EUROPEAN MEDICINES AGENCY
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Committee on Herbal Medicinal Products (HMPC)

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

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Filipendula ulmaria* (L.) Maxim., herba *Filipendula ulmaria* (L.) Maxim., flos
Herbal preparation(s)	**Herb:** a) Comminuted herbal substance b) Powdered herbal substance c) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% (V/V) **Flowers:** Comminuted herbal substance
Pharmaceutical forms	**Herb:** Comminuted herbal substance as herbal tea for oral use. Powdered herbal substance in solid dosage forms for oral use. Herbal preparation in liquid dosage form for oral use. **Flowers:** Comminuted herbal substance as herbal tea for oral use.
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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. 6th ed. 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 *et al.,* 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 *et al.,* 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[1]:
a1) Comminuted herbal substance for tea preparation

a2) Powdered herbal substance

b1) Dry extract (DER unknown), water

[1] For details please refer to 'Qualitative and quantitative composition in the Monograph on Filipendula ulmaria herba or indications 1-4 as specified under section 2.2, page 10 and section 2.3, page 11/12 of this AR.

b2) Dry extract (DER unknown), water (may be identical to b1)

b3) Liquid extract (1:1; ethanol 25% V/V)

c) Tincture (1:5; ethanol 45% V/V)

Flowers[2]:
a1) Comminuted herbal substance for tea preparation

b) Dry extract (DER unknown), ethanol (concentration unknown)

- 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 (1974/1983), Filipendulae ulmariae herba is used in combinations with *Althaea officinalis* 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)[2].

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. 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

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	

[2] For details please refer to 'Qualitative and quantitative composition in the Monograph on Filipendula ulmaria herba or indications 1-4 as specified under section 2.2, page 10 and section 2.3, page 11/12 of this AR.

	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 unknown), water, hard capsule 200 mg	MA
	Comminuted herbal substance, sachet 1.5 g	MA
	Dry extract (DER unknown), water, hard capsule 169 mg	MA
	Also available in combination products (herbal teas)	- (?)
	Flowers:	
	Dry extract (DER unknown), ethanol (concentration unknown), 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
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:	

Member State	Regulatory Status				Comments
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify: as food supplement	No products with MA on 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

The electronic databases of PubMed, Embase and International Pharmaceutical Abstracts were searched with the search terms 'Filipendula' and/or 'ulmaria'. The search was carried out on 28 September 2009.

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 from 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 the literature sources, mainly herbal tea preparations are described, however, Van Hellemont (1988) also mentions a tincture. A tincture (1:5 in 45% V/V alcohol) of the herb is used against rheumatic muscle and joint pains (British Herbal Pharmacopoeia, 1974). A product containing 250 mg of dried, powdered flowering tops in hard capsules was 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. This product 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 a fragmented herb have been marketed since 1990 as a traditionally used medicine in the symptomatic treatment of minor painful joint conditions. In some countries of the EU, tinctures or possible tincture-based products containing alcoholic extracts of Filipendula herba are on the market as food supplements used for complaints such as rheumatic and arthritic pain.

Assessor's comment:
With regards to the comminuted herbal substance for tea preparation, the powdered herbal substance and the tincture (1:5 in 45% V/V alcohol), 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. However, with respect to dry and liquid extracts and other tinctures, the available information is not sufficient.

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

Whereas in the British Herbal Pharmacopoeia (1974/1983) stomachic, mild urinary antiseptic, antirheumatic and antacid actions are listed, the British Herbal Pharmacopoeia (1990) and British Herbal Compendium (BHC; Bradley, 1992) describe the action of Filipendula herba as anti-inflammatory. In addition, BHC (1992) 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 therapeutic actions have been accepted: Oral use: "Traditionally used to facilitate renal and digestive elimination functions, for febrile and influenza conditions, as an analgesic (headache, toothache), in the symptomatic treatment of minor painful articular conditions 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 Commission E monograph (Blumenthal *et al.*, 1998) mentions the use of both herb and flowers as supportive therapy for colds. In the ESCOP Monographs (2003), it is stated: "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, 1974/1983	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, 1974/1983	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, astringent, woundhealing, in adipositas, cellulitis	H: infusion, tincture
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), sachets containing 1.5 g of comminuted herbal substance for tea preparation (2) and tinctures (2; DER and ethanol concentration unknown).

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, 1974; 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 unknown), water

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

b2) Dry extract (DER unknown), 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, 1974/1983; 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, 1974/1983; 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 unknown), ethanol (concentration unknown)

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

Assessor's comment:
The information on the use/dosages of Filipendula ulmaria in children is limited to only one reference for the herb (ESCOP, 2003 [original reference: Dorsch et al., 1998]) and completely lacking for flowers. No exposure data in children are available. It is therefore 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 / flos nor their preparations. However, since data on prolonged use are lacking, the products should not be used for more then seven 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 (Tunón *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) 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 *et al.*, 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 not to be 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 compounds, however,

were 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 have been described (Halkes, 1998; ESCOP, 2003; Barnes *et al.,* 2007). 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 has been described (Barnes *et al.,* 2007).
A heparin-like complex from the flowers showed *in vivo* anticoagulant and fibrinolytic properties in animals after intramuscular and intravenous injection (Kudriashov *et al.,* 1990; Kudriashov *et al.,* 1991).
Isolated rugosin D demonstrated to possess a high capacity for binding to bovine serum albumine (BSA) *in vitro* (Beart *et al.,* 1985; ESCOP, 2003).

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 German Commission E monograph (Blumenthal et al., 1998) describes the same use for both herbal substances, with only a different daily dosage: 2.5–3.5 g of the flowers is considered equivalent with 4–5 g of the 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, amongst others 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 on 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 determined 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).

Overall conclusion on toxicological data

Assessor's comment:
There are only limited preclinical safety data on 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 cannot 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

Powdered meadowsweet herb as well as the comminuted herb and flowers for preparation of an 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 have been 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 amongst others 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 a 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

Clinical data are limited to a 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, the 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 categorises 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 McGuffin *et al.* (1997), the Filipendulae ulmariae herba is a herb that can be safely consumed when used appropriately.

5.2. Patient exposure

No clinical human data are 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 July 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 are 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 is not recommended.

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 as 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) (EMEA/HMPC/295337/2007), 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. 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. However, 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 *(Blumenthal et al., 1998)* describes the same use for both herbal substances, with only a different daily dosage: 2.5–3.5 g of flowers is considered equivalent to 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 have been 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 amongst others 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 support the plausibility of long-standing use and experience, as required by Art 16a 1 (e) of Directive 2004/24/EC.

For the (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.

For the tincture of the herb (1:5; ethanol 45% V/V) in a daily adult dosage of 2-12 ml, the period of traditional use is considered to be elapsed only with respect to the following indication:

- 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
- tincture: daily adult dosage 2-12 ml; single dose: 2-4 ml

Flowers:

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

No experimental data are 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 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