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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Filipendula ulmaria* (L.) Maxim. *(= Spiraea ulmaria* (L.)), herba and *Filipendula ulmaria* (L.) Maxim. (= *Spiraea ulmaria* (L.)), flos

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)	*Filipendula ulmaria* (L.) Maxim. (= *Spiraea ulmaria* (L.)), herba *Filipendula ulmaria* (L.) Maxim. (= *Spiraea ulmaria* (L.)), flos
Herbal preparation(s)	Herb: a) Comminuted herbal substance b) Powdered herbal substance Flowers: Comminuted herbal substance
Pharmaceutical forms	(Comminuted) herbal substance for herbal tea or other herbal preparations in solid or liquid dosage forms for oral use.

Note: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Filipendula ulmaria* (L.) Maxim. *(= Spiraea ulmaria* (L.)), herba and *Filipendula ulmaria* (L.) Maxim. (= *Spiraea ulmaria* (L.)), flos. It should be noted that this document is a working document, not yet fully 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)

Filipendulae ulmariae herba consists of the whole or cut, dried flowering tops of *Filipendula ulmaria* (L.) Maxim. (syn.: *Spiraeae ulmaria* (L.)). The material complies with the Ph. Eur. monograph (ref.: 01/2008:1868)

For Filipendulae ulmariae flos no Ph. Eur. monograph is available. Descriptions are derived from Wichtl (1994) and the Complete German Commission E. (Blumenthal, 1998). Wichtl defines Spiraeae flos as the dried flowers of *Filipendula ulmaria* (L.) Maxim. and provides extensive macroscopic and microscopic descriptions. According to the Commission E monograph Spiraeae flos consists of the dried flower of *Filipendula ulmaria* (L.) Maxim. (syn.: *Spiraeae ulmaria* (L.)) as well as its preparations in effective dosage (Blumenthal, 1998).

In the European countries *Filipendula ulmaria* is designated as follows: English: Meadowsweet, Bittersweet, Bridewort, Goat's beard, Honey-sweet, Queen of the meadows, Sweet hay; French: Reine des prés, Barbe de bouc, Barbe de chèvre, Belle des prés, Ulmaire; German: Echtes Mädesüß, Bocksbart, Geißbart, Spierstaude, Sumpfkraut, Wiesenkönigin; Dutch: Moerasspiraea, Bloeiende olm, Geitenbaard, Kamerkruid, Koningin der weide, Olmkruid, Torkruid (Halkes, 1998).

Constituents: (Wichtl, 1994; Zeylstra, 1998; ESCOP, 2003; Barnes et al., 2007):

The European Pharmacopoeia requires minimum 1 ml/kg of steam-volatile substances for Filipendulae ulmariae herba. Salicylates are the main components of the volatile oil, mainly salicylaldehyde (up to 70%). According to ESCOP monograph "Steam distillation of the dried flowers yields a small amount (0.2%) of volatile oil arising from the phenolic glycosides during drying and storage".

The amount of salicylates, mostly present in the form of glycosides, is assumed to be less than 0.5% (Zeylstra, 1998; ESCOP, 2003).

Flavonoids, from 3-4% in the flowering herb up to 6% in the fresh flowers, in particular spiraeoside (quercetin-4'-glucoside), also hyperoside, other quercetin and kaempferol derivatives, as kaempferol-4'-glucoside.

Tannins (hydrolysable type, ranging from 1% in ethanolic extracts to 12% in aqueous extracts), predominantly the dimeric compound rugosin D.

Miscellaneous: coumarin (trace), mucilage, carbohydrates, ascorbic acid.

- Herbal preparation(s)

Herb:
A1) Comminuted herbal substance for tea preparation

A2) Powdered herbal substance

B1) Dry extract (DER not available), water

B2) Dry extract (DER not available), water (may be identical to B1)

B3) Liquid extract (1:1; ethanol 25% v/v)

C) Tincture (1:5; ethanol 45% v/v)

Flowers:
A1) Comminuted herbal substance for tea preparation

B) Dry extract (DER not available), ethanol ? % (v/v)

- 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.

According to the British Herbal Pharmacopoeia (1983) Filipendulae ulmariae herba is used in combinations with *Althaea* and *Melissa* (for gastric conditions), and with *Ballota* (anti-emetic). At present combination products containing Filipendulae ulmariae herba are on the market in several EU Member States, amongst others: Czech Republic (combinations with Salicis cortex, Violae tricoloris herba, Harpagophyti radix, Equiseti herba, Solidaginis herba, Callunae herba, herbal tea for oral use; indications 1) as an adjuvant for inflammatory and degenerative diseases of locomotors apparatus (rheumatism, arthrosis, arthritis and gout), 2) adjuvant therapy in flu like symptoms, France (about 10 combination products as herbal teas; indications 1) Traditionally used to promote urinary and digestive elimination functions, 2) Traditionally used as analgesic (headache, toothache), 3) Traditionally used in the symptomatic treatment of minor painful joint conditions, and Spain (in combination products as herbal teas).

Filipendulae ulmariae flos is an ingredient of 6 herbal teas in Germany, each one consisting of Filipendulae ulmariae flos, Tiliae flos and Sambuci flos. According to Wichtl (1994) the flowers are a component of some mixed herbal teas as remedies for influenza, rheumatism and kidney-bladder teas. In the UK some multi-ingredient products containing the flowers or extracts are on the market.

- Vitamin(s): not applicable
- Mineral(s) :not applicable

1.2. Information about products on the market in the Member States

According to the information provided by the National Competent Authorities

Table 1. Specified products on the market in the European Member State

Member State	**Medicinal Product**	**Regulatory Status**
Austria	no medicinal product on the market containing *Filipendula* alone or in combination	
Bulgaria	no products with MA	
Czech Republic	no product containing *Filipendula* as a single herbal substance/ herbal preparation is authorised/registered. Herb: only available in combination products as food supplements, e.g. a herbal tea, on the market since 1999.	
Danmark	no products with MA	
Estonia	no medicinal product on the market	
France	Herb:	

	Arkogélules Reine des Près, powdered herbal substance of dry flowering tops, hard capsules 300 mg	MA 1988
	Dry extract (DER?), water, hard capsule 200 mg	MA
	Comminuted herbal substance, sachet 1.5 g	MA
	Dry extract (DER?), water, hard capsule 169 mg	MA
	Also available in combination products (herbal teas)	- (?)
	Flowers:	
	Dry extract (DER?), ethanol ? % (v/v), hard capsule 50 mg	-
Germany	Herb: no products on the market Flowers: single active ingredient: 3 herbal teas combination products: 6 herbal teas	
Greece	no authorised or marketed products containing *Filipendula*, neither as single active ingredient, nor in combination products	
Hungary	Herb: only in combinations in "healing products", a.o. herbal tea and gel for topical use	
Latvia	no authorised or registered medicinal products containing *Filipendula*. However, several food supplements containing *Filipendula* on the market	
Netherlands	no products containing *Filipendula* on the market	
Slovak republic	no products authorised , neither as a single active ingredient nor as combination products	
Slovenia	no authorised/registered medicinal product containing Filipendulae ulmariae flos and Filipendulae ulmariae herba.	
Spain	Herb: powdered herbal substance of dry flowering tops, hard capsules 250 mg	MA 1993
	Also available in combination products (herbal teas)	- (?)
Sweden	no products containing *Filipendula* on the market	

Regulatory status overview

H = herb
F = flowers

Member State	Regulatory Status				Comments (not mandatory field)
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal product on market
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products with MA on market
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: as food supplement	H: only in combination products, a.o. herbal tea F: No products on market
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products with MA on market
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No medicinal products on market
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☒ TRAD	☒ Other TRAD	☒ Other Specify:	H: trad.: products with MA on market; also in combination products as. herbal tea F: trad.: products without MA
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	F: WEU (German Standard MA): single and in combination products (all herbal teas) H: No products on market
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on market
Hungary	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	H: only in combinations in "healing products", a.o. herbal tea and gel for topical use
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:	No products with MA on

Member State	Regulatory Status				Comments (not mandatory field)
				as food supplement	market
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:	No products on market
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:	No products with MA on market
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products with MA on market
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	H: single and in combination products (herbal teas)
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	No products on market
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

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

1.3. Search and assessment methodology

Databases assessed (date, search terms) and other sources used: to be completed.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The medicinal use of *Filipendula ulmaria* has been described from the late 16th and 17th century (Halkes, 1998). In general, preparations form herb and/or flowers have been used traditionally in inflammatory diseases (Madaus, 1938; Gessner and Orzechowski, 1974; Van Hellemont, 1988; Wichtl, 1994; Zeylstra, 1998; Halkes, 1998) and as a diuretic (Madaus, 1938; Gessner and Orzechowski, 1974; Van Hellemont, 1988; Wichtl, 1994; Zeylstra, 1998; Halkes, 1998). Zeylstra (1998) concludes that the uses of *Filipendula* shifted over the years from a diuretic towards an antirheumatic.

In most literature herbal tea preparations are described, however Van Hellemont (1988) also mentions a tincture. A product containing 250 mg of dried, powdered flowering tops in hard capsules which has

been authorised in France in 1988 as a traditionally used medicine in the symptomatic treatment of minor painful articular conditions and to facilitate renal and digestive elimination functions, has been on the market since 1980 and was already mentioned in a price list dated January 1981 of the French firm Laboratoires Arkochim. Dry aqueous extracts of the herb in capsules containing 200 mg (indications: "traditionally used as an analgesic (headache, toothache)" and "traditionally used in the symptomatic treatment of minor painful articular conditions") have been marketed since 1986. Sachets containing 1.5 g of fragmented herb have been marketed since 1990 as a traditionally used medicine in the symptomatic treatment of minor painful joint conditions.

Assessor's comment:
Conclusion: Only for the comminuted herbal substance for tea preparation and the powdered herbal substance a period of at least 30 years of medical use as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product can be considered fulfilled. With respect to dry and liquid extracts and tinctures older information is limited, sufficient details on extraction solvent and drug-extract ratio are only available from 1983.

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

Whereas in the British Herbal Pharmacopoea (1983) stomachic, mild urinary antiseptic, antirheumatic and antacid actions are listed, the British Herbal Pharmacopoeia (1990) and British Herbal Compendium (1992) describe the action of Filipendula herba as anti-inflammatory. In addition, BHC mentions diuretic, stomachic and astringent actions. As indications BHC (1992) describes "Atonic and acid dyspepsia, gastritis and peptic ulceration", as other uses "Rheumatic and arthritic pains (internally and topically). In Belgium, according to regulatory guidelines, the indication must be stated as: "Traditionally used for painful articular conditions although its activity has not been proved in accordance with current evaluation criteria for medicines", whereas in France the following therapetic actions have been accepted: Oral use: "Traditionally used to facilitate renal and digestive elimination functions, for febrile and influenzal conditions, as an antalgesic (headache, toothache), in the symptomatic treatment of minor painful articular comditions and to promote the renal elimination of water". Topical use: "Traditionally used in the symptomatic treatment of minor painful articular conditions" (BHC, 1992). The German Commision E monograph (Blumenthal, 1998) mentions the use of both herb and flowers as supportive therapy for colds. ESCOP Monographs: Herb is used as supportive therapy for the common cold and to enhance the renal elimination of water.

Diaphoretic, colds, flu and chills

reference	**indication**	**preparation**
Van Hellemont, 1988	H: diaphoretic, in flu and colds F: diaphoretic, in flu and colds	H: infusion, tincture F: infusion
British Herbal Pharmacopoeia, 1990	H: Anti-inflammatory	
Wichtl, 1994	F: diaphoretic for colds, chills etc.	F: infusion
Halkes, 1998	F: diaphoretic, as an additional treatments for colds	F: aqueous decoctions and infusions, alcoholic extracts
Blumenthal, 1998	H, F: supportive therapy for colds	H, F: comminuted herb and other galenical preparations for infusions
Zeylstra, 1998	F: diaphoretic	H: infusion, liquid extract, tinctures

Schulz et al., 1998	F: supportive therapy of colds	F: infusion
ESCOP, 2003	H: supportive therapy for colds	H: infusion, liquid extract, tincture

Antirheumatic, anti-arthritic, analgesic, in diseases of muscles and joints

reference	**indication**	**preparation**
British Herbal Pharmacopoeia, 1983	H: rheumatic muscle and joint pains	H: infusion, liquid extract (1:1 in 25% alcohol), tincture (1:5 in 45% alcohol)
Van Hellemont, 1988	H: antirheumatic, in diseases of muscle and joints F: gout and rheumatic diseases	H: infusion, tincture F: infusion, also for topical use
British Herbal Pharmacopoeia, 1990	H: Anti-inflammatory	
British Herbal Compendium, 1992	H: rheumatic and arthritic pains	H: dried herb or infusion, liquid extract (1:1 in 25% alcohol), tincture (1:5 in 45% alcohol) Also for topical use
Wichtl, 1994	F: against rheumatism of muscles and joints and against arthritis	F: infusion
Zeylstra, 1998	H: rheumatoid arthritis, osteoarthritis, gouty conditions, muscular rheumatism, lumbago, sciatica	H: infusion, liquid extract, tinctures
Barnes et al., 2007	H: Antirheumatic, rheumatic muscle and joint pains	H: infusion, liquid extract (1:1 in 25% alcohol), tincture (1:5 in 45% alcohol)

Renal elimination function

reference	**indication**	**preparation**
Van Hellemont, 1988	H: diuretic F: diuretic	H: infusion, tincture F: infusion
Wichtl, 1994	F: diuretic	F: infusion
Zeylstra, 1998	H: diuretic, against albuminuria and oliguria, uricosuric, stimulates excretion of urea	H: infusion, liquid extract, tinctures
ESCOP, 2003	H: to enhance the renal elimination of water	H: infusion, liquid extract, tincture

Others

reference	**indication**	**preparation**
British Herbal Pharmacopoeia, 1983	H: atonic dyspepsia with heartburn and hyperacidity, acute catarrhal cystitis, prophylaxis and treatment of peptic ulcer, diarrhoea in children	H: infusion, liquid extract (1:1 in 25% alcohol), tincture (1:5 in 45% alcohol)
Van Hellemont, 1988	H: antispasmodic, cholagogum. F: in cystitis, pyelitis, nephritis,	H: infusion, tincture

	astringent, woundhealing, in adipositas, cellulitis	
British Herbal Compendium, 1992	H: atonic and acid dyspepsia, gastritis and peptic ulceration	H: dried herb or infusion, liquid extract (1:1 in 25% alcohol), tincture (1:5 in 45% alcohol)
Zeylstra, 1998	H: antiseptic (cystitis, pyelites, nephritis), against scarlet fever.. F: antacid, treatment of peptic ulcers, gastritis	H: infusion, liquid extract, tinctures
Barnes et al., 2007	H: stomachic, mild urinary antiseptic, astringent, antacid, atonic dyspepsia with heartburn and hyperacidity, acute catarrhal cystitis, prophylaxis and treatment of peptic ulcer, diarrhoea in children	H: infusion, liquid extract (1:1 in 25% alcohol), tincture (1:5 in 45% alcohol)

Currently, the following specified products based on *Filipendula ulmaria* have been reported to be on the market in the European Member States (indication numbers between brackets):

Herb: hard capsules for oral use containing 250–300 mg of powdered herbal substance (1, 2, 3), hard capsules for oral use containing 169–200 mg of dry aqueous extract (s) (2, 3, 4) and sachets containing 1.5 g of comminuted herbal substance for tea preparation (2).

Flowers: hard capsules for oral use containing 50 mg of dry ethanolic extract (3).

Indications mentioned:

1. relief of symptoms of common cold
2. relief of minor articular pain, traditionally used in the symptomatic treatment of minor painful articular conditions
3. traditionally used to facilitate renal and digestive elimination functions
4. traditionally used as an analgesic (headache, toothache)

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

Indication numbers 1-4 refer to 2.2 under Indications mentioned:
p.c. = personal communication
n.m. = not mentioned

Herb:

A1) Comminuted herbal substance (for tea preparation)

reference	**single dose**	**daily dose**	**indication**
France, p.c.	1.5 g	3 – 4.5 g	2
BHP, 1983; Barnes et al., 2007	4-6 g	12-18 g	2
Comm. E, 1998	n.m.	4-5 g	1
BHC, 1992	2-6 g	2-18 g	2

ESCOP, 2003	n.m.	Adults: 2-6 g Children 1-4 years: 1-2 g Children 4-10 years: 2-3 g Children 10-16 years: 2-6 g	1, 3

A2) Powdered herbal substance

reference	single dose	daily dose	Indication
Spain, p.c.	250-500 mg	250-1500 mg	1, 2
France, p.c.	300 mg	900-1500 mg	2, 3

B1) Dry extract (DER?), water

reference	single dose	daily dose	Indication
France, p.c.	200 mg	400 mg	2, 4

B2) Dry extract (DER?), water

reference	single dose	daily dose	Indication
France, p.c.	169-507 mg	169-507 mg	2, 3

B3) Liquid extract (1:1; ethanol 25% v/v)

reference	single dose	daily dose	indication
BHP, 1983; Barnes et al., 2007	1.5-6.0 ml	4,5-18,0 ml	2
BHC, 1992	2-6 ml	2-18 ml	

C) Tincture (1:5; ethanol 45% v/v)

reference	single dose	daily dose	indication
BHP, 1983; Barnes et al., 2007	2-4 ml	6-12 ml	2
BHC, 1992	2-4 ml	2-12 ml	

Flowers:

A1) (Comminuted) herbal substance (for tea preparation)

reference	single dose	daily dose	indication
Comm. E, 1998	n.m.	2.5-3.5 g	1
Wichtl, 1994	n.m.	3-6 g	1, 2, 3
Czech Republic, p.c.	3.0 g	n.m.	n.m.

B) Dry extract (DER?), ethanol ? % (v/v)

reference	single dose	daily dose	indication
France, p.c.	100-150 mg	200-450 mg	3

Assessor's comment:
Since the information on the use of *Filipendula ulmaria* in and dosages for children is limited to only one reference (herb; ESCOP, 2003, original reference: Dorsch et al., 1998) or completely lacking

(flowers), and no exposure data in children are available, it is proposed not to include dosages for children in the respective monographs.

No restriction on the duration of use has been mentioned for Filipendulae ulmariae herba or flos or their preparations. However, since data on prolonged use are lacking the products should not be used for more then ten days to four weeks, depending on the indication. Moreover the remark should be added that if the symptoms persist during the use of these medicinal products, a doctor or a qualified health care practitioner should be consulted.

3. Non-Clinical Data

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

Anti-inflammatory and antipyretic activity and related effects; effects on gastric ulcers

An aqueous leaf extract was reported to inhibit both prostaglandin biosynthesis and platelet activation factor (PAF)-induced exocytosis/release of elastase (Tunon et al., 1995). The elastase inhibiting properties of 50% (v/v) ethanolic flower and leaf extracts were attributed to the presence of tannins (Lamaison et al., 1990).

Methanolic flower extracts (with flavonoids as main constituents) were demonstrated to strongly inhibit xanthine oxidase activity *in vitro* (Kazazi et al., 2009).

Preparations of Filipendulae ulmariae flos have been reported to cause lowering of motor activity and rectal temperature, myorelaxation and potentiation of narcotic action (Barnaulov et al., 1977), to prolong life expectancy of mice, lower vascular permeability and prevent the development of stomach ulcers in rats and mice (Barnaulov et al., 1977; Halkes, 1998).

Antiulcerative effects were also documented for other parts of the plant (Halkes, 1998; Barnes, 2007). On the other hand, a flower decoction appeared to potentiate the ulcerogenic properties of histamine in guinea-pigs. The greatest anti-ulcer activity is associated with aqueous flower extracts (Halkes, 1998; Barnes et al., 2007). Orally administered flavonoids, as well as flower extracts from *Filipendula ulmaria*, appeared to have a protective effect against reserpine-induced lesions of the rat stomach (Halkes, 1998).

Immunomodulatory activity

Different extracts of both herb and flowers were shown to strongly inhibit luminol-dependent chemiluminescence, T-cell proliferation and the classical pathway of the complement system, the latter activity appearing to be not attributable to tannins (Halkes et al., 1997a). From a range of flower extracts, prepared with different solvents, the ethyl acetate extract was found to exert the strongest inhibition towards the classical pathway of complement activation, the active compound (s) however being not identified (Halkes et al., 1997b). A flower decoction has been documented to enhance the growth-stimulating activity of mice peritoneal macrophages, both *in vitro* and *in vivo* (Bespalov et al., 1992).

Antibacterial activity

In vitro bacteriostatic activity of several 70% ethanolic and aqueous flower extracts against a range of urinary tract pathogens (Halkes, 1998; ESCOP, 2003; Barnes et al., 2007) have been described. Growth-inhibitory effects (in vitro) against a variety of bacteria were also demonstrated for a combination of 70% ethanolic and aqueous extracts (Csedõ et al., 1993).

Anticarcinogenic activity

Flower decoctions have been reported to show anticarcinogenic activity against chemically induced tumours in rats and mice (Bespalov et al., 1992; Halkes, 1998) and against transplanted tumours in mice (Bespalov et al., 1992). Isolated rugosin D displayed antitumour activity against transplanted tumours in mice (Miyamoto et al., 1987).

Other effects

An increase of bronchial tone in cats and a potentiation of bronchospastic properties of histamine in guinea-pigs by ethanolic and aqueous preparations of Filipendulae ulmariae flos have been observed (ESCOP, 2003; Barnes et al., 2007). Furthermore, *in vitro* enhancement of intestinal tone in guinea-pigs and of uterine tone in rabbits (Barnes et al., 2007) has been described.

A heparin-like complex from the flowers showed *in vivo* anticoagulant and fibrinolytic properties in animals after IM and IV injection (Kudriashov et al., 1990; Kudriashov et al., 1991).

Isolated rugosin D has been demonstrated to possess a high capacity for binding to bovine serum albumine (BSA) *in vitro* (Beart et al., 1985; ESCOP, 2003).

3.1.1. Overall conclusion on pharmacology:

Assessor's comment:

In general, there seems to be no clear distinction between the pharmacological effects of (preparations of) Filipendulae ulmariae herba (= flowering tops) and Filipendulae ulmariae flos. Also the Commission E monograph describes the same use for both herbal substances, with only a different daily dosage: 2.5–3.5 g of flowers is considered equivalent with 4–5 g of herb.

Results from *in vitro* and animal studies suggest anti-inflammatory/immunomodulatory, antibacterial and anticarcinogenic activities. *In vivo* effects on the CNS in various animals include a.o. a reduction of rectal temperature. The effects on gastric ulcers seem contradictory. No effects on renal and digestive elimination functions have been reported.

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

No data with regard to absorption, distribution, metabolism, elimination or pharmacokinetic interactions with other medicinal products are available.

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

Intraperitoneal LD_{50} in mice and intravenous LD_{50} in rabbits have been detemined as 1770 mg/kg and 75.7 mg/kg, respectively for an ethanolic flower extract (Barnaulov et al., 1977). For a flower decoction (1:20) the intraperitoneal LD_{50} in male and female mice and the intravenous LD_{50} in rabbits were determined as 535 mg/kg, 1050 mg/kg and 141.5 mg/kg respectively (ESCOP, 2003).

No influence on liver function of flowers and aqueous and ethanolic flower extracts could be observed in pharmacological studies in rats and rabbits (Barnaulov et al., 1977; Halkes, 1998; ESCOP, 2003).

3.3.1. Overall conclusion on toxicological data

Assessor's comment:

There are only limited preclinical safety data for preparations of Filipendulae ulmariae herba or flos. In view of the lack of data on mutagenicity, carcinogenicity and reproductive and developmental toxicity,

a list entry for Filipendulae ulmariae herba or flos can not be recommended. In addition, the use during pregnancy and lactation should be avoided.
Due to the presence of salicylates, *Filipendula ulmaria* should not be used in cases of hypersensitivity to salicylates (Meier and Meier-Liebi, 1993; Wichtl, 1994).

3.4. Overall conclusions on non-clinical data

Assessor's comment:
Powdered meadowsweet herb as well as comminuted herb and chopped flowers for preparation of herbal tea are used therapeutically in (commercially available) preparations in Europe for relief of minor articular pain, supportive treatment of symptoms of common cold and to facilitate renal and digestive elimination functions.

In general, there seems to be no clear distinction between the pharmacological effects of (preparations of) Filipendulae ulmariae herba (= flowering tops) and Filipendulae ulmariae flos.

From *in vitro* and animal studies anti-inflammatory/immunomodulatory and anticarcinogenic activities could be documented. In addition, antibacterial activity of flower extracts against a large number of microorganisms was shown *in vitro*.
In vivo effects on the CNS in various animals include a.o. a reduction of rectal temperature. This antipyretic activity, together with the anti-inflammatory/immunomodulatory and antibacterial effects, supports the use of the specified herbal preparations in the context of inflammatory diseases such as painful articular conditions and common colds.
The effects on gastric ulcers seem contradictory. No effects on renal and digestive elimination functions have been reported.

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

4.2.1. Dose response studies

No data available.

4.2.2. Clinical studies (case studies and clinical trials)

Effect on cervical mucosa

Local application of an ointment containing a flower decoction resulted in an improvement of cervical dysplasia in 32 of 48 patients (67%), including 25 cases (52%) of complete regression. Within 10 months, no recurrence was observed in 10 completely cured patients (Halkes, 1998; ESCOP, 2003).

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

No data available.

4.3. Overall conclusions on clinical pharmacology and efficacy

Assessor's comment:
Clinical data are limited to the study of the use of a flower decoction in cervical dysplasia as described. Available data are considered insufficient to evaluate quality and design of the study. On this basis, assessment of the efficacy in accordance with current guidance is not feasible.

No clinical data are available to contribute to the plausibility of efficacy for the specific indications of Filipendulae ulmariae herba and flos in the context of inflammatory diseases such as painful articular conditions and common colds.

5. Clinical Safety/Pharmacovigilance

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

No specific data available.

The Council of Europe categorizes Filipendulae ulmariae herba as a natural source of food flavouring that can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product (Barnes et al., 2007). According to the Botanical Safety Handbook Filipendulae ulmariae herba is an herb that can be safely consumed when used appropriately (McGuffin, 1997).

5.2. Patient exposure

No clinical human data is available.

So far, no pharmacovigilance actions have been reported by any of the responding Member States (based on information received from 15 MS, situation on 15-07-2010).

5.3. Adverse events and serious adverse events and deaths

No data available.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

No specific data is available on drug interactions, use in pregnancy and lactation, overdose, drug abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability. However, as safety during pregnancy and lactation has not been established, the use of *Filipendula ulmaria* during pregnancy and lactation should be avoided.

Due to the presence of salicylates, *Filipendula ulmaria* should not be used in cases of hypersensitivity to salicylates.

5.6. Overall conclusions on clinical safety

Pregnancy and lactation:
As safety during pregnancy and lactation has not been established, the use during pregnancy and lactation should be avoided.

Use in children:
Data on *Filipendula ulmaria* are scarce. Use in children and adolescents under 18 years of age is not recommended because data are not sufficient and medical advice should be sought.

Drug interactions adverse effects and contra-indications:
No drug interactions are documented clinically. Theoretically, as preparations of *Filipendula ulmaria* may contain salicylates there might be a potential for interactions with other salicylate containing products or other NSAID medicines administered concurrently. However, the amount of salicylates, mostly present in the form of glycosides, is assumed to be less than 0.5 % (Zeylstra, 1998; ESCOP, 2003). According to Schulz et al. (1998) infusions contain only trace amounts of salicylates, so meadowsweet tea is considered an aromatic remedy rather than a salicylate medication. Indeed, there appears to be some doubt whether salicylates will play an important role in experimental or clinical effects (Steinegger and Casparis, 1945; Halkes, 1998). With respect to adverse effects and contra-indications, for willow bark (containing 0.5-10% of salicylates) (HMPC, 2009) it was concluded that "there is no evidence that the types of reactions known to be associated with the pharmaceutical salicylates is observed with Salix" (McGuffin, 1997). In addition, according to Wichtl (1994) "salicylate side effects are not to be expected with the amount of salicylate derived from the drug (2-3 g of willow bark) administered" and "there should be no increased interaction with blood coagulants". Hence, for (preparations of) *Filipendula ulmaria*, containing even less salicylates than *Salix, salicylates-related* interactions, adverse effects and contra-indications, can be considered unlikely. Nevertheless, although side effects commonly associated with aspirin have not been observed with salicin-rich plants, *Filipendula ulmaria* should not be used in cases of hypersensitivity to salicylates.

Assessor's comment:
Clinical safety data are very limited. On the other hand, no safety problems concerning the traditional use of *Filipendula ulmaria* or its preparations have been reported. Although side effects, interactions and contra-indications commonly associated with aspirin are considered unlikely, *Filipendula ulmaria* should not be used in cases of hypersensitivity to salicylates, In addition, the use during pregnancy and lactation and in children and adolescents under 18 years of age is not recommended. In other situations, *Filipendula ulmaria* preparations are considered not harmful when used in the recommended dosages for the specified indications.

6. Overall conclusions

In general, there seems to be no clear distinction between the pharmacological effects of (preparations of) Filipendulae ulmariae herba (= flowering tops) and Filipendulae ulmariae flos. Also the Commission E monograph describes the same use for both herbal substances, with only a different daily dosage: 2.5–3.5 g of flowers is considered equivalent with 4–5 g of herb.

As no adequate clinical studies are available, preparations of neither Filipendulae ulmariae herba nor Filipendulae ulmariae flos can be qualified for well-established use indications.

Since data on genotoxicity, mutagenicity and carcinogenicity studies are lacking, a list entry for neither Filipendulae ulmariae herba nor Filipendulae ulmariae flos is considered to be applicable.

Also the amount of preclinical scientific data for *Filipendula ulmaria* preparations appears to be limited. From *in vitro* and animal studies anti-inflammatory/immunomodulatory and anticarcinogenic activities could be documented. In addition, antibacterial activity of flower extracts against a large number of microorganisms was shown *in vitro*.
In vivo effects on the CNS in various animals include a.o. a reduction of rectal temperature. This antipyretic activity, together with the anti-inflammatory / immunomodulatory and antibacterial effects, support the use of the specified herbal preparations in the context of inflammatory diseases such as painful articular conditions and common colds. Their pharmacological effects or efficacy are considered plausible on the basis of long-standing use and experience, as required by Art 16a 1 (e) of Directive 2004/24/EC.

For (comminuted) herbal substance (for tea preparation) in a daily adult dosage of 2-18 g (herb) or 2.5-6 g (flowers), respectively as well as for powdered herbal substance (herb) in a daily adult dosage of 250-1500 mg, the period of traditional use as required by art. 16a 1 (d) and laid down in art. 16c 1 (c) of Directive 2004/24/EC is considered to be elapsed with respect to the following indications (for both Filipendulae ulmariae flos and Filipendulae ulmariae herba, as well as their specified preparations):

- Traditional herbal medicinal product for the supportive treatment of common cold.
- Traditional herbal medicinal product for the relief of minor articular pain.

The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

These indications are considered as appropriate "…for use without the supervision of a medical practitioner…" and subsequently to fulfil the requirements of art. 16a 1 (e) of Directive 2004/24/EC.

Recommended posology:

Herb:
- (comminuted) herbal substance (for tea preparation): daily adult dosage of 2-18 g; single dose: 1.5-6 g
- powdered herbal substance (herb): daily adult dosage 250-1500 mg; single dose: 250-500 mg

Flowers:
- herbal substance (for tea preparation): daily adult dosage of 2.5-6 g; single dose: 2.5-3 g.

No experimental data is available on possible toxicity of (preparations of) *Filipendula ulmaria*.
However, in view of the results of the preclinical studies and the long period of marketing experience without reports of adverse reactions, the specified *Filipendula ulmaria* herbal preparations can be considered as proved not to be harmful in the specified conditions of use as required by Art. 16a 1 (e) of Directive 2004/24/EC.

Annex

List of references