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EMA/HMPC/576232/2010
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Fumaria officinalis* L., 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)	<i>Fumaria officinalis</i> L., herba
Herbal preparation(s)	a) Comminuted herbal substance b) Powdered herbal substance c) Dry extract (DER 3.5-4.5:1), extraction solvent water d) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V e) Tincture (1:5), extraction solvent ethanol 45% V/V f) Juice of fresh plant
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use. 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 *Fumaria officinalis* L., herba. 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)

Fumariae herba, common fumitory herb, consists of the dried, above-ground parts of *Fumaria officinalis* L. (fam. *Fumariaceae*), gathered during the flowering season, as well as their preparations in effective dosages (Blumenthal 1998).

Fumitory is an annual plant of somewhat variable characteristics, often resembling a bush but also growing as a low trailing shrub. It has a gray, pointed leaves that at a distance give the plant a wispy appearance of smoke (hence the common name). The pink-purple flower blooms in spring. The plant is a widely dispersed and can be found in gardens, slopes and in wastelands.

According to the European Pharmacopoeia (6.2. 2008), the whole or fragmented dried aerial parts of *Fumaria officinalis* are harvested in full bloom. They contain a minimum of 0.40% of total alkaloids, expressed as protopine ($C_{20}H_{19}NO_5=353.4$).

Fumitory comprises of the dried or fresh flowering plant *Fumaria officinalis* (*Papaveraceae*) and is used in herbal medicine. It is an ingredient of preparations used mainly for gastrointestinal and biliary-tract disorders (Ph. Eur. 6.2. 2008; Martindale 1996).

Erdrauchkraut; Fumaria; Fumariae herba; Fumeterre; Zemědymová nat'; Ziele dymnicy; Дымовая Трава; Дымянка Лекарственная

According to Goetz et al. (2009), British Herbal Pharmacopoeia (1976), British Herbal Compendium (1992) and Paris & Moyses (1981) chemical constituents are:

- Alkaloids (0.3-1% calculated as protopine (0.13%) even though several different types of alkaloids have been isolated and structurally elucidated derivatives

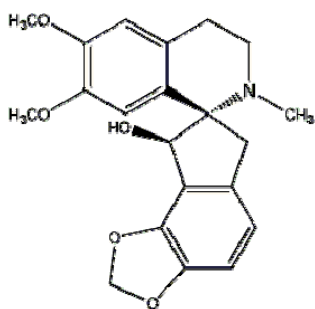
Protopines, the quantitatively predominant type, as protopine (fumarine) and cryptopine

Protoberberines: aurotensine, stylophine, N-methylsinactine and others

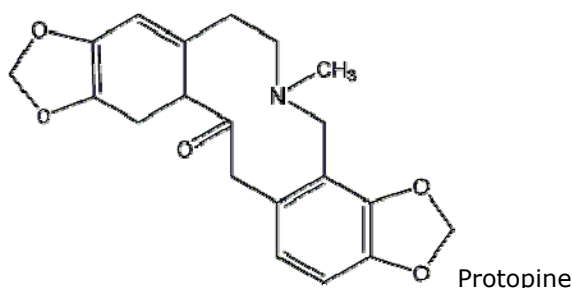
Spirobenzylisoquinolines: fumaritine, fumaricine and fumariline and others

Benzophenanthridines such as sanguinarine and corydamine (traces)

Indenobenzazepines: fumaritrididine and fumaritrine (Preininger 1975; Forgacs et al. 1982, 1986; Wawrzynowicz et al. 1968; Hermansson & Sandberg 1973; Mardirossian et al. 1983)



Fumaricine



Protopine

- Flavonoids: principally glucosides of quercetin such as isoquercitrin, rutin, quercetin-3,7-diglucoside-3-arabinoglucoside (Torck et al. 1971; Massa et al. 1971)
- Acids: chlorogenic and caffeic acids, also fumaric acid, caffeoylmalic acid and other aliphatic acids (Massa et al. 1971; Boegge et al. 1995; Hahn & Nahrstedt 1985)
- Other constituents: bitter principles, mucilage, resin and potassium salts (Barnes et al. 2002)
- Herbal preparation(s)
 - a) Comminuted herbal substance
 - b) Powdered herbal substance
 - c) Dry extract (DER 3.5-5:1), extraction solvent water
 - d) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V
 - e) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% V/V
 - f) Juice of fresh plant
- 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.

This monograph refers only to *Fumariae herba*.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Dry water extract, DER 5:1, since 1978
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
France	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	1) Powdered aerial parts 2), 3) Dried water extract (DER: 3.5-4.5:1) Since: 1) 1982, 2) 1963, 3) 1987
Germany	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Only two herbal teas
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market

Member State	Regulatory Status				Comments
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	1) Powdered herbal substance as herbal tea 2) Powdered herbal substance for oral use in capsules Since: 1) 1985, 2) 1993
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products registered
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known

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.

Analytically

Member State	Regulatory Status
Member state	Products, indications
Austria	<p><u>WEU</u></p> <p>Preparations</p> <p>1) Dry extract, extraction solvent water, DER not specified, not less than 1.5% alkaloids calc. as protopine. 1 film-coated tablet contains 250 mg extract</p> <p>2) Dry extract, extraction solvent water, DER 5:1, not less than 2.5 mg alkaloids calc. as protopine per film coated tablet. 1 film-coated tablet contains 250 mg extract</p> <p>3) Combination 275.1 mg dry extract, extraction solvent water, DER 4-6:1, not less than 1.5% alkaloids calc. as protopine. 83.1 mg dry extract of <i>Silybi marianae fructus</i> (no more details) Combination</p> <p>Since</p> <p>1) 1992 2) 1978 3) 1988</p> <p>Pharmaceutical form</p> <p>1), 2) Film coated tablet 3) Hard capsules</p> <p>Posology for oral use in adults</p> <p>1), 2) 3 times daily 1-2 tablets 3) 3 times daily 2 tablets</p> <p>Indications</p> <ol style="list-style-type: none"> Dyskinesia of the biliary duct; pain in case of cholelithiasis when surgery is not possible; pain in case of cholecystitis and cholangitis; postcholecystectomy syndrome; posthepatic syndrome with cholestasis. Pain in the biliary system in case of dyskinesia of the biliary duct, complaints after cholecystectomy, cholelithiasis when surgery is not possible. Supportive treatment of dyskinesias of the biliary duct (also after cholecystectomy) in cases of an impairment of the liver.
Belgium	Not known
Bulgaria	Not known
Cyprus	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Czech Republic	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Denmark	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Estonia	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Finland	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
France	<p><u>TU</u></p> <p>Preparations</p>

Member State	Regulatory Status
	1) Powdered aerial parts 2) Dried extract (DER: 3.5-4.5:1), solvent water 3) Dried extract (DER: 3.5-4.5:1), solvent water Since 1) 1982 2) 1963 3) 1987 Pharmaceutical form 1), 3) Hard capsules 2) Coated tablet Posology for oral use in adults 1) 3-5 times daily (containing 220 mg powder each), (1100 mg maximum daily) 2) 4 times daily 250 mg of extract /tablet (1000 mg daily) 3) 2 times daily 200 mg of extract /capsule Indications 1) Traditionally used to promote urinary and digestive elimination functions. Traditionally used as a choloretic and cholagogoue. 2), 3) Traditionally used to promote urinary and digestive elimination functions.
Germany	Only two herbal teas
Greece	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Hungary	Not known
Iceland	Not known
Ireland	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Italy	Not known
Latvia	Not known
Lithuania	Not known
Luxembourg	Not known
Malta	Not known
Netherlands	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Norway	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Poland	Not known
Portugal	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Romania	Not known
Slovakia	Not known
Slovenia	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
Spain	Preparations 1) Powdered herbal substance for oral use as herbal tea or 2) Powdered herbal substance for oral use in capsules (160 mg) up to three times daily

Member State	Regulatory Status
	<p>Since</p> <p>1) 1985 2) 1993</p> <p>Posology for oral use in adults</p> <p>1) 2g/250 ml divided in 2-3 times daily, 2-6 g/day 2) 6-8 capsules daily, 960-1280 mg/day</p> <p>Indications</p> <p>1) Traditionally used digestive complaints, difficult digestions. 2) Dyspeptic symptoms; THMP to facilitate difficult digestions; spastic discomfort in the gastrointestinal tract (gall bladder).</p>
Sweden	No authorized herbal medicinal products containing <i>Fumariae herba</i> as a single drug preparation are on the market
United Kingdom	Not known

1.3. Search and assessment methodology

Search terms: *Fumaria officinalis* L., *Fumariae herba*, fumitory, fumitory alkaloids

Databases: Pubmed, Medline, HealLink, Scopus

Libraries: University of Athens, Lab. Of Pharmacognosy of the University of Athens

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

The name of fumitory is said to be derived either from the fact that its whitish, blue-green colour gives it the appearance of smoke rising from the ground, or according to Pliny and Olivier de Serres (XIV century) because the juice of the plant brings on such a flow of tears that the sight becomes dim as with smoke (Delaveau 1980), and hence its reputed use in affections of the eye. The leaves have no odour but a bitter and salty taste.

Fumitory has been known since antiquity and was described in herbals from the Middle-Ages. It was a predominantly the Mediterranean genus that was once used medicinally.

Traditionally the plant has been used as digestive and diuretic.

Fumaria extracts may be useful in the management of disorders of hepatobiliary tract, spastic discomfort in the area of the gallbladder bile ducts as well as gastrointestinal tract.

Unproven uses: in folk medicine, the herb has been used for skin diseases, constipation, cystitis, arteriosclerosis, rheumatism, arthritis, as a blood purifier, for hypoglycaemia and infections (PDR 2007).

Traditional preparation involved expressing the juice and evaporating, while the plant has also been used to treat chronic eczema, cutaneous eruptions and other dermatological conditions (The Review of Natural Products 2005). The use as an eye lotion in conjunctivitis has been reported (British Herbal Pharmacopoeia 1976).

Physicians and writers from Dioscorides to modern times value its depurative properties. The herbal drug has been monographed in old official pharmacopoeias (e.g. Codex Medicamentarius Gallicus Pharmacopée Française 1908; British Herbal Pharmacopoeia 1976; Madaus 1979; Les Cahiers de l'Agence 2008; Wichtl 1998; HagerROM 2006; Blumenthal 1998; The British Herbal Pharmacopoeia 1976; British Herbal Compendium 1992). It was also included in the Pharmacopée Française of 1908 for its diuretic and depurative properties.

Fumitory was officially recognized in 1986 by the French Health authorities (Bulletins Officiels N° 86/20 bis and N° 90/22 bis, Direction de la Pharmacie et du Médicament) as an herbal remedy traditionally used in renal and digestive elimination functions and to help digestion. Moreover, fumitory is on the United Kingdom General Sales List (GSL) and is approved by the German Commission E Monograph (Blumenthal 1998). It has been used as a traditional remedy for a long time without safety problems, in Europe and worldwide, for more than 30 years.

The flowers are used to make a yellow dye for wool.

Fumitory is listed by the Council of Europe as a natural source of food flavouring (category N3). This category indicates that fumitory can be added to foodstuffs in the traditionally accepted manner, although there is insufficient information available for an adequate assessment of potential toxicity (Barnes et al. 2002).

Type of tradition: European.

Fumitory (shatara) has been used in Afghanistan for the treatment of asthma (Delaveau 1980), while in India fumitory is widely used against dyspeptic disorders (Fiegel 1971).

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

- Herbal preparations

According to the overview of the European market, the herbal preparations a), b) and c) fulfil the criteria of the thirty years at least in Europe. The herbal preparations d), e) and f) were found in many literature references, also for at least 30 years (British Herbal Pharmacopoeia 1976).

For *Fumariae herba*, a period of at least 30 years in medicinal use, as requested by Directive 2004/24 EC for qualification as a traditional herbal medicinal product, is easily fulfilled. The evidence on traditional medicinal use is supported by a large number of publications providing consistent information.

a) Comminuted herbal substance

b) Powdered herbal substance (in France since 1982)

c) Dry extract (DER 3.5-5:1), extraction solvent water (in France since 1963 and in Austria since 1978)

From the literature (British Herbal Pharmacopoeia 1976; Van Hellemont 1986; British Herbal Compendium 1992; Barnes et al. 2002; PDR 2007; Goetz et al. 2009)

d) Liquid extract (1:1), extraction solvent ethanol 25% V/V

e) Tincture (1:5), ethanol 45% V/V

f) Juice of fresh plant

Herbal preparations in solid or liquid dosage forms for oral use or Comminuted herbal substance as herbal tea for oral use.

- Indications

Traditional herbal medicinal product used to promote urinary and digestive elimination functions (France).

Traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence (Spain).

Dyskinesia of the biliary duct, pain in case of cholelithiasis when surgery is not possible, pain in case of cholecystitis and cholangitis, postcholecystectomy syndrome and posthepatic syndrome with cholestasis (Austria).

Pain in the biliary system in case of dyskinesia of the biliary duct, complaints after cholecystectomy, cholelithiasis when surgery is not possible (Austria).

Supportive treatment of dyskinesias of the biliary duct (also after cholecystectomy) in cases of an impairment of the liver (Austria).

The indication by MLWP-HMPC: Traditional herbal medicinal product used to increase bile flow for the relief of symptoms of indigestion (such as sensation of fullness, flatulence and slow digestion).

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

Posology

Adults and elderly

a) Comminuted herbal substance

2-4 g/day (2 g/250 ml), 2-3 times daily

To be taken 30 min before meals

b) Powdered herbal substance

Single dose of 220 mg, up to 1100 mg of herbal substance daily

c) Dry extract (DER 3.5-4.5:1), extraction solvent water

Single dose of 250 mg of extract, up to 1000 mg daily

d) Liquid extract (1:1, solvent alcohol 25% V/V)

2-4 ml (30-50 drops) before meals

e) Tincture (1:5 alcohol 45% V/V)

Daily dose 1-4 ml before meals

f) Juice of fresh plant

Daily dose 3.5-4 g

Duration of use

Up to 2-3 weeks.

3. Non-Clinical Data

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

In vitro and animal studies

The herb has been used as amphotoleretic (Boucard & Laubenheimer 1966; Fiegel 1971; British Herbal Compendium 1992), mild antispasmodic on smooth muscle, mild diuretic and laxative (Reynier et al. 1977).

Amphocholeretic activity

The amphocholeretic activity of fumitory has been demonstrated in animals, showing that it has no effect on normal choleresis but modified bile flow which was artificially increased or decreased (Boucard & Laubenheimer 1966; Reynier et al. 1977), slowing down artificially increased flow and increasing reduced flow.

Fumitory extract inhibited the formation of gall bladder calculi in animals (Lagrange & Arousseau 1973).

Antispasmodic activity

Antispasmodic activity on smooth muscle has been reported by Reynier et al. (1977). Extracts inhibited formation of gallbladder calculi in animals (Lagrange & Arousseau 1973).

Antibacterial activity

Bactericidal activity against the Gram-positive organisms *Bacillus anthracis* and *Staphylococcus* has been reported (Preininger 1975).

Antiallergic and choloretic activity

In *in vivo* (rats) studies, preparations of the herb had no effect on normal choleresis but modified bile flow that had been artificially increased or decreased (Boucard & Laubenheimer 1966).

Plantago major together with *Fumaria officinalis* ethanolic extracts appeared to be of interest because of their antiallergic and choloretic properties in a study in the Tunisian population (Denden et al. 2010).

Bioactivities of secondary metabolites from Fumaria

The alkaloid protopine has a contractile action on Oddi's sphincter in animals (Van Hellemont 1986). One preparation of the total alkaloids of *Fumaria officinalis* L. (no further information) has shown arrhythmic activity (Gorbunov et al. 1977).

The major alkaloid protopine has antihistaminic, hypotensive, bradycardic and sedative activities in small doses in animals (Goetz et al. 2009), whereas larger doses cause excitation and convulsions (Preininger 1975).

All these observations of such bioactivities help to account for some of the existing clinical effects.

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

No data on *Fumaria* extracts have been found or reported, while there is only the following reference on protopine alkaloids purified from *Fumaria* extracts.

The alkaloid protopine, the major secondary metabolite was extracted from *Fumaria officinalis* and purified by column chromatography. Urine samples were collected from horses and a human volunteer that had been administered either *F. officinalis* or protopine free base. Plant and urine samples were acetylated and analysed by GC-MS after solid-phase extraction (SPE). The urinary metabolites of protopine were identified as 4,6,7,13-tetrahydro-9,10-dihydroxy-5-methyl-benzo[e]-1,3-benzodioxolo[4,5-1][2] benzazecin-12(5H)-one, 4,6,7,13-tetrahydro-10-hydroxy-9-methoxy-5-methyl- benzo[e]-1,3-benzodioxolo[4,5-1][2] benzazecin-12(5H)-one and 4,6,7,13-tetrahydro-9-hydroxy-10-methoxy-5-methyl-benzo[e]-1,3-benzodioxolo[4,5-1][2] benzazecin-12(5H)-one, chelianthifoline, isochelianthifoline and 2-O-desmethylchelianthifoline. The metabolic formation of the

tetrahydroprotoberberines by closure of the bridge across N5 and C13 is rate limited and protopine-like metabolites accumulate only when the route is overloaded. Metabolism was qualitatively similar in the horse and human (Wynne et al. 2004).

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

The main constituents of fumitory include:

- alkaloids, principally protopines, protoberberines, spirobenzylisoquinolines, benzophenanthridines and indenobenzazepines types;
- flavonoids, principally glycosides of quercetin;
- acids: chlorogenic and caffeic acids, fumaric acid and other aliphatic acids.

Single-dose and repeated-dose toxicity studies

No data available.

Genotoxicity studies

No genotoxicity studies have been carried out on fumitory according to available scientific literature.

Carcinogenicity studies

No carcinogenicity studies have been carried out on fumitory according to available scientific literature.

Reproduction and developmental toxicity studies

No reproductive and developmental toxicity studies have been carried out on fumitory according to available scientific literature.

The safety of fumitory during pregnancy and lactation has not been established. In accordance with general medical practice, the herbal medicinal products (herbal teas or finished products) should not be used during pregnancy and lactation without medical advice.

3.4. Overall conclusions on non-clinical data

Fumitory was officially recognized in 1986 by the French Health authorities (Bulletins Officiels N° 86/20 bis and N° 90/22 bis, Direction de la Pharmacie et du Médicament) as an herbal remedy traditionally used in renal and digestive elimination functions and to help digestion. Moreover, fumitory is on the United Kingdom General Sales List (GSL) and is approved by the German Commission E Monograph. It has been used as a traditional remedy for a long time without safety problems, in Europe and worldwide, for more than 30 years.

The published data that refers to the indications and preparations is limited, but on the basis of existing data the pharmacological activities (choleric amphocholeric, mild antispasmodic on smooth muscle, mild diuretic and laxative antispasmodic activity *on smooth muscle* (Reynier et al. 1977; Lagrange & Arousseau 1973; Boucard & Laubenheimer 1966; Fiegel 1971; British Herbal Compendium 1992) support the traditional use of *Fumaria officinalis* and preparations thereof in the proposed indication:

Traditional herbal medicinal product used to increase bile flow for the relief of symptoms of indigestion (such as sensation of fullness, flatulence and slow digestion).

The efficacy of traditional herbal medicinal products is only plausible but not proven by clinical data. Nevertheless, the safety must be guaranteed.

The lack of genotoxicity, carcinogenicity as well as reproductive and developmental toxicity studies do not allow the establishment of a Community List Entry.

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)

There is a lack of clinical research assessing the effects of fumitory; therefore, rigorous randomised controlled clinical trials are required.

The following data on clinical studies has been found in the literature:

Clinical trials

In a clinical study involving 105 patients with biliary disorders (hepatopathy, cholelithiasis, post-operation cholecystectomy syndrome) favourable results were claimed (British Herbal Compendium 1992; Fiegel 1971). Doses of 2 tablets containing sprayed water extract (3-6:1) in tablets of 250 mg each, in a proposed dose of 2 tablets 3 times per day were used for a period of 2-6 months. No detailed response has been given but an excellent tolerability was reported.

In another clinical trial by Müscher (1971) an amphotoleretic herbal medicinal product (Fumitory herb water extract 4-6:1, in tablets containing 250 mg of sprayed water extract) was used for one year in a group of 178 patients with biliary disorders. Ninety six treated patients (20-70 years old) were suffering from biliary disorders (especially dyskinesia), taking doses of 3 tablets per day (two before the meals and the 3rd before sleep). The safety and tolerability was proven and for 64 patients the results were characterised as successful, especially against the symptoms of fullness and flatulence. Another 43 patients (40-70 years old) with diagnosed cholelithiasis and post-operation syndrome were treated with 2 tablets containing 250 mg, 3 times daily for a period of 3 weeks, showing for 36 among them successful results, good tolerability and safety. In total, 125 patients among the 176 treated claimed favourable results. In all cases the tablets were taken before meals and the safety and tolerability were proven.

Roux (1977): In that clinical study 31 patients (16 men and 15 women, 25-78 years old) with biliary syndrome (either dyskinesia or low digestion and digestive complains (diarrhoea) have shown very positive amphocholeretic effects. The treatment lasted 15-30 days (depending on the problem) with doses of 2 dragees containing 250 mg of a water extract of fumitory (no further data given).

The clinical experience with a *Fumaria officinalis* nebulisate (water extract of 4-6:1) as an amphocholinergic agent used in 64 patients suffering from biliary disorders (dyskinesia, hepatopathy etc) has been published by Zawodsky (1974). All patients were treated with 3 tablets containing 250 mg of the extract daily, for 21 days. No adverse effects were noticed and an excellent tolerability was reported.

Hunold (1975): The clinical experience with *Fumaria officinalis* (water extract of 4-6:1) in primary and secondary, organic or functional affections of the gall bladder and biliary system was checked in a group of 85 patients with no detailed information on the doses used during the trial.

Heully et al. (1969): The effect of a water extract of Fumitory herba has been studied in a group of 20 persons vis-a-vis the choloretic result in a dose containing 500 mg of direct infusion in duodenal. The results appeared very variable and not comparable. The tolerability to the extract was very good.

Bourjat (1974): A clinical study has been carried out on the effect of trials of treatment with a water extract sprayed in tablets (nebulizate) of *Fumaria officinalis* against Xerostomia due to radiotherapy, because of pathological sclerose of salivary glands. The results were excellent using 2 tablets containing 250 mg of water extract before each meal and before sleep.

Salembier (1967): A study on the effect of the aerosol 'Fumeterre' on choleresis has been carried out in a group of 33 patients with external biliary drainage (no further information available).

Fablet et al. (1968): The therapeutic activity of the extract of *Fumaria officinalis* against the hepatobiliary syndrome and the depending migraines has been studied in a group of 101 patients (82 women and 19 men of 16-79 years old).

Double blind placebo clinical trial

One double blind placebo clinical trial was performed in a group of 30 patients (20 women, 10 men of 26-57 years old) with different biliary disorders (dyskinesia, cholecystitis, hepatopathy, chololithiasis, post-operation cholecystectomy syndrome) taking doses of 3 tablets of 'Fumaria-Nebulizat' (water extract 4-6:1) 250 mg per day (two before the meals and the 3rd before sleep) for 28 days. The safety and tolerability was proven, and for all 30 patients the results were described as successful, especially against the symptoms of fullness and flatulence (Kopp 1979).

Open studies

Kopp (1979): The Choloretic activity of an herbal medicinal product containing an extract of fumitory was studied in an open study in 18 patients for 10 days with favourable results. No data on the exact preparation or the posology are provided.

Zacharewicz et al. (1979): In an open study 45 patients (30 women and 15 men 28-59 years old) among them 27 with biliary dyskinesia problems (20 hypertonic, 7 hypotonic), were treated with 3 tablets containing 250 mg of extract per day (water extract not further specified), for 16 days. In some cases the daily doses reached 2000 mg. No adverse effects were reported, while 80% of the participants of the open study improved their daily life and their symptoms were clearly reduced.

However, the methodological limitations of these studies do not allow attributing the reported effects to the administration of fumitory (Barnes et al. 2002).

Irritable bowel syndrome

Neither fumitory nor Javanese turmeric was effective in a study in patients with irritable bowel syndrome (Brinkhaus et al. 2005).

The aim of this study was to determine the efficacy of two herbal remedies used in the treatment of IBS. In a randomized, double-blind, placebo-controlled trial, IBS patients were randomly assigned to one of three treatment groups: 1) *Curcuma xanthorrhiza* 60 mg daily (curcuma group) (n=24), 2) *Fumaria officinalis* 1500 mg daily (fumitory group) (n=24) and 3) placebo (n=58). The study treatment was applied three times a day for 18 weeks. The main outcome parameters were changes in global patient ratings of IBS-related pain and distension on a visual analogue scale (0-50 mm) between baseline and at the end of treatment. Additional outcome parameters included global assessments of changes in IBS symptoms and psychosocial stress caused by IBS.

A total of 106 patients (mean age 48±12 years, 63% F) were included in the intention-to-treat group. IBS-related pain decreased by -0.9 ± 11.5 (mm±SD) in the fumitory group, -0.3 ± 9.9 in the placebo group and increased by 2.0 ± 9.5 in the curcuma group ($p=0.81$). IBS-related distension decreased by -1.4 ± 12.5 in the curcuma group, -2.1 ± 9.2 in the placebo group and increased by 0.3 ± 9.3 in the fumitory group ($p=0.48$). Additionally, the global assessment of changes in IBS symptoms and psychological stress due to IBS did not differ significantly among the three treatment groups. Neither fumitory nor curcuma showed any therapeutic benefit over placebo in patients with IBS. Therefore, the use of these herbs for the treatment of IBS cannot be recommended.

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

None reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

Eight existing clinical studies in 617 patients (British Herbal Compendium 1992; Fiegel 1971; Müscher 1971; Roux 1977; Zawodsky 1974; Hunold 1975; Bourjat 1974; Salembier 1967; Fablet et al. 1968) as well as one existing double blind placebo trial (30 patients) (Kopp 1979) and two open studies in 63 patients (Kopp 1979; Zacharewicz et al. 1979) fully support the traditional use with intended choleric and digestive effects of fumitory. However, there is a lack of rigorous clinical research assessing the effects of preparations of fumitory.

It is obvious, that according the published *in vitro* and *in vivo* studies as well as the existing clinical trials an antispasmodic effect on the upper digestive tract is sufficiently documented.

5. Clinical Safety/Pharmacovigilance

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

Eight existing clinical studies in 617 patients (British Herbal Compendium 1992; Fiegel 1971; Müscher 1971; Roux 1977; Zawodsky 1974; Hunold 1975; Bourjat 1974; Salembier 1967; Fablet et al. 1968) as well as one existing double blind placebo trial (30 patients) (Kopp 1979) and two open studies in 63 patients (Kopp 1979; Zacharewicz et al. 1979) fully support the traditional use with intended choleric and digestive effects of fumitory. A very good tolerability was proven and no adverse effects have been reported, showing enough safety data for the proposed traditional use of fumitory.

5.2. Patient exposure

No data available.

5.3. Adverse events and serious adverse events and deaths

Raised intraocular pressure and oedema have been reported as possible effects (Anderson & Phillipson 1986).

One case of an acute hepatitis probably induced by product containing *Fumaria* and *Vitis vinifera* has been recently reported by Bonnet et al. (2007).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Special patient population

In the absence of data, *Fumaria* is intended only for adults.

Use in pregnancy and lactation

In the absence of data and in accordance with general medical practice, it is recommended not to use the herbal medicinal products containing fumitory during pregnancy and lactation.

Overdose

No cases of overdose have been reported in the scientific literature.

Drug abuse

No data available.

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

No data available.

5.6. Overall conclusions on clinical safety

In the absence of data in special patient populations, *Fumaria* is intended only for adults.

In the absence of data and in accordance with general medical practice, it is recommended not to use the herbal medicinal products containing fumitory during pregnancy and lactation.

Seven hundred and ten patients were treated with water extracts of fumitory (mainly 1 500 mg daily) for a period from 10 days to 21 weeks with variable results, but showing very good tolerability (British Herbal Compendium 1992; Fiegel 1971; Müscher 1971; Roux 1977; Zawodsky 1974; Hunold 1975; Bourjat 1974; Salembier 1967; Fablet et al. 1968; Kopp 1979; Zacharewicz et al. 1979). The results fully support the traditional use of fumitory for its choleric and digestive effects.

There is only one published report suggesting that a raised intraocular pressure and oedema have been reported as possible effects (Anderson & Phillipson 1986) during the use of an herbal medicinal product containing fumitory. No further data are available. Also one case of an acute hepatitis probably induced by *Fumaria* and *Vitis vinifera* products has been recently reported by Bonnet et al. (2007).

A good tolerability in all clinical trials was proven and no adverse effects have been reported, showing enough safety data for the proposed traditional use of fumitory.

As there is no available data on genotoxicity, carcinogenicity and reproducibility on fumitory extracts, the establishment of a Community List Entry is not possible for safety reasons.

6. Overall conclusions

The positive effects of fumitory aerial parts on digestive and hepatobiliary problems have long been recognised empirically. The use is made plausible by pharmacological data. There is a lack of controlled clinical studies, using herbal preparations, containing the herbal substance of *Fumariae herba*.

In conclusion, *Fumariae herba* and its preparations can be regarded as traditional herbal medicinal products in the indications:

Traditional herbal medicinal product used to increase bile flow for the relief of symptoms of indigestion (such as sensation of fullness, flatulence and slow digestion).

In the absence of data in special patient populations, *Fumaria* is intended only for adults.

In the absence of data and in accordance with general medical practice, it is recommended not to use the herbal medicinal products containing fumitory during pregnancy and lactation.

Seven hundred and ten patients have been treated with water extracts of fumitory (mainly 1 500 mg daily) from 10 days up to 21 weeks with very good tolerability.

No adverse effects have been reported in the above referred clinical studies except one report suggesting that a raised intraocular pressure and oedema (Anderson & Phillipson 1986). Also one case of an acute hepatitis probably induced by *Fumaria* and *Vitis vinifera* plant therapy products has been recently reported by Bonnet et al. (2007).

As there is no available data on genotoxicity, carcinogenicity and reproducibility on fumitory extracts, the establishment of a Community List Entry is not possible for safety reasons.

Annex

List of references