicity are available a List Entry is not proposed.

3.4. Overall conclusions on non-clinical data

Non-clinical data on anti-proliferative activity and potential effects on prostate cells growth as well as anti-inflammatory and analgesic activity were mostly obtained from *in vitro* experiments. Especially the investigations on metabolites of oenothein A and B and their effects on prostate cancer cells seem to be of interest with respect to the plausibility of the traditional use. However, to draw firm conclusions on the supportive character of such data more information on the metabolism and bioavailability of these substances in humans would be necessary.

Specific data on pharmacokinetics and interactions of *E. angustifolium* and *E. parviflorum* extracts are not available.

Non-clinical information on the safety of *Epilobium angustifolium* and *Epilobium parviflorum* is scarce.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended. Moreover the proposed indication is not applicable for women.

Oral administration of the herbal tea *of Epilobium angustifolium* and/or *Epilobium parviflorum* can be regarded as safe at traditionally used doses.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. Therefore, a List Entry is not proposed.

4. Clinical Data

4.1. Clinical pharmacology

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

No data available.

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

No data available.

4.2. Clinical efficacy

No data available.

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

No data available.

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

As there is no data available no conclusions on clinical pharmacology and efficacy can be drawn.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

Aside from market presence there are no concrete data concerning patient exposure.

If patients with known intolerance to *Epilobium* species are excluded, a traditional use is possible if administration follows the instructions as specified in the monograph.

5.3. Adverse events, serious adverse events and deaths

Adverse events, serious adverse events and deaths have not been reported so far.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No data available.

5.5.1. Use in children and adolescents

No data available.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special Warnings and precautions for use

To ensure a safe use the following statement should be labelled:

If complaints worsen or if symptoms such as fever, spasms or blood in the urine, painful urination, or urinary retention occur during the use of the medicinal product, a doctor should be consulted.

5.5.4. Drug interactions and other forms of interaction

Drug interactions from clinical trials or case studies have not been reported so far.

5.5.5. Fertility, pregnancy and lactation

No data available.

The use in pregnancy and lactation is not applicable due to the indication.

5.5.6. Overdose

No data available.

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

No data available.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

Adverse events serious adverse events and deaths have not been reported so far. Furthermore, drug interactions from clinical trials or case studies have not been reported so far.

6. Overall conclusions (benefit-risk assessment)

The aerial parts of *Epilobium angustifolium* L. and/or *Epilobium parviflorum* Schreb. have been used medicinally in several countries in the European Union for more than 30 years. Based on the available data from various literature sources supported by data on the market presence of the herbal substance and medicinal products thereof the legal requirements for traditional use are regarded fulfilled for the comminuted herbal substance as a herbal tea for oral use in the following indication: Relief of lower urinary tract symptoms related to benign prostatic hyperplasia, after serious conditions have been excluded by a medical doctor.

According to the indication the use in women, during pregnancy and lactation as well as in children is not applicable.

So far adverse events, serious adverse events and deaths as well as drug interactions from clinical trials or case studies have not been reported. Furthermore, no concerns arise from the few available data from toxicity studies. Due to the widespread traditional medicinal use for more than 30 years the safety of *Epilobium angustifolium* and *Epilobium parviflorum* can be assumed.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. As no data on genotoxicity are available a List Entry is not proposed.

Annex