07 July 2021
EMA/HMPC/113793/2021
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Agropyron repens* (L.) P. Beauv., rhizoma

Draft

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)		*Agropyron repens* (L.) P. Beauv., rhizoma
Herbal preparation(s)		a) Comminuted herbal substance b) Liquid extract (DER 1:1), extraction solvent ethanol 20-25% V/V c) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 40% V/V
Pharmaceutical form(s)		Comminuted herbal substance as herbal tea for oral use. Herbal preparations in liquid dosage forms for oral use.
First assessment	Rapporteur	E Widy-Tyszkiewicz
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Note: This draft assessment report is published to support the public consultation of the draft European Union herbal monograph on *Agropyron repens* (L.) P. Beauv, rhizoma. 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 public statement.

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1. Introduction

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

- Herbal substance(s)

Couch grass rhizome (*Graminis rhizoma*) is defined in the European Pharmacopoeia monograph ref. 04/2011:1306, as the whole or cut, washed and dried rhizome of *Agropyron repens* (L.) Beauv. (*Elymus repens* (L.) Gould); the adventitious roots are removed (Pharm. Eur. 10.0).

On a base of new classification of grasses growing in California by Gould FW (1947) it was suggested to rename also *Agropyron repens* (L.) P. Beauv. for *Elymus repens*. The change was accepted by many botanists in Europe (Devey, 1983; Melderis & McClintock, 1983; Szczepaniak, 2009), was implemented by international plant databases and started to be used in Europe. Botanical database (IPNI) uses a name Elymus repens (L.) Gould as a correct botanical name. The new classification included growing in Europe *Agropyron repens* species into *Elymus* genus.

Couch grass rhizome (*Agropyri rhizoma*, *Graminis rhizoma*) consist of rhizomes collected as underground parts of perennial grasses (couch grass), based on Beauvois classification (1812). The new classification is not easy for use when the herbal substance is harvested. Field observations in Europe don't give us solid evidence for easy differentiation of the two groups of genus Elymus and the Agropyron (Mizianty & Szczepaniak 1997). They rather form mixed complexes. Plants of both groups are closely related, moreover extensively hybridize (Hansen, 1960; Kasaeva, 1970; Szabo,1981; Szczepaniak et al. 2007, Urfusova, 2020). The European Pharmacopoeia in a couch grass rhizome monograph uses the name *Agropyron repens* (L.) P. Beauv. although botanical databases (IPNI) uses a name *Elymus repens* (L.) Gould as a correct botanical name.

The review refers to data on the species which are covered by the European Pharmacopoeia monograph: *Agropyron repens* (L.) P. Beauv. and *Elymus repens* (L.) Gould (=*Triticum repens* (L.) Beauv.; = *Elytrigia repens* (L.) Nevski; = *Elytrigia repens* (L.) Desv. ex Nevski).

The material of commerce in European Union is mostly distributed from Eastern and South-Eastern European countries. Commonly used in Europe material is described as the shiny yellowish, light brown or yellowish brown rhizome and stem pieces are hollow, longitudinally furrowed and about 2-3 mm thick. At the unthickened nodes are the remains of very thin, more or less branched roots and fiber-like scales. The taste is bland and slightly sweet (Wichtl 1994).

Constituents

Polysaccharides: Polysaccharide fructosan, known earlier and named by Müller (1873) as triticin, was studied by Arni and Percival (1951) through chemical derivatisation. It constitutes about 12% of dried couch grass rhizome mass (extracted with cold water); its molecule is built of about 30 fructose units and the fructofuranose aggregate is terminated by linked glucose residue. The polysaccharide easy hydrolyses in hot or boiling water.

Mono- and disaccharides: Extraction of the dried powdered couch grass rhizome with 80% of water ethanol by Arni and Percival (1951) gave 17.1% of fructose and 3.4 % of glucose and a disaccharide hydrolizing mainly to glucose and fructose with xylose.

Sugar alcohols: Mannitol (suggested to be formed by boiling) and inositol, were mentioned by Berger in his manual (1960) after the former authors. The information have been cited in Hänsel (1992), Nagell A in Wichtl (2004). The information on mannitol (2-3%) was cited by Stoop et al. (1996). There is no more recent data.

Free and binded phenolic acids: Small amounts of vanillin monoglucoside (Karrer, 1958), vanillic acid, hydroxycinnamic acid alkyl ester are reported by Hagers Handbuch (1992), Hiller (1999), Bruneton (1999). Whitehead et al. (1982, 1983) detected p-hydroxybenzoic, vanilic and p-coumaric acids (p-hydroxycinnamic acid) in alkalic extracts of soils and of roots of *Agropyron repens*. More than half of it was in binded forms. In Siberian couch grass *Elytrigia repens* (L.) Nevski, Petrova et al. (2009) also detected (by chromatography) free chlorogenic and p-hydroxycinnamic (p-coumaric) acids.

Phenolic acid esters: Light petroleum and dichloromethane extracts of *Agropyron repens* dried rhizomes, chromatographed by CircularTLC gave: (E)-and (Z)-p-coumaric acid hexadecyl ester and (E)-and (Z)-p-coumaric acid-16-hydroxyhexadecylester (Koetter et al. 1993) and bis-(E)- and bis-(Z)-diesters of analogous structure (Koetter et al. 1994). Acetone extract separated by centrifugal partition chromatography gave also (E)-p-coumaric acid octyl ester and (E)-cinnamic acid hexadecyl ester (Beydokhti et al. 2017).

Flavonoids: Weston LA et al. (1987), searching for couch grass substances responsible for their allelopathic activity (detrimentous influence on other plants), found in ether fraction of water extract, tricin (5,7,4'-trihydroxy-3',5'-dimethoxyflavone). Petrova et al. (2009) detected rutin, hyperoside and baicaleine (by chromatography), in the Siberian couch grass.

Plant growth regulators: Hagin (1989), found the 5-hydroxyindole-3-acetic acid (5-HIAA) and 5-hydroxytryptophane (5-HTP) accumulated in a whole couch grass plant in a glycosidic forms (Mw range 353 – 4159). The compounds are known to be plant regulators and may be responsible for the observed inhibitory effects for growth of seedling of corn and bean. Korhammer and Haslinger (1994) identified the 3-indole acetic acid, which may be responsible for disturbing seeds germination in surrounding soil. However there is no evidence for influence of the plant regulators to animal and human health.

Silicic acid and silicates: Total Si level in dried rhizome of Agropyron repens gathered at various stages of its vegetation between June and October was measured in the range of 0.34-0.43 %. The maximum silicates concentrations in decoction of 3 g of rhizomes in a glass (200 ml) of water was estimated to contain 2.6 mg of assimilable silicon equivalent to 5.6 mg of $Si0_2$ (Pasławska and Piękoś, 1976).

Antraquinones: They were detected in small amounts (RP18-HMPL with LCMS or GCMS) in *Graminis rhizoma* (Mueller et al. 1999): total (0.2-0.7 mg/kg): emodin (0.06-0.2 mg/kg), chrysophanol 0.05-0.2 mg/kg, physcion 0.08-0.3 mg/kg.

Volatiles: Treibs (1947) obtained of "Queckenwurzel" volatile oil almost exclusively consisted of aromatic en-yne hydrocarbon named "agropyren" (suggested to be 1-phenylhex-2-en-4-yne, $C_{12}H_{12}$). The substance was supplied to several laboratories and exhibited promising antibiotic and antifungal activities. Boesel and Shilcher (1989) repeating the distillation of Graminis rhizoma failed in obtaining agropyrene in the essential oil. Their essential oil fraction (0.017%) contained 43.9% of compounds of the essential oil and 36% of fatty acids. The essential oil contained 10.8% of carvacrol, trans-anethole (6.8%), carvone, (5.5%) thymol (4.3%), menthol (3.5%), menthone (1.4%) and and p-cymene (1.1%) and sesquiterpenes (0.85%). (In later years the Treibs's "agropyren" was found only in Asian wormwoods oils, like *A. scoparia* (Goryaev et al, 1981).

- Herbal preparations
  - Comminuted herbal substance
  - Liquid extract (1:1) extraction solvent: ethanol 20-25% V/V
  - Tincture (1:5) extraction solvent: ethanol 40% V/V

- 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.

The herbal substance is commonly used as a part of herbal tea combinations. See also a monograph for Species diureticae.

Agropyri repentis rhizoma (*Graminis rhizoma*) is contained in typical herbal tea combinations contained in national monographs of Polish Pharmacopoeia.

Species laxantes contains: 30.0 parts of *Graminis rhizoma*, together with *Frangulae cortex* 20.0 p., *Carvi fructus* 20.0 p., *Lini semen* 10.0 p., *Menthae piperitae folium* 20.0 p.

Species metabolicae I contains: 30.0% of *Graminis rhizoma*, together with *Violae tricoloris herba* 20.0 p., *Cichorii radix* 20.0 p., *Urticae folium* 17.0 p., *Phaseoli pericarpium* 10.0 p., *Rhei radix* 3.0 p. *Species metabolicae* II contains: *Graminis rhizoma* 35.0 p., *Equiseti herba* 34.0 p., *Taraxaci officinalis herba cum radice* 20.0 p., *Taraxaci officinalis radix* 20,0 p., *Frangulae cortex* 1.0 p.

1.2. Search and assessment methodology

The search was undertaken to find all new available data, specially of the period of the last decade, but also data unavailable earlier.

The search covered: Books, Book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations (see List of references).

Search engines used: Google, Google Scholar, Bing

Scientific databases: Scopus, ScienceDirects, Clarivate Web of Science, SciFinder, EBSCOhost

Medical databases: Embase, Medline, PubMed, The Cochrane Library, Polska Bibliografia Lekarska

Toxicological databases: PubMed. Extensive bibliographic search for with different combinations of key words: Agropyron (Elymus) repens + safety, Agropyron (Elymus) repens + toxicity, Agropyron (Elymus) repens + poisoning.

Pharmacovigilance resources: Pharmacovigilance data (data from EudraVigilance, VigiBase, national databases, EVDAS EMA)

Data from EU and non-EU regulatory authorities: European Union pharmaceutical market overview (with the use of exchange information) showed one more product which is now present on the German market. The product was present under a former national law called 'Standard Marketig Authorisation', with the dosage based on German Commission E.

Other resources: Extensive bibliographic search for with different combinations of key words: Agropyron repens, Elymus repens, Elytrigia repens, Tritici + rhizoma, Agropyri +rhizoma, Graminis + rhizome, couch grass, Quackgrass, Twich, Agropyron repens + safety, Agropyron (Elymus) repens + toxicity, Agropyron (Elymus) repens + poisoning, Agropyron (Elymus) clinical, Agropyron (Elymus) + trials, triticin, tricin, agropyren, agropyrene.

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

Active substance	Indication	Pharmaceutical form	Regulatory Status
WEU			
Agropyri repentis rhizoma	To achieve flushing of the urinary tract and for prevention of renal gravel.	Herbal tea Adults and adolescents ≥ 12 years: Pour about 150 ml boiling water over about 2 to 3 teaspoons (about 5 to 10 g) of dried coach grass rhizome. Steep for 10 min. and then pass through a tea strainer. Unless otherwise prescribed, drink 1 freshly prepared cup of tea infusion four times daily. [Single Dose 5-10 g, Daily Dose 20-40 g] 3 g of comminuted herbal substance in 150 ml boiling water as a herbal infusion 2-3 times daily corresponding to a daily dose of 6-9 g. [Single Dose 3 g, Daily Dose 6–9 g] If the symptoms persist longer than 7 days, a doctor should be consulted.	1986, DE, Standard Marketing Authorisation (Anl. St. Zul. 1986, 154 *Queckenwurzelstock* Published March 12, 1986) 1986 - 2004 2004- 2020
TU			
Agropyron repens (L.)	Traditional herbal	Oral liquid (100 ml	1970, DE, 2007 TUR

Active substance	Indication	Pharmaceutical form	Regulatory Status
Bouv., rhizoma, liquid extract (1:1), extraction solvent: ethanol 20% V/V	medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.	contain 100 ml liquid extract) Adults: 3 ml 3 times daily, corresponding to a daily dose 9 g of herbal substance If the symptoms get worse or persist longer than 14 days, a doctor should be consulted.	
Agropyron repens (L.) Bouv., rhizoma, cut substance for herbal tea	Traditional herbal medicinal product used as an adjuvant in mild urinary complaints as a mean increasing of amount of urine and improving flow in urinary ways.	Since 2016 in line to the EU monograph. 5 g of couch grass rhizome pour with a glass of boiling water, infuse 15 min under cover and strain. Drink a glass of the infusion up to 4 times a day.	1992, PL, TUR 2016
Agropyron repens (L.) Bouv., rhizoma, cut substance for herbal tea	Supplementory as mild diuretic in minor inflammatory states of urinary ways	Two teaspoons[1] (claimed to be about 3 g) in 1 cup of tea (claimed to be 100 ml) for infusion; 3 times a day.	1992, PL, NA

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

Assessor's comment: The herbal tea which is now reported to be authorized in Germany, was declared also during the first assessment but was not included. Single dose of this product is 3 g, daily dose 6 – 9 g. The daily dosage of this product in the declared indications is lower than in the current monograph (10-20 g) and lower than in a regulation on Standard Marketing Authorisation (Graminis rhizoma. Anl. St. Zul. 1986, March 12 1986) where was of 2-3 teaspoons. Taking into account that the average filled teaspoons, used over a period of last 5 decades in Poland corresponded to 6.6 - 9.4 g and even if the 2-3 teaspoons were flat filled, as referred by Nagell in Wichtl manual, they corresponded to 3.0-4.5 g and the use of it 3 times daily gives a daily dose 9.0 – 13.5 g.

The use of products in similar single doses was found also in other products over a period of last 30 years in European Union countries. The dosage of the product was included changing the monograph in the point 4.2. Posology and method of administration, from:

a) Herbal tea: 3-6 g of comminuted herbal substance in 250 ml boiling water as a herbal infusion several times daily corresponding to a daily dose of 10-20 g.

[1] One average teaspoon corresponded to 3.3±0.2 g to 4.7±0.3g of couch grass root.

to: Herbal tea: 3 - 6 g of comminuted herbal substance in 250 ml boiling water as a herbal decoction or infusion 2 to 4 times daily corresponding to a daily dose of 6 - 24 g.

The product available in Germany is accepted for use by adolescents and needs consultation with a doctor after one week of use.

The liquid extract in the current monograph have been used in a dosage of 4 – 8 ml 2 – 4 times daily, on a base of British tradition. Nowthe liquid extract (DER 1:1), prepared with 20% (V/V) ethanol is reported to be registered in Germany in a dosage of 3 ml, used 3 times daily. Due to the presence of this product on the market, an appropriate extension of the range of doses can be proposed: 3 – 8 ml 2 – 4 times daily.

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

The herbal substance is commonly used as a part of herbal tea combinations. See also a monograph for Species diureticae.

Agropyri repentis rhizoma (=*Graminis rhizoma*) is contained in typical herbal tea combinations contained in national monographs of Polish Pharmacopoeia. *Species laxantes* contains: 30.0 parts of *Graminis rhhizoma*, together with *Frangulae cortex* 20.0 p., *Carvi fructus* 20.0 p., *Lini semen* 10.0 p., Menthae piperitae folium 20.0 p. *Species metabolicae* I contains: 30.0% of *Graminis rhizoma*, together with *Violae tricoloris herba* 20.0 p., *Cichorii radix* 20.0 p., *Urticae folium* 17.0 p., *Phaseoli pericarpium* 10.0 p., *Rhei radix* 3.0 p. *Species metabolicae* II contains: *Graminis rhizoma* 35.0 p., *Equiseti herba* 34.0 p., *Taraxaci officinalis herba cum radice* 20.0 p., *Taraxaci officinalis radix* 20,0 p., *Frangulae cortex* 1.0 p.

In Poland and Latvia a herbal preparation have been traditionally used in a form of oral paste containing in one 5 g dose 3.36 g of soft combined extract (1:1.3-1.6) of: *Agropyri repentis rhizoma* 12.5 parts; *Allium cepae squamata* 5.0 p.; *Betulae folium* 10.0 p.; *Foenugraeci semen* 15.0 p.; *Petroselini radix* 17.5 p.; *Solidaginis virgaureae herba* 5.0 p.; *Equiseti herba* 10.0 p.; *Levistici herba* 10.0 p.; *Polygoni avicularis herba* 15.0 p. Extraction solvent : ethanol 45% (V/V). The product have been on the market since 06.01.1961.

In Belgium Agropyri repentis rhizoma (under the old name *Triticum repens*) was been in use as a component of a herbal tea combination containing: *Hyssopus officinalis*, herb 100 mg/g; Senna, leaf 300 mg/g; *Rosmarinus*, leaf 150 mg/g; *Triticum repens*, rhizom 150 mg/g; *Vitis vinifera* L., leaf 300 mg/g. Single dose 2g. Indication: Herbal tea for circulatory disorders. The product was been on the market from 01.04.2007 until 14.04.2017.

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

In Italy is on the market dietary supplement, declared to containin couch grass dry extract (Agropyrum repens P.B.) 1:4, extraction solvent: water, 100mg/tablet and potassium citrate 24 mEq/tablet. Posology: two times daily. Product was clinically tested in Italy (Brardi S et al., 2012).

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

Not applicable

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

The herbal substance have been used commonly along Europe in folk medicine, in Greece for urinary tract disorders (cystitis, kidney stones, prostate enlargement) and also for gastrointestinal diseases like gallstones, in arthritis and rheumatism and to reduce increased cholesterol levels (Hanlidou et al.

2004); in Bulgaria and Italy, couch grass rhizome was traditionally used mainly as diuretic and also laxative (Leporatti and Ivancheva 2003, Pieroni et al. 2002).

The herbal substance is well known for many centuries and mentioned in several pharmacognosy and phytotherapeutical handbooks such as: Jaretzky (1937), Madaus (1938), Barnes et al. (2002), Bradley (2006), Duke's Handbook of Medicinal Herbs (2002), Hagers Handbuch (1949), Wallis (1955), Karsten (1956), Hoppe (1958), Berger (1960), British Herbal Pharmacopoeia (1974 and 1983), Borkowski (1974), Ożarowski (1976 and 1978), Schulz et al. (1998), Newall et al. (1996), Hiller and Melzig (1999), Wichtl (1994, 2004), PDR for Herbal Medicines (2000, 2004).

The herbal substance used in European countries met the definition in the national pharmacopoeias; Polish [*Rhizoma Agropyri*] (1954), German, Austrian, Swiss [*Rhizoma graminis*], French [*Chiedent*], Belgian [*Tritici Rhizoma*] (Hänsel, 1992) and later was included in the European Pharmacopoeia. *Couch grass rhizome* consists of the whole or cut, washed and dried rhizomes of *Agropyron repens* (L.) P. Beauv. It was a subject of national pharmaceutical regulations: German *Standardzulassung* 154 *Queckenwurzelstock* (1986), German Commission E Monograph (1990, 1992), reference ESCOP Monograph (2009).

A general rule in pharmacognosy was that hard herbal substances like *lignum*, *cortex*, *root*, *rhizoma*, were decocted (Muszyński 1954). The same it is seen in Karsten Pharmacognosy and, Hager's Handbook.

Table 2: Overview of historical data

Herbal preparation	**Documented use / Traditional use**	**Strength, posology duration of use**	**Reference**
Agropyron repens (L.) Beauv., herbal tea decoction	Mild diuretic and diaphoretic. Used also in chronic kidney and liver diseases	20g/250 ml, use up to 4 times daily. SD 20 g, DD 80 g	Muszyński 1954 (bibliographic)
Agropyron repens (L.) Beauv., herbal tea decoction (1:10)		20 g/200 ml (decoction 1:10). SD 20 g	Farmakopea Polska III 1954 (regulatory)
Agropyron repens (L.) Beauv., herbal tea decoction (1:10).		20 g/200 ml (decoction 1:10). Used up to 4 times daily. SD 20 g, DD 80 g	Informator Terapeutyczny USL 1955 (regulatory)
Agropyron repens (L.) Beauv., herbal tea decoction 10-20 g/200ml	Used in gastrointestinal disorders, liver and kidney diseases, especially in urolithiasis	Decoction 10-20 g/200 ml. SD 10-20 g, DD 40-80 g	Informator Terapeutyczny USL 1959 (regulatory)
Rhizoma agropyri FPIII), dried, 1 tablespoon of cut rhizome in 250 ml of water in decoction	Diureticum, metabolicum, depurativum	½ of the glass of the decoction (corresponding to 1/2 tablespoon) taken 2 – 3 times a day. SD 5.6 g, DD 11.3-16.9 g	Gobiec K (red.) 1963 Receptariusz Zielarski (bibl.)

Herbal preparation	Documented use / Traditional use	Strength, posology duration of use	Reference
Rhizoma agropyri, dried, cut in infusion 1 tablespoon (average 11.3g[2])/250 ml	Diuretic in mild kidney diseases and oedemas. Supplementary in cystitis and urelithiasis	Drink 1/3-2/3 of the glass, 2 – 4 times daily. SD 5.3-11.3 g DD 6.6-40 g	Ożarowski 1976 (bibl.)
Rhizoma agropyri, dried, cut in decoction 10-15g g/250 ml	*Metabolicum* in mild hepatic insufficiency and in a weak diuresis. Diuretic adjuvant after chemotherapy and therapy with antibiotics	Drink 1/2-2/3 of the glass of decoction 2 – 4 times a day. SD 5.6-11.3 g, DD 11.3-45.2 g	Ożarowski 1978 (bibl.)
Rhizoma agropyri (=Rhizoma tritici), dried, cut; decoction or infusion, 1 spoon (11.3 g) in 250 ml	Urolithiasis, cystitis in children	Infusion or decoction of 1 spoon (11.3 g) of the herbal substance in 250 ml of water, used up to 4 times. DD up to 40 g	Olechnowicz-Stępień, 1986 (bibl.)
Rhizoma tritici, dried rhizome in a dose 4-8g.	Indications: cystitis, urethritis, prostatitis. Benign prostatic hypertrophy. Renal calculus. Lithuria. Specific indications: Cystitis with irritation or inflammation of the urinary tract.	4-8 g thrice daily. SD 4-8 g, DD 12-24 g	British Herbal Pharmacopoeia, 1974, 1983 (bibl.)
Rhizoma tritici, dried rhizome in a dose 4-8g in decoction.	Indications: cystitis, urethritis, prostatitis. Benign prostatic hypertrophy. Renal calculus. Lithuria. Specific indications: Cystitis with irritation or inflammation of the urinary tract.	4-8 g thrice daily. SD 4-8 g, DD 12-24 g	British Herbal Pharmacopoeia, 1974, 1983 (bibl.)
Rhizoma tritici, liquid extract 1:1 in 25% ethanol.	Indications: cystitis, urethritis, prostatitis, . Benign prostatic hypertrophy. Renal calculus. Lithuria. Specific indications: Cystitis with irritation	Dose 4-8 ml, thrice daily	British Herbal Pharmacopoeia, 1974, 1983 (bibl.)

[2] 1 tablespoon of a dried cut couchgrass rhizome, on a base of the average content of spoons used in last 30 years in Poland can be estimated between 11.8 ± 0.8 g and 10,8 g ± 0.8. The spoon contented in average about 11.3 g.

Herbal preparation	Documented use / Traditional use	Strength, posology duration of use	Reference
	or inflammation of the urinary tract.		
Rhizoma tritici, tincture: 1:5 in 40% ethanol	Indications: cystitis, urethritis, prostatitis. Benign prostatic hypertrophy. Renal calculus. Lithuria. Specific indications: Cystitis with irritation or inflammation of the urinary tract.	Dose 5-15 ml, thrice daily	British Herbal Pharmacopoeia, 1971, 1983 (bibl.)
Graminis rhizoma for herbal tea, decoction	To increase the amount of urine in inflammatory states of the lower urinary tract and as a complement to the treatment of the upper respiratory tract inflammations	About 2 to teaspoons l (approx. 5 to 10 g) of couch grass are covered with boiling water (approx. 150 ml) and passed through a tea strainer after 10 minutes. Unless otherwise prescribed, up to 4 times a day. Daily dose 20-40 g	German Standard License (*Anl. St. Zul.*) (regulatory) 1986 (Wichtl 2004)
Graminis rhizoma. Comminuted herb, decoctions and other galenical preparations for internal use	Irrigation therapy for inflammatory diseases of the urinary tract and for the prevention of kidney gravel	Daily dosage 6 – 9 g	German Commission E. *BAnz*, Feb. 1 1990 (regulatory)
Agropyri repentis rhizoma, comminuted dried rhizome for infusion or decoction	Traditionally in inflammatory ailments and infections of the urinary tract, particularly cystitis but also urethritis, prostatitis and irritable bladder	Dose 4-8 g for infusion or decoction used 3 times daily. DD 12-24 g	British Herbal Compendium Bradley P. (red.) Vol. II, 2006
Graminis rhizoma, herbal tea infusion	Irritable bladder and other urinary tract disorders	Adults and children over 12 years. 5-10 g daily as an infusion.	ESCOP Monographs. Second edition. Supplement. 2009
Graminis rhizoma. Fluid extract (1:1), 20-25% etnhanol (V/V)	Irritable bladder and other urinary tract disorders	Adults and children over 12 years. 2-4 ml three times daily	ESCOP Monographs. Second edition. Supplement. 2009
Graminis rhizoma.	Irritable bladder and	Adults and children	ESCOP Monographs.

Herbal preparation	Documented use / Traditional use	Strength, posology duration of use	Reference
Tincture (1:5), ethanol 40% (V/V)	other urinary tract disorders	over 12 years. 5-15 ml three times daily	Second edition. Supplement. 2009

2.3. Overall conclusions on medicinal use

Couch grass rhizome have been undoubtedly used in medical traditions and folk medicine over the European countries for many decades.

Daily dosing of the couch grass rhizome in continental Europe, in the period from the 1950s to the 1990s was at the dosage of 40 g and was lowered 4 times, to the dosage of 6-9g daily, as a result of regulatory activity in Germany, being the consequence of use the Commission E monograph. The reports justifying this change were not available. Some countries followed the German regulatory action, reducing dosages accordingly. Despite of this, traditional dosages are still recommended in textbooks based on *Standardzulassung* for *Queckenwurzelstock* of 1986. In the British tradition, for the entire period of 30 years, the daily dose was 24 g. In the first edition of HMPC monograph daily dosage was established at a level of 10-20g of herbal substance.

The point 4.2 Posology and method of administration, is changed accordingly from:

a) Herbal tea: 3-6 g of comminuted herbal substance in 250 ml boiling water as a herbal infusion several times daily corresponding to a daily dose of 10-20 g.

to: Herbal tea: 3-6 g of comminuted herbal substance in 250 ml boiling water as a herbal decoction or infusion 2 to 4 times daily corresponding to a daily dose of 6-24 g.

The product is accepted for use in adolescents.

During the review period from Germany, the liquid extract (DER 1:1), prepared with 20% (V/V) ethanol, was reported to be registered with the posology of a single dose of 3 ml, used 3 times daily. In the current monograph it have been used in a dosage of 4–8 ml 2–4 times daily. As a result, it is also proposed to change the lower range of single doses in the monograph at the point 4.2 Posology and method of administration, from

b) Liquid extract: Single dose: 4-8 ml, 2 to 4 times daily

to: Liquid extract: Single dose: 3-8 ml, 2 to 4 times daily.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
Agropyron repens (L.) Bouv., rhizoma, cut substance for herbal tea, infusion	Traditional herbal medicinal product used as an adjuvant in mild urinary complaints as a mean increasing of amount of urine and improving flow in urinary ways.	5g of couch grass rhizome pour with a glass of boiling water, infuse 15 min under cover and strain. Drink a glass of the infusion up to 4 times a day.	1992, NA, PL 2016, TUR, PL, 5 years

Herbal preparation Pharmaceutical form	**Indication**	**Posology, Strength**	**Period of medicinal use**
Agropyron repens (L.) Bouv., rhizoma, cut substance for herbal tea, infusion	Supplementary as mild diuretic in minor inflammatory states of urinary ways	Two teaspoons (claimed to be 3 g) in 1 cup of tea (claimed to be 100 ml) for infusion; 3 times a day.	1992, NA, PL, 29 years
Agropyri repentis rhiozoma. Cut or comminuted herbal substance for herbal tea, infusion	To achieve flushing of the urinary tract and for prevention of renal gravel.	Pour about 150 ml boiling water over about 2 to 3 teaspoons (about 5 to 10 g) of dried coach grass rhizome. Steep for 10 min. And then pass through a tea strainer. Unless otherwise prescribed, drink 1 freshly prepared cup of tea infusion four times daily. [SD 5-10 g, DD 20-40 g] (*Standardzulassung* 1986) Adults and adolescents ≥ 12 years: 3 g of herbal substance in 150 ml boiling water 2-3 times daily, corresponding to a daily dose of 6-9 g. [SD 3g, DD 6-9g]	1986-2004, DE, NA 2004 - 2020, DE, WEU
Agropyri repentis rhizoma, cut or comminuted herbal substance for herbal tea, decoction	Cystitis. Urethritis. Prostatitis. Benign prostatic hypertrophy. Renal calculus. Lithuria. Specific indication: Cystitis with irritation of inflammation of the urinary tract. (BHP 1971-2021)	Dose: 4-8 g in decoction. Dosage: Thrice daily. [SD 4 - 8g, DD 12-24g]	1971-2021, bibl>30 years
Graminis rhizoma	Irritable bladder or other urinary tract disorders (Wichtl M 2002, BHP 1983, cited in ESCOP 2009)	5-10g daily as an infusion	1983-2021, >30 years
Agropyri rhizoma (*Graminis rhizoma*) Fluid extract (1:1), 20-25% ethanol	Cystitis. Urethritis. Prostatitis. Benign prostatic hypertrophy. Renal calculus. Lithuria. Specific indication: Cystitis with irritation of inflammation of the urinary tract.	Adults and adolescents over 12 years. 2-4ml three times daily	>30 years

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use
(V/V)	(BHP 1971-2021) Irritable bladder or other urinary tract disorders (Hautmann C, Scheithe K 2000; BHP 1983, cited in ESCOP 2009) Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints. (HMPC 2011-2021)	2-4ml, three times daily	12 years 10 years
Agropyri repentis rhizoma. Liquid extract (1:1), extraction solvent: ethanol 20% V/V	Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.	Oral liquid (100 ml contain 100 ml liquid extract). Adults: 3 ml 3 times daily corresponding to a daily dose of 9 ml	Corresponding product 1970, TUR 2007-2021, DE
Agropyri rhizoma (*Graminis rhizoma*) Tincture (1:5), ethanol 40% (V/V)	Cystitis. Urethritis. Prostatitis. Benign prostatic hypertrophy. Renal calculus. Lithuria. Specific indication: Cystitis with irritation of inflammation of the urinary tract. (BHP 1971-2021) Irritable bladder or other urinary tract disorders (BHP 1983, cited in ESCOP 2009) Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints. (HMPC 2011-2021)	Adults and adolescents over 12 years. 5-15ml three times daily 5-15 ml, three times daily	>30 years >30 years 10 years

3. Non-Clinical Data

There no available systematic non-clinical data. Couch grass rhizome was well known for its traditional use in folk medicines along Europe and outside from times when animal test were not required. There are only few pharmacological data connected to the area of indications assigned by the HMPC to the herbal substance in the monograph.

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

3.1.1. Primary pharmacodynamics

Diuretic activity

Diuretic activity was shown by Racz-Kotilla and Mozes (1971) in rats after oral administration of an aqueous extract (1% macerate). After receiving 50 ml/kg body weight, diuretic index increased by 1.42 compared to control rats receiving water only. Some stronger diuretic effect (index of 1.62) was observed after i.p. administration of an equivalent dose of the dry hydroalcoholic (unknown concentration) extract dissolved in water corresponding to 10% of dried rhizome at 5 ml/kg body weight.

Assessor's comment: Macerate is not a form commonly used in couch grass traditional herbal medicinal products due to pharmacopoeial microbiological requirements. The cold macerate may contain more unhydrolised polyfructan in compare to better water soluble mono- and disaccharides and sugar alcohols. Hot water infusions or decoctions contains more hydrolysed products. It was the only bibliographic source where the diuretic effect of couch grass rhizome preparation was observed.

Effects on the calcium oxalate urolithiasis urinary risk factors.

Grases et al. (1995) tested the influence of couch grass rhizome infusion on calcium oxalate urolithiasis risk factors in Wistar rats fed with standard commercial diet, high protein diet and high glucidic diet. High protein diet contained 34 % of proteins and 52.8 % of carbohydrates; high glucidic diet contained 76.8% and 4.3% of proteins. Urine samples collected between 25 and 90 day of life were regarded as a standard. After 90 day a water supply was replaced with a herbal infusion of 3g herbal substance in 1L. Then rats were fed with high protein diet and with drinking water for 7 days and two 24h urine samples were collected (in eight and ninth days). After this, water was replaced by a herbal infusion for 7 days and two urine 24 h samples were collected. This was followed by 7 days period with a high glucidic diet and water, with collection of two urine samples what was followed by 7 day period with the herbal infusion, ending with collection of two 24 h urine samples. The authors compared: the volumes of consumed diets, excreted urine volumes, urine density, urine pH, calcium and magnesium, phosphates, citrates, creatinine, to the samples obtained of rats fed with standard diet, high protein diet, high glucidic diet of rats given with water or Agropyron repens infusion. The authors observed that citruria slightly decreased ($p<0.01$) when the herbal infusion was combined with a high glucidic diet, calciuria was increased and magnesiuria decreased. The authors concluded that the possible effects of the Agropyron repens infusion can't be assigned to any positive effect of the main urolithiasis risk factors studied.

Assessor's comment: The concentration of the infusion was lower than used in humans. There was no observed positive effects of the Agropyron repens infusion on the urolithiasis risk diets.

Anti-adhesive activity against Escherichia coli to the urinary epithelial bladder cells

Beydokhti et al., 2017, tested the extracts of powdered *Agropyron repens* rhizomes on the antiadhesive abilities on human epithelial bladder cells infected with *E. coli* strains NU14 and 2980. The herbal substance was extracted with following consecutive extraction solvents: water (15% of residue), methanol (1.5%), ethanol-water (1:1) (16.1%), ethanol-water (9:1)(9%), acetone (1.3%) and only in the acetone fraction the activity was found; more hydrophilic fractions were inactive. Further chromatography led to isolation and characterisation of the compound exhibiting antiadhesive activity: hexadecyl-3-(hydroxyphenyl)-acrylate which was earlier known from couch grass rhizome as p-coumaric acid hexadecyl ester. The compound exhibited antiadhesive activity against *E. coli* strains

2980 infecting human epithelial T24 bladder cells, in concentrations 0.5 and 1mM/ml. The authors notice that although the observed antiadhesive activity of the isolated compound in the co-incubation with the bladder cells and the bacteria is clear, the substance is lipophilic, is present in the herbal substance in small quantity and its pharmacokinetics need to be studied to confirm whether is able to come in any active form to the urinary ways.

3.1.2. Secondary pharmacodynamics

Anti-inflammatory activity

Moderate inhibition of carrageenin foot oedema of the rat hind-paw (14%) was found after oral administration of 80% ethanol extract of rhizomes of Agropyron repens (100 mg/kg) compared to indometacin effects (45% of inhibition) at 5 mg/kg (Mascolo et al. 1987).

In the model of allergic contact dermatitis induced by topical applications of 0.1 ml of 5% alcoholic solution 2.4-dinitrochlorobenzene (DNCB) in rats, the cream containing dry couch grass extract was tested. Couch grass extract cream was applied 3 days after the beginning of sensitization. Evaluation of the anti-inflammatory activity of the cream was monitored 4, 6 and 10 days after the experiment started. Plasma lipid peroxidation parameters: malondialdehyde (MDA), diene conjugates (DC) and catalase activity were registered. After 2 days of treatment with couch grass cream (4th day of experiment) decrease of erythema, oedema and infiltration was seen. On the 6th day of experiment the skin of rats treated with cream containing couch grass returned to baseline values with reduction of oedema and erythema. The visual symptoms of recovery of the control untreated rats were seen at 10 days. The activity of the antioxidant enzyme catalase increased by 30% at the 4th day and by 15% at the 6th day of experiment, compared to the control. At the end of the experiment on the 10th day increased levels of MDA and the activity of catalase (a major antioxidant defence enzyme). The couch grass cream application accelerated the recovery by 4-5 days as compared to the untreated control animals although was less effective than the standard glucocorticoid cream (Petrova et al. 2009).

Effect on lipid metabolism and antidiabetic effects

The effect of single and repeated oral administration of lyophilized decoction of couch grass, in a dose 20 mg/kg, on lipid metabolism in normal and streptozotocin-induced diabetic rats was studied by Maghrani et al (2004). The tested extract was prepared of 1g of dried *Triticum repens* (L.) Beauv., rhizoma, in 100ml of water and lyophilized with the yield 14%. In normal rats the extract induced significant decrease in the plasma triglycerides concentrations, observed 4 days and 1 week after repeated oral administration. The treatment caused a significant decrease of plasma cholesterol levels was observed only 1 week after repeated oral administration to diabetic rats. The decrease was observed 6 hours after a single oral administration of the extract. Four days after repeated oral administration of the extract, the plasma cholesterol level was significantly decreased and it remained so after 2 weeks. The repeated oral administration of the aqueous extract caused also significant decrease in body weight 2 weeks after oral treatment. In rats with sever hyperglycaemia the extract treatment induced reduction of lipid levels and body weight (Maghrani et al. 2004).

The hypoglycaemic effect of an lyophilised aqueous extract of *Triticum repens* (L.) Beauv., rhizomes harvested and in the same location in Maroc than in the former publication, dried in 40°C and processed by decoction of 1 g in 10 ml boiling water, filtration and lyophilsation, was investigated in normal and streptozotocin-induced diabetic rats. After a single oral administration of dose 20 mg/kg of the extract (dissolved 1 g/100 ml of water) a significant decrease in blood glucose levels in diabetic rats was observed. The blood glucose levels were normalized after 2 weeks of daily oral administration of 20 mg/kg of the extract. Significant reduction of blood glucose levels were also noticed in normal rats after acute and chronic treatment. No changes were observed in basal plasma insulin

concentrations after treatment in either normal or diabetic rats. The authors remarked that the couch grass rhizome aqueous extract is traditionally used in Maroc as antidiabetic treatment (Eddouks et al. 2005; 2007).

Effect on motility

Experiments were performed on rota-rod with male mice (20-30 g body weight). Each group of mice (N=30) received either orally or i.p. 10% infusion of *Rhizoma graminis* (either 40 or 80 mg/20 g mouse). Control mice received orally or i.p. 0.9% NaCl solution. Motility tests were performed after 2 and 8 hours after administration of the tested solutions. Other groups of mice received equivalent doses of Valerianae radix or Radix Heleniae infusum. All tested plant products induced comparable significant dose-dependent inhibition of motility. Similar comparable effects were obtained with use of the ether extracts of plants tested. The unspecific "sedative" effects on rotarod motility assayed plants with an unknown mechanism of action are discussed by the authors (Kiesewetter and Müller 1958).

Assessor's comment: 10% infusion is rather high concentrated even for humans (25 g of the herbal substance (about two spoons) in a glass of water). It may contain high sugar/sugar alcohol concentration, containing metabolic troubles in rodents. The result of the experiment inspired many authors to several hypothesis but seems to stay unclarified nor repeated. The "sedative" effect was not observed in rabbits fed with dried couch grass rhizomes.

3.1.3. Safety pharmacology

Not available

3.1.4. Pharmacodynamic interactions

No data are available concerning couch grass rhizome pharmacokinetics; the complex phytochemical composition is acknowledged.

3.1.5. Conclusions

Non-clinical data on *Agropyron repens* (L.), Beauv., rhizoma, are scarce. There are no plausible data from animal studies confirming the diuretic activity of herbal tea infusion or decoction. The experiment conducted with infusion (in a concentration 3g in 1L) failed in the confirmation of diuretic activity. One available experiment conducted with couch grass herbal macerate showed a mild diuretic activity but this type of preparation was not used traditionally as traditional herbal medicinal product.

Among less polar couch grass fractions p-coumaric esters were found with antiadhesive activity against Escherichia strains in vitro. The substances were present in acetone fraction; because of its low hydrophility, may be present only in ethanolic extracts. Although it is not known whether the coumaric esters may reach sufficient concentrations in the urinary tract, this effect may be taken into account also.

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

No data available. There is not known substance of known therapeutic activity in a couch grass rhizome, so there is no base for monitoring of pharmacokinetic parameters.

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

Systematic toxicological studies have not been conducted.

3.3.1. Single dose toxicity

No studies on acute toxicity have been performed with couch grass rhizome and couch grass rhizome preparations.

3.3.2. Repeat dose toxicity

No studies on repeated dose toxicity have been performed with couch grass rhizome and couch grass rhizome preparations.

One observation is available. Wilson (1945) compared feeding of 18 domestic rabbits (Beveren type), with rough grass hay (control) or couch grass rhizome for 25 weeks. The first 18 weeks was used dried couch grass rhizome and the last - fresh rhizomes, washed and air dried. Throughout the period of feeding with dried couch grass rhizomes the group maintained a slight advantage in live weight over the control. After the change to fresh air dried rhizomes the couch grass group continued to give slightly heavier body weight (3 weeks spite the reduced dry matter intake). 25 weeks of feeding with couch grass as a substitute of hay, the average weight increased in a the control group by 3.7 oz (≈105 g) and in a rhizome group 4.9 oz (≈139 g). During the observation in each group, hay and couch grass, 1 rabbit died, with symptoms typical to age.

3.3.3. Genotoxicity

Schimmer et al. (1994) showed no mutagenic potential of the fluid extract (1:1, 20% ethanol) of the Agropyron repens rhizome in the Ames test with Salmonella typhimurium strains TA98 and TA100 with and without S9 mix from induced rat liver microsomes up to maximal dose tested of 200 µl/plate.

3.3.4. Carcinogenicity

No published data could be found on the carcinogenicity of the couch grass rhizome and couch grass rhizome preparations. There are no substances with known carcinogenic potential in a couch grass rhizome.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

No data available.

3.3.7. Other special studies

No data.

3.3.8. Conclusions

There are no systematic toxicity studies on couch grass rhizome herbal substance nor preparations in the literature.

There are no data on the presence of constituents with safety concerns to humans in couch grass rhizome used for medicinal purposes.

Due to the lack of data on acute and chronic toxicity, repeated dose toxicity, carcinogenicity, reproductive and developmental toxicity, a list entry for Agropyron repens rhizome cannot be recommended.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on *Agropyron repens* (L.) Beauv., rhizoma, infusions, decoctions and ethanolic extract, which could support the proposed indications, are very limited.

Although diuretic effect of infusions or decoctions of couch grass rhizome extract can't be confirmed on a base of available bibliographic data, it was observed antiadhesive effects of some substances contained in the herbal substance or its preparations against urinary pathogens, which is not considered contradictory to the area of traditional uses.

As there are not known constituents with known therapeutic activity, specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of couch grass rhizome is scarce.

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

Oral administration of couch grass rhizome or its preparations can be regarded as safe at traditionally used doses with the exception of patients with severe renal or cardiac disease e.g. renal and heart failure.

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

4. Clinical Data

4.1. Clinical pharmacology

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

No clinical pharmacology data available

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

There is no base for pharmacokinetic data because constituent with known therapeutic activity have not been identified.

4.2. Clinical efficacy

Publications with results of efficacy, based on well controlled clinical trials, for couch grass rhizome preparations containing products, were not found in a public domain.

4.2.1. Dose response studies

No data available

4.2.2. Clinical studies (case studies and clinical trials)

Effect of fluid extract in urinary tract infections and irritable bladder

In the open clinical observation in 99 patients with different micturition disorders (87 male and 12 female), a 20% ethanol fluid extract of *Agropyron repens* were administered for 28-31 days (60 drops 3 times daily). The complaints of urge incontinence, dysuria, nycturia and tenesmus due to adenoma of prostate, prostatitis and cystitis were significantly reduced in 44.4-100 % of patients. Laboratory markers of inflammation (protein, epithelia, leucocytes and erythrocytes in urine) were also normalised. 96% of patients estimated results were good or very good. Adverse effects were not recorded (Barsom 1981).

Assessor's comment: This pilot observation was not a well-controlled clinical study.

A multicentered post-marketing surveillance evaluated the effects of use of couch grass fluid extract in 313 patients with urinary tract infections or irritable bladder. The patients with diagnosis of irritable bladder, urethritis, cystitis and prostatitis were included. The patients were administered 50-60 drops of 20% fluid ethanolic extract of couch grass rhizome for 12 days. Primary "efficacy criterion" i.e. the subject of the observation was the clinically relevant improvement and change of following urologic symptoms during the course of therapy: urge incontinence, painful micturition, dysuria, pollakiuria, nycturia and tenesmus. At the end of the observation, dependent on the urologic diagnosis, between 32% and 53% of the patients were free of symptoms following treatment (32% of patients with irritable bladder, 44% with urethritis, 53% with cystitis and 42% with prostatitis) No side effects were reported (Hautmann and Scheithe 2000).

Assessor's comment: This observation met the criteria for surveillance study but not for efficacy assessment because of lack of control.

Observation on combinations of diuretics with food supplement containing couch grass extract and potassium citrate

The aim of the study was to evaluate by a prospective randomized controlled study the efficacy of the association of potassium citrate 24 mEq and 100 mg of dry extract of couch grass (*Agropyrum repens*) (CalcoMEV) in renal stone treatment.

50 patients with at least 2 renal calculi, documented during the previous 2 years, associated with one or more active metabolic alterations that constitute an indication to the use of potassium citrate, were randomly divided in two equal unblinded treatment groups. Exclusions: renal failure, contraindication to potassium citrate, hypoadrenocorticism, bladder stones, cystinuria, pregnancy. The study was a parallel observation of four groups of patients (19 males, 6 females) obtaining diuretic medicines plus food supplement (containing extract of couch grass rhizome of not pharmaceutical quality): the tested product + allopurinol 300mg 4 x a day), product + allopurinol + thiazide (amiloride 5 mg + hydrochlorothiazide 50 mg, 4 x a day), product + thiazide + pyridoxine (300 mg, 4 x a day), product + allopurinol + pyridoxine; and four comparative groups (20 males, 5 females) obtaining the same combinations of diuretic medicines used in urolithiasis, with added potassium citrate, potassium citrate + allopurinol, potassium citrate + allopurinol + thiazide, potassium citrate + thiazide + pyridoxine, potassium citrate + pyridoxine.

All patients were advised to drink 2 liters of water during the study. The authors claim that the combinations of diuretics with added couch grass extract with potassium citrate was better in reducing

number and diameter of stones than compared combinations with potassium citrate alone (Brardi et al 2012).

Assessor's comment: There was no groups treated with couch grass alone or couch grass +potassium citrate alone nor placebo group. Study was declared to be not blinded, treatment subgroups were small and divided as comparable as possible. From this study and based on conditions described any conclusions about the efficacy of product or on couch grass preparation itself can't be drown.

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

Study in children with renal calculi

Alosy et al. (2019), reported on a parallel comparative study (two arm, treated v. control, without placebo) on 50 children with renal calculus, in age between 5 and 14 years (inclusion criteria not described in details) from hospital and private medical practice in Iraq. 25 were treated with an *Agropyron repens* extract in capsules, dissolved before use in water, in a dose 5 mg/kg. Strength of the examined product was not declared in a EU way. Comparative group obtained "normal" care (not described). Patients of the both groups were encouraged to drink water. Randomisation is declared, although not described. The patients were observed for 60 days, with number and size of stones evaluated by ultrasonographic examination every 14 days. Symptoms were noted: renal colics, haematuria and sepsis (infections). Liver function, renal function and haematological parameters were evaluated for any abnormality or side effects. After a 60 days in 22+/-2.12 (88%) (p=0.001) in patients of the treated group was observed decline in number of stones but in 3+/-1.02 (12%) was not observed. In a control group in 23+/-2.01 (92%) patients number of stones not declined; in 3+/-1.02 declined. Size of stones was declined in 23+/-1.09 patients (p=0,002) of treated group, not declined in 2+/-1.09 patients (12%). Renal colics were reduced in 19.4+/-1.72 patients (77.6%) in Agropyron group v. 4.1+/-1.02 (16.4%) in control group. Haematuria was reduced in 21.49+/-1.06 (85.9%) in Agropyron group v. 6.04+/-1.06 (24.1%) in control group. Urinary infections were reduced in 22.2+/-1.9 (88.8) v. 3.2+/-1.02.

Assessor's comment: The study presents some methodological shortcomings (the inclusion criteria was not defined, control treatment was not well characterized, study has a small size and was not blinded, the biochemical study is unavailable). It is not enough to be considered for the development of a WEU-monograph.

4.4. Overall conclusions on clinical pharmacology and efficacy

Available clinical data include two studies where effects of administration of a liquid extract preparation were observed in patients with different urological diseases. Over the 12 day studies with the administration of the liquid extract preparation, trends to reduction symptoms of inflammatory states and urinary infections (in cystitis 53% were free of symptoms, in prostatitis 42% of patients, in irritable bladder 33%) were observed. In children with urolithiasis, after 60 days using the water extract, the number of stones declined (88%), haematuria and infections were reduced (85% and 88%). Although conclusions on clinical efficacy can't be drown, some positive effects of use of couch grass preparations were observed.

5. Clinical Safety/Pharmacovigilance

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

There are no toxicological data from available clinical trials or observations.

5.2. Patient exposure

Aside from market presence and data from studies, 412 patients were treated with fluid extract and 25 paediatric patients were treated with extract in capsules. In the observation of 25 patients administered with combined dietetic product, declared to contain water couch grass extract with potassium citrate, adverse events were not recorded.

Among 313 patients of post surveillance study using a liquid extract product, adverse effects were not reported. There are no concrete data concerning the whole patient exposure.

Data obtained from 313 patients, tested for safety during clinical trials of Hautmann and Scheithe (2000), showed no adverse effects.

5.3. Adverse events, serious adverse events and deaths

VigiLyze (WHO) recorded 3 reports over a period 2011-2020. There was a case of abdominal pain after use of unidentified part of *Elymus repens* by 50 year old man in Maroc in 2014. However, as the symptoms did not resolved after withdrawing the use of the product, the role of *Elymus repens* product was noted to be possible. There were no details on herbal substance, posology or dose used.

Two historical cases, where herbs were suspected to be involved, were reported to the VigiLyze database in 2011. The case of a 59 year old female, using *Filipendula ulmaria, Fraxinus excelsior, Tilia cordata, Elymus repens* with captopril and hydrochlorothiazide, that experienced jaundice, fulminant hepatitis and died in 1998. The case was spontaneously reported to the WHO 13 years later (in 2011) by a doctor from France. It was not assessed in 1998, the narrative description in the WHO database is absent and the assessment report or justification was not available. The second case, also spontaneously reported by a doctor from France in 2011 was a 36 old female taking between 15 March 2000 and 20 April 2000, the herbs: *Senna alexandrina, Elymus repens* and *Equisetum* with Zolpidem, for one day, Meteospasmyl and DL methionine. After this experienced leukopenia, monocytosis, jaundice, hepatitis, rash and pruritus. The role of the previously used herbs was suspected by the rapporteur. Narrative description of doses, data on conditions, sequences of symptoms were not available from the database. For any of the cases their cause-relationship between the use of any *Agropyron repens* preparation and adverse effects were not confirmed.

5.4. Laboratory findings

No data available

5.5. Safety in special populations and situations

No data available

5.5.1. Use in children and adolescents

Herbal tea: Children under 12 years of age should not use the medicinal product due to lack of adequate data.

Fluid extract and tincture: The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.

5.5.2. Contraindications

Hypersensitivity to the active substance(s), Herbal tea: Conditions where a reduced fluid intake is recommended (e.g. severe cardiac or renal disease).

5.5.3. Special warnings and precautions for use

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

5.5.4. Drug interactions and other forms of interaction

Not known

5.5.5. Fertility, pregnancy and lactation

No data available.

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

5.5.6. Overdose

No data available.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

There are no data from humans on the influence of couch grass preparations on ability to drive or operate machines.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

Available post-marketing surveillance study on couch grass fluid extract did not identify any special safety concerns for the use of the preparation.

Available clinical data on the use of herbal teas in paediatric population with urolithiasis are too limited (25 treated patients) for safety assessment.

6. Overall conclusions (benefit-risk assessment)

The indication established in the monograph in 2012 was:

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

Results from relevant experimental studies on *Agropyron repens* (L.) Beauv., rhizoma, infusions, decoctions and ethanolic extract, which could support the proposed indications, are very limited.

Although some clinical data on couch grass preparations are available, none of the publication describes well-designed, controlled clinical trials enabling the efficacy assessment. On a base of the data, no conclusion can be drown on an well-established medicinal use.

Available post-marketing surveillance study on couch grass liquid extract did not identify any special safety concerns for the use of the preparation in adults and elderly. The use in children and adolescents of the tincture and the liquid extract under 18 years of age can not been established due to lack of adequate data. The use in children under 12 years of the herbal tea of age has not been established due to the lack of adequate data.

The available data are sufficient to establish a EU herbal monograph on the traditional use of couch grass rhizome. Couch grass rhizome fulfils the requirement of medicinal use for at least 30 years (including at least 15 years within the European Union, Directive 2004/24/EC).

Due to the lack of data on acute and chronic toxicity, repeated dose toxicity, carcinogenicity, reproductive and developmental toxicity, a list entry for *Agropyron repens* cannot be recommended.

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

Annex 1

List of references