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EMA/HMPC/524623/2011
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)

Draft

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Levisticum officinale</i> Koch, radix Lovage root
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical forms	Comminuted herbal substance as herbal tea for oral use
Rapporteur	
Assessor(s)	

Note: This Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Levisticum officinale* Koch, radix. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.



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1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

Composition

According to Toulemonde and Noleau (cited by Bradley 2006), 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-butyldiene-4,5-dihydrophthalide 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.

Blank *et al.* (1993) described presence of the flavour compound 3-hydroxy-4,5-dimethyl-2(5H)-furanone (sotolone) 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).

The results of supercritical CO₂ extraction in constant pressure revealed the presence: *cis*-ligustilide (52.0%), *trans*-ligustilide (3.95%), 3n-butyldiene phtalide E (1.75%), 3n-butyldiene phtalide Z (0.73%), β -phellandrene (0.28%), α -terpinyl acetate (0.08%) (Daukšas *et al.* 2002). Moreover palmitic acid (2.81%), phytol (2.62%), linoleic acid (3.52%), stigmaterol1 (11%), and β -sitosterol (1.28%) were found (Daukšas *et al.* 2002).

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

Phtalides are flavour compounds giving characteristic flavour in some species of *Apiaceae*, also in *Levisticum officinale* root. The phtalides have been isolated in 40 species of plants within family *Apiaceae* and to date 71 phtalides have been isolated (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-butyldienephtalide, E- and Z-ligustilide, senkyunolide and validene-4,5-dihydrophthalide; *isosenkyunolide* and propylidienephtalide. As the guiding 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-butyldiene-4,5-dihydrophthalide) 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-butyldienephtalide, (*E*)-ligustilide and the dimer levistolide A. Simultaneous determination of ligustilide and butyldienephtalide by use the GC-MS-SIM method was described by Chen *et al.* (2010) with tested ranges of 20 – 1.000 μ /ml for ligustilide and 2–100 μ g/ml for butyldienephtalide.

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

fertilisation value of 33.6% was obtained when lovage plants were fertilised with chemical NPK, the highest amount of falcarinol (32.6% 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 harvesting time. Andruszczak (2007) observed that harvesting leaves in the vegetation season has a negative influence on the accumulation of essential oil in the roots. Leaving the above ground parts of *Levisticum* until autumn significantly increased the amount of essential oil from 0.52 - 0.85%.

Better effects were also obtained after direct seeding and not propagation of the plants from direct sowing with leaf cutting in autumn (Andruszczak 2004).

According to Hogg (2001), literature sources present following composition of lovage root oil as % of oil yield - α -terpinyl acetate: 0.1-0.2, β -phellandrene: 1.7-15.5, α -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 ~0.6), angelicin (R_f ~0.5), umbelliferone (R_f ~0.45) and 3-butylidenphtalide at R_f ~0.85. When compared to *Imperatoriae radix* and *Angelicae radix*, *Levistici radix* varied by a largely lower coumarin content (Wagner and Bladt, 2001). In 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 total amount of coumarins for 3.2%, umbelliferone, coumarin and others (angelicin and scopoletin) included. Again generally lower coumarin content than in *Angelicae* and *Imperatoriae radix* was established. Apterin(8-(glucosyloxy)isopropyl-9-hydroxy-8,9-dihydroangelicin) has been isolated in small amounts from nine plants of *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

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 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) achieving the amounts between 19% and 46%. Moreover the presence of farnesene, phellandrene, elemene, heptanal and octanal was found.

- Herbal substance(s)
- Herbal preparation(s)
- 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.

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 avail in combin 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 avail in combin 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 avail in combin 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 avail in combin 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 avail in combin 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 Alpine region of Italy in Liguria (Dioskurides).

Lovage preparations were used during the Middle Ages mainly as a emmenagogue, carminativum, direticum 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* of 9th century contains lovage as one of many culinary and medical plants that should be cultivated in every imperial garden (Arnold 1923). For centuries it is known as carminative and spasmolytic folk medicine. In cosmetic medical treatise of Trotula de Ruggiero of the Schola Medica Salernitana from 11th century garden lovage is indicated for skin lightening (Cavallo *et al.* 2008).

In Germany, it was approved in inflammatory conditions of 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.

Lovage therapeutic activity is presented in Madaus (1938) and in many other sources: Awang 2009; Berger 1960; Bradley 2006; Chevallier 1996; Duke 2002; Evans 2009; European Pharmacopoeia 5th and 6th 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

Combination products

In the Czech Republic, there are authorised combination products.

Average number of combination substances: 2-3 3-5 >5

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

Other information on relevant combination product:

Herbal tea for oral use; indications: Traditionally used in temporary loss of appetite and t mild gastrointestinal complaints such as bloating, and flatulence-on the market since 1995

Additional comments:

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

Preparations: None, but 1 German Standard Marketing Authorisation (herbal tea)

Is the Herbal Substance on the market? Yes No

1 German Standard Marketing Authorisation, herbal tea

Status Authorised products Registered products Food supplements

What are the main combination substances? Rosmarini folium, Ononidis radix

Combination products: In DE 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

Preparations: Comminuted herbal substance

Since when are the preparations on the market? At least since 1967

Pharmaceutical form (Standard Terms): 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.

Is the Herbal Substance on the market? Yes No

Status: Authorised products Registered products Food supplements

Spain

Combination products

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

United Kingdom

The herbal substance is only available in combination product Yes No

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.

Posology: 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, dysmenorrhoea, 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 photodermatosis; 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 has the 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 compared to 25 essential oils tested.

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

S. typhimurium, *Salmonella enterica* serotype *typhimurium*; Lo, chloroform extract of *Levisticum officinale* extract.

^bBold text indicates synergistic combinations (i.e. MICs for the combination lower than for the antibiotic alone).

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 total inhibition of spore germination of faltarindiol against *Alternaria brassicicola* and *Septoria nodorum* at a concentration 20 µg/ml, however faltarinol even at the concentration of 200 µg/ml did not affect his fungi.

Polyacetylene faltarindiol has been identified as a phytoalexin in tomato leaves infected by fungi.

Hadacek and Greger (2000) tested activity of faltarindiol 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.

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 MIC: 64 µg/ml. Further fractionation resulted in two active polyacetylenes: (1) 3(R)-faltarinol and (2) 3(R)-8 (S)-faltarindiol with MICs against *M. fortuitum*, 30.4 µm (1), 16.4 µm (2) and against *M. aurum*, 60.8 µm (1) , 16.4 µm MICs of standard chemiotherapeutics 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

Methanolic extract of lovage roots (20 g of powdered herbal substance with 200 ml of absolute methanol) inhibited in 55% activity of pancreatic lipase at concentration range of 0.05 and 0.15 mg/ml of the extract (Gholamhoseinian *et al.* 2010).

Isolated constituents of lovage essential oil

Antifungal activity

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

Spasmolytic activity

Ligustilide in the concentration dependent manner relaxed isolated rat mesenteric artery rings precontracted with potassium chloride. *In vitro* experiments showed that the β-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 CaCl₂ in Ca²⁺ -free medium. The pD₂ value of ligustilide (the negative logarithm of the drug concentration that elicited 50% relaxation) to CaCl₂ was 4.45±0.02. Contractions induced by caffeine were also inhibited, therefore the ryanodine receptors were involved through inhibition of intracellular Ca²⁺ 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 spasmolytic activity of **butylidenephtalide** in comparison of papaverine activity in isolated guinea pig ileum, guinea pig vas deferens and guinea pig taenia coli. Butylidenephtalide non competitively inhibited contractions induced by ACh, K⁺ and Ba²⁺ in normal Tyrode solutions and to administered exogenous Ca²⁺ in high K⁺, Ca²⁺ free Tyrode solution. However butylidenephtalide pD₂ values were significantly inferior to those of papaverine (p<0.001). In author opinion butylidenephtalide probably inhibits Ca²⁺ release from cellular membrane and from intracellular calcium storage and/or inhibits Ca²⁺ influx from extracellular fluid.

In other experiments Ko *et al.* (1997) separated two geometric isomers, the *Z*- and the *E*- forms of synthetic butylidenephtalide and checked their inhibition of voltage-dependent calcium channels in depolarised guinea-pig ileum longitudinal smooth muscle. It was found that **E- butylidenephtalide** (2-100 µM) inhibited contractions with pD₂ value 4.56±0.18. **Z- butylidenephtalide** non-competitively induced significantly lower inhibition of Ca²⁺ as compared to E-butylidene phtalide with contractions at the range 50 – 100 µM and the pD₂ value of 3.88±0.20 (p<0.05).

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

Butylidenephtalide induced concentration-dependent (1-300 µM) vasorelaxing effect in the rat isolated aorta constricted with use of 60 mM of kalium chloride (KCl) and 30 nM of 9,11-dideoxy-9α,11α-methanoepoxyprostaglandin H₂. (EC₅₀ is the effective concentration of the test compound to cause 50% of its maximal response; 1- EC₅₀: 4.00±0.03, n=5; 2- EC₅₀:P 4.29±0.03, n=5 respectively (Chan *et al.* 2006). The authors suggest that spasmolytic effect is dependent on modulation of L-type voltage operated and prostanoid receptor operated Ca²⁺ channels.

Both **ligustilide** and **senkyunolide A** induced vasorelaxation effects in rat isolated aorta with cumulative concentrations to set with a range of 1 - 300µ (Chan *et al.* 2007). Both compounds had similar spasmolytic activity against contractions induced by 9,11-dideoxy-9α,11α-methanoepoxyprostaglandin F_{2α}, phenylephrine, 5-hydroxytryptamine and KCl with pD₂: 4.14±0.08, pD₂: 4.39±0.11, pD₂ 4.56±0.12, pD₂: 4.43±0.08, n=6 respectively (Chan *et al.* 2007).

Ligustilide inhibited the spontaneous periodic contractions of isolated rat uterus in a concentration dependent manner (EC₅₀ = 4.4±2.7-6.1) µg/ml and antagonised prostaglandin F_{2α} (95.3% at 8 µg/ml) and acetylcholine induced contractions (73.9% at 8 µg/ml) Du *et al.* (2006).

In other experiment performed also in the model of rat experiment aorta Chan *et al.* (2009) reported synergistic myorelaxant activity with NO-donor sodium nitropruside in the rat isolated aorta constricted with use of 9,11-dideoxy-9α,11α-methanoepoxyprostaglandin H₂. According to authors this relaxant synergism is related to modulation of the Ca²⁺ 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 rat carotid artery on neointimal hyperplasia. In the cell culture of rat aorta derived cell line n-butylidenphtalide in concentrations of 25-100 µg/ml significantly inhibited the proliferation and arrested the cell cycle in G₀/G₁ phase. In rats with balloon injured carotid artery treatment with n-butylidenphtalide (150 - 300 mg/kg) after 2 weeks after injury significantly reduced proliferation of intima compared to the control group. Immunohistochemical tests revealed significant decrease of proliferative activity in the 60 - 300 mg/kg treated rats. In contrary apoptotic activity was significantly increased in animals receiving 60 - 300 mg/kg of n-butylidenphtalide. Authors suggest that dose dependent up-regulation of Nur77 gene (nerve growth factor IB) implicated in cell growth/survival and apoptosis is related to antiproliferative activity of n-butylidenphtalide.

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

Falcarindol blocks 5-LO product synthesis at the range of IC₅₀ concentrations 2 – 10 µM (Alanko *et al.* 1994; Schneider and Bucar 2005; Werz 2007).

Inhibition of TNF-α

Liu *et al.* (2005) described dose and time dependent inhibition of transcription of TNF-α mRNA by Z-ligustilide and senkyunolide A in monocytes. Moreover, two phtalides suppressed TNF-α mediated NF-κB activation.

GABAergic activity

Deng *et al.* (2006) have shown that a new phtalide dimer gelispirolide composed of Z-ligustilide and Z-butylidenephtalide induces inhibitory effects on the binding of [³H] diazepam to the GABA_A receptors with IC₅₀ 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).

Volatile oil present in roots in amount from 0.6 - 1 %. Up to 70% of the oil consists of alkylphtalides which are mainly responsible for the characteristic odour. Butylidenphtalide 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 *Levistici radix* showed slight increase of urine volume and concentration of chloride ions. Previously tested lovage root effects in rats with 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 Allen-Doisy criterion (measures of vaginal cornification as the end point) estrogenic effects were seen after lovage extract administration with activity: 1 g of the 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 acetic acid induced writhing response and formalin-induced licking time in mice, ligustilide given intragastrically significantly dose-dependently reduced writhing response and formalin –induced licking time (Du *et al.* 2007). **Ligustilide** at the dose 10 mg/kg induced the same range of analgesia as very high dose of aspirin (200 mg/kg) in the acetic acid induced writhing movements.

Neuroprotective activity.

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

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 rat carotid artery on neointimal hyperplasia. In the cell culture of rat aorta derived cell line n-butylidenphtalide with 25-100 $\mu\text{g/ml}$ significantly inhibited the proliferation and arrested the cell cycle in G_0/G_1 phase. In rats with balloon injured carotid artery treatment with n-butylidenphtalide (150-300 mg/kg) after 2 weeks after injury significantly reduced proliferation of intima compared to the control group. Immunohistochemical tests revealed significant decrease of proliferative activity in the 60-300 mg/kg treated rats. In contrary apoptotic activity was significantly increased in animals receiving 60-300 mg/kg of n-butylidenphtalide. Authors suggest that dose dependent up-regulation of Nur77 gene (nerve growth factor IB) implicated in cell growth/survival and apoptosis is related to antiproliferative activity of n-butylidenphtalide.

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 administered intranasal rapidly enters the central nervous system through 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 weak estrogenic activity lovage extract appears of concern for reproductive and developmental toxicity. However in the absence of sufficient data the use during pregnancy and lactation is not recommended.

Acute toxicity and skin irritation

Tisserand and Balacs (1998) present summary of data on acute oral toxicity and skin irritation of lovage root oil. In their opinion the oil is non-toxic and is safe to use unless there are other reasons not to: rodent oral LD_{50} values are in the range 2 - 5 g/kg, and causes very mildly irritation of the skin at >5 g/kg.

Cytotoxicity

No data concerning cytotoxicity of herbal substance are available.

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 IC₅₀ approximately 30 µM. However falcarinol was more active against CEM-C7H2 line with IC₅₀ value of 3.5 µM. Activity of falcarindiol against HRT-18 and HT-2912 was in the range of IC₅₀ >100 µM, but IC₅₀ 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⁺) mutant strain of green algae *Chlamydomonas reinhardtii* (Schimmer 1983; Schimmer *et al.* 1980). Bergapten was tested for photomutagenicity under long-wave ultraviolet light (NUV). Concentration of bergapten 5 µg/ml, with application of NUV (dose of 2 – 2.7 W/m², fluence rate of 2.7 W/m² for 10 to 15 minutes) resulted with maximum number of Arg⁺ from 1 400 to 3 000 revertants/10⁸ 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 10⁸ surviving cells (UVA dose of 3 kJ/m², fluence rate 5.1 W/m²) (Schimmer 1997).

Photomutagenic effects of concentration of 0.25% *Levisticum radice* extract, (NUV dose 2W/m² with fluence rate 7.2 kJ/m² for 60 minutes) induced the number of 7 revertants/10⁸ 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 LD₅₀ 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 toxicity of substances present in the roots of lovage 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 indications.

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 concern is needed with UV radiation exposure due to furanocoumarins photoactivation

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 has to be regarded as traditional.

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 *Apiaceae* family should be considered, particularly with UV exposure.

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 ± 0.64 and 4.02 ± 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 by molding 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.

The 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.

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).

Indications for treatment: 1) 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 acute and chronic toxicity, repeated dose toxicity, mutagenicity, carcinogenicity, reproductive and developmental 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.

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