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SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

## Assessment report on *Levisticum officinale* Koch, radix

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)	<i>Levisticum officinale</i> Koch, radix
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical forms	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)

According to Toulemonde and Noleau (cited by Bradley 2006), the chemical composition of different extracts of *Levisticum officinale* revealed more than 190 volatiles, in prevalence monoterpene carbons and phtalides (Bylaite *et al.* 1998; 2000; Raal *et al.* 2008; Stahl-Biskup and Wichtmann 1991). They found, that n-butylidene-4,5-dihydrophtalide is the major constituent at 67% concentration range (Eskin and Tamir 2006). Cichy *et al.* (1984) after Bradley (2006) found in lovage roots phtalide dimers: levistolide A, levistolide B.

The volatile oil is present in the roots in amounts of 0.6-1%. Up to 70% of the oil consists of alkylphtalides which are mainly responsible for the characteristic odour (Wichtl 1994, 2004). Blank *et al.* (1993) described the presence of the flavour compound 3-hydroxy-4,5-dimethyl-2(5H)-furanone (sotolone) as responsible for intense odour which was described as "hydrolyzed vegetable protein-like" or "curry-like". Sotolone presence was recognised also in urine of patients with maple syrup urine disease leading to neurological damage and mental retardation (Podebrad *et al.* 1999).

Supercritical CO<sub>2</sub> extraction using constant pressure revealed the presence of *cis*-ligustilide (52.0%), *trans*-ligustilide (3.95%), 3n-butylidene phtalide E (1.75%), 3n-butylidene phtalide Z (0.73%),  $\beta$ -phellandrene (0.28%),  $\alpha$ -terpinyl acetate (0.08%) (Daukšas *et al.* 2002). Moreover palmitic acid (2.81%), phytol (2.62%), linoleic acid (3.52%), stigmasterol (11%), and  $\beta$ -sitosterol (1.28%) were found (Daukšas *et al.* 2002).

Fehr (1980) identified the following substances in lovage root essential oil:  $\alpha$ -pinen (4.5-4.6%), camphene (1.0-1.1%),  $\beta$ -pinene (7.1-8.0%), myrcene (0.9%),  $\alpha$ -phellandrene 0.4-0.5%),  $\alpha$ -terpinene (0.1%), limonene (0.8-1,2%),  $\beta$ -phellandrene (8.7-10.7%), *cis*-ocimene (0.2-0.4%),  $\gamma$ -terpinene/*trans*-ocimene (0.2-0.3%), terpinolene (1.2-1.5%), pentylcyclohexadiene (7.4-12.7%), pentylbenzene (0.1-0.3%), 3n-butylidene-phtalide (31.5-32.0%) and 3n-butylidene-4,5-dihydrophtalide (23.5-24.9%).

**Phtalides** are compounds that give characteristic flavours to some species of *Apiaceae*, including *Levisticum officinale* root. To date 71 Phtalides have been isolated from 40 species of the *Apiaceae* family (Naves 1943; Beck and Chou 2007; Nunes *et al.* 2009). By combining analytical and preparative separation methods Gijbels *et al.* (1980, 1982) identified E- and Z-butylidenephtalide, E- and Z-ligustilide, senkyunolide and validene-4,5-dihydrophtalide; *isosenkyunolide* and propylidenephtalide. As the lead component of *Levisticum officinale* roots was described (*Z*)-Ligustilide (Segebrecht and Schilcher 1989). From *Levisticum officinale* roots 20 phtalides have been isolated and their content in the essential oil was 64-80%. Z-ligustilide (*cis*-3-n-butylidene-4,5-dihydrophtalide) was described by Mitsuhashi *et al.* (1960; 1966). Kobayashi *et al.* (1984; 1987) and they investigated phtalides in *Levisticum officinale* and described senkyunolide B, senkyunolide C, senkyunolide E, senkyunolide F, senkyunolide G, senkyunolide H, senkyunolide I and senkyunolide J. Other phtalides were identified after isolation by Liu *et al.* (2005): specifically (*E*)-3-butylidenephtalide, (*E*)-ligustilide and the dimer levistolide A. The simultaneous determination of ligustilide and butylidenephtalide using GC-MS-SIM was described by Chen *et al.* (2010) with tested ranges of 20-1,000  $\mu\text{g/ml}$  for ligustilide and 2-100  $\mu\text{g/ml}$  for butylidenephtalide.

According to Ezz El-Din and Hendawy (2010) lovage root oil is characterised by a high content of Z-ligustilide followed by falcarinol. In control plants the Z-ligustilide value was 23.4%, while after

fertilisation (chemical NPK ) a value of 33.6% was obtained. The highest amount of falcarinol (32.6% vs: from 26.1% in control) resulted from plants fertilised with compost. In contrary, Najda and Wolski (2003) found that the monocyclic terpenes and phtalides comprised the major components of the essential oil from lovage roots.

The essential oil content in lovage roots depends on the harvesting time. Andruszczak (2007) observed that harvesting the leaves during the vegetation season has a negative influence on the accumulation of essential oil in the roots. Keeping the above ground parts of *Levisticum* until autumn, significantly increased the amount of essential oil from 0.52 to 0.85%.

According to Hogg (2001), literature sources present following composition of lovage root oil as % of oil yield -  $\alpha$ -terpinyl acetate: 0.1-0.2,  $\beta$ -phellandrene: 1.7-15.5,  $\alpha$ -phellandrene: 0.2-0.5, myrcene: 0.3-0.9, (Z)-ligustilide: 37.0-67.5 and pentylcyclohexadiene: 7.4-29.3.

**Coumarins.** Thin-Layer chromatographic analysis of lovage root methanolic extract provided semi-quantitative information on the presence of bergapten ( $R_f \sim 0.6$ ), angelicin ( $R_f \sim 0.5$ ), umbelliferone ( $R_f \sim 0.45$ ) and 3-butylidenphtalide at  $R_f \sim 0.85$ . When compared to *Imperatoriae radix* and *Angelicae radix*, *Levistici radix* had a lower coumarin content (Wagner and Bladt, 2001). Using LC-DAD analysis of the chloroform extracts of lovage root, Paszkiewicz *et al.* (2008) detected both coumarins and furanocoumarins (psoralen and bergapten). Bradley (2006) estimates a total amount of coumarins of 3.2%, umbelliferone, coumarin and others (angelicin and scopoletin) included. Apterin (8-(glucosyloxy)isopropyl-9-hydroxy-8,9-dihydroangelicin) has been isolated in small amounts from nine plants of the *Apiaceae* family, *Levisticum officinale* enclosed (Fischer and Svendsen 1976).

### Phenylpropanoids

Some amounts of chlorogenic, caffeic and ferulic acids were found (Baerheim Svendsen 1951; Bradley 2006).

### Polyacetylenes

The aliphatic C17 polyacetylene falcarindiol was found by Cichy *et al.* (1984) and Zschocke *et al.* (1998) at the range of 0.14-0.2% of the dry drug. The ratio between Z-ligustilide and falcarindiol in lovage root was found to be (falcarindiol: Z-ligustilide) 1:2, Zschocke *et al.* (1998). The other polyacetylene Z-falcarinol was detected by Santos *et al.* (2005) with amounts between 19% and 46%. Moreover the presence of farnesene, phellandrene, elemene, heptanal and octanal was found.

- Herbal preparation(s)

Comminuted herbal substance

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

Not applicable

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

### Regulatory status overview

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Herbal substance only available in combination products
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Herbal substance only available in combination products
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Germany	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Herbal substance only available in combination products
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Hungary	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Poland	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Spain	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Herbal substance only available in combination products

Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input checked="" type="checkbox"/> Other Specify:	Herbal substance only available in combination products

MA: Marketing Authorisation

TRAD: Traditional Use Registration

Other TRAD: Other national Traditional systems of registration

Other: If known, it should be specified or otherwise add 'Not Known'

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

### **1.3. Search and assessment methodology**

Databases assessed up to April 2011:

Science Direct, PubMed, Embase, Medline, Academic Search Complete, Toxnet

Search terms: *Levisticum officinale*, lovage root

## **2. Historical data on medicinal use**

### **2.1. Information on period of medicinal use in the Community**

Lovage has a long history: thousands of years of traditional medicinal use to treat a wide range of complaints (Colombo *et al.* 2011; De Voss 2010). The traditional use of *Levisticum officinale* in different diseases has been thoroughly documented in several handbooks and in folk tradition. Its use is mentioned in the ancient times by Dioscorides as Greek: *ligusticon*, Latin: *ligusticum*, the plant grown in the Alpine region of Liguria in Italy (Dioskurides).

Lovage preparations were used during the Middle Ages mainly as an emmenagogue, carminativum, diureticum and remedy for various skin ailments and were mentioned by Lonicerus (1564) and Matthiolus (1501-1577) according to Madaus (1938). The medieval sourcebook: the *Capitulary de Villis* (9th century) contains lovage as one of many culinary and medicinal plants that should be cultivated in every imperial garden (Arnold 1923). For centuries it is known as carminative and spasmolytic folk medicine. In the cosmetic/medical treatise of Trotula de Ruggiero of the Schola Medica Salernitana from the 11<sup>th</sup> century, garden lovage is indicated for skin lightening (Cavallo *et al.* 2008).

In Germany, it was approved in inflammatory conditions of the urinary tract and in kidney stones (Schimpfky 1900; Hogg 2001). In France, lovage was used as digestive and carminative (Goetz 2007) and as a confectionary ingredient.

The therapeutic activity of lovage is described in Madaus (1938) and in many other sources: Awang 2009; Berger 1960; Bradley 2006; Chevallier 1996; Duke 2002; Evans 2009; European Pharmacopoeia 5<sup>th</sup> and 6<sup>th</sup> ed.; Frohne 2006; Hänsel *et al.* 1994; Kohlmünzer 2000; Ożarowski 1976; Ożarowski and Jaroniewski 1987; Peter 2004; Raghavan 2007; Robbers and Tyler 1997; Roeske 1955; Schulz *et al.* 1998; Wagner and Wiesenauer 1995; Wiesenauer 2008; Weiss 1988; Weiss and Fintelman 2000; Wichtl 1994 and 2004; Wren 1975., Zehui and Watson 2005.

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

According to the information provided by the National Competent Authorities:

## Czech Republic

Authorised combination products

Average number of combination substances: 3-5

The main combination substances are: Absinthii herba, Millefolii herba, Menthae piperitae herba, Levistici radix, Hyperici herba, Liquiritiae radix, Foeniculi fructus

Herbal tea for oral use;

indications: Traditionally used in temporary loss of appetite and mild gastrointestinal complaints such as bloating, and flatulence

on the market since 1995

Levistici radix has been a subject of Czechoslovak Pharmacopoeia since 1987, recommended dosage in the last version of the Czech Pharmacopoeia (2009, Supplement 2010): single dose 2 g, daily dose 4-8 g

## Germany

Well-Established Use

One German standard marketing authorisation, herbal tea

The main combination substances are: Rosmarini folium, Ononidis radix

Combination products: In Germany there are 3 authorised combination products

Number of combination substances	Number of authorised combination products
2-3	2
4-5	1
>5	0

All preparations for which marketing authorisations for traditional use have been granted (with reference to former national regulations) are mentioned, regardless of the fact that some of them are not in accordance with current community law (as defined in Directive 2004/24/EC). Traditional preparations were authorised in 10-50% of well-established use doses when in parallel the same preparations were authorised under well-established use.

## Poland

Traditional Use

Preparation: Comminuted herbal substance

On the market at least since 1967

Pharmaceutical form: Herbal teas (three)

Posology: Dose for decoction: 4-5 g in 1 cup (200 ml) of hot water/15 minutes.

Indications: To increase amount of urine to achieve flushing of the urinary tract.

Risks (adverse drug effects, literature)

Avoid an excessive exposure to the sun or UV light. Not recommended in hypersensitivity.

## Spain

### Combination products

A combination product has been submitted as a THMP (coated tablets) to the Spanish Agency, but at the moment it is still under assessment and therefore it isn't on the market yet.

## United Kingdom

The herbal substance is only available in combination product.

A combination product was granted recently as a Traditional Herbal MP.

One coated tablet contains: *Levisticum officinale* Koch, radix, *Centaurium erythraea* Rafn. herba, *Rosmarinus officinalis* L., folium.

Indication: A traditional herbal medicinal product used to help flushing of the urinary tract and to assist in minor urinary complaints associated with cystitis in women only, based on traditional use only.

## Search and assessment methodology

Databases assessed up to April 2011:

Science Direct, PubMed, Embase, Medline, Academic Search Complete, Toxnet

Search terms: *Levisticum officinale*, lovage root

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

#### **British Herbal Compendium (Bradley 2006)**

Indications based on tradition: Inflammatory complaints of the lower urinary tract and renal gravel or lithuria. Menstrual disorders including dysmenorrhea, delayed menses, have menstrual bleeding and period pain. Digestive disorders including flatulent colic, heartburn and loss of appetite.

Contraindications: \_Pregnancy. Inflammatory disorders of the kidney; oedema due to impaired cardiac or renal function.

Side effects: none known

Interactions: None known

Dosage: Dried root, 1-3 g as an infusion or decoction; liquid extract 1:1 in 45% ethanol, 1-3 ml, up to 3 times daily.

#### **British Herbal Pharmacopoeia (1983)**

Indications: flatulent colic, dyspepsia, oedema, renal, dysmenorrhea, delayed menses, lithuria, cystitis

Dosage: Dose of 0.5-2 g as decoction in water or milk. Liquid extract 1:1 in 45% alcohol. Dose 0.5-2 ml.

Duration of use: no information



**Commission E Monograph. *Levistici officinale* L.  
(Bundesanzeiger No 101, published June 1, 1990)**

Indications: Irrigation therapy for inflammation of the lower urinary tract and for prevention of kidney gravel.

Contraindications: Preparations of lovage should not be used if acute inflammation of the kidney parenchyma with impaired kidney function exists.

No irrigation therapy in cases of oedema due to limited heart and kidney function.

Side effects: None known

Interactions with other drugs: None known

Dosage: Unless otherwise prescribed: 4-8 g of drug and equivalent preparations daily.

Duration of use: no information

**Hagers Handbuch der Pharmazeutischen Praxis (Hänsel et al. 1994)**

Indications: Irrigation therapy for inflammation of the lower urinary tract and for prevention of kidney gravel.

Side effects: Allergic contact reactions.

Warnings: With prolonged use of lovage root, exposure to ultraviolet light and intense sun bathing should be avoided.

Contraindications: Not to be used in cases of acute inflammation of the kidney or with impaired kidney function. No irrigation therapy in cases of oedema due to impaired heart and kidney functions.

Dosage: Tea: 1.5 g in a 150 ml of hot water, steep for 10-15 minutes, then strain. Drink between meals.

Daily dose: 4-8 g of the drug

Duration of use: no information.

**Herbal Drugs and Phytopharmaceuticals (Wichtl 2004)**

Indications: For irrigation therapy in cases of inflammatory diseases of the lower urinary tract and for prevention of kidney gravel

Contraindications: Should not be used in cases of acute inflammation of the kidney parenchyma or with impaired kidney function. No irrigation therapy in cases of oedema due to limited heart and kidney functions.

Side effects: None known

Interactions: None known

Dosage: The daily dosage is 4-8 g of dried root or corresponding preparations.

Note: For use in irrigation therapy, abundant fluid intake is necessary.

Warning: With prolonged use of lovage root, exposure to ultraviolet light and intense sun bathing should be avoided.

Duration of use: no information

### **Herbal Medicine (Weiss and Fintelman 2000).**

Indications: As a diuretic for treatment of unspecific inflammatory diseases of the efferent urinary passages and renal gravel.

Daily dose: Pour one cup of boiling water onto one to two teaspoonful of the finely chopped drug, cover and allow to steep for 10-15 minutes, then strain. Drink one cup of the hot tea before meals, several times a day.

Duration of use: No information

### **Lehrbuch der Biologischen Heilmittel (Madaus 1938)**

Indications: Diuresis to treat oedema, inflammation of the lower urinary tract and prevention of kidney gravel. As carminative to improve digestion, as expectorant and emmenagogue.

Dosage: Orally: 5-8 g in hot water (cup). Drink up to 3-4 times daily.

Maximum dose is not described.

Duration of use: No information

### **Medicinal Plants of the World (Wyk and Wink 2004)**

Indications: Inflammation of the lower urinary tract. Kidney gravel, oedema.

Traditionally: Used as stomachic and carminative, as expectorant and emmenagogue.

Mode of use: A tea is made by pouring boiling water over 1.5-3 g of the dry herb.

Drink two or three times a day as a diuretic, half an hour before a meal as stomachic.

Duration of use: No information.

### **Medicinal Herbs: A Compendium (Gehrmann et al. 2005)**

Indications: Cleansing therapy with bacterial and inflammatory illness of urinary tract, as a prophylaxis for kidney gravel; also for dyspeptic complaints such as indigestion, heartburn, feelings of fullness, flatulence

Dosage: 2-4 g (1 teaspoon)/150 ml, 10-15 minutes, 1 cup several times/day between meals;  
stomachic: 1 cup 30 minutes before meals

Daily dose: 4-8 g

Warning: Ensure sufficient fluid intake, minimum 2 litre/day

Contraindications: Inflammatory diseases of the kidneys or urinary drainage passages, reduced cardiac and renal function; pregnancy

Side effects: Individual cases of photodermatitis; long-therapy → avoid exposure to direct sunlight or intensive UV radiation

Duration of use: No information

### **Normdosen gebräuchlicher Arzneistoffe und Drogen(Haffner et al. 2009)**

Oral route: Drug, 2 g 2-3 times daily; Extractum siccum: 0.3 g, 2-3 times daily,  
Extractum fluidum: 2 g, 2-3 times daily

## **PDR for Herbal Medicines, Gruenwald et al. editors (2000, 2004)**

The medicinal parts are the dried rhizome and roots.

Indications: Infections of the urinary tract. Kidney and bladder stones.

Irrigating therapy for inflammation of the urinary tract and irrigating therapy for prevention of kidney gravel.

Mode of use: Comminuted herb for internal use.

Tea is prepared by using 2-4 g drug to 1 cup, several times a day between meals.

Contraindications: Not to be used during pregnancy

Side effects: The drug possesses a low potential for sensitisation. An elevation of UV-sensitivity among light-skinned people is possible (Phototoxic effect of the furocoumarins).

Duration of use: No information.

## **Receptariusz Zielarski (1967)**

Indications: Stomachicum, diureticum, carminativum

Dosage: Decoctum: 1 tablespoon of the drug in 1 glass of hot water

Oral route: Drink half a glass (100 ml) two-three times daily

## **Ziółolecznictwo, Ożarowski (1976)**

Indications: Irrigating therapy for inflammation of the urinary tract.

Dosage: Decoctions: 10-20 g of the drug in 400 ml of hot water.

Drink half a glass (100 ml) three times daily

Duration of use: No information

## **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 experiments***

##### ***Lovage root essential oil***

##### **Antimicrobial activity**

According to Deans and Ritchie (1987) after Ceylan and Fung (2004) lovage essential oil shows antibacterial activity against both Gram positive and Gram-negative bacteria and is one of ten essential oils (thyme, cinnamon, bay, clove, almond-bitter, pimento, marjoram, angelica, nutmeg) with strongest activity from total 25 essential oils tested.

The fractionated methanolic extract of *Levisticum officinale* (10 g) was tested against bacterial strains of isolates of Gram-negative bacteria (Garvey *et al.* 2011). The extract was fractionated to active compounds yielding faltarindiol (450 mg), levistolide A (69 mg) and oleic and linoleic acids. The lovage extract showed synergistic activity with five antibiotics (ciprofloxacin, tetracycline, chloramphenicol,

erythromycin and ethidium bromide) against several *Salmonella typhimurium* isolates with innate efflux pump multidrug resistance AcrAB-TolC and was found the most active from eighty four extracts from 21 plants. Bioassay screening was carried out with ciprofloxacin in the absence or presence of the chloroform extract of *Levisticum officinale* on agar plates. A zone of inhibition of the ciprofloxacin (0.5, 1 and 2 mg/l) plus plant extract (100 mg/l) larger than that of antibiotic alone was estimated as synergy (Table 1). However no synergism was observed with the fractions and purified substances, implying that a composition of active substances is needed for efflux inhibition.

Table 1. Minimum inhibitory concentrations (MICs) of ciprofloxacin (CIP) in the absence and presence of *Levisticum officinale* extracts against Gram-negative bacteria (modified after Garvey et al. 2011)

Strain	MIC (mg/l) <sup>b</sup>	
	CIP	CIP+Lo
<i>S. typhimurium</i> L354	0.03	<b>0.008</b>
<i>S. typhimurium</i> L828	0.03	<b>0.008</b>
<i>S. typhimurium</i> L 829	0.008	<b>0.004</b>
<i>S. typhimurium</i> L3	0.008	<b>0.002</b>
<i>S. typhimurium</i> L10	0.06	<b>0.03</b>
<i>Enterobacter cloacae</i> A1	0.12	<b>0.06</b>
<i>Serratia marcescens</i> B14	0.06	0.06
<i>Pseudomonas aeruginosa</i> G1	1	1
<i>Klebsiella pneumoniae</i> H42	0.06	<b>0.03</b>
<i>Escherichia coli</i> I114	0.06	<b>0.03</b>
<i>Morganella morgani</i> J29	0.015	<b>0.008</b>

*S. typhimurium*, *Salmonella enterica* serotype *typhimurium*; Lo, chloroform extract of *Levisticum officinale* extract.  
<sup>b</sup>Bold text indicates synergistic combinations (i.e. MICs for the combination lower than for the antibiotic alone).

### Antimycobacterial activity

The dichloromethane extract of the root of *Levisticum officinale* was tested in a microtiter plate dilution method against *Mycobacterium fortuitum* and *Mycobacterium aurum* with a MIC of 64 µg/ml. Further fractionation resulted in two active polyacetylenes: (1) 3(R)-falcarinol and (2) 3(R)-8 (S)-falcarindiol with MICs against *M. fortuitum*, 30.4 µm (1), 16.4 µm (2) and against *M. aurum*, 60.8 µm (1), 16.4 µm (2). MICs of standard chemotherapeutics were as follows: ethambutol: 115.5 µm (*M. fortuitum*) and 14.6 µm (*M. aurum*); isoniazid: 3.4 µm (*M. fortuitum*) and 29.2 µm (*M. aurum*), respectively (Schinkovitz et al. 2008).

### Inhibition of activity of pancreatic lipase

The methanolic extract of lovage roots (20 g of powdered herbal substance with 200 ml of absolute methanol) inhibited by 55% the activity of pancreatic lipase at a concentration range of 0.05-0.15 mg/ml of the extract (Gholamhoseinian et al. 2010).

## ***Isolated constituents of lovage essential oil***

### **Antifungal activity**

**Polyacetylenes of falcarindiol type** constitutively present in *Apiaceae* have been identified as antifungal substances acting as prevention against infections (Garrod *et al.* 1979). They inhibit spore germination of different fungi at the concentration range of 20-200 µg/ml. It has also been shown that falcarindiol have anti-inflammatory, antiplatelet, and cytotoxic activity (Christensen and Brandt 2006b).

Acetylenes from *Apiaceae* have been shown to be toxic to bacteria and fungi and play a role in resistance and protection of plants against infection. Kemp (1978) found a total inhibition of spore germination using falcarindiol against *Alternaria brassicicola* and *Septoria nodorum* at a concentration of 20 µg/ml. However falcarinol even at the concentration of 200 µg/ml did not affect the fungi themselves.

The polyacetylene falcarindiol has been identified as a phytoalexin in tomato fruits and leaves infected by fungi (Christensen and Brandt 2006a).

Hadacek and Greger (2000) tested the activity of falcarindiol in various dilutions and diffusion bioassays against three selected plant filamentous microfungi, *Botrytis cinerea*, *Cladosporium herbarum* and *Fusarium avenaceum*. MIC defined as the lowest concentration/spot causing mycelium-free zones was found as follows: for *Botrytis cinerea*: 25 µg/ml, for *Cladosporium herbarum*: 12 µg/ml and for *Fusarium avenaceum*: 50 µg/ml.

### **Spasmolytic activity**

**Ligustilide** in concentration dependent manner relaxed isolated rat mesenteric artery rings precontracted with potassium chloride. *In vitro* experiments showed that the  $\beta$ -receptors, ATP sensitive potassium channels, calcium activated potassium channels and inwardly rectifying potassium channels were not involved in the myorelaxation. It was found, that ligustilide (10, 30, 100 µM) concentration-dependently (more than 10 µM) inhibited vasoconstrictive effects of Na and CaCl<sub>2</sub> in Ca<sup>2+</sup>-free medium. The pD<sub>2</sub> value of ligustilide (the negative logarithm of the drug concentration that elicited 50% relaxation) to CaCl<sub>2</sub> was 4.45±0.02. Contractions induced by caffeine were also inhibited, therefore the ryanodine receptors were involved through inhibition of intracellular Ca<sup>2+</sup> release. The authors conclude that the vasorelaxant effect of ligustilide in rat mesenteric artery is related to inhibition the voltage-dependent calcium channel and receptor-mediated calcium ryanodine receptors (Cao *et al.* 2006).

In *in vitro* experiments Ko (1980) tested the spasmolytic activity of **butylidenephthalide** in comparison to the papaverine activity in isolated guinea pig ileum, guinea pig vas deferens and guinea pig taenia coli. Butylidenephthalide non competitively inhibited contractions induced by ACh, K<sup>+</sup> and Ba<sup>2+</sup> in normal Tyrode solutions and to administered exogenous Ca<sup>2+</sup> in high K<sup>+</sup>, Ca<sup>2+</sup> free Tyrode solution. However butylidenephthalide pD<sub>2</sub> values were significantly inferior to those of papaverine (p<0.001). In the author's opinion butylidenephthalide probably inhibits the Ca<sup>2+</sup> release from the cellular membrane and from the intracellular calcium storage and/or inhibits the Ca<sup>2+</sup> influx from the extracellular fluid.

In other experiments Ko *et al.* (1997) separated two geometric isomers, the *Z*- and the *E*- forms of synthetic butylidenephthalide and checked their inhibition of voltage-dependent calcium channels in depolarised guinea-pig ileum longitudinal smooth muscle. It was found that ***E*-butylidenephthalide** (2-100 µM) inhibited contractions with a pD<sub>2</sub> value of 4.56±0.18. ***Z*-butylidenephthalide** non-competitively induced significantly lower inhibition of Ca<sup>2+</sup> as compared to *E*-butylidene phtalide with contractions at the range 50-100 µM and the pD<sub>2</sub> value of 3.88±0.20 (p<0.05).

**Butylidenephthalide** inhibited the calcium release from calcium stores in isolated rat aortic rings probably due to an independent mechanism not related to the production of inositol-1,4,5-trisphosphate (Ko *et al.* 1998).

**Butylidenephthalide** induced a concentration-dependent (1-300  $\mu\text{M}$ ) vasorelaxing effect in the rat isolated aorta constricted by use of **(1)** 60 mM of kalium chloride (KCl) and **(2)** 30 nM of 9,11-dideoxy-9 $\alpha$ ,11 $\alpha$ -methanoepoxyprostaglandin H<sub>2</sub> (EC<sub>50</sub> is the effective concentration of the test compound to cause 50% of its maximal response; **(1)** - EC<sub>50</sub>: 4.00 $\pm$ 0.03, n=5; **(2)** -EC<sub>50</sub>: P 4.29 $\pm$ 0.03, n=5, respectively (Chan *et al.* 2006). The authors suggest that the spasmolytic effect is dependent on the modulation of the L-type voltage operated and prostanoid receptor operated Ca<sup>2+</sup> channels.

Both **ligustilide** and **senkyunolide A** induced vasorelaxation effects in rat isolated aorta with cumulative concentrations within a range of 1 – 300  $\mu\text{M}$  (Chan *et al.* 2007). Both compounds had a similar spasmolytic activity against contractions induced by 9,11-dideoxy-9 $\alpha$ ,11 $\alpha$ -methanoepoxyprostaglandin F<sub>2 $\alpha$</sub> , phenylephrine, 5-hydroxytryptamine and KCl with pD<sub>2</sub>: 4.14 $\pm$ 0.08, pD<sub>2</sub>: 4.39 $\pm$ 0.11, pD<sub>2</sub> 4.56 $\pm$ 0.12, pD<sub>2</sub>: 4.43 $\pm$ 0.08, n=6, respectively (Chan *et al.* 2007).

**Ligustilide** inhibited spontaneous periodic contractions of the isolated rat uterus in a concentration dependent manner (EC<sub>50</sub>=4.4 $\pm$ 2.7-6.1)  $\mu\text{g}/\text{ml}$  and antagonised prostaglandin F<sub>2 $\alpha$</sub>  (95.3% at 8  $\mu\text{g}/\text{ml}$ ) and acetylcholine induced contractions (73.9% at 8  $\mu\text{g}/\text{ml}$ ) (Du *et al.*, 2006).

From another experiment performed in the rat isolated aorta model, Chan *et al.* (2009) reported a synergistic myorelaxant activity with NO-donor sodium nitroprusside in the rat isolated aorta constricted by use of 9, 11-dideoxy-9 $\alpha$ ,11 $\alpha$ -methanoepoxyprostaglandin H<sub>2</sub>. According to the authors this relaxant synergism is related to the modulation of the Ca<sup>2+</sup> sensitisation-mediated tone.

### Antiproliferative activity

Liu *et al.* (2011) tested the inhibitory effects of **n-butylidenphtalide** on proliferation *in vitro* and *in vivo* in the model of balloon injured a rat carotid artery on neointimal hyperplasia. In the cell culture of a rat aorta derived cell line, **n-butylidenphtalide** at concentrations of 25-100  $\mu\text{g}/\text{ml}$  significantly inhibited the proliferation and arrested the cell cycle in the G<sub>0</sub>/G<sub>1</sub> phase. Treatment with **n-butylidenphtalide** (150-300 mg/kg) significantly reduced the proliferation of the intima compared to the control group in rats with balloon injured carotid artery 2 weeks after injury. Immunohistochemical tests revealed a significant decrease of the proliferative activity in the 60-300 mg/kg treated rats. In contrary, the apoptotic activity was significantly increased in animals receiving 60-300 mg/kg of **n-butylidenphtalide**. The authors suggest that dose dependent up-regulation of the Nur77 gene (nerve growth factor IB) implicated in cell growth/survival and apoptosis is related to the antiproliferative activity of **n-butylidenphtalide**.

### Inhibition of 5-lipoxygenase (5-LO) products synthesis

**Falcarindol** blocks 5-LO product synthesis at the range of IC<sub>50</sub> concentrations 2-10  $\mu\text{M}$  (Alanko *et al.* 1994; Schneider and Bucar 2005; Werz 2007).

### Inhibition of TNF- $\alpha$

Liu *et al.* (2005) described the dose and time dependent inhibition of the transcription of TNF- $\alpha$  mRNA by **Z-ligustilide** and **senkyunolide A** in monocytes. Moreover, the two phtalides suppressed the TNF- $\alpha$  mediated NF- $\kappa\text{B}$  activation.

## **GABAergic activity**

Deng *et al.* (2006) have shown that a new phthalide dimer **gelispirolide** composed of Z-ligustilide and Z-butyridenephtalide induces inhibitory effects on the binding of [<sup>3</sup>H] diazepam to the GABA<sub>A</sub> receptors with IC<sub>50</sub> values of 29 μM.

## ***In vivo* experiments**

### ***Lovage root and lovage root essential oil***

#### **Diuretic activity**

Lovage root is used as diuretic in urinary tract infections (Bag *et al.* 2008; Combest *et al.* 2005; Yarnell 2002).

Butyridenephtalide and ligustilide possess spasmolytic properties (Wichtl 1994, 2004).

Early experiments performed in rabbits and mice (Vollmer and Weidlich 1937; Vollmer and Hübner 1937) with an infusion of *Levisticum radix* showed a slight increase of the urine volume and the concentration of chloride ions. However, in previous tests lovage root (0.25-1 g of crude drug per animal) , did not induce diuresis (Bradley 2006).

According to Vollman (1988), diuretic effects of the oil is due to activity of the terpene derivatives.

#### **Oestrogenic activity**

San Martin (1958) observed in experiments performed *in vivo* with female ovariectomised rats estrogenic effects on the vagina and on the uterus (the production of cornified epithelial cells in the vaginal smear of a castrated animal) after subcutaneous injection of the aqueous extract (1: 8) of *Levisticum officinale*. According to the Allen-Doisy criterion (measures of vaginal cornification as endpoint) estrogenic effects were seen after lovage extract administration with an activity of 1 g drug equivalent to 8 IU of estradiol. In comparison, according to San Martin (1958) 1 g of *Humulus lupulus* extract induces estrogenic effects equivalent to 200-300 UI of estradiol.

### ***Isolated constituents of lovage essential oil***

#### **Analgesic activity**

In two mice models, the acetic acid-induced writhing response and the formalin-induced licking time, ligustilide given intragastrically significantly and dose-dependently reduced the writhing response and licking time (Du *et al.* 2007). **Ligustilide** at the dose 10 mg/kg induced the same range of analgesia as a very high dose of aspirin (200 mg/kg) in the acetic acid induced writhing movements.

#### **Neuroprotective activity.**

Using the model of forebrain ischemia/reperfusion injury in mice, Kuang *et al.* (2006) demonstrated for **ligustilide** significant protection against brain damage. Transient ischemia was produced by the bilateral common carotid artery occlusion. After intraperitoneal administration, ligustilide dose dependently significantly decreased the infarction volume of the brain tissue. The infarction volume was without ligustilide: 22.1±2.6%, after 5 mg/kg: 11.8±5.2%(p<0.05) and after 20 mg/kg: 2.60±1.5% (p<0.01).

## Antiproliferative activity

Liu *et al.* (2011) tested the inhibitory effects of **n-butylidenphthalide** on proliferation *in vitro* and *in vivo* in the model of balloon injured a rat carotid artery on neointimal hyperplasia. In the cell culture of a rat aorta derived cell line, **n-butylidenphthalide** at concentrations of 25-100 µg/ml significantly inhibited the proliferation and arrested the cell cycle in the G<sub>0</sub>/G<sub>1</sub> phase. Treatment with **n-butylidenphthalide** (150-300 mg/kg) significantly reduced the proliferation of the intima compared to the control group in rats with balloon injured carotid artery 2 weeks after injury. Immunohistochemical tests revealed a significant decrease of the proliferative activity in the 60-300 mg/kg treated rats. In contrary, the apoptotic activity was significantly increased in animals receiving 60-300 mg/kg of **n-butylidenphthalide**. The authors suggest that dose dependent up-regulation of the Nur77 gene (nerve growth factor IB) implicated in cell growth/survival and apoptosis is related to the antiproliferative activity of **n-butylidenphthalide**.

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

No data are available concerning lovage root on pharmacokinetics due to its complex phytochemical composition.

Ligustilide intranasally administered rapidly enters the central nervous system through the nasal cavity (Guo *et al.* 2009). In contrary, after oral administration only 2.6% is absorbed in the rat (Yan *et al.* 2008). Ligustilide can be detected in brain tissue samples already after 5 minutes of the application.

#### Overview of pharmacokinetics

Due to lack of data on pharmacokinetics of lovage root no conclusions can be drawn.

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

No published studies could be found concerning reproductive and development toxicity, carcinogenicity and immunotoxicity of lovage root.

Due to the weak estrogenic activity, lovage extract appears of concern for reproductive and developmental toxicity. In the absence of sufficient data the use during pregnancy and lactation is not recommended.

#### Acute toxicity and skin irritation

Tisserand and Balacs (1998) published a summary of data on the acute oral toxicity and the skin irritation of lovage root oil. In their opinion, the oil is non-toxic and is safe to use unless there are other specific reasons: rodent oral LD<sub>50</sub> values are in the range 2-5 g/kg, and cause a very mild irritation of the skin at >5 g/kg.

#### Cytotoxicity

No data concerning cytotoxicity of the herbal substance are available.

The cytotoxic activity of polyacetylenes present in *Apiaceae* vegetables was tested *in vitro* against different human cancer cell lines: CEM-C7H2, T-ALL – acute lymphoblastic leukaemia, U937- human histiocytic lymphoma, HRT-18 and HT-2912, colorectal carcinoma cell lines (Zidorn *et al.* 2005).

**Falcarinol** and **falcarindiol** exhibited medium level cytotoxicity against leukaemia, lymphoma and



myeloma tested cell lines in the range of IC<sub>50</sub> approximately 30 µM. However falcarinol was more active against CEM-C7H2 line with IC<sub>50</sub> value of 3.5 µM. Activity of falcarindiol against HRT-18 and HT-2912 was in the range of IC<sub>50</sub> >100 µM, but IC<sub>50</sub> of falcarinol against HRT-18 was 42.3 µM and against HT2912 – 63.9 µM.

Falcarinol in low concentrations (0.5-10 µM) increased significantly the proliferation of CaCo cell line and decreased expression of caspase-3 with decreased basal DNA strand breakage (Young *et al.* 2007). Contrary, in higher concentrations. twenty µM falcarinol induced an increase of caspase activity and decreased proliferation of the CaCo cell line.

### Genotoxicity and mutagenicity

Bergapten and lovage extract exhibited strong **photomutagenicity** in an arginine-requiring (Arg<sup>+</sup>) mutant strain of green algae *Chlamydomonas reinhardtii* (Schimmer 1983; Schimmer *et al.* 1980). Bergapten was tested for photomutagenicity under long-wave ultraviolet light (NUV). A bergapten concentration of 5 µg/ml, with application of NUV (dose of 2-2.7 W/m<sup>2</sup>, fluence rate of 2.7 W/m<sup>2</sup> for 10 to 15 minutes) resulted with a maximum number of Arg<sup>+</sup> from 1 400 to 3 000 revertants/10<sup>8</sup> surviving cells (Schimmer *et al.* 1980). Some experiments with preincubation in the dark enhanced the number of revertants. In this conditions bergapten induced >1100 revertants per 10<sup>8</sup> surviving cells (UVA dose of 3 kJ/m<sup>2</sup>, fluence rate 5.1 W/m<sup>2</sup>) (Schimmer 1997).

*Levistici radices* extract (0.25%), (NUV dose 2W/m<sup>2</sup> with fluence rate 7.2 kJ/m<sup>2</sup> for 60 minutes) induced the number of 7 revertants/10<sup>8</sup> surviving cells (Schimmer 1983).

Photoactivated furanocoumarins (psoralens) are linked to gene mutations and chromosomal aberrations. They have been shown as mutagenic and carcinogenic (Bruneton 1995, Diawara *et al.* 1999). In the absence of ultraviolet light the toxicity of furanocoumarins is low, with an LD<sub>50</sub> in mammals of 300 to 600 mg/kg body weight. However, even 1 mg/kg body weight in humans can be harmful in the presence of UV radiation. The lowest observed adverse effect (LOAEL) was 0.14-0.38 mg/kg body weight. Therefore, furanocoumarins intake should be limited (Hsu and Friedlander 2010; Schulzova *et al.* 2007).

### Regulatory status

*Levisticum officinale* extract has been recognised as GRAS (Botanicals Generally Recognized As Safe (<http://www.biologie.uni-hamburg.de/b-online/ibc99/dr-duke/gras.htm>) for use as a flavour ingredient. Presently lovage extract is used at levels below 100 ppm in selected brands of cigarettes. It is administered directly to the tobacco and can undergo pyrolysis when smoked.

EFSA Scientific Cooperation (ESCO, 2009) in 'Compendium of botanicals that have been reported to contain toxic, addictive, psychotropic, or other substances of concern' classifies the toxicity of substances present in lovage roots and recommends restrictions for use for: coumarin, furocoumarins (mainly bergapten, umbelliferone, psoralen); root seeds: imperatorin 12.82 mg/kg, 5-methoxypsoralen 6.38 mg/kg, psoralen 3.8 mg/kg, 8-methoxypsoralen 0.5 mg/kg.

### 3.4. Overall conclusions on non-clinical data

The published data on pharmacological activities support the traditional use of preparations containing lovage root in the proposed indication.

However, despite daily intake of lovage root as common vegetable, the therapeutic importance of the plant can be overestimated.

*Levisticum officinale* root oil is relatively nontoxic following acute exposure both by oral or topical administration.

Adequate genotoxicity studies have not been performed. Due to the presence of furanocoumarins, photoactivation by UV radiation is seen as a concern.

No published data could be found on the carcinogenicity of the lovage root and the lovage root preparations.

Lovage root use is not recommended during pregnancy and lactation. Moreover, some caution is needed in combination with UV radiation exposure due to possible photoactivation caused by furanocoumarins

## **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**

There are no data on human pharmacodynamics.

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

There are no data on human pharmacokinetics.

### **4.2. Clinical Efficacy**

#### **4.2.1. Dose response studies**

There are no specific data available on dose-response studies.

#### **4.2.2. Clinical studies (case studies and clinical trials)**

None were published on mono-preparations of lovage root.

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

No information available.

### **4.3. Overall conclusions on clinical pharmacology and efficacy**

There are no data available from controlled clinical studies, therefore the medicinal use of *Levisticum officinale* root is not suitable for well-established use authorisation.

## **5. Clinical Safety/Pharmacovigilance**

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

There are no adverse effects reported from the Member States, however allergic reactions to the *Apiaceae* family should be considered, particularly with UV exposure.

Concerns regarding phototoxicity are not supported by clinical data or pharmacovigilance signals to be relevant for the use of lovage root as recommended in the monograph.

There are no data from clinical trials available.

## **5.2. Patient exposure**

None reported.

## **5.3. Adverse events and serious adverse events and deaths**

**Allergy.** The extensive handling of lovage during harvest under prolonged exposure to strong sunlight induced dermatitis within a few hours with itching and erythema (Wolf 1995). After 36 hour on exposed arms and legs bullae and vesicles were formed with marked hyperpigmentation after 3 weeks. In the fresh lovage specimens appreciable amounts of furanocoumarins were found:  $3.12 \pm 0.64$  and  $4.02 \pm 0.64$   $\mu\text{g/g}$  wet weight  $\pm$  SE) for psoralen and 5-methoxypsoralen, respectively (Ashwood-Smith *et al.* 1992). A similar case of dermatitis was described Vollman (1988) after contact with lovage oil.

### **Laboratory findings**

No data available.

## **5.4. Safety in special populations and situations**

There are no reports of use *Levisticum officinale* root in children. The use of lovage root is not recommended in children and adolescents younger than 18 years of age.

### **Drug interactions**

None reported for *Levisticum officinale* preparations.

Coumarin present in the plant, devoid of anticoagulant activity, can be transformed e.g. by moulding to the anticoagulant dicoumarol. Abnormal clotting values and bleeding can be expected after drinking the herbal tea prepared from several plants with coumarin as active constituent present (Aronson 2009).

A theoretical risk for potentiation activity of warfarin exists, as lovage root contains coumarin or coumarin derivatives, bergapten and imperatorin which inhibit platelet aggregation (Ebadi 2007; Heck *et al.* 2000; Herr 2005; Nutescu 2006; Patel and Gohil 2008; Shehadeh 2007).

Moreover, herbal products containing lovage should be discontinued in advance in patients undergoing surgery (Heyneman 2003).

### **Use in pregnancy and lactation.**

Lovage root should not be used during pregnancy and lactation.

*Levisticum officinale* is in the list of plants that should not be used during pregnancy because of their potential uterine stimulating and emmenagogue properties (Belew 1999; Ernst 2002). However this recommendation is discussed and questioned (Guba 2000).

Chuchupate lovage (*Ligusticum porteri*, *Apiaceae*), but not *Levisticum officinale*, was used by Spanish and Mexicans in New Mexico as an emmenagogue and abortifacient (Conway and Slocumb 1979).

## Overdose

None reported.

## Effect on ability to drive or operate machinery or impairment of mental ability

None reported.

### 5.5. Overall conclusions on clinical safety

The allergic reactions in patients allergic to *Apiaceae* should be considered.

Concerns regarding phototoxicity are not supported by clinical data or pharmacovigilance signals to be relevant for the oral use of lovage root as recommended in the monograph.

## 6. Overall conclusions

The available data are sufficient to include the traditional use of specified preparations of lovage root in a monograph of the European Community. *Levisticum officinale* root fulfils the requirement of therapeutic use for at least 30 years (15 years within the Community, Directive 2004/24/EC).

Indication: Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

Due to the lack of data on mutagenicity and carcinogenicity toxicity, a list entry for *Levisticum officinale* root cannot be recommended.

### Benefit/risk assessment

There are some concerns about side effects with *Levisticum officinale* root due to presence of furanocoumarins (psoralens) or interaction with oral anticoagulants.

There are reported side effects concerning allergic reactions due to the contact with *Levisticum officinale*, particularly after prolonged exposure to strong sunlight or UV radiation.

Concerns regarding phototoxicity are not supported by clinical data or pharmacovigilance signals to be relevant for the use of lovage root as recommended in the monograph.

No serious adverse events with a therapeutic posology of the herbal preparations are reported.

Despite the insufficiency of toxicological data base, levels of exposure associated with the use of lovage root most probably do not result in significant risk to human health.

It can be concluded that the benefit/risk assessment for *Levisticum officinale* preparations is positive for use as an adjuvant in minor urinary complaints.

## Annex

### List of references