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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Ononis spinosa* L., 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>Ononis spinosa</i> L., radix (Restharrow root)
Herbal preparation(s)	Comminuted herbal substance (cut dried roots)
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 *Ononis spinosa* L. 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.



Table of contents

Table of contents	2
1. Introduction	3
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof	3
1.2. Information about products on the market in the Member States	6
1.3. Search and assessment methodology.....	12
2. Historical data on medicinal use	13
2.1. Information on period of medicinal use in the Community	13
2.2. Information on traditional/current indications and specified substances/preparations	14
2.3. Specified strength/posology/route of administration/duration of use for relevant preparations and indications	15
3. Non-Clinical Data	18
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	18
3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	21
3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof	21
3.4. Overall conclusions on non-clinical data.....	22
4. Clinical Data	22
4.1. Clinical Pharmacology	22
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents	22
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents	22
4.2. Clinical Efficacy	22
4.2.1. Dose response studies.....	22
4.2.2. Clinical studies (case studies and clinical trials)	22
4.2.3. Clinical studies in special populations (e.g. elderly and children).....	23
4.3. Overall conclusions on clinical pharmacology and efficacy.....	23
5. Clinical Safety/Pharmacovigilance	23
5.1. Overview of toxicological/safety data from clinical trials in humans.....	23
5.2. Patient exposure	23
5.3. Adverse events and serious adverse events and deaths.....	23
5.4. Laboratory findings.....	23
5.5. Safety in special populations and situations	23
5.6. Overall conclusions on clinical safety.....	24
6. Overall conclusions	24
Annex	25

1. Introduction

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

- Herbal substance(s)

In the Ph. Eur. monograph 7.0 ref. 01/2008:1879, Restharrow root (*Ononidis radix*) is defined as the whole or cut, dried root of *Ononis spinosa* (L.).

Restharrow root is more or less flattened, twisted and bent with a grayish brown to dark brown outer surface and deep longitudinal grooves. Characteristic of the transversely cut surface is the conspicuously radiate structure of the xylem due to the unequal width of the medullary rays. The fracture of the root is short and fibrous. It has bitter taste resembling that of liquorice and is regarded as an aperitive, diuretic, antiinflammatory and astringent [Thurzová 1973; Wichtl 2004; European Pharmacopoeia monograph 7.0; Gruenwald *et al.* 2004].

In some older literature two species - *Ononis spinosa* L. and *Ononis arvensis* L. have been mentioned as botanical name of plant for *Ononidis radix*. According to information from Member States only products containing *Ononis spinosa* L., radix are available on the European market. In many other well-known European handbooks and Pharmacopoeias only *Ononis spinosa* L. is mentioned as source for *Ononidis radix*. *Ononis arvensis* L. can be mainly found in the literature from the former USSR, for instance in the Pharmacopoeia of former USSR [USSR Pharmacopoeia 1990]. Taking into account the above mentioned considerations and also the definition of European Pharmacopoeia, **this assessment report and the following monograph reflects information regarding *Ononis spinosa* L, radix only.**

Ononidis radix is known under the following common names: English: Restharrow root, Spiny restharrow root; German: Hauhechelwurzel, Haudornwurzel, Ochsenbrechwurzel; Dutch: Kattedoorn, Stalkruid; Czech: Kořen jehlice trnité; French: Racine de bugrane; Arrête-boeuf; Italian: Ononide radice, Latvian: blaktenes saknes; Polish: Korzeń wilżyny.

Other names: Raiz de gatuña, busktörnerot, Krageklo, Jooksjarohi, Dirvenių šaknys, Gatunha, Koreň ihlice, Гръмотрън, корен.

Description and origin of the plant:

Leguminosae is the second largest family of flowering plants containing 600 genus and about 12 000 species. It is divided into three subfamilies – the Papilionaceae (377 genus), the Mimosoideae (40 genus) and Caesalpinoideae (133 genus). To Papilionaceae subfamily belongs *Ononis* genus including 75 species [Evans 2002; Kloda *et al.* 2008]. *Ononis spinosa* (L.) is native throughout in Europe, western Asia and northern Africa, widely distributed mainly in semi-arid grasslands, alternately dry meadows and pastures [Wichtl 2004; Wyk and Wink 2005; Kloda *et al.* 2008]. In the literature can be found several subspecies and one nothosubspecies of *Ononis spinosa* L. [Hocking 1997; Wichtl 2004; The database of the International Plant Names Index; Flora Europea]. The word *Ononis* essentially derives from Greek word *onos* which means donkey that in their diet consumed by this plant [Brem 2010]. The material of commerce is reported to originate usually from wild collection in southeastern Europe [Wichtl 2004].

Ononis spinosa L. (Spiny restharrow) is a perennial, spiny subshrub up to 80 cm tall. The branches of the plant are spreading, villous, and densely covered short shoots, which terminate in straight thorns. The lower leaves are ternate while the upper ones are single and papilionaceous, pinkish white flowers generally flowered from June-July, followed by the small seed pods. Spiny restharrow has an unpleasant smell [Wichtl 2004].

Constituents:

The following chemical constituents were identified in Restharrow root:

Isoflavones (compounds characteristic of the roots of member of the Fabaceae), particularly formononetin (aglycone), ononin (formononetin 7-O-glucoside), pseudobaptigenin glucoside, genistein (1.7 – 3.8 mg/100g herbal substance), biochanin A 7-O-glucoside, biochanin A 7-O-glucoside 6"-malonate (biochanin A 0.08 – 0.70 mg/100g), formononetin 7-O-glucoside 6"-malonate (3.2 – 5.9 mg/100g), 2.3-Dihydro-ononin and also tectoridin, trifolirhizin, rothinidin [Háznagy *et al.* 1978; Pietta 1983; Köster *et al.* 1983; Blaschek *et al.* 1998; Klejdus *et al.* 2007; Benedec *et al.* 2012].

Glucosides Spinonin, a glucoside with unusual structure has been detected, as well as medicarpin, a pterocarpan derivative [Kirmizigül *et al.* 1997; Wichtl 2004].

Triterpenes (terpenes) include particularly α -onocerin (4.1 mg/1g herbal substance), also known as onocol [Barton & Overton 1955; Fujise *et al.* 1965; Rowan *et al.* 1972; Blaschek *et al.* 1998; Pauli 2000].

Sterols mainly β -sitosterol, stigmasterol, campesterol, cholesterol, α -spinasterol [Blaschek *et al.* 1998].

Saponin triterpenoid saponin (e.g. 3-O-[α -L-rhamnopyranosyl-(1 \rightarrow 2)- β -D-xylopyranosyl-(1 \rightarrow 2)- β -D-glucuronopyranosyl]-3 β ,22 α -dihydroxyolean-13-en-11). Saponin is the active ingredient responsible for the diuretic effect. In normal subjects the diuretic action of Restharrow root containing saponin is considerable increasing urinary output by more than 20% [Weiss 1988; Shaker *et al.* 2004].

Phenolic acids p-hydroxybenzoic, vanillic acid, caffeic acid, syringic acid, p-coumaric acid, cinnamic acid, sinapic acid, salicylic acid, gentisin acid etc. can be detected in the *Ononis spinosa* L., radix [Blaschek *et al.* 1998; Klejdus *et al.* 2008].

Lectins Index Nomenclature LECp.Ono.Spi.ro.Hga1 [Horejsi and Kocourek 1978; Uhlenbruck *et al.* 1978].

Small amounts of essential oil (0,02- 0.2%) are found, containing *trans*-anethole as the major constituent, with carvone, menthol, menthone, isomenthone, linalool, estragole, borneol and *cis*-anethole [Jaretsky 1940; Hilp *et al.* 1974; Wren *et al.* 1988; Gruenwald *et al.* 2004, 2007; ESCOP Monographs 2003;].

Other constituents are: tannins, sucrose, lipids, citric acid.

- Herbal preparation(s)

According to information from member states and literature. Restharrow root is used as a comminuted herbal substance for single herbal tea preparation and also as a component of combination herbal tea products. Tea infusions are prepared by pouring boiling water over 2-3 g of the coarsely powdered dried root, steeped for 20-30 min and strained.

It is reported that the root of Restharrow contains two antagonistic constituents. The one volatilizes in the steam having diuretic properties whereas other that is not soluble in water does not volatilize exerting antidiuretic activity. Therefore not to lose volatile component for exertions of the diuretic activity it is important to use infusion of the Restharrow root and not a decoction [Weiss 1988].

The ESCOP Monograph (2003), Herbal drugs and phytopharmaceuticals by Wichtl (2004), The complete German Commission E monograph (Blumenthal *et al.* 1998) reports that extracts (not specified) of Restharrow root are components of phytotherapy in tablet and coated tablets form.

Following extracts are included in combination products authorised or registered in EU member states:

- dry extract from *Ononidis radix* (DER 6-9: 1), extraction solvent: ethanol 20% (m/m);
- dry extract from *Ononidis radix* (DER 5-8: 1), extraction solvent: water;
- liquid extract from *Ononidis radix* (DER 1: 1, extraction solvent: ethanol about 23%).

As extracts are included in combination products only and no data is available from literature regarding use of mono-products with extracts, this assessment report and the community herbal monograph cover the comminuted herbal substance for tea preparation only.

- 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.

Restharrow root is often used in combinations with many other diuretic herbal substances/herbal preparations (*Betulae folium*, *Ilex paraguariensis folium/mate*, *Orthosiphonis folium*, *Solidaginis herba*, *Urticae herba*, *Uvae ursi folium* etc) as bladder and kidney teas [Muszyński 1954; Weiss 1998, 1999; Schulz *et al.* 2004].

Vitamin(s): not applicable.

Mineral(s): not applicable.

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

In European Member States, the herbal substance (*Ononis spinosa* L., radix) is available in Poland as single herbal substance products (2 products as herbal teas) and in Germany as authorised single herbal substance products (German Standard Marketing Authorisations; single active ingredient in 66 herbal teas).

Restharrow root (*Ononis spinosa* L.) is also included in combinations products with many other herbal substances/herbal preparations (for instance: *Betulae folium*, *Phaseoli fructus*, *Fumaria officinalis* L. flos, *Herniariae herba*, *Ilex paraguariensis folium* / mate, *Menthae piperitae herba*, *Millefolii herba*, *Orthosiphonis folium*, *Petroselinii radix*, *Polygonii avicularis herba*, *Sambuci nigrae flos*, *Solidaginis herba*, *Urticae herba*, *Uvae ursi folium* etc). and available on the Austrian, Belgian, Czech, German and Italian market.)

Information about products on the market in the Member States

Single preparations:

Germany	German Standard Marketing Authorisations	Preparations: <u>herbal teas</u>	single active ingredient: 66 herbal teas
Poland	Registration /MA	Preparations: <u>Herbal teas as single active ingredient products</u>	<p><u>Pharmaceutical form:</u> <i>Herbal teas</i> containing comminuted roots of <i>Ononis spinosa</i> L., radix 3 g (1 teaspoon) for one cup of tea; 2-3 times daily</p> <p><u>Indication:</u> Traditionally used as a diuretic medicine for treatment of symptoms of mild lower urinary tract inflammatory conditions and as an aid in preventing of kidney gravel.</p> <p><u>Contraindications:</u> in case of oedema due to impaired heart and kidney function.</p> <p><u>Interaction with other drugs and adverse events:</u> Unknown.</p> <p><u>Use in pregnancy and lactation:</u> Due to lack of data is not recommended for use.</p> <p><u>Legal status:</u> On market 2 single active ingredient products <u>Since when is on the market:</u> at least 20 years on the Polish market</p>

Combination products:

Austria		<p><u>Preparations:</u> Herbal teas (only combination products)</p>	<p><u>Pharmaceutical form:</u> Herbal teas <u>The main combination substances:</u> Urticae herba, Betulae folium, Solidaginis herba, Equiseti herba, Orthosiphonis folium. Available 75 herbal teas containing Ononidis radix.</p>
Belgium	<p><i>Traditional herbal medicinal products</i></p>	<p><u>Preparations:</u> Herbal teas (only combination products) with more than 5 substances.</p>	<p><u>Pharmaceutical form:</u> Herbal teas <u>The main combination substances:</u> 1) Ilex paraguariensis, folium, 76.42 mg/g, Valerianae officinalis, radix 76.42 mg/g, Glycyrrhiza, radix 23.57 mg/g, Crataegus oxyacantha 215.71 mg/g, Viscum album, herba 76.42 mg/g, Pix liquida Betulae 215.71 mg/g, Petroselinum sativum 44.28 mg/g, Ononis spinosa 133.57 mg/g, Leonurus cardiaca, herba 104.28 mg/g 2) Ilex paraguariensis, folium 41.33 mg/g, Juniperus communis 94.66 mg/g, Equisetum arvense 75.33 mg/g, Glycyrrhiza, radix 28.00 mg/g, Spiraea ulmaria, flores 95.33 mg/g, Pix liquida Betulae 214.66 mg/g, Petroselinum sativum 94.66 mg/g, Ononis spinosa 176.00 mg/g, Herniaria glabra 111.33 mg/g, Leonurus cardiaca, herba 41.33 mg/g 3) Pterocarpus santalinus vel indicus, lignum 60.00 mg/g, Glycyrrhiza, radix 60.00 mg/g, Aloe 100.00 mg/g, Frangulae corticis extractum 100.00 mg/g, Gentiana 100.00 mg/g, Curcuma longa L. 60.00 mg, Pix liquida Betulae 40.00 mg/g, Citrum oil 60.00 mg/g, Solanum dulcamara 100.00 mg/g, Salix alba 60.00 mg/g, Petroselinum sativum 60.00 mg/g, Ononis spinosa 100.00 mg/g, Acorus calamus 100.00 mg/g 4) Senna, folium 308.00 mg/g, Mentha piperita, folium 81.33 mg/g, Pterocarpus santalinus vel indicus, lignum 22.00 mg/g, Fucus vesiculosus, extracta fluidum et siccum 111.33 mg/g, Spiraea ulmaria, flores 81.33 mg/g, Pix liquida Betulae 222.00 mg/g, Phaseoli fructus sine semine 44.66 mg/g, Petroselinum sativum 22.00 mg/g, Ononis spinosa 81.33 mg/g 5) Senna, folium 76.92 mg/g, Pterocarpus santalinus vel indicus, lignum 30.70 mg/g, Equisetum arvense 66.15 mg/g, Solidago 76.92 mg/g, Centaurium cyanus L. 113.84 mg/g, Pix liquida Betulae 338.40 mg/g, Phaseoli fructus sine semine 92.30 mg/g, Solanum dulcamara 76.92 mg/g, Ononis spinosa 92.30 mg/g 6) Erica vulgaris 33.57 mg/g, Pterocarpus santalinus</p>

			<p>vel indicus (lignum) 47.14 mg/g, Equisetum arvense 76.42 mg/g, Solidago 3.35 mg/g, Arctostaphylos uva-ursi 115.71 mg/g, Spiraea ulmaria, flores 92.85 mg/g, Pix liquida Betulae 3.35 mg/g, Phaseoli fructus sine semine 67.14 mg/g, Petroselinum sativum 42.85 mg/g, Ononis spinosa 76.42 mg/g, Herniaria glabra 110.00 mg/g</p>
Czech Republic	<i>Traditional herbal medicinal products</i>	<p><u>Preparations:</u> Herbal tea (only combination products) with more than 5 substances</p>	<p><u>The main combination substances:</u> Betulae folium, Uvae ursi folium, Ononidis radix, Petroselini radix, Polygonii avicularis herba, Sambuci nigrae flos, Urticae herba, Millefolii herba Betulae folium, Uvae ursi folium, Herniariae herba, Menthae piperitae herba, Ononidis radix, Petroselini radix <u>Pharmaceutical form:</u> 1) and 2) as herbal teas <u>Therapeutic indication and posology:</u> and 2) are used as an adjuvant for treatment of symptoms of mild lower urinary tract infections such as burning sensation during urination and frequent urination Preparation on the market: herbal tea 1) on the market since 1969 and herbal tea 2) on the market since 1995.</p>
Germany	<i>Traditional herbal medicinal products</i>	<p><u>Preparations:</u> Extract (only combination products) with 3 substances</p>	<p><u>The main combination substances:</u> 14 mg dry extract from Fructus Phaseoli sine semine (8-14:1); extraction solvent: water <u>Indication:</u> Traditionally used to support the elimination function of the kidney <u>Legal status:</u> 1 authorised herbal medicinal combination product</p>

Germany	<i>Herbal medicinal product with well-established use</i>	<u>Preparations:</u> only combination products with 2-3 substances	<u>The main combination substances:</u> 1) 1 film-coated tablet contains: 80 mg dry extract from <i>Ononidis radix</i> (5-8:1), extraction solvent: water; 90 mg dry extract from <i>Orthosiphonis folium</i> (5-7:1), extraction solvent: water; 180 mg dry extract from <i>Solidaginis herba</i> (4-7:1), extraction solvent: water 2) 1 tea-sachet of 1.8 g contains: 0.68 g <i>Orthosiphonis folium</i> , cut 0.68 g <i>Ononidis radix</i> , cut 257 herbal teas <u>Indication:</u> 1) as a purging of the urinary tract 2) to increase the amount of urine to achieve flushing in bacterial and inflammatory disorders of the lower urinary tract. As a purging for preventive treatment and treatment in urolithiasis and renal grave <u>Legal status:</u> 2 authorised herbal medicinal combination product
Italy	<i>Herbal medicinal product with well-established use</i>	<u>Preparations:</u> <i>Ononis spinosa</i> radix liquid extracts (DER 1:1, extraction solvent ethanol about 23%: only as combination products	<u>The main combination substances:</u> 1) solution for oral use 100 g of oral solution contain: <i>Ononis spinosa</i> radix liquid extract (DER 1:1, extraction solvent ethanol about 23% - formomonethin content nlt 0.02%) 0.0104 g <i>Fumaria officinalis</i> L. flos liquid extract (DER 1:1, extraction solvent ethanol about 26% - protopine title nlt 0.005%) 0.0120 g <i>Piscidia erythrina</i> L. cortex of the radix liquid extract (DER 1:1 extraction solvent about 55% - jamaicine title nlt 0.005%) 0.0016 g Glycerol 10.70 g 2) solution for oral use 100 g of oral solution contain: <i>Ononis spinosa</i> radix liquid extract (DER 1:1, extraction solvent ethanol about 23% - formononetine content nlt 0.02%) 0.0229 g <i>Fumaria officinalis</i> L. flos liquid extract (DER 1:1, extraction solvent ethanol about 26% - protopine title nlt 0.005%) 0.0264 g <i>Piscidia erythrina</i> L. cortex of the radix liquid extract (DER 1:1 extraction solvent about 55% - jamaicin title nlt 0.005%) 0.0035 g Glycerol 23,540 g

			<p><u>Pharmaceutical form:</u> Oral solution</p> <p><u>Posology:</u></p> <p>1) Adults 50 g 4-6 times daily corresponding to 0.006 g of <i>Ononis</i> extract Children: 25 g 1-2 times daily corresponding to 0.003 g of <i>Ononis</i> extract</p> <p>2) Adults: 50 g 4-6 times daily corresponding to 0.0132 of <i>Ononis</i> extract Children: 25g 1-2 times daily corresponding to 0.0066 g of <i>Ononis</i> extract</p> <p><u>Indication:</u></p> <p>As an adjuvant in spasmodic and painful complaints of the biliary and urinary ways</p> <p><u>Legal status:</u> Authorized herbal medicinal product</p> <p><u>Since when is on the market:</u> since 1951 (1) and 1961 (2)</p> <p><u>Other information on relevant combination products:</u></p> <p>The presence of <i>Ononis spinosa</i> liquid extract in the combination is justified by the following pharmacological action: relevant diuretic activity with increase of urinary elimination of chloride and urea nitrogen.</p>
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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:	Combination products as herbal teas only
Belgium	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combination products as herbal teas with more than 5 substances; food supplements marketed
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Czech Republic	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combination products as herbal teas only with more than 5 substances
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Estonia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
France	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	One combination product
Germany	<input checked="" type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combination product only with 2-3 substances and German Standard Marketing Authorisations (single active ingredient and combination products as herbal teas)
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Italy	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Two combination products since 1951 and 1961 on the market
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Lithuania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market

Member State	Regulatory Status				Comments
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Poland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input checked="" type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	2 medicinal products on the market, single ingredient as herbal tea (infusion)
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Not known
Slovenia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Spain	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	No products on the market

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 (date, search terms) and other sources used to research available pharmaceutical, non-clinical and clinical data on *Ononis arvensis* L., *Ononis spinosa* L, *Ononidis radix*

or its relevant constituents:

- Search terms: *Ononis arvensis* L., *Ononis spinosa* L, *Ononidis radix*, combination
- Articles and references retrieved from data bases: Pubmed, Medline, Scopus, SciFinder, Science direct, Web of Science etc.
- Handbooks, textbooks and Pharmacopoeias
- Libraries: EMA library, University of Latvia, Rigas Stradinu University, The State Agency of Medicines of Latvia, Central library in Riga.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Ononis spinosa L, radix (Restharrow root) has been widely used since ancient times and mentioned in many old documents such as Dioskurides (increases diuresis and breaks stones), Plinius (the root expels bladder-stones), Matthiolus (stimulates diuresis, powerfully breaks the stones), Lonicerus (expels the stone and urine) Schroder (stimulates diuresis and against kidney- and bladder-stones) [Benedum *et al.* 2006] and has been traditionally used for the treatment of the lower urinary tract disorders in the irrigation therapy as a diuretic medicine for inflammatory conditions of the lower urinary tract and for preventing and treating kidney and bladder disorders, gravel and small stones [Pharmacopoea Germanica 1884; Deutsches Arzneibuch 1926; Deutsches Arzneibuch. Kommentar 1928; Jaretsky 1940; Československý lékopis (Pharmacopoeia Bohemoslovenica) 1954, 1970, 1987; Österreichisches Arzneibuch 1960; Farmakopea Polska 1970; Wren *et al.* 1988; European Pharmacopoeia 7.0 2010; ESCOP Monographs 2003; Blumenthal *et al.* 1998) etc. and in several well known handbooks such as Hoppe 1942; Bergen 1960; Thurzová 1973; Borkowski 1974; Schilcher 1997; Hocking 1997; Blaschek *et al.* 1998; Bartram 1998; Weiss 1998, 1999; Evans 2002; A Guide to Traditional Herbal Medicines 2003; Wichtl 1997, 2004; Gruenwald *et al.* 2004, 2007; Wyk and Wink 2005; Gehrman *et al.* 2005; Benedum *et al.* 2006; Fintelman and Weiss 1999; Quer 2008; Braun 2011 etc].

In folk medicine, Restharrow root is also used for gout and rheumatic complaints and skin disorders [Wichtl 2004]. *Ononis* species have been used for centuries as folk remedies in Turkey as diuretic, antiseptic and antimicrobial. In Turkey *Ononis spinosa* L. is known as kayışkiran and found in Central Anatolia. *Ononis spinosa* L. has been reported to have diuretic, antibacterial, analgesic, anti-inflammatory, antiviral, cytotoxic, and antifungal effects.

In USA Restharrow root is a dietary supplement and in Canada approved active ingredient in a few OTC Traditional Herbal Medicines and homeopathic medicines [Wichtl 2004].

Restharrow root has been traditionally used in Poland with an evidence in the literature going back at least to the middle of the last century [Muszyński 1954; Roeske 1955; Deryng 1961; Farmakopea Polska 1970; Borkowski 1974; Ożarowski 1976; Ożarowski 1978]. Currently two medicinal products as single ingredient herbal teas are available for more than 20 years on the Polish market.

Restharrow root is offered as a single herb tea (German Standart License) and as a component of 'bladder and kidneys' tea formulas, extracts of Restharrow root are components of phytomedicines in tablet and dragée form [Wichtl 2004].

In the Czech Republic, Restharrow root is available on the market in multicomponent herbal teas since 1969. Extracts of Restharrow roots in combination products are present on the market more than 30 years (e.g. since 1951 in Italy).

Overall conclusion on the traditional medicinal use

Preparations from Restharrow root have been traditionally used as an infusion for diuresis stimulation. Literature data supporting the medicinal use of Restharrow root in Europe goes back at least as far as to the beginning of the 20th century. Therefore, for the above mentioned, it can be stated that the Restharrow root evidence a period of at least 30 years in medical use as requested by Directive 2004/24/EC for qualification as a traditional herbal medicinal product is fulfilled.

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

The following indications have been reported in the literature for Restharrow root (*Ononis spinosa* L.)

Lehrbuch der Pharmakognosie für Hochschulen (Karsten 1949)

Uses and properties: diuretic

Zarys Fitoterapii. Farmakologia i receptura ziół leczniczych. Radix Ononidis – Korzeń wilżyny [Roeske 1955]

Uses and properties: diuretic

Österreichisches Arzneibuch [1960]

Uses and properties: diuretic

Handbuch Der Drogenkunde [Bergen 1960]

Usage: diuretic

Farmakopea Polska IV [1970]

Uses and properties: diuretic

The Complete German Commission E Monographs [Blumenthal *et al.* 1998]

Indications: Irrigation therapy for inflammatory diseases of the lower urinary tract and for the prevention and treatment of kidney gravel.

Hagers Handbuch [Drogen L-Z, Blaschek *et al.* 1998]

Indications: Irrigation therapy for inflammatory diseases of the lower urinary tract and for the prevention and treatment of kidney gravel.

ESCOP Monographs [2003]

Indications: Irrigation of the urinary tract, especially in cases of inflammation and renal gravel, and as an adjuvant in treatment of bacterial infections of the urinary tract.

Herbal Drugs and Phytopharmaceuticals [Wichtl, 2004]

Indications: As a mild diuretic.

PDR For Herbal Medicines [Gruenwald *et al.* 2004; 2007]

- Infections of the urinary tract
- Kidney and bladder stones

Preparations of the drug are used for irrigation therapy for inflammatory diseases of the lower urinary tract and also for prevention and treatment of kidney gravel.

Medicinal Plants of the World [Wyk and Wink 2005]

Indications: Irrigation therapy as a diuretic medicine for inflammatory conditions of the lower urinary tract and for preventing and treating kidney gravel.

Medicinal Herbs: A Compendium [Gehrmann *et al.* 2005]

Usage: Irrigation therapy for inflammatory diseases of the lower urinary tract; prophylaxis and treatment of renal gravel.

Standardzulassungen für Fertigarzneimittel [Braun 2011]

Indications: Herbal medicinal product used to increase the amount of urine to achieve flushing of the urinary tract; prophylaxis and treatment of renal gravel.

Plantas Medicinales [Quer 2008]

Uses and properties: diuretic.

Literature data support the traditional use of Restharrow root as an traditional herbal medicinal product for traditional use and the specified indication exclusively based upon long-standing use.

The current indications are:

- In Poland:

Traditionally used as a diuretic medicine (2 products as single ingredient herbal tea) for treatment of symptoms of mild lower urinary tract inflammatory conditions and as an aid in preventing of kidney gravel.

- In Germany:

Traditionally used to support the elimination function of the kidney.

Based on the available literature data the following text on the indication in the Monograph is recommended:

Traditional herbal medicinal product used to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary tract complaints. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

For more detailed information see section: Information about products on the market in the Member States.

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

The following posologies have been reported in the literature for Restharrow root (*Ononis spinosa* L.):

Österreichisches Arzneibuch [1960]

Dosage: the recommended dose is 1.5 g for one tea cup.

Route of administration: Oral administration.

Farmakopea Polska [1970]

Dosage: the recommended dose is 1-2.5 g for one tea cup.

Route of administration: Oral administration.

The Complete German Commission E Monographs [Blumenthal *et al.* 1998]

Dosage: the daily dose is 6-12 g of comminuted herb or equivalent preparations.

Route of administration: Oral administration. Comminuted herb for teas or other galenic preparations for internal use.

Duration of use: no information.

Contraindication: No irrigation therapy in case of oedema due to impaired heart and kidney function.

Interaction with other drugs: none known.

Hager's Handbuch [Drogen L-Z, Blaschek *et al.* 1998]

Dosage: the recommended dose is 3-4 g two to three times per day between meals.

Route of administration: Oral administration. Comminuted herb for teas, boiling water (150 ml) is poured over the material and the mixture strained after 30 min.

ESCOP Monographs [2003]

Dosage: For adults the recommended dose is an infusion of 2-3 g of dried material two to three times per day; equivalent preparations.

Route of administration: Oral administration. For infusion, boiling water is poured over the material and the mixture strained after 20-30 min.

Duration of use: no restriction.

Contraindication: none known.

Interaction with other drugs: none reported.

PDR For Herbal Medicines [Gruenwald *et al.* 2004; 2007]

Dosage: 2-2.5 g finely cut or coarsely powdered drug and strain 20-30 min, daily dosage: 6-12 g of drug.

Route of administration: Teas and other galenic preparations for internal use. Ample liquid intake (at least 2 litres per day) should accompany the use of the drug.

Contraindication: Should not be used in the presence of oedema resulting from reduced cardiac or renal activity.

Duration of use: no information.

Precautions and adverse events: No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages.

Herbal Drugs and Phytopharmaceuticals [Wichtl, 2004]

Dosage: Pour boiling water over 2 – 2.5 g of finely cut or coarsely powdered dried root. Steep for 20-30 min and then strain. 1 teaspoon = about 3 g

Route of administration: Oral administration.

Medicinal Plants of the World [Wyk and Wink 2005]

Dosage: to prepare a tea, boiling water poured over 2-2.5 g of the coarsely powdered root and taken several times a day. The recommended daily dose is 6-12 g of the herb.

Route of administration: Oral administration.

Medicinal Herbs: A Compendium [Gehrmann *et al.* 2005]

Dosage: 2-2.5 g (1 scant teaspoon) in 150 ml boiled water steeped for 20-30 min, 1 cup 3-4 times/day, daily dose: 6-12 g.

Route of administration: Oral administration. Ensure sufficient liquid intake, minimum 2 l/day.

Duration of use: acute complaints > 1 week or recurring illness: consult medical practitioner.

Contraindication: Not to be used in dehydration or oedema due to reduced heart and renal activity.

Interaction with other drugs: Unknown.

Adverse events: Unknown.

Standardzulassungen für Fertigarzneimittel [Braun 2011]

Dosage: For adults and adolescents the recommended dose is 2 g (1 scant teaspoon) of dried material 3 to 6 times per day.

Route of administration: Oral administration. For infusion, boiling 150 ml water is poured over the material and strained after 20-30 min.

Duration of use: 1 week.

Contraindication: none known.

Interaction with other drugs: Unknown.

Adverse events: Unknown.

Posology in children and adolescents up to 14 years of age:

A posology for children and adolescents is provided in *Kinderdosierungen von Phytopharmaka* [Dorsch *et al.* 1998] for Restharrow root and is based on calculations.

	0 – 1 year	> 1-4 years	> 4-10 years	> 10 -14 years
Dorsch <i>et. Al.</i> 1998	-	2 – 4 g	4 – 6 g	6 – 12 g

Posology in adolescents from age of 12 years:

The usage of Restharrow root for adolescents is mentioned in Braun [2011].

	0 – 1 year	> 1 – 4 years	> 4 – 10 years	> 12 years
Braun (2011)	-	-	-	6 – 12 g

1 teaspoon = approximately 2 g, 3-6 times daily.

The dosage recommendation for adolescents from the age of 12 years found in a handbook: 2 g (1 scant teaspoon) of dried material 3 to 6 times per day [Braun 2011] are similar to those for adults recommended in the monographs: 2-3 g of dried material two to three times per day [ESCOP Monographs 2003] and 6-12 g daily [Blumenthal *et al.* 1998]. According to the literature the maximum daily dosage for adolescents over 12 years of age, adults and elderly is 12 g.

No data for a posology in children from clinical trials are available. Therefore *Ononidis radix* should not be used in children under 12 years of age.

Duration of use:

Adolescents, adults, elderly

In generally Restharrow root infusions should be given on a short-term basis as the diuretic effect will decrease with continued use [Weiss 1988]. In Braun [2011] the following is mentioned: if urinary tract complaints worsen and symptoms such as fever or blood in the urine occur during the 7 days use of medicinal product, a doctor or a qualified health care practitioner should be consulted. In other source of literature the duration of application is suggested: acute complaints > 1 week or recurring illness [Gehrmann *et al.* 2005].

Based on the duration of use recommended in other monographs on herbal substances with similar effect and data for *Ononis spinosa* (L.), radix available in the literature, e.g. Medicinal Herbs. A Compendium [Gehrmann *et al.* 2005] and Braun [2011], the duration of use for 1 week is recommended in the Community Monograph: if the symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

3. Non-Clinical Data

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

In vivo experimental studies on the diuretic effect of *Ononidis radix* were performed and described in a dissertation thesis of Wilhelm Bulow already in 1891 [Bulow 1891].

In the late 1930's and early 1940's the studies done by Jaretzky and Vollmer had established the pharmacology of *Ononis spinosa* L, radix showing the diuretic effects in animal experiments [Vollmer und Hübner 1937b; Jaretzky and Neuwald 1938; Jaretzky 1940; Vollmer 1940a,b]. Vollmer described that an aqueous extract of Restharrow root administered *per os* to rats (0.250 g, 0.5 g and 1g/animal) induced the most pronounced diuretic effect at the dose of 1 g [Vollmer and Hübner 1937b]. An infusion of Restharrow root that was administrated orally to rabbits showed an increase in urinary output by 26% [Vollmer 1937a].

Primary Pharmacodynamics

Aqueous extracts:

An aqueous extract prepared from roots of *Ononis spinosa* L. was administered intragastrically to male Wistar rats (250±50 g, n=4 per group) at the dose of 0.3 g/per animal in 20ml of water. The controls were the same rats, that several days later have received distillate (5 ml) water or theophylline (5 mg/kg in 5 ml).

Every hour over a 5-hour period the samples of urine were collected from the rats following administration of aqueous infusion 21.4 ml, compared to 15.1 ml for distillate water and 17.9 ml for theophylline. The obtained results are summarized in Table 1.

Table 1: Effects of intragastrical administration of aqueous extract (0.3 g/animal), ash (0.3 g/animal) of the Restharrow root on excretion of urine volume expressed as ml and percentage in male Wistar rats. Distillate water and theophylline used for controls [Rebuelta *et al.* 1981].

Time, h	Distillate water controls	Theophylline controls	Aqueous extract
	ml urine ± SEM; excretion of urine volume in %	ml urine ± SEM; excretion of urine volume in %	ml urine ± SEM; excretion of urine volume in %
1 h	6.38 ml ± 0.28; 31.9 %	10.39 ml ± 0.40; 51.95 %	10.94 ml ± 0.24; 54.7 %
2 h	9.45 ml ± 0.31; 47.25 %	12.62 ml ± 0.36; 63.1 %	14.08 ml ± 0.33; 70.4 %
3 h	11.37 ml ± 0.27; 56.85 %	14.53 ml ± 0.35; 72.65 %	17.15 ml ± 0.38; 85.8 %
4 h	13.44 ml ± 0.31; 67.2 %	16.31 ml ± 0.231; 81.55 %	19.74 ml ± 0.33; 98.7 %
5 h	15.11 ml ± 0.37; 75.55 %	17.92 ml ± 0.26; 89.6 %	21.43 ml ± 0.38; 107.15 %

The amounts of sodium in the urine collected over 5 hours were 23.55 mg for an aqueous extract compared to 6 and 16 mg of sodium with water and theophylline controls respectively. The amounts of potassium was 62.20 mg compared to 43.87 and 60.95 mg of potassium with water and theophylline controls respectively. The amounts of sodium and potassium were determined by the atomic absorption spectrophotometry. The experiment was repeated several times (according to the paper 50) thus confirm the diuretic activity of the Restharrow root. The results demonstrated moderate diuretic and saluretic activity of preparation and higher than that produced by theophylline (5 mg/kg). The

conclusion was made that the diuretic activity of Restharrow root was caused by its content of potassium salts and flavonoid glycosides. [Rebuelta *et al.* 1981].

Hilp (1976) confirmed a diuretic activity *in vivo* studies. Oral administration of infusions of the Restharrow root caused slight diuresis (average of 12%) and decoctions an antidiuretic effect of 7-20% in rats.

Other extracts:

Bolle *et al.* (1993) showed that an ethanolic extract (not further defined) at a dose corresponding to 2 g/kg of drug administered p.o. significantly increased urinary volume by 103% (p<0.05) in mice and rats during 2 h observation time compared to saline control whereas no influence was observed on sodium or potassium elimination. This diuretic activity was not confirmed by intraperitoneal injection of the drug at doses up to 500 mg/kg/animal [Bolle *et al.* 1993].

A moderate diuretic activity (see Table 2) was shown following intragastrical administration of dried methanolic extract 19.9 ml, ash 18.7 ml, a mixture of methanolic extract and ash 20.9 ml of Restharrow root at the dose being equivalent to 0.3 g of root. The amount of urine was evaluated every hour over a 5-hour period in male Wistar rats.

Table 2: Effects of intragastrical administration of dried methanolic extract (0.3 g/animal), ash (0.3 g/animal) and a mixture of methanolic extract and ash (0.3 g/animal) of the Restharrow root on excretion of urine volume expressed as ml and percentage in male Wistar rats [Rebuelta *et al.* 1981]

Time, h	Methanolic extract	Ash	Mixture of methanolic extract and ash
	ml urine ± SEM; excretion of urine volume in %	ml urine ± SEM; excretion of urine volume in %	ml urine ± SEM; excretion of urine volume in %
1 h	8.42 ml ± 0.33; 42.1 %	8.94 ml ± 0.37; 44.7 %	12.18 ml ± 0.34; 60.9 %
2 h	12.31 ml ± 0.33; 61.55 %	11.94 ml ± 0.34; 59.7 %	14.45 ml ± 0.30; 72.25 %
3 h	14.93 ml ± 0.18; 74.65 %	14.75 ml ± 0.26; 73.75 %	16.66 ml ± 0.37; 83.3 %
4 h	17.45 ml ± 0.29; 87.725 %	16.80 ml ± 0.27; 84 %	18.63 ml ± 0.35; 93.15 %
5 h	19.87 ml ± 0.19; 99.35 %	18.66 ml ± 0.21; 93.39 %	20.85 ml ± 0.37; 104.25 %

In the study the controls were the same male Wistar rats, that several days later were administered with water or theophylline (5 mg/kg). The controls data with water or theophylline see above at aqueous extract description [Rebuelta *et al.* 1981]. The amounts of sodium in urine were 20.31 mg for dried methanolic extract, 32.69 mg for ash and 20.97 mg for mixture of methanolic extract and ash determined by atomic absorption spectrophotometry and compared to 6 and 16 mg of sodium with water and theophylline controls respectively. The potassium levels were 95.50 mg for dried methanolic extract, 78.89 for ash and 65.87 mg for mixture of methanolic extract and ash, compared to 44 and 61mg with water and theophylline [Rebuelta *et al.* 1981].

Essential oil:

In Hilp (1976) it was said that aqueous residue of an aqueous preparation after steam distillation expressed an antidiuretic effect (7-16%) that was depending on the duration of distillation, whereas 0.5-1.0 ml of the essential oil obtained by steam distillation (2-4 hours) produced a diuretic effect. The conclusion of this study was that the essential oil of Restharrow root exhibits diuretic activity [Hilp 1976].

Vollmer and Jaretzky discussed the role of the essential oil for the diuretic action of Restharrow root [Vollmer 1940a; Vollmer 1940b; Jaretzky 1940].

Isolated compounds:

A study performed by Melzig and Schmidt (1972) indicates that genistein, a component of Restharrow root has a diuretic action comparable to furosemide [Melzig and Schmidt 1972].

Secondary Pharmacodynamics

Aqueous extracts:

Joksić *et al.* (2003) assessed the cytogenetic effects of the aqueous extract from *Ononidis radix* on the micronuclei formation *in vitro* studies by using an irradiated human blood lymphocytes obtained from healthy, non-smoking, young male donor. In the study was examined the acquired micronucleus formation in unirradiated and irradiated samples of cultured blood lymphocytes using the cytochalasin block micronucleus test (CBMN). Centromere-positive micronuclei (MNC⁺) were recognized by fluorescence *in situ* hybridization using DNA probe labelled with α -satellite digoxigenin. *Ononidis radix* (0.2mg/ml) potentiated the yield of radiation-induced micronuclei up to 1.7-fold. [Joksić *et al.* 2003].

Extracts of Restharrow root have been shown to exert antifungal activity [Wolters 1966].

Other extracts:

In vitro studies shown that a methanolic Restharrow root extract (6:1) selectively inhibited 5-lipoxygenase with an IC₅₀ of 7.8 $\mu\text{g/ml}$ and the isolated pterocarpan medicarpin inhibited leukotriene B₄ formation with an IC₅₀ of 6.7 μM [Dannhardt *et al.* 1992].

The application of acetylcholinesterase inhibitors is currently the only approved therapy for Alzheimer's disease. Petroleum ether, dichloromethane and methanol extracts of Restharrow root (from *Ononis spinosa* L.) at the concentration of 100 $\mu\text{g/extract/ml}$ using Ellman's reagent in a microplate assay showed no significant inhibitory activity on acetylcholinesterase not even with the isolated α -onocerin [Rollinger *et al.* 2005].

In vivo studies using the hot plate test no analgesic effects were obtained after oral or intraperitoneal (i.p.) administration of an ethanol Restharrow root extract (not further defined) in mice. Restharrow root extract reduced reaction to pain by up to 80% at doses of 100 and 500 mg/kg after i.p. injection, while no effect was observed after oral administration of extract in mice followed by the phenylquinone writhing test. The same extract induced a significant ($p < 0.05$) reduction of an oedema (46%) in the carrageenan-induced rat paw oedema test after 3 hours following i.p. injection of Restharrow root at the dose of 500 mg/kg in mice while no significant effects were obtained at the dose of 100 mg/kg [Bolle *et al.* 1993].

Dried and powdered roots of *Ononis spinosa* subsp. *leiosperma* was extracted with methanol and then evaporated *in vacuo*. The crude extract washed with hexane and Me₂CO was applied on a *Si* gel column for isolation of spinonin. The applied paper-disk diffusion method was chosen to test activity of compounds against the Gram-positive bacteria *B. subtilis* ATCC 6633, *S. aureus* ATCC 6538P, *S.*

epidermidis ATTC 12228, *E. faecalis* ATCC 29212, beta-hemolytic *Streptococcus* 48 and the Gram-negative bacteria *P. mirabilis* ATTC 9027 and *K. pneumonia* ATCC 4352, and the yeast *C. albicans* ATCC 10231. Isolated spinonin and pterocarpan produced weak (MIC 200 µg/ml) activity against *Pseudomonas aeruginosa*. Ononin was more active (MIC = 25 µg/ml) against β-hemolytic *Streptococcus*. Spinonin was tested against human cancer cell lines (BC1, Lu1, KB-V(+VLB) and HIV-1 reverse transcriptase in which it was inactive [Kirmizigül *et al.* 1997].

Isolated compounds:

Restharrow root contains the isoflavone genistein that is reported in the literature to produce a mild estrogenic effect [Gruenwald *et al.* 2004, 2007]. No studies on particular extract of restharrow root are available. Farmakalidis *et al.* (1985) have described the oestrogenic response to 1.5 mg genistin was equivalent to that of 1 mg genistein, giving a 1:1 molar relationship in oestrogenic activity between genistin and genistein in the mouse B6D2F1 strain [Farmakalidis *et al.* 1985].

Safety Pharmacology

No data available.

Pharmacodynamic interactions

No data available.

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

There is no Restharrow root specific data on pharmacokinetics and interactions available.

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

Acute toxicity

No data available.

Repeated dose toxicity

An ethanolic extract at a daily dose of 2g/kg per drug injected orally or intraperitoneally for 14 days in rats and mice did not produce any visible toxic effect [Bolle *et al.* 1993].

Genotoxicity

Aqueous extracts

In vitro cytogenetic effects of aqueous extracts of *Ononidis radix* were examined with cytochalasin block micronucleus test and centromere-positive micronuclei were identified by fluorescence *in situ* hybridization using a DNA probe labelled with α-satellite digoxigenin. The aqueous extracts (concentration ranging from 0.025 to 0.1 mg/ml) of *Ononidis radix* showed clastogenic properties inducing 5- to 6-fold increase in the incidence of micronuclei compared to the control. Concentration of 0.2mg/ml decreased slightly the incidence of micronuclei and was followed by lesser proliferation of the cells (CBPI=1.81). The percentage of MNC⁺ micronuclei ranged from 18.8 to 23.8%. The name of species from the genus *Ononis* was not specified by the authors of this paper [Joksić *et al.* 2003]. Thus it is difficult to use these findings in the assessment of safety of *Ononidis spinosa*.

Carcinogenicity, reproductive and developmental toxicity

No studies concerning carcinogenicity and reproductive toxicity have been reported for the Restharrow root or Restharrow root preparations.

3.4. Overall conclusions on non-clinical data

Limited pharmacodynamic data on Restharrow root aqueous extracts and other extracts indicate diuretic, anti-inflammatory and antimicrobial effects. Restharrow root specific data on pharmacokinetics and interactions are not available.

The data on toxicology of Restharrow root and Restharrow root preparations are limited. The repeated dose toxicity study was performed with ethanol extracts but studies with aqueous preparations of the roots are lacking. No adverse toxic reactions have been reported in scientific literature.

Neither the chemical composition nor the long-term widespread use in the European Community suggests that there is a high risk associated with the use of Restharrow root preparations.

Tests on reproductive toxicity and carcinogenicity and adequate tests on genotoxicity have not been performed. Therefore, a list entry for *Ononis spinosa* L. radix from a non-clinical point of view cannot be recommended.

The published non-clinical data with respect to preparation diuretic activity is mostly limited to old scientific papers and mainly from the beginning of the 20th century. Diuretic effects of *Ononis spinosa* L, radix aqueous extracts are discussed in more detail for a more recent study from 1981. Available information on diuretic activity indicates the use of Restharrow root in the short-term treatment as a mild diuretic for the lower urinary tract disorders.

4. Clinical Data

4.1. Clinical Pharmacology

No relevant data are available.

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No relevant data are available on human pharmacodynamics.

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

No relevant data are available on human pharmacokinetics.

4.2. Clinical Efficacy

No studies for clinical efficacy were found.

4.2.1. Dose response studies

No dose-response studies were performed to support the posology and daily dose proposed in the literature.

4.2.2. Clinical studies (case studies and clinical trials)

No relevant data are available.

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

No clinical studies in special populations are reported.

4.3. Overall conclusions on clinical pharmacology and efficacy

No relevant data are available on clinical research assessing the effects of Restharrow root. Therefore the well-established use cannot be supported.

Overall, the medicinal use of Restharrow 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 specific data available.

5.2. Patient exposure

There are no specific data on patient exposure to Restharrow root available.

5.3. Adverse events and serious adverse events and deaths

No side effects are known in conjunction with the proper administration and therapeutic dosages.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

The safety of Restharrow root in humans is based on the traditional use. Without any further specification it is mentioned that Restharrow root should not be used in the presence of accumulation of water (oedema) due to impaired cardiac or renal function and dehydration [Blumenthal *et al.* 1998; Wichtl 2004; Herbal Medicines 2004; Medicinal Herbs. A Compendium 2005].

Sufficient liquid intake should be ensured, minimum 2 l/day [Medicinal Herbs. A Compendium 2005].

Intrinsic (including elderly and children)/extrinsic factors

No clinical studies in children or adolescents are available. A posology for children and adolescents for Restharrow root in Dorsch *et al.* (1998) is based only on calculations.

In the marketed preparations and in Braun (2011), the dosages are recommended for adolescents above 12 years of age and adults. The dosage for adolescents over 12 years of age is the same as for adults and elderly.

Due to the lack of sufficient data the use is not recommended for children under 12 years of age.

Drug interactions

In phytotherapeutic books such as ESCOP Monographs (2003), Blumenthal *et al.* (1998), interactions with other drugs are not mentioned.

Use in pregnancy and lactation

Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use of the Restharrow root during pregnancy and lactation is not recommended.

Overdose

From literature, monographs and databases of the Member States, no case reports on overdose of *Ononis spinosa* preparations are available. Therefore it is stated in the monograph that no case of overdose has been reported.

Drug abuse

There are no reports on drug abuse of *O. spinosa* preparations.

Withdrawal and rebound

There are no reports on withdrawal of *O. spinosa* preparations.

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

No studies on the ability to drive and use machines have been performed. There are no reports on impairment of mental ability. No conclusions can be drawn on potential concern arising from effects on ability to drive or operate machinery by the known ingredients of Ononis.

5.6. Overall conclusions on clinical safety

No data for a posology in children from clinical trials are available. As the use of diuretic treatment in self-medication for the children under age of 12 years is not appropriate, the use of Restharrow root in children under age of 12 is not recommended.

The duration of use is limited to one week. There are no data on reproductive and developmental toxicity, therefore the use during pregnancy cannot be recommended.

Available information up to now shows no reports of side effects from Member States of the European Union. The traditional use over a long period has shown that Restharrow root is not harmful used in the specified indications.

6. Overall conclusions

The medicinal application of the Restharrow root has been consistently described to be used for a long period of time in many European pharmacopeias, relevant handbooks and scientific papers. Restharrow root (comminuted herbal substance as herbal tea) as included in the monograph fulfills the requirement of Directive 2004/24/EC for use in traditional herbal medicinal products (medicinal use for at least 30 years including at least 15 years within the European Union). The use in the treatment of minor urinary complaints is considered plausible on the bases of bibliography and pharmacological data available.

In the absence of clinical studies using relevant herbal preparations, the well-established use cannot be supported for the herbal substance or extracts.

Due to the lack of sufficient data on genotoxicity, carcinogenicity and reproductive and developmental toxicity, a Community list entry for *Ononis spinosa* (L.), radix cannot be established.

Oral administration of Ononidis radix can be regarded as safe at traditionally described and used doses in adults and adolescents over 12 years of age. Due to lack of data Restharrow root cannot be recommended in children under age of 12 years and in pregnancy and lactation. The use is

contraindicated in conditions where a reduced fluid intake is recommended (e.g. cardiac or renal diseases) and in patients with hypersensitivity to the active substance. [Blumenthal *et al.* 1998; Wichtl 2004; Gruenwald *et al.* 2004, 2007; Medicinal Herbs. Gehrman *et al.* 2005].

In the documentation of medicinal use no adverse effects have been mentioned. Toxicological data on *Ononidis radix* are very limited and available data do not indicate a noteworthy risk associated with the *Ononidis radix* treatment.

Based on literature data and information received from the Member States, *Ononis spinosa* L, radix can be recommended for use in adolescents over 12 years of age, adults and elderly as a traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

Available data are sufficient to establish a Community herbal monograph on the traditional use of Restharrow root.

Annex