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)

Final

<table>
<thead>
<tr>
<th>Herbal substance(s) (binomial scientific name of the plant, including plant part)</th>
<th><em>Fumaria officinalis</em> L., herba</th>
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</thead>
<tbody>
<tr>
<td>Herbal preparation(s)</td>
<td>a) Comminuted herbal substance</td>
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<tr>
<td></td>
<td>b) Powdered herbal substance</td>
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<tr>
<td></td>
<td>c) Dry extract (DER 3.5-4.5:1), extraction solvent water</td>
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<td></td>
<td>d) Liquid extract (DER 1:1), extraction solvent ethanol 25% V/V</td>
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<tr>
<td></td>
<td>e) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 45% V/V</td>
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<tr>
<td></td>
<td>f) Juice of fresh plant</td>
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<tr>
<th>Pharmaceutical forms</th>
<th>Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid dosage forms for oral use.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapporteur</td>
<td>Dr Ioanna Chinou</td>
</tr>
</tbody>
</table>
Table of contents

1. Introduction .......................................................................................................................3
   1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof .3
   1.2. Information about products on the market in the Member States ......................... 4
   Regulatory status overview ......................................................................................... 4
   1.3. Search and assessment methodology .................................................................... 7

2. Historical data on medicinal use ........................................................................................7
   2.1. Information on period of medicinal use in the Community ................................. 7
   2.2. Information on traditional/current indications and specified substances/preparations ... 8
   2.3. Specified strength/posology/route of administration/duration of use for relevant
       preparations and indications ............................................................................... 9

3. Non-Clinical Data .............................................................................................................10
   3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal
       preparation(s) and relevant constituents thereof ..................................................... 10
   3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal
       preparation(s) and relevant constituents thereof ..................................................... 11
   3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal
       preparation(s) and constituents thereof .................................................................. 11
   3.4. Overall conclusions on non-clinical data ............................................................ 11

4. Clinical Data .....................................................................................................................12
   4.1. Clinical Pharmacology ...................................................................................... 12
       4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s)
           including data on relevant constituents ................................................................ 12
       4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s)
           including data on relevant constituents ................................................................ 12
   4.2. Clinical Efficacy ............................................................................................... 12
       4.2.1. Dose response studies .................................................................................... 12
       4.2.2. Clinical studies (case studies and clinical trials) .................................................. 12
       4.2.3. Clinical studies in special populations (e.g. elderly and children) .................... 14
   4.3. Overall conclusions on clinical pharmacology and efficacy ................................... 14

5. Clinical Safety/Pharmacovigilance ...................................................................................15
   5.1. Overview of toxicological/safety data from clinical trials in humans...................... 15
   5.2. Patient exposure ................................................................................................. 15
   5.3. Adverse events and serious adverse events and deaths ........................................ 15
   5.4. Laboratory findings ............................................................................................ 15
   5.5. Safety in special populations and situations ......................................................... 15
   5.6. Overall conclusions on clinical safety ................................................................. 16

6. Overall conclusions ..........................................................................................................16

Annex .................................................................................................................................. 16
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 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 widespread and can be found in gardens, slopes and in wastelands.

According to the European Pharmacopoeia (6th ed. 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 (European Pharmacopoeia 6th ed. 2008; Reynolds 1996).

Some synonyms are: Erdrauchkraut; Fumaria; Fumariae herba; Fumeterre; Zemědýmová nat'; Ziele dymnicy; Дымовая Трава; Дымянка Лекарственная

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

- Alkaloids (0.3-1% calculated as protopine (0.13%); several different types of alkaloids have been isolated and structurally elucidated derivatives:
  - Protopines, the quantitatively predominant type, as protopine (fumarine) and cryptopine,
  - Protoberberines: aurotensine, stylopine, N-methylsinactine and others,
  - Spirobenzylisoquinolines: fumaritine, fumaricine anf fumariline and others (Murav'eva *et al.* 1974),
  - Benzophenanthridines such as sanguinarine and corydamine (traces),
- 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 et al. 1985)

- Other constituents are: 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 the 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

<table>
<thead>
<tr>
<th>Member State</th>
<th>Regulatory Status</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Austria</td>
<td>☒ MA ☐ TRAD ☐ Other TRAD ☐ Other Specify:</td>
<td>Dry water extract, DER 5:1, since 1978</td>
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<td>Estonia</td>
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<td>Finland</td>
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<td>France</td>
<td>☐ MA ☒ TRAD ☐ Other TRAD ☐ Other Specify:</td>
<td>1) Powdered aerial parts 2), 3) Dried water extract (DER: 3.5-4.5:1) Since: 1) 1982, 2) 1963, 3) 1987</td>
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<tr>
<td>Germany</td>
<td>☐ MA ☒ TRAD ☐ Other TRAD ☒ Other Specify:</td>
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<td>Greece</td>
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<td>Lithuania</td>
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<td>Malta</td>
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<td>The Netherlands</td>
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<td>Poland</td>
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<td>Portugal</td>
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<td>Romania</td>
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<td>Slovak Republic</td>
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<td>Slovenia</td>
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<tr>
<td>Spain</td>
<td>□ MA □ TRAD</td>
<td>□ Other TRAD □ Other Specify: 1) Powdered herbal substance as herbal tea 2) Powdered herbal substance for oral use in capsules Since: 1) 1985, 2) 1993</td>
</tr>
<tr>
<td>Sweden</td>
<td>□ MA</td>
<td>□ TRAD □ Other TRAD □ Other Specify: No products registered</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>□ MA</td>
<td>□ TRAD □ Other TRAD □ Other Specify: Not known</td>
</tr>
</tbody>
</table>

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.
### Austria

**Products, indications**

| WEU  | Prep. | 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  
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  
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 Silybi marianae fructus (no more details), combination |
|------|-------|--------------------------------------------------|
| **Since** | 1) 1992  
2) 1978  
3) 1988 | |
| **Pharmaceutical form** | 1), 2) Film coated tablet  
3) Hard capsules | |
| **Posology** | for oral use in adults | |
| 1), 2) 3 times daily 1-2 tablets  
3) 3 times daily 2 tablets | |
| **Indications** | 1. 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.  
2. Pain in the biliary system in case of dyskinesia of the biliary duct, complaints after cholecystectomy, cholelithiasis when surgery is not possible.  
3. Supportive treatment of dyskinesias of the biliary duct (also after cholecystectomy) in cases of an impairment of the liver. | |

### France

**TU  
Preparations**

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 | |
<p>| <strong>Posology</strong> | for oral use in adults | |
| 1) 3-5 times daily (containing 220 mg powder each), (1100 mg maximum daily) | |</p>
<table>
<thead>
<tr>
<th>Member State</th>
<th>Products, indications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2) 4 times daily 250 mg of extract /tablet (1000 mg daily)</td>
</tr>
<tr>
<td></td>
<td>3) 2 times daily 200 mg of extract /capsule</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>1) Traditionally used to promote urinary and digestive elimination functions. Traditionally used as a choleretic and cholagogue.</td>
</tr>
<tr>
<td></td>
<td>2), 3) Traditionally used to promote urinary and digestive elimination functions.</td>
</tr>
</tbody>
</table>

**Germany**

Only two herbal teas

**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

**Since**

1) 1985
2) 1993

**Posology** for oral use in adults

1) 2 g/250 ml divided in 2-3 times daily, 2-6 g/day
2) 6-8 capsules daily, 960-1280 mg/day

**Indications**

1) Traditionally used digestive complaints, difficult digestions.
2) Dyspeptic symptoms, THMP to facilitate difficult digestions, spastic discomfort in the gastrointestinal tract (gall bladder).

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### 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

The regulatory status of Fumariae herba preparations in EU was requested by e-mail.

### 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 predominantly the Mediterranean genus that was once used as medicine. 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 experimental 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 (Gruenwald *et al.* 2007; Duke 2002).
The traditional preparation involved expressing the juice and evaporating. The plant has also been used to treat chronic eczema, cutaneous eruptions and other dermatological conditions (DerMarderosian et al. 2005; Duke 2002). The use as an eye lotion in conjunctivitis has also 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. Pharmacopée Française; Codex Medicamentarius Gallicus Pharmacopée Française 1908; British Herbal Pharmacopoeia 1976; Madaus 1979; Bulletins Officiels N° 86/20 bis and N° 90/22 bis 1986; Les Cahiers de l’Agence 2008; Wichtl 1998; Blaschek et al. 2006; Blumenthal 1998; Goldberg et al. 2000; British Herbal Pharmacopoeia 1976; Bradley 1992). It is included in the Pharmacopée Française of 1908, for its diuretic and depurative properties.

Fumitory was officially recognised in 1986 by the French Health authorities (Bulletins Officiels N° 86/20 bis and N° 90/22 bis 1986) 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; Goldberg et al. 2000). It has been used in Europe and worldwide as a traditional remedy for more than 30 years without safety problems. (British Herbal Pharmacopoeia 1976; Madaus 1979)

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 for 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 below listed herbal preparations a), b) and c) fulfil the criteria of at least 30 years 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 these preparations, a period of at least 30 years in medicinal use, as requested by Directive 2004/24 EC (British Herbal Pharmacopoeia 1976; Madaus 1979) 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, in Austria since 1978)

  From the literature (British Herbal Pharmacopoeia 1976; Van Hellemont 1986; Bradley 1992; Barnes et al. 2002; Gruenwald et al. 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

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

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

Austria
- 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
- 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 liver impairment

The indication accepted 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), 1-2 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 4 times 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 the fresh plant
   Daily dose 3.5-4 g
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 amphocholeretic (Boucard & Laubenheimer 1966; Fiegel 1971; Bradley 1992), mild antispasmodic, mild diuretic and laxative (Reynier et al. 1977; Reynier et al. 1977a).

Amphocholeretic activity

The amphocholeretic activity of fumitory has been demonstrated in animals, showing no effect on normal choleresis. However, it modified the bile flow when it was artificially increased or decreased (Boucard et al. 1966; Reynier et al. 1977; Reynier et al. 1977a).

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

Antibacterial activity

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

Antiallergic and choleric 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 et al. 1966).

Plantago major together with Fumaria officinalis ethanolic extracts appeared to be of interest because of their antiallergic and choleric properties showed 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 (Dil 1973), 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 observed 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 with either *F. officinalis* or protopine free base. Plant and urine samples were acetylated and analysed by GC-MS after solid-phase extraction. The urinary metabolites of protopine were identified as 4,6,7,13-tetrahydro-9,10-dihydroxy-5-methyl-benzo[e]-l,3-benzodioxolo[4,5-l][2] benzazecin-12(5H)-one, 4,6,7,13-tetrahydro-10-hydroxy-9-methoxy-5-methyl-benzo[e]-1,3-benzodioxolo[4,5-l][2] benzazecin-12(5H)-one and 4,6,7,13-tetrahydro-9-methoxy-5-methyl-benzo[e]-1,3-benzodioxolo[4,5-l][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 was rate limited and protopine-like metabolites accumulated only when the route is overloaded. The metabolism was qualitatively similar in 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**

**Single-dose and repeated-dose toxicity studies**

No data available.

**Genotoxicity studies**

According to available scientific literature, no genotoxicity studies have been carried out on fumitory.

**Carcinogenicity studies**

According to available scientific literature, no carcinogenicity studies have been carried out on fumitory.

**Reproduction and developmental toxicity studies**

According to available scientific literature, no reproductive and developmental toxicity studies have been carried out on fumitory.

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 recognised in 1986 by the French Health authorities (Bulletins Officiels N° 86/20 bis and N° 90/22 bis 1986) 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, in Europe and worldwide, as a traditional remedy for more than 30 years without safety problems.

The published data that refers to the indications and preparations are limited, but existing data on the pharmacological activities (choleretic amphocholeretic, mild antispasmodic on smooth muscle, mild
diuretic and laxative antispasmodic activity) (Reynier et al. 1977; Reynier et al. 1977a; Lagrange et al. 1973; Boucard et al. 1966; Fiegel 1971; Bradley 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, no safety problems have been found.

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 fumitory water extract (3-6:1) in tablets of 250 mg each, in a proposed dose of 2 tablets 3 times daily were used for a period of 2-6 months. No detailed response has been given but a good tolerability was reported.

In another clinical trial by Müscher (1971), an amphocholeretic 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 of 178 treated patients (20-70 years old) were suffering from biliary disorders (especially dyskinesia) taking doses of 3 tablets daily (two before 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 chololithiasis and post-operation syndrome were treated with 2 tablets containing 250 mg, 3 times daily for a period of 3 weeks, showing successful results, good tolerability and safety for 36 of them. In total, 125 patients out of 178 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 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 (no detailed information on the doses used during the trial).

Heullly *et al.* (1969): The effect of a water extract of fumitory herb has been studied in a group of 20 persons vis-à-vis toward the choleretic activity in a dose of 500 mg by direct infusion into the duodenum. The results appeared very variable and not comparable. The tolerability of the extract was very good.

Bourjat (1974): A clinical study has been carried out on the effect of a water extract sprayed in tablets (nebulizate) of *Fumaria officinalis* against Xerostomia due to radiotherapy (because of pathological sclerosis of salivary glands) 2 tablets containing 250 mg of water extract were taken before each meal and before sleep (no further information on the type of the extract is available). The authors reported the results as ‘very good’.

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) (no further information available).

**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). Patients were taking 3 tablets of 'Fumaria-Nebulisat' (water extract 4-6:1) 250 mg daily (two before 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 Choleretic 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 nor the posology were provided.
Zacharewicz et al. (1979): In an open study, 45 patients (30 women and 15 men 28-59 years old), 27 of them with biliary dyskinesia problems (20 hypertonic, 7 hypotonic), were treated with 3 tablets containing 250 mg of extract daily (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 (IBS) (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 daily for 18 weeks. The main outcome parameters were changes in global patient ratings of an 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. An 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 between 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 (Bradley 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 choleretic and digestive effects of fumitory. However, there is a lack of rigorous clinical research assessing the effects of preparations of fumitory.

In view of 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 (Bradley 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) support the traditional use with intended choleretic 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 undesired effects (Anderson et al. 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 (Bradley 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 support the traditional use of fumitory for its choleretic and digestive effects.

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

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

**Annex**

**List of references**