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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Ononis spinosa* L., radix

Draft – Revision 1

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Ononis spinosa* L., radix
Herbal preparation(s)	Comminuted herbal substance
Pharmaceutical form(s)	Herbal tea
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Ononis spinosa* L., radix. It is a working document, not yet edited, and shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.

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1. Introduction

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

- Herbal substance(s)

In the Ph. Eur. monograph 11.0 ref.: 07/2014:1879, Restharrow root (Ononidis radix) is defined as the whole or cut, dried root of *Ononis spinosa* L.

- Herbal preparation(s)

No official quality standard available.

- Relevant constituents for this assessment report

Isoflavones: formononetin 7-O-β-D-glucoside, formononetin 7-O-β-D-glucoside 6”-malonate (3.2 – 5.9 mg/100g), formononetin (aglycone) malonate, calycosin 7-O-β-D-glucoside and calycosin 7-O-β-D-glucoside-6”-malonate, genist, ononin (formononetin 7-O-glucoside), pseudobaptigenin 7-O β-D-glucoside, pseudobaptigenin 7-O β-D-glucoside 6”-ein (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), maackianin 3-O β-glucoside, ononigenin 7-O-β-D-glucoside, 2.3-dihydro-ononin and also tectoridin, trifolirhizin, rothinidin (Háznagy et al.1978; Pietta and Calatroni 1983; Köster et al. 1983; Blaschek et al. 1998; Klejdus et al. 2007; Benedec et al. 2012, Gampe et al. 2016).

Phenolic acids with p-hydroxybenzoic, vanillic acid, caffeic acid, syringic acid, p-coumaric acid, cinnamic acid, sinapin acid, salicylic acid, gentisin acid were reported in the (Blaschek et al. 1998; Klejdus et al. 2008).

Glucosides: Spinonin, a glucoside with specific structure has been detected, as well as medicarpin, a pterocarpan derivative (Kirmizigül et al. 1997; Blaschek 2016)

Saponins: triterpenoid saponin (e.g. 3-O-[α-L-rhamnopyranosyl-(1→2)-β -D-xylopyranosyl-(1→2)- β -D-glucuronopyranosyl]-3β,22α-dihydroxyolean-13-en-11) (Shaker et al. 2004).

Small amounts of essential oil (0.02 - 0.2%), containing *trans*-anethole as the major constituent, with carvone, menthol, menthone were found in the *Ononis spinosa* L., radix Hilp (1974), ESCOP monograph (2015). Also constituents with low water solubility were found, triterpenes, particularly α-onocerin [onocol] (4.1 mg/1g herbal substance) (Barton and Overton 1955, Fujise et al. 1965, Rowan et al. 1971, Blaschek et al. 1998, Pauli 2000); sterols, mainly β-sitosterol, stigmasterol, campesterol, cholesterol, α-spinasterol (Blaschek et al. 1998); polyketide lactones, cyclic polyketide 7,9,11-trihydroxytetracos-2-eneoic acid d-lactone (Abu Zarga et al. 2021).

1.2. Search and assessment methodology

Scientific databases

☒ Scientific/Medical/Toxicological databases

Scientific data of the period 2013 -2022 was reviewed using Google Scholar browsing machine and sources available in library of Warsaw Medical University (Medline Complete, PubMed, Reaxys, SciFinder, Scopus, The Cochrane Library, Web of Science, Polska Bibliografia Lekarska, ScienceDirect. Open Access system containing Directory of Open Access Journal (DOAJ), BioMed Central Journals, PLoS Journals, Hindawi, Elsevier Open Access, SAGE Open Access, Free Medical Journals. Search terms “Ononidis + radix”, “Ononis + spinosa”, “Restharrow + root”.

☒ Pharmacovigilance databases

☒ data from EudraVigilance

☒ from other sources (e.g. data from VigiBase)

☐ Other: Not applicable

Books

☒ Old books and a new edition, which were not included in the first report were added.

Regulatory practice

☒ Old market overview in AR (i.e. check products fulfilling 30/15 years of TU or 10 years of WEU on the market)

☒ New market overview (including pharmacovigilance actions taken in member states)

☒ PSUSA

☒ Feedback from experiences with the monograph during MRP/DCP procedures

☒ Ph. Eur. monograph

☐ Other: Not applicable

Consistency (e.g. scientific decisions taken by HMPC)

☒ Public statements or other decisions taken by HMPC

☒ Consistency with other monographs within the therapeutic area

☒ Other: Not applicable

Other

☐ Not applicable

1.3. Main changes introduced in the 1st revision

The monograph and consequently the assessment report has been harmonised with other monographs in the same therapeutic area. This includes the indication, contraindication and warning sections.

To be in line with the monographs of other herbal substances with a similar scope of diuretic use, the indication was expressed in the same way: "Traditional herbal medicinal product for the relief of symptoms associated with mild urinary tract symptoms in addition to the general recommendation of adequate fluid intake to increase urine volume. The product is a traditional herbal medicinal product for use in certain indications based exclusively on long-term use".

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on medicinal products marketed in the EU/EEA

Table 1. Overview of data obtained from marketed medicinal products.

Herbal substance/ preparation	**Indication**	**Posology and method of administration**	**Regulatory status**
Ononidis radix, comminuted herbal substance	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.	Preparation of herbal tea, infusion. 1 teaspoon (declared value: 2-3 g; measured values 3.5-5 g*) pour with a glass (200mL) of boiling water, infuse under cover for 15 min., strain. Use of the fresh prepared infusion 2-3 times a day. Pay attention on significant amount of fluids. If symptoms persist for more than a week while using the medicinal product, consult a doctor.	Two products registered in 03.1995 and 02.2003, PL, National registration
Ononidis radix, comminuted	To increase the amount of urine in the case of renal pelvis and bladder catarrh, urinary gravel and to prevent urinary stones.	Herbal tea Single dose: 3-4 g, 2-3 times daily Daily dose: 6-12 g Duration of use: Tea made from restharrow root should only be used for a few days as its effectiveness wears off. Use can be continued after a break of several days.	1986-2004, DE, Standard Marketing Authorisation

* Average content of Ononidis radix in spoons and teaspoons from years 1960-2010 in Dymowski & Jackiewicz (2020).

Information on relevant combination medicinal products marketed in the EU/EEA

According to the information from the Member States and literature restharrow root, as comminuted herbal substance, is also used as a constituent of combination herbal tea products.

Restharrow root 30 years ago was used in Germany in different diuretic combination products with Orthosiphonis folium, Solidaginis herba, Levistici radix and Santali rubri lignum and in other herbal urological combinations with Urticae radix and Scillae bulbus (Rote Liste 1992).

Information on other products marketed in the EU/EEA (where relevant)

No relevant data available

2.1.2. Information on products on the market outside the EU/EEA

In the USA, restharrow root is a dietary supplement and in Canada approved as an active ingredient in a few OTC Traditional Herbal Medicines and homeopathic medicines (Blaschek 2016). Ononis species has been used for centuries as folk remedies in Turkey as diuretic, antiseptic and antimicrobial aids. No detailed data are available.

2.2. Information on documented medicinal use and historical data from literature

Ononis spinosa L, radix (restharrow root) has been widely used since ancient times and mentioned in many old manuals 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 as a diuretic medicine for inflammatory conditions of the lower urinary tract and for preventing and treating kidney and bladder disorders, urinary gravel and small stones (Jaretzky 1940, Deutsches Arzneibuch 1947; Československý lékopis (Pharmacopoeia Bohemoslovenica) 1954, 1970, 1987; Österreichisches Arzneibuch 1960; Farmakopea Polska 1970; Wren et al. 1988; Blumenthal et al. 1998, ESCOP Monograph 2015; Hoppe 1942; Berger 1960; Thurzová et al. 1973; Borkowski 1974; Weiss 1988, Schilcher 1997; Hocking 1997; Blaschek et al. 1998; Bartram 1998; 1999; Evans 2000; Wichtl 1997, Blaschek 2016; Gruenwald et al. 2004, 2007; Wyk and Wink 2005; Gehrmann et al. 2005; Fintelmann and Weiss 2006; Fintelmann et al. 2024, Quer 2008.

Restharrow root has been traditionally used in Poland with evidence in a literature dating back at least to the mid-twentieth century (Muszyński 1954; Roeske 1955; Farmakopea Polska 1970; Borkowski 1974; Ożarowski 1976; Ożarowski 1978). Restharrow root preparations have been known to increase daily urine output (from about 1.0 to 1.5 l daily in adults, Muszyński 1954). Restharrow root has been on pharmaceutical market in Germany as a single herb tea (*Standardzulassung*, 1986), in Poland (*Informator Terapeutyczny do Urzędowego Spisu Leków*, 1954, 1959) and as a constituent of 'bladder and kidneys' tea formulas (*Standardzulassung*, 1988). Restharrow root has been components of phytomedicines in tablet and dragée form (Rote Liste 1992, Chapters 35 and 81; Blaschek 2016).

Currently medicinal products as single ingredient herbal teas have been available on the market in Poland since 1995 and 2003 and in Germany with a tradition since 2004. The term of *flushing therapy* appeared in the *Standardzulassung* published in 2004.

Comparison of daily dosages in children and adolescents up to 14 years of age in Germany.

The daily dosages for children and adolescents provided in the manual Kinderdosierungen von Phytopharmaka (Dorsch et al. 1998) for restharrow root, based on calculations. The daily dosages in adolescents from age of 12 years as have been regulated since Standardzulassung 2004, Nr 105 Hauhechelwurzel (Braun 2011).

Age range	0 – 1 year	1 - 4 years	4 - 10 years	>10 - 14 years
Dorsch 1998	-	2 – 4 g	4 – 6 g	6 – 12 g
Age range	0 – 1 year	1 – 4 years	4 – 12 years	>12 years
Braun 2011	-	-	-	6 – 12 g

1 teaspoon according to the Standardzulazssung 1986 has been about 3-4 g, daily dose 6 – 12 g.

1 teaspoon since *Standardzulassung* 2004 (Braun 2011) have been approximately 2 g. To give a single dose 2 g the teaspoon should be very scant filled and to maintain daily dose 6-12 g should have been used 3-6 times daily.

The daily dosage recommendation for adolescents from the age of 12 years found in a handbook: 2 g of dried material 3 to 6 times per day (Standardzulassung 2004 in Braun 2011) are similar to those for adults given in ESCOP monograph (2015): an infusion of 2-3 g of dried material two to three times per day and in the Commission E monograph (*Blumenthal* et al. 1998): 6-12 g daily. According to the literature the maximum daily dosage for adolescents over 12 years of age, adults and elderly is 12 g.

The following posology for 'traditional herbal medicines' is recommended in the European Union herbal monograph: 2 – 3 g of comminuted herbal substance in 150 – 200 ml of boiling water as a herbal infusion up to 3 - 4 times daily corresponding to the maximum daily dose of 12 g.

For children under 12 years the use of diuretic drugs in self medication is not appropriate. Therefore the use for children is not recommended without medical consultation. Oral administration of Ononidis radix can be regarded as safe at traditionally described and used doses in elderly, adults and adolescents.

Duration of use:

Adolescents, adults, elderly

Documented medicinal use of all traditional herbal medicinal products which were reported to be present on the EU pharmaceutical market give evidence for the use of the products for a period of 7 day (or one week) without of the need of medical consultation (Table 1). Restharrow root infusions should be given on a short-term basis as the diuretic effect will decrease with continued use (Weiss 1988). In Standardzulassungs 2004 (Braun, 2011) is mentioned that 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. Gehrmann et al. (2005) in acute complaints suggested the duration of application 1 week or recurring illness.

The discussion on the duration of use has been moved to the Chapter 5.5.3 on Special warnings.

Table 2. Overview of historical data.

Herbal substance/ preparation	**Documented use / Traditional use**	**Posology and method of administration**	**Reference and date of the reference**
Ononidis radix comminuted (Radix Ononidis)	mild diuretic	Single oral dose 2 g of comminuted herbal substance increase daily diuresis in patients from about 1000 to 1500 ml	Zarys Fitoterapii. Farmakologia i receptura ziół leczniczych (Roeske 1955)
Ononidis radix (Radix Ononidis)		Single dose: 1.5 g in 1 teacup	Österreichisches Arzneibuch 9. Ausgabe (1960)
Ononidis radix (Radix Ononidis)	diuretic	Single oral dose in preparations: 1.0 - 2.5 g	Farmakopea Polska IV (1970)

Herbal substance/ preparation	Documented use / Traditional use	Posology and method of administration	Reference and date of the reference
Ononidis radix (Radix ononidis)	diureticum	Single oral dose: 1.5 g in a form of decoction	Československy Lékopis (Ed. III 1970, Ed. IV 1987)
Ononidis radix	Irrigation therapy for inflammatory diseases of The lower urinary tract and for the prevention and treatment of kidney gravel.	Daily dose in preparations: 6 g - 12 g Observe ample fluid intake.	Blumenthal et al. (1998)
Ononidis radix	Increase of urine output, known and described for a long time	Single dose 3-4 g (volume of about two teaspoons) infuse for a 30 min., used two to three times a day, between meals	Blaschek et al. (1998)
Ononidis radix	Aquaretic	1 teaspoon of the herbal substance infuse for 30 min. in teacup of boiling water. Several times daily one cup.	Weiss & Fintelmann (1999)
Ononidis radix, comminuted herbal substance	For irrigation therapy for inflammatory diseases of the lower urinary tract (infections of the urinary tract) and also for prevention and treatment of kidney gravel.	Herbal tea of 2.0-2.5 g comminuted herbal substance, infused 20-30 minutes Daily dose: 6-12 g	Gruenwald et al. (2004; 2007)
Ononidis radix	Indications: Irrigation therapy as a diuretic medicine for inflammatory conditions of the lower urinary tract and for preventing and treating kidney gravel.	Herbal tea, infusion made of 2-2.5 g comminuted herbal substance. Daily dose 6-12 g	Wyk and Wink (2005)
Ononidis radix	Irrigation therapy for inflammatory diseases of the lower urinary tract; prophylaxis and treatment of renal gravel.	Herbal tea of 2-2.5 g/150 ml. One cup 3-4 times a day. Daily dose 6-12 g. Ensure sufficient liquid intake (minimum 2 L per day)	Gehrmann et al. (2005)

Herbal substance/ preparation	Documented use / Traditional use	Posology and method of administration	Reference and date of the reference
Ononidis radix	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.	Adults: infusion of 2-3 g of dried material (the mixture being strained after 20-30 minutes) two to three times per day. Preparations in equivalent doses. Method of administration: For oral administration. No restriction. If symptoms persist or worsen, medical advice should be sought.	ESCOP monograph (2015)
Ononidis radix comminuted	Indications as HMPC, ESCOP, and Commission E monograph	Herbal tea, infusion. 2.0-2.5 g of comminuted herbal substance infused for 20-30 minutes. Daily dose: 6-12 g	Blaschek (2016)

2.3. Overall conclusions on medicinal use

Overview of evidence on period of medicinal use of Ononidis radix is presented in Table 3 below.

Table 3. Overview of evidence on period of medicinal use.

Herbal substance/ preparation	Indication	Posology and method of administration	Period of medicinal use
Ononidis radix. Comminuted herbal substance	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.	Preparation of herbal tea, infusion. 2-3 g with 200 mL of boiling water, infuse under cover for 15 min., strain. Use of the fresh prepared infusion 2-3 times a day. Notices: Pay attention on adequate amount of fluids. If symptoms persist for more than a week while using the medicinal product, consult a doctor.	Since 1995

Herbal substance/ preparation	Indication	Posology and method of administration	Period of medicinal use
Ononidis radix. Comminuted herbal substance	Increase of urine output,	Single dose 3-4 g infusion (for a 30 min.), used two to three times a day, between meals	Blaschek et al. (1998)
Ononidis radix, comminuted	To increase the amount of urine in the case of renal pelvis and bladder catarrh, urinary gravel and to prevent urinary stones.	Herbal tea Single dose: 3-4 g, 2-3 times daily Daily dose: 6-12 g Duration of use: Tea made from restharrow root should only be used for a few days as its effectiveness wears off. Use can be continued after a break of several days.	1986-2004, DE, Standard Marketing Authorisation

Clinical safety for preparations that fulfil the criteria of medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, i.e. traditional medicinal use based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC is further evaluated in chapter 5 'Clinical Safety/Pharmacovigilance'. The non-clinical safety is evaluated in chapter 3 'Non-clinical data'.

Infusions of restharrow root have been traditionally used as mild diuretics. A long presence of herbal medicinal products on the market together with regulatory and bibliographic sources support the traditional medicinal use of restharrow root in Europe, therefore 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.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Aqueous extracts

In the late 1930's and early 1940's Vollmer and Hübner (Vollmer 1937, 1939, 1940; Vollmer and Hübner 1937) described that an aqueous extract of restharrow root (no further information) administered *per os* to rats (0.250 g, 0.5 g and 1 g/animal) and compared with water, induced diuretic effect. An infusion of restharrow root (5 g) that was administrated orally to rabbits showed an increase in urinary output by 25,9% (Vollmer 1937).

Rebuelta et al. (1981) studied infusion prepared of roots of *Ononis spinosa* L. (according to the Pharmacopoea Española 1954), administered intragastrically to male Wistar rats (250±50 g, n=4 per group), in a dose corresponding to 0.3 g/per animal, in a tested volume of 5 ml. To check the influence

of the potassium on the diuretic activity one group of animals obtained ash solution in 5 ml of water. The controls were the same rats, that several days later have received distillate water (5 ml per animal or theophylline (5 mg/kg in 5 ml). Every hour for 5-hours after the administration, the samples of urine were collected. The urinary output volume in a distillate water group was 15.1 ml, in theophylline group 17.9 ml, in the ash group 18.7 ml and in the infusion 21.4 ml. 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 experiment was repeated several times, thus confirm the activity. The results demonstrated moderate diuretic and saluretic activity of the preparation (at the tested level similar to the theophylline in dose 5 mg/kg). The authors suggested that the diuretic activity of restharrow root was caused by its content of potassium salts and other constituents as flavonoid glycosides.

Other extracts

In the same experiments as above (Rebuelta et al. 1981) administered to male Wistar rats 5 ml of solution of the dry methanol extract residue (46.3 mg, of 20 ml, corresponding to the 300 mg of the herbal substance), and the mixture of the extract with the ash. The same Wistar rat's groups (n=4), several days later were administered with water (negative control) or theophylline (5 mg/kg) as positive control. The amounts of sodium excreted in urine were 20.31 mg for dried methanolic extract group, 32.69 mg for ash and 20.97 mg for mixture of the extract and ash group; in distilled water and theophylline controls were 6 and 16 mg respectively. A moderate urinary 5h output was found following administration of the dried extract 19.9 ml; the ash solution 18.7 ml and the mixture of the extract with the ash solution 20.9 ml. The controls: water 15.1 ml, theophylline 17.9 ml. Bolle et al. (1993) communicated on test on ethanolic extract (not further defined) at a dose corresponding to 2 g/kg per animal, 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.

Essential oil

Jaretzky and Neuwald (1937) observed that aqueous residue after steam distillation of Ononidis radix have weakened diuretic effect (by 7-16%) depended on the duration of boiling, while the essential oil obtained by steam distillation (2-4 hours, in a dose of 0.5-1.0 ml) produced some diuretic effect. The observation induced discussion on possible active substance which could be involved in the diuretic effects (Vollmer 1939, 1940; Jaretzky 1940). Later Hilp et al. (1974) found in the essential oil trans-anethole, carvon and menthol but the phenomenon of influence of water boiling/distillation on the diuretic activity was not further studied.

Isolated compounds

A study performed by Giménez et al (1998) indicated that genistein, a component of restharrow root has a diuretic and saluretic activity in perfused rat kidneys similar to furosemide but 3-5 times weaker (potent).

The main non-clinical on data on *Ononis spinosa* L., radix, preparations are presented in Table 4.

Table 4. Overview of the main non-clinical data.

Herbal preparation tested	Concentration / Dosage	Experimental model	Reference	Main outcome(s) according to the authors
Infusions, hot water extract				
Infusion/decoction	0.25 g; 0.5 g;1.0 g /animal	*In vivo* p.o. Rats in laboratory conditions, 5 animals in group urea N and chlorides excretion were compared to the "standard values"	Vollmer & Hübner (1937)	Maximal growth in the urine quantity at 0.5g. Influence on growth of urea N excretion: 13.5%, 47.9%, 83.3% and growth in urinary chlorides excretion: 93.6%, 104.5%, 209.7%.
Infusion (according to the Farmacopoea Espanola IX)	2 ml/100 g (in 5 ml) or distilled water. Corresponding to 0.3 g herbal substance per animal negative control: distilled water (5 ml) positive control: theophylline (5 mg/kg)	*In vivo* Oral administration Wistar rats (300±20 g), 4 animal per group. (0.3g of the herbal substance per animal) administered later. Urine collected by 5 following hours. Sodium and potassium in the urine were measured by spectrophotometric method.	Rebuelta et al. (1981)	After 5 h volume of urine excreted was in water group 15.1 ml (75.5% growth), in theophylline group 17.9 (89.6%) and in the infusion group 21.4 ml (107.15%). Natriuretic effect was observed. Excretion of sodium was 5.9 mg/5 h in water group, 16.3 mg/5 h in theophylline group, 23.5 in the Ononis infusion group. Absolute diuretic activity 1.41 (Vmeasured/Vwater). Relative diuretic activity of infusion was 1.19 after 5h (Vmeasured/Vtheophylline)
Hot water (70°C) extract (DER 6.5:1) under 2h of stirring	Concentrations: 125-1000 µg/ml	*In vitro* models: Influence on the proliferation of uropathogenic *Escherichia coli* (UPEC) UT189; anti-adhesive activity assessed by flow cytometry;	Deipenbrock et al. (2020)	No influence on the proliferation of *E. coli* cells of the water extract in tested concentrations. No influence on the cell viability of T24 bladder cells. Significant, concentration dependent inhibition of bacterial adhesion to T24 cells

Herbal preparation tested	Concentration / Dosage	Experimental model	Reference	Main outcome(s) according to the authors
		evaluation of fluorescent-Labelled pathogenic UTI189 cells to human T24 bladder carcinoma cells; internalization of E. coli cells monitored by an invasion assay.		(p>0.001) leading to Lowered internalization *E. coli* to the host cells. Extract did not interact with FimH-mediated adhesion of *E. coli* cells.
Alcohol extracts				
Dry methanolic extract (DER 6.5:1)	46.3 mg per rat (corresponding to 300 mg of herbal substance); negative control: distilled water (5 ml); positive control: theophylline (5 mg/kg)	*In vivo* Wistar rats (300±20 g), 4 animal per group. Intra-gastric administration. As a control served distilled water or theophylline solution) administered later. Urine collected by 5 following hours. Sodium and potassium in the urine were measured by spectrophotometric method.	Rebuelta et al. (1981)	The important amounts of sodium were excreted in urine: 20.31 mg for dried methanolic extract, 32.69 mg for ash and 20.97 mg for mixture of the extract and ash as compared to 6 and 16 mg of sodium in water and theophylline controls. A moderate urinary 5h output was found following administration of dried methanolic extract 19.9 ml; for the ash solution 18.7 ml and the mixture of methanolic extract with the ash solution 20.9 ml. The authors presumed the role of potassium content in the herbal substance
Ethanol extract (not characterised)	p.o. doses corresponded to 1 g and 2 g of herbal substance/kg; i.p. doses corresponded to 100 mg and 500 mg of herbal substance/kg	*In vivo* Rats (no details of the experiment) p.o. and i.p. Urine collection for 2 hours.	Bolle (1983)	p.o.: Urine excretion enhanced by +103% without affecting sodium and potassium in the urine during 2 h collection. i.p.: did not modify diuresis

Herbal preparation tested	Concentration / Dosage	Experimental model	Reference	Main outcome(s) according to the authors
Volatile fraction (with essential oil)				
Ononidis radix	The herbal substance was boiled with so much water that 100 g of the obtained decoction corresponded to 10g of the drug. The residue was filtered and administered to rats for checking its diuretic activity.	*In vivo* Rats In order to determine whether non-volatile ingredients, in the residue of boiling of the drug also have an influence on urine excretion in rats, the residue was administered to the animals and the diuretic output was measured with volumetric method.	Jaretzky and Neuwald (1937)	The decoction freed from the volatile ingredients had a diuretic output decreased with the time of boiling: 46% within 45 minutes, 34.5% within one hour and 17.3% within four hours. The authors supposed that restharrow root contains volatile substances which promote diuresis and water-soluble non-volatile substances which inhibited diuresis.

Assessor's comment:
Old pharmacological studies in rodents indicated dose-dependent aquaretic activity of restharrow root herbal teas. Based on comparison of the diuretic effect of infusions and the solution of the ash from the restharrow root, a possible influence of potassium salts in the effect was suspected. More recent studies on the diuretic effect of restharrow root infusion and on its detailed mechanism of action are not available.

3.1.2. Secondary pharmacodynamics

Analgesic activity *in vivo* carried out by hot plate test in mice, 1 h after i.p. and p.o. doses 100 and 500 mg/kg of a restharrow extract (no close data) not indicated statistical difference in the reaction time. Although the i.p. dose of phenylquinone (used as positive control) reduced the writing response (-80%) while oral response was ineffective (Bolle et al. 1993).

Anti-inflammatory activity, carried by the paw oedema test, induced by carrageenin in rats, was significantly ($p<0.05$) reduced (46%) by i.p. injection of the same restharrow extract after 3 hours following the dose of 500 mg/kg while no significant effects were obtained at the oral dose of 100 mg/kg (Bolle et al. 1993).

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Restharrow root hot water extracts and infusions in non-clinical studies exhibited diuretic effect (measured as urinary output) and saluretic effect (measured as urine sodium and potassium elimination) in rats and rabbits.

Direct antibacterial activity from *in vitro* studies of the restharrow extracts against bacterial species *E. coli* (uropathogenic) was found as moderate to weak although it was observed inhibition of adhesion of bacteria to urinary cells *in vitro* what needs further studies.

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

3.3.1. Single dose toxicity

No systematic data are available. Ethanol extract of *Ononis spinosa* root (no further information) showed no toxicity during the 14 days of observation when administered in rats and mice up to doses of 2 g/kg p.o. and i.p. (Bolle et al. 1993).

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

Aqueous extracts

Ononidis radix was tested for micronuclei formation in human cells *in vitro*. Micronuclei formation, in non–irradiated and radiated samples of isolated human lymphocytes with added dry 70% ethanol extract of Ononidis radix (DER and strength not described) was examined by Joksić et al. (2003) with the use of cytochalasin block micronucleus test (CBMN). Centromere-positive micronuclei were identified by fluorescence in situ hybridization with the use of DNA labelling with α-satellite digoxigenin. The extract, tested in lower concentrations (0.025, 0.05, 0.1 mg/ml) showed clastogenic properties inducing 5- to 6 fold increase in the incidence of micronuclei compared to the control although in a concentration of 0.2 mg/ml decreased slightly the incidence of micronuclei. The percentage of MNC+(fluorescent) micronuclei ranged from 18.8 to 23.8%, indicated that micronuclei originate by clastogenic mechanism (Joksić et al, 2003)

Table 6. Genotoxicity studies. Chromosomal aberrations (clastogenicity) study *in-vitro*.

Type of test/reference	**Test system**	**Herbal substance / preparatio**	**Concentrations/Concentration range/ Metabolising system**	**ResultsPositive/negative/ equivocal**

		n/ isolated compound		
Micronucleus test in non-irradiated and irradiated human lymphocytes *ex vivo*. Joksić et al. (2003)	PHA-stimulated human blood lymphocytes, micronuclei spontaneously occurring (negative control) and irriadiated and (positive control). The extract was added to the non-irradiated and irradiated samples	Dry herbal substance extracted with ethanol 70%, evaporated to dryness and added 20% lactose monohydrate.	Water solution of the ethanol 70% extract (+ lactose) in concentrations 0.025, 0.05, 0.1, 0.2 mg/ml (in vol. 50 µl) added to the irradiated and radiated sample. Irradiation dose as absorbed energy by the sample sample 2Gy (J/kg).	In the non-irradiated samples, the extract of Ononidis radix exhibited clastogenic properties at lower concentrations 0.025-0.1 mg/ml (5-to 6-fold increase of micronuclei when compared to the control with max. at 0.05 mg/ml. (Fluorescent micronuclei 18.7-23.8%). In higher concentration 0.2 mg/ml lowered slightly the incidence of micronuclei. In the irradiated samples added extract potentiated frequency at all concentration; at a concentration 0.2mg/ml 1.7-fold. (Fluorescent micronuclei 22.5%). Result positive/equivocal.

Assessor's comment:

The ethanol extract of Ononidis radix stimulated the formation of micronuclei in the experiment, although the level of clastogenic chromosomes was similar (about 20%) in both irradiated and non-irradiated human lymphocytes. The test system used in this study is not a standard procedure which is used for testing of the new medicines. The experiment has not been repeated, discussed or confirmed by the other authors, although isoflavones present in other legumes are also known to have clastogenic activity in vitro. The compounds responsible for the positive test in this experiment have not been identified.

To the best of our knowledge, the restharrow root residual does not contain any compound with known safety issue. At this time potential impact of the experiment on human safety has not yet been conclusively determined.

3.3.4. Carcinogenicity

No studies concerning carcinogenicity have been reported for the restharrow root or its preparations.

3.3.5. Reproductive and developmental toxicity

No studies concerning reproductive toxicity have been reported for the restharrow root or restharrow root preparations.

3.3.6. Local tolerance

No data on dermal route of administration are available

3.3.7. Other toxicity studies

Not available

3.3.8. Conclusions on toxicological data

Non-clinical information on the safety of *Ononis spinosa* L., radix, is scarce. Neither in the herbal substance nor in its preparations were identified constituents for which there would be any safety concerns.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

The following text is included in the monograph section 4.6 Fertility, pregnancy and lactation*: Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data available.*

The following text is included in the monograph section 5.3: *Adequate tests on genotoxicity with herbal teas have not been performed. Tests on reproductive toxicity and carcinogenicity have not been performed.*

3.4. Overall conclusions on non-clinical data

Limited pharmacodynamic data on restharrow root aqueous extracts and other extracts indicate moderate diuretic effect. Possible anti-adhesive effects on bacteria in tests in vitro need confirmation in urinary ways *in vivo*. Restharrow root specific data on pharmacokinetics and interactions are not available.

The data on toxicology of restharrow root and restharrow root preparations are very limited. Only data on one single dose 2 g/kg of ethanol extract are available. Studies with aqueous preparations of the roots are lacking.

Neither the chemical composition nor the long-term use widespread in the European Union suggests a risk associated with the use of restharrow root or its preparations. Tests on reproductive and developmental toxicity and carcinogenicity have not been reported in the scientific literature.

The published non-clinical data on preparations with diuretic activity are mostly limited to old scientific papers and mainly from the 20th century. Diuretic effects of *Ononis spinosa* L, radix aqueous extracts are discussed in more detail in a 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.

Results from relevant experimental studies on restharrow root are limited and not required.

Specific data on pharmacokinetics and interactions are not available.

As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. Due to a lack of conclusive genotoxicity testing a list entry cannot be recommended.

4. Clinical Data

There are no clinical studies performed with mono-preparations of *Ononis spinosa* L., root.

4.1. Clinical pharmacology

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

No relevant data are available.

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 pharmacodynamics.

4.2. Clinical efficacy

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 clinical data on mono-component products containing Ononidis herba preparation have been available before and over a review period since 2014 to 2023.

Vahlensieck et al. (2019) reanalysed data from placebo-controlled, parallel-group, double-blind trial (phase III) comparing a fixed combination of extracts of Ononidis radix (80 mg), Orthosiphonis folium (90 mg) and Solidaginis herba (180 mg) to placebo in 200 women with acute lower uncomplicated UTI (posology: 3 times daily for 7 days). When the authors used new definition of the Acute Cystitis Symptom Score (ACSS) in a group of patients with evaluable microbiologic data (n = 122), they found the decrease of the mean sum-score of three typical ACSS-adjusted symptoms significantly superior in the herbal product over placebo already after Day 1 ($p = 0.0086$) and on Day 7, with the average difference −1.9 score points ($p < 0.0001$). The superior therapeutic effect was mainly caused by better response rates on 'dysuria' (group difference: −29.4%, $p = 0.0042$) and significantly fewer patients of the product group required antibiotic therapy (15.3% vs. 49.2%, $p = 0.0001$).

Assessor's comment:

The only referred clinical trial was on combination product containing restharrow root extract and the contribution of this constituent to the therapeutic effect has not been measured.

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

No clinical studies in special populations are reported.

4.4. Overall conclusions on clinical pharmacology and efficacy

No relevant data are available on clinical research assessing the effects of restharrow root. Therefore, available data do not meet the criteria for "well established medicinal use" in accordance with Directive 2001/83/EC, so the well-established use cannot be supported.

Overall, the medicinal products of Ononidis radix (restharrow root) are based on long-standing use and has to be regarded on the traditional use.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from market overview

No data available.

5.2. Patient exposure

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

5.3. Adverse events, serious adverse events and deaths

A search in the EudraVigilance database was done in August 2023. It resulted in 1 report on Ononidis radix (restharrow root). The case was reported by the pharmacist to German authority in September 2018 on a woman (74 years, with the history of gastrectomy) who used an unknown product with restharrow root for peripheral swellings and experienced gastric pain, nausea and vomiting. The symptoms resolved after discontinuing of the therapy. Overall, no new safety issues could be identified from reports in the EudraVigilance database up to August 2023.

A search in VigiBase resulted in two reports. One report on patient in Korea with symptoms of belching after use of restharrow root, classified as suspected and second was on a combination product and also upper mentioned case of in Germany. No new safety issues could be identified from reports.

Mazzanti et al. (2019) reviewing data on monitoring herbal supplements in Italy (Phytovigilance system, from July 2010 till October 2017) mentioned three cases with concomitant use of restharrow. In one case of woman (29 years old) hospitalized because of acute hepatitis. the patient had taken products: food supplement declared to contain *Ononis spinosa* root, together with 17 other herbs, which were consumed for 15 days, concomitantly medicinal products with ketoprofen and acethyl salicylic acid and other propolis products. In second case, female patient (61 years old) took a food supplement with undeclared part of restharrow, and product contain also gymnema, coleus, butcher's-broom, chitosan, griffonia, Garcinia cambogia, boldo and gotu cola. After 150 days of consumption, abnormal thyroid function was observed as adverse reaction. Patient also used other mediciations: atorvastatin, olmesartan plus hydrochlorothiazide, and cardio-aspirin. Third case was noticed in 19 years old female patient with adverse reaction: multiple spontaneous ecchymoses caused after 28 days of use a food supplement with more that 6 plants extracts and vitamins and minerals, including undefined restharrow root dry extract.

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

Assessor's comments:

Due to the simultaneous use of medicinal products such as ketoprofen, acethyl salicylic acid, atorvastatin, olmesartan plus hydrochlorothiazide, it is not possible to confirm the casual relationship with one of the ingredients of the supplement used at the same time. The adverse reactions occur with food supplements with complex ingredients in which restharrow was only one ingredient among others.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

No clinical studies in children or adolescents are available.

In the marketed preparations and in *Standardzulasssungen* (Braun, 2011), the dosages are recommended for adolescents and adults only. The dosage for adolescents is the same as for adults and elderly.

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

5.5.2. Contraindications

Contraindications were not known, with a note: No irrigation therapy in case of oedema due to impaired heart and kidney function (Blumenthal et al. 1998). Gehrmann et al. (2005) gives information that restharrow is not useful for dehydration or oedema due to reduced heart or renal activity. Gruenwald et al. (2004) also included the warning to contraindications stating that the drug should not be used in the presence of oedema resulting from reduced cardiac and renal activity. This was reflected on labelling of products available on the markets (Table 1) and included in the first version of the monograph section 4.4 i.e. as follows: "Conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease)."

In the revision of the monograph, to harmonise with other EU herbal monograph with the same therapeutic area, the information: *Because adequate fluid intake is required during treatment, the use of Ononis spinosa L., radix, is not recommended for patients with conditions where reduced fluid intake was advised,* was placed in section 5.5.3 on warnings, below.

The only contraindication is proposed: *Hypersensitivity to the active substance*.

5.5.3. Special warnings and precautions for use

The single Restharrow root product available on pharmaceutical market in Europe (registered nationally in March 1995 in Poland) has been used in a form of infusion and its use does not need additional watering. Also, in historical sources the Restharrow root has been decocted and taken as a diuretic in single doses 50-180 ml, up to a daily dose volume of about 360 ml (Muszyński 1954, Gobiec & Konieczny 1963, Ożarowski 1978), without suggestion that the additional fluid intake as such is necessary for *the flushing therapy* in the traditional use. However, the use of sufficient fluid intake during the use of the Restharrow root herbal teas is included in the established indication: *Traditional*

herbal medicinal product used for the relief of symptoms associated with minor urinary tract complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine. Normal reference values for daily water intake in EC countries are 2.0 L in woman and 2.5 L in man (EFSA, 2010). The traditional use of the infusions remains within the range of normal water consumption. Additional water consumption or reducing fluid intake is advised to be consulted with a doctor because it is binded with proper daily intake of electrolytes.

In bibliographic sources is mentioned, without any further specification, that restharrow root should not be used in the presence of water retention symptom (oedema) due to impaired cardiac or renal function and dehydration (Blumenthal et al. 1998; Blaschek 2016; Gruenwald et al. 2004; Gehrmann et al. 2005) and also in Standardzulassung 2004 (*If there is fluid retention [edema] as a result of restricted heart or kidney activity, flushing therapy is not indicated*).

In the present Monograph the following warnings are included:

The use in children under 12 years of age has not been established due to lack of adequate data.

Because adequate fluid intake is required during treatment, the use of Ononis spinosa L., radix, is not recommended for patients with conditions where reduced fluid intake was advised.

If urinary tract complaints worsen and symptoms such as fever, dysuria, spasm, or blood in the urine occur during the use of medicinal product, a doctor or a qualified health care practitioner should be consulted.

Duration of use

In the monograph adopted in 2014 in p. 4.2. Posology and method of administration it was established, on a base of documented medicinal use of products present on the EU market, the following duration of use: *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*. In the Standardzulassung 2004 the warning concerned situations when blood was in the urine, or a fever or the symptoms persisted for more than 7 days, and patient was advised to consult a doctor. Although in the Stadardzulassung from 1986 was also general information justifying the period of use: p. 6.4 Duration of use: *Tea made from restharrow root should only be used for a few days as its effectiveness wears off. Use can be continued after a break of several days.* This is a specific feature of the restharrow root and the data on documented use did not change over the review period (2014-2024).

5.5.4. Drug interactions and other forms of interaction

No data are reported.

5.5.5. Fertility, 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.

5.5.6. 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.

5.5.7. Effects 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 restharrow root.

5.5.8. Safety in other special situations

Not available.

5.6. Overall conclusions on clinical safety

No data for a posology in children from clinical trials are available. As the use 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.

If the symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

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 commonly accepted handbooks and confirmed by presence in use of products with restharrow root; and aspects of medicinal use were regulated on national level. Comminuted herbal substance of restharrow root used as herbal tea, as included in the monograph, fulfils the requirement of Directive 2004/24/EC for being in medicinal use in traditional herbal medicinal products 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 availability of pharmacological data.

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

No studies on carcinogenicity and reproductive and developmental toxicity have been reported in the scientific literature. Due to lack of adequate genotoxicity data, as proposed in the HMPC guideline, a European Union list entry for *Ononis spinosa* (L.), radix cannot be recommended. Oral administration of Ononidis radix can be regarded as safe at traditionally described and used doses in adults and adolescents. As no data for a posology in children (and no data from clinical trials) are available for diuretic treatment, the use of restharrow root in self-medication for the children under age of 12 years is not recommended.

Due to lack of data restharrow root cannot be recommended in pregnancy and lactation.

One contraindication is for products on the market: Hypersensitivity to the active substance.

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.

Based on product on the market, regulatory and bibliographic data *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 used for the relief of symptoms associated with minor urinary tract complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine.

Available data are sufficient to establish a European Union herbal monograph on the traditional use of restharrow root.

Traditional use monograph

The requirements for traditional medicinal use according to Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC are considered fulfilled. It has been demonstrated that *Ononis spinosa* L., radix (restharrow root) has been in traditional medicinal use throughout a period of at least 30 years, including at least 15 years within the EU/EEA, with an acceptable level of safety for:

Herbal substance/ preparation	**Indication**	**Therapeutic area for browse search**	**Posology and method of administration**	**Duration of use**
Ononis spinosa L., radix (restharrow root) Herbal preparations: Comminuted herbal substance	Traditional herbal medicinal product used for the relief of symptoms associated with minor urinary complaints in addition to the general recommendation of a sufficient fluid intake to increase the amount of urine.	Urinary disorders and genital disorders	Adolescents, adults and elderly Herbal tea: 2 – 4 g of comminuted herbal substance in 150 ml of boiling water as an herbal infusion up to 3 - 4 times daily corresponding to the maximum daily dose of 12 g. The use in children under 12 years of age is not recommended Method of administration Oral use.	Duration of use 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.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC.

Annex

List of references