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EMA/HMPC/563395/2010
Committee on Herbal Medicinal Products (HMPC)

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

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

Final

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Rhizome of *Agropyron repens* (L.) P. Beauv.
Herbal preparation(s)	Comminuted herbal substance Liquid extract (DER 1:1), extraction solvent ethanol 20-25% V/V 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.
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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 ref. 01/2008:1306, couch grass rhizome (Graminis rhizoma) is defined as the whole or cut, washed and dried rhizome of *Agropyron repens* (L.) Beauv. (*Elymus repens* (L.) Gould); the adventitious roots are removed (Ph. Eur. 2008).

Couch grass rhizome is known under the following common names:

English: Scutch, Twitch grass root, Quack grass root, Triticum;

German: Queckenwurzelstock, Laufqueckenwurzel, Schließgraswurzel, Graswurzel, Kriechwurzel;

French: Rhizome de chiendent, Chiendent rampant;

Spanish: Rizoma de grama de las boticas, Rizoma de grama del Norteo grama oficinal.

Polish: Kłącze perzu

Other names: Agropyron, Dogs Grass, Grama, Graminis Rhizoma, Juolavehnänjuurakko, Kvickrot, Pýrový oddenek, Tarackbúza-gyökértörzs, Triticum, Twitch, Varpučių šakniastiebiai and Пырей Ползучий

The herbal substance can also be defined as the whole or cut, washed and dried rhizomes and short pieces of stem of *Agropyron repens* (L.) P. Beauv. (synonyms: *Agropyron caesium* J.U.C. Presl., *Bromus glaber* Scop., *Elymus repens* L., *Elymus dumetorium* Hoffm., *Elytrygia repens* Desv. ex Nevski, *Triticum arundinaceum* Poulsen ex Fries, *Triticum repens* L., *Triticum sepitum* Thuill.), *Poaceae* (Hänsel 1992).

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).

Couch grass is a widely distributed weed throughout the Northern hemisphere. The material of commerce is imported from Eastern and South-Eastern European countries.

Constituents:

Couch grass contains 3-8% triticin (similar to inulin), which yields fructose upon hydrolysis. The drug also contains 3-4% fructose, 2-3% sugar alcohols (mannitol, inositol). The presence of agropyrene has been disputed. Furthermore, small amounts of vanillin monoglucoside, vanillic acid, phenolic carboxylic acids, hydroxycinnamic acid alkyl ester, silicic acid and silicates are present. Small amounts of anthraquinones were also detected (Steinegger 1972, Hoppe 1958, Frerichs *et al.* 1949, Karsten 1956, Jaretzky 1937, Claus 1956, Wallis 1955, Hänsel 1992, Hiller 1999, Bruneton 1999, Newall 1996, Borkowski 1952; 1974, Koetter *et al.* 1993 and Müller *et al.* 1999).

Carbohydrates: The rhizome is free of starch.

Polysaccharides: The active substances of the aqueous extract of couch grass rhizome consisted of: polysacharide fraction (45.3 ± 0.3%), flavonoids (0.96 ± 0.03%), tannins (4.9 ± 0.4%). Polysaccharides were separated by fractional extraction for: monosaccharides-glucose, D-fructose,

rhamnose, pectins and hemicelluloses A and B (Petrova *et al.* 2009, Steinegger & Hänsel 1972). About 10% mucilage and possibly saponins occur (haemolytic activity is detectable) (Steinegger 1972, Hänsel 1992).

Sugar alcohols: Inositol, mannitol (2-3%) (Stoop *et al.* 1996).

Fructans: (storage carbohydrates) 3-10% (Arni & Percival 1951, Bruneton 1999, Biggs & Hancock 2001, Steinegger 1972).

Triticin: Laevorotatory carbohydrate high-branched out polysaccharide resembling inulin (3-18%) (Steinegger 1972).

Free fatty acids: 36% (particularly palmitic acid).

Phenol compounds: P-hydroxybenzoic, vanilic and p-coumaric acids (Whitehead *et al.* 1982), Chlorogenic acid, p-hydroxycinnamic acids (Petrova *et al.* 2009), P-hydroxycinnamic acid esters: (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). Presence of agropyrene has been disputed.

Essential oil: (0.01-0.02%): 25% monoterpens (carvacrol, carvon, trans-anethole, thymol and menthol, among others), 0.85% sesquiterpenes (Boesel & Schilcher 1989) and other compounds including 2-hexyl-3-methyl-maleic acid anhydride.

Flavonoids: Tricin, rutin, baicaleine, hyperoside (Petrova *et al.* 2009).

Anthraquinones: Sum of anthraquinones (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 (Müller *et al.* 1999).

Steroids: Oestrogen, androstenone, progesterone and androgens in trace amounts (Simons & Grinwich 1989).

Lectins: Can be found in the seedlings and leaves of *Agropyron repens* and may also be present in the rhizome. Purified leaf lectin (ARLL) corresponds to a M_r of 19,500 compared to M_r of 18,000 for the embrio lectins (AREL). ARLL polypeptide is slightly larger than cereal embrio lectins. They also exhibit different agglutination properties: ARLL is GalNAc-specific and agglutinates preferentially red blood cells of group A, since AREL is GlcNAc-specific and has no blood group specificity at all (Cammue *et al.* 1985).

Saponins: Presence has not been confirmed.

Microelements: Concentrations of an iron and zinc in infusions prepared from raw *Agropyron repens* rhizomes was estimated in the range of 3.78-6.84 μg/g and 7.12-10.80 μg/g respectively (Arceusz *et al.* 2009).

Silicic acid and silicates: Total Si level (%) in rhizomes of *Agropyron repens* at various stages of its vegetation between June and October increased in the range of 0.37-0.43. The maximum concentrations in decoction were obtained after boiling 3 g of rhizomes in a glass of water for 2 hours under a cover. One glass of decoction contains 2.6 mg of assimilable silicon equivalent to 5.6 mg of Si02 (Pasławska & Piekos 1976).

- Herbal preparation(s)

1. Comminuted herbal substance
2. Liquid extract (1:1) extraction solvent: ethanol 20-25% V/V
3. 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 also available in combination products. Main plants used in combination are: *Achillea millefolium*, *Allium cepa* , *Althea officinalis*, *Betula pendula*, *Calendula officinalis*, *Carum carvi*, *Cichorium intybus*, *Cynara scolymus*, *Equisetum arvense*, *Frangula alnus*, *Levisticum officinale*, *Linum usitassimum*, *Matricaria chamomilla*, *Mentha piperita*, *Petroselinum crispum*, *Phaseolus vulgaris*, *Polygonum avicularis*, *Rheum officinale*, *Ribes nigrum*, *Sambuccus nigra*, *Silybum marianum*, *Solidago virgaurea*, *Taraxacum officinalis*, *Tilia cordata*, *Trigonella foenum-graecum*, *Urtica dioica* and *Viola tricolor*.

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

Estonia

There are no products containing *Agropyron repens* rhizome as a single active ingredient or in combination.

Germany

*Traditional Use**

- Preparations (kind of extract, extraction solvent, DER)

Liquid extract (1:1), extraction solvent: ethanol 20% V/V

- Since when are the preparations on the market?

At least since 2007

- Pharmaceutical form (Standard Terms)

Oral liquid

- Posology (Route of administration in Standard Terms + daily dosage)

For oral use in adults > 18 years: 3 times daily 3 ml containing 100% of liquid extract

- Indications

Traditionally used to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

- Risks (adverse drug effects, literature)

Use in children and adolescents below the age of 18 years and during pregnancy and lactation is not recommended because of insufficient data.

- Is the Herbal Substance on the market?

☒ Yes ☐ No

- Status

☐ Authorised products ☒ Registered products ☐ Food supplements

- Were pharmacovigilance actions taken on medicinal products containing the herbal substance?

☐ Yes ☒ No.

Combination products

In Germany, there is 1 authorised combination product.

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

Additional comments: German Standard Marketing Authorisations

Single active ingredient: 1
Combination products: 7
All of them are herbal teas

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

Latvia

One authorised medicinal combination product containing *Agropyron repens* rhizome (extractum Agropyri rhizoma) is available on the Latvian market, as a paste for oral use, in cases of urinary tract infections and nephrolithiasis.

There are also products with *A. repens* on the Latvian market as food supplements (one product with *A. repens* as single ingredient and a few combination products).

Poland

Traditional Use

- Preparations (kind of extract, extraction solvent, DER)

Herbal substance (herbal tea), single ingredient

- Since when are the preparations on the market?

At least since 1994

- Pharmaceutical form (Standard Terms)

Herbal tea

- Posology (Route of administration in Standard Terms + daily dosage)

1.5-3.0 g of comminuted herbal substance in 200 ml of boiling water for 15 min, 4 times daily

- Indications

Traditionally in troubles with urination to increase the amount of urine and to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

- Risks (adverse drug effects, literature)

Use in children and adolescents below the age of 18 years and during pregnancy and lactation is not recommended because of insufficient data.

- Contraindications

Do not use in oedema in renal/cardiac insufficiency.

- Is the Herbal Substance on the market? ☒ Yes ☐ No

- Status

☒ Authorised products ☐ Registered products ☐ Food supplements

- Were pharmacovigilance actions taken on medicinal products containing the herbal substance?

☐ Yes ☒ No

Combination products

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

a) Communited herbal substances: *Graminis rhizoma, Equiseti herba, Taraxaci herba, Taraxaci radix* and *Frangulae cortex*

b) Communited herbal substances: *Frangulae cortex, Graminis rhizoma, Carvi fructus* and *Lini semen*

c) Communited herbal substances: *Graminis rhizoma, Violae tricoloris herba, Cichorii radix, Urticae folium, Phaseoli pericarpium* and *Rhei radix*

d) Communited herbal substances: *Silybi mariani fructus, Cynarae herba, Taraxaci radix, Urticae folium, Calendulae anthodium* and *Graminis rhizoma*

e) Communited herbal substances: *Menthae piperitae folium, Graminis rhizoma, Matricariae flos, Taraxaci radix cum herba, Carvi fructus* and *Frangulae cortex*

f) Paste: Extractum compositum (1:1.3-1.6) ex: *Graminis rhizomate, Allii cepae squama, Betulae folio, Foenugraeci semen, Petroselini radix, Solidaginis herba, Equiseti herba, Levistici radix* and *Polygoni avicularis herba*; extraction solvent – ethanol 45% (V/V)

g) Extractum compositum fluidum (1:1) ex: *Phaseoli pericarpio, Betulae folio, Graminis rhizomate, Rubi fruticose folio* and *Rosae fructus;* extraction solvent – ethanol 70% (V/V)

Since when are the preparations on the market?

a) 8 years
b) 5 years
c) 6 years
d) 21 years
e) 17 years
f) 49 years (since 1961)
g) 8 years

Pharmaceutical form (Standard Terms)

a) Herbal tea (comminuted herbal substances)
b) Herbal tea (comminuted herbal substances)
c) Herbal tea (comminuted herbal substances)
d) Herbal tea (comminuted herbal substances)
e) Herbal tea (comminuted herbal substances)
f) Oral paste (dry extract)
g) Oral liquid (liquid extract)

Posology (Route of administration in Standard Terms + daily dosage)

a) Oral use: 2 g (0.7 g of *Graminis rhizoma*) 1-2 times daily
b) Oral use: 1 g (0.25 g of *Graminis rhizoma*) daily
c) Oral use: 2 g (0.6 g of *Graminis rhizoma*) 2-3 times daily
d) Oral use: 5-10 g (0.375-0.75 g of *Graminis rhizoma*) 2-3 times daily
e) Oral use: 5 g (1 g of *Graminis rhizoma*) 1-3 times daily
f) Oral use: 5 g (3.36 g of extract corresponds to 0.42 g of *Graminis rhizoma*) 3-4 times daily
g) Oral use: 5 ml (0.92 g of *Graminis rhizoma*) up to 4 times daily

A. repens can also be found in combination with *Achillea millefolium, flos; Allium cepa, bulbus; Althea officinalis, radix; Calendula officinalis, flos; , Ribis nigrum; Sambuccus nigra; Tilia cordata, flos.*

Other information on relevant combination products: the herbal substance is included in compositions *Species laxantes* and *Species metabolicae.*

Additional comments:
On the Polish market, there are 7 single active ingredient products and 7 combination products containing couch grass.

Portugal

There are no authorised products (single or in combination) with *Agropyron repens*. Products with *Agropyron repens* could be on the market as food supplements.

Slovak Republic

There are no registered medicinal products containing *Agropyron repens* L. as a single ingredient or in combination.

Sweden

There are no products containing *Agropyron*.

United Kingdom

Traditional Use

- Preparations (kind of extract, extraction solvent, DER)

1. Blended chopped herb
2. Dry extract (5:1)
3. Liquid extract (1:1), extraction solvent: ethanol 21%

- Since when are the preparations on the market?

Since 1968

- Pharmaceutical form (Standard Terms)

1. Herbal substance
2. Dry extract
3. Liquid extract

- Posology (Route of administration in Standard Terms + daily dosage)

1. 6 g infused in 0.5 l of boiling water and taken daily in portions when cool enough
2. Two tablets 3 times daily (containing 12 mg of *Agropyron repens* dry extract) after meals
3. One 5 ml teaspoonful three times daily containing 0.875 ml of liquid extract of couch grass

- Indications

1. A herbal remedy traditionally used for short term symptomatic relief of urinary and bladder discomfort and associated backache.
2. A herbal remedy traditionally used for symptomatic relief of urinary or bladder discomfort.
3. A traditional herbal remedy for the symptomatic relief of urinary or bladder discomfort.

- Risks (adverse drug effects, literature)

Adults and elderly only; not recommended for children. Avoid in early pregnancy and lactation.

- Is the Herbal Substance on the market?

☒ Yes ☐ No

- Status

☐ Authorised products ☒ Registered products ☐ Food supplements

- Were pharmacovigilance actions taken on medicinal products containing the herbal substance?

☐ *Yes* ☒ *No*

Combination products

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

What are the main combination substances?
Barosma betulina, folium; *Asperugo procumbens, folium*;*Equisetum arvense, herba; Arctostaphylos uva ursi, folium; Cassia angustifolia, folium; Capsella bursa-pastoris, herba; Althea officinalis, radix* and *Juniperus communis, pseudofructus.*

Regulatory status overview

Member State	**Regulatory Status**				**Comments**
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Belgium	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not present
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	The herbal substance is also available in combination products
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

Member State	Regulatory Status				Comments
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Latvia	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	The herbal substance is available in combination product
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Poland	☒ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	The herbal substance is also available in combination products
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not present
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not present
Slovenia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Not present
United Kingdom	☐ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	The herbal substance is available in combination products

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
Other: If known, it should be specified or otherwise add 'Not Known'
This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.

1.3. Search and assessment methodology

The following databases were assessed in August 2010: PubMed, The Cochrane Library, OvidMedline and Embase.

Search terms: *Agropyron repens*, *Elymus repens*, *Elytrygia repens*, *Triticum repens*, *Graminis rhizome*, Couch grass and Quack grass

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Couch grass rhizome has been traditionally used as diuretic, mainly in compositions (Borkowski 1952; 1974, Claus 1956, Frohne 1994, Hiller 1999, Oppermann 1995 and Receptariusz Zielarski 1963; 1967).

Agropyron repens has been traditionally used in treatment since ancient times. Its name was mentioned in the publications of Dioskurides, Plinius, Tabermontanus-Bauhinus 1588 and Matthiolus 1626, according to Madaus (1938).

The herbal substance is mentioned in several well known handbooks such as Barnes (2002), Bradley (2006), Duke (2002), ESCOP Monographs (2009), German Commission E Monograph (1990), Hänsel (1992), Frerichs (1949), Hiller (1999), Hoppe (1958), Madaus (1938), Martindale (2009), Jaretzky (1937), Karsten (1956), Newall (1996), PDR for Herbal Medicines (2000; 2004), Schulz (1998), Wallis (1955) and Wichtl (1994; 2002).

In Greece, according to ethnobotanical tradition, *Agropyron repens* is used not only in urinary tract disorders (cystitis, kidney stones, prostate enlargement) but also in gastrointestinal problems (gallstones), in arthritis and rheumatism and to reduce increased cholesterol levels (Hanlidou *et al.* 2004).

In Bulgaria and Italy, couch grass rhizomes are traditionally used as diuretic and laxatives (Leporatti & Ivancheva 2003). They are also used as a diuretic by ethnic Albanian communities living in the Vulture area in Southern Italy (Pieroni *et al.* 2002).

In Bosnia and Herzegovina, a traditional use of couch grass as diuretic and in rheumatic complaint is described (Redžić 2007).

Agropyron repens (L.) rhizomes, dried, ground into flour to make bread or thick soup in famine conditions were used in Poland until the mid-20th century and might have been used to make beer until the 18th century (Łuczaj & Szymański 2007, Łuczaj 2008).

The pulverised rhizomes of *Agropyron repens* (2-3 g 3 times daily for 10-12 days) were used in order to reduce irritable condition of bladder and to promote urination (Ballabh *et al.* 2008).

Agropyron repens is also used in ethnoveterinary medicine to treat endoparasites and gastrointestinal problems in Italy and in Canada (Lans *et al.* 2007, Viegi *et al.* 2003).

Overall conclusion on the traditional medicinal use

Preparations from *Agropyron repens* rhizome have long been used for diuresis stimulation. The traditional medicinal use is made plausible by pharmacological data.

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

See section 2.3.

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

British Herbal Compendium (Bradley 2006)
Traditionally used in inflammatory ailments and infections of the urinary tract, cystitis, urethritis, prostatitis and irritable bladder. It has also been used in the treatment of renal stones, gout and rheumatic disorders and chronic skin complaints.
Daily dose: dried rhizome, 4-8 g usually as decoction or infusion, liquid extract 1:1 in 25% alcohol: 4-8 ml, tincture 1:5 in 40% alcohol: 5-15 ml.
Duration of use: no information

British Herbal Pharmacopoeia (1971)
Action: diuretic
Indications: Cystitis, urethritis, prostatitis, benign prostatic hypertrophy, renal calculus, lithuria
Combination used: May be combined with Agathosma in cystitis and with Hydrangea in prostatic enlargement.
Specific indications: Cystitis with irritation or inflammation of the urinary tract
Preparations and dosage: Dried rhizome, dose 4-8 g, tincture 1:5 in 40% alcohol, dose 5-15 ml, 3 times daily.

German Commission E Monograph (1990)

Irrigation therapy for inflammatory diseases of urinary tract and for the prevention of kidney gravel.
Daily dose: 6-9 g of comminuted herb or equivalent preparations.
Duration of use: no information.

ESCOP Monograph (2009)

Indications: Irritable bladder and other urinary tract disorders. Efficacy is plausible on the basis of tradition and long-standing use.
Dosage: Oral administration
Adults and children over 12 years: Herbal substance: 5-10 g as herbal tea daily, fluid extract (1:1, 20-25% ethanol V/V): 2-4 ml, three times daily, tincture (1:5, ethanol 40% V/V): 5-15 ml, 3 times daily.
Duration of use: No restriction.

If symptoms persist or worsen, medical advice should be sought.

Hager's Handbuch (Hänsel 1992)
Irrigation therapy for inflammatory diseases of urinary tract and for the prevention of kidney gravel.
Other traditional indications: Rheumatic complaints, diabetic nutrition (fructosans)
Dosage:
Tea:
6-9 g of comminuted herbal substance daily (according to Commission E);
either 20-40 g (Standardzulassungen für Fertigarzneimittel, Nr. 1169.99.99, 1988) or 12-24 g (BHP 1983) as herbal tea daily.
Tea preparation: Pour boiling water over the comminuted herbal substance and strain after 10 minutes.
Fluid extract (1:1): 4-8 ml, 3 times daily
Tincture (1:5): 5-15 ml, 3 times daily
Warnings: Do not use in oedema in renal/cardiac insufficiency.

Herbal Drugs and Phytopharmaceuticals (Wichtl 2002)
Diuretic in cases of bladder inflammation and bladder and kidney stones. According to folk tradition as a cough remedy to alleviate the irritation in bronchial catarrh and in rheumatic disorders, gout and chronic skin conditions.
Dosage: 5-20 g of the chopped drug in boiling water, after 5-10 minutes passed through a tea strainer. It is also recommended to put the herbal substance in cold water and slowly bring it to the boil (1 teaspoon = ca. 1.5 g). Unless otherwise prescribed, a cup is drunk up to 4 times daily.

Lehrbuch der Biologischen Heilmittel (Madaus, 1938)
Indications: urinary tract complaints, renal stones and rheumatic ailments.
Dosage: 14 g (4 teaspoons) fresh herbal tea daily, 1 g comminuted herbal substance 3 times daily, 1 teaspoon of the fresh powdered herbal substance 4 times daily.

Maximal dose is not described.
Duration of use: no information.

Martindale (2009)
Agropyron repens is a mild diuretic that has been used in herbal medicine in the treatment of urinary-tract disorders.
Dose: no information.
Duration of use: no information.

PDR for Herbal Medicines (2000, 2004)
The medicinal part is the rhizome collected in spring and autumn.
Indicated in infections of the urinary tract and kidney and bladder stones.
Comminuted herbal substance: 3-10 g/day (1 teaspoon corresponds to 3 g of drug).
Tea: 3-10 g in 1 cup (250 ml) of boiling water, strain after 10 minutes. Drink fresh several times a day.
Liquid extract: 4 to 8 ml, 3 times daily.
Tincture: 5 to 15 ml, 3 times daily.
Storage: the drug must be kept in sealed containers, protected from light and moisture.
Duration of use: no information.

3. Non-Clinical Data

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

In vivo experiments

Diuretic activity

A diuretic activity was shown by Racz-Kotilla *et al.* (1974) 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. A stronger diuretic effect (index of 1.62) was observed after i.p. administration of an equivalent dose of the dry hydroalcoholic extract dissolved in water corresponding to 10% of dried rhizome at 5 ml/kg body weight.

Effects on the calcium oxalate urolithiasis urinary risk factors

The effects on the calcium oxalate urolithiasis urinary risk factors of administration of *Agropyron repens* (*Gramineae*), in an herb infusion form, combined with different diets (standard, high glucidic, high protein) have been studied using Wistar rats. From this study, the authors concluded that administration of the *Agropyron repens* infusion cannot be associated to any positive effects on the main urolithiasis risk factors. According to the authors, some significant diuretic effects ($p<0.005$) with the infusion of *Agropyron repens* were registered with calciuria increased ($p<0.005$) and magnesiuria decreased ($p<0.005$) when a standard diet was used. Moreover, citratruria decreased when couch grass infusion was associated with a high glucidic diet (Table 1). The authors concluded that the conditional diuretic effect of couch grass infusion cannot be attributed to the diet (Grases *et al.* 1995).

Table 1 Volume consumed, diuresis and urinary biochemical parameters for different diets, without herb (control) with *Agropyron repens* infusion (Grases *et al.* 1995)

	Volume consumed (ml)	Diuresis	pH	Ca	Mg	Phos (mg/l)	Creat	Cit
Standard diet								
Control	37.0±3.5	17.0±2.3	7.8±0.5	187±76	572±82	4384±972	56±87	3787±677
Agropyron repens	34.2±8.4	21.7±4.7**	7.4±0.6	277±77**	448±125**	4966±856	768±171	3151±980
High protein diet								
Control	34.3±5.0	27.9±4.5	6.5±0.8	191±61	258±42	7176±609	520±51	176±57
Agropyron repens	33.8±9.0	24.6±4.0	5.9±0.1*	218±54	163±20***	12120±1792***	571±101	180±43
High glucidic diet								
Control	29.8±7.9	21.5±8.3	5.8±0.3	130±61	228±89	5225±1197	831±272	195±59
Agropyron repens	27.5±8.4	22.5±6.9	5.9±0.5	178±66	222±51	4845±1348	590±116**	118±78*

The values are expressed as mean ± SD of 12 animals; *p<0.01, **p<0.005, *** p<0.0005

Anti-inflammatory activity

Moderate inhibition of carrageenan foot oedema of the rat hind-paw (14%) was found after an 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 animal model of allergic contact dermatitis induced topically in rats after depilation with two applications of 0.1 ml of 5% alcoholic solution 2.4-dinitrochlorobenzene (DNCB), the cream containing dry couch grass extract was tested. After DNCB use, the skin was hyperaemic, oedematous with serious purulent changes and itching. 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 (4^{th} day of experiment), a decrease of erythema, oedema and infiltration was seen. On the 6^{th} day of the experiment, the skin of rats treated with the cream containing couch grass returned to baseline values with a reduction of oedema and erythema. The visual symptoms of recovery of the control untreated rats were seen at day 10. The activity of the antioxidant enzyme catalase increased by 30% at the 4^{th} day and by 15% at the 6^{th} day of the experiment, compared to the control. Biochemical parameters showed, at the end of the experiment on the 10th day, control levels of MDA and increased the activity of catalase, a major antioxidant defence enzyme. The couch grass cream application resulted in quickening the recovery by 4-5 days as compared with untreated control animals. The anti-inflammatory effects of the couch grass cream were comparable to the standard glucocorticoid cream activity (Petrova *et al.* 2009).

Effect on lipid metabolism

The effect of single and repeated oral administration of the lyophilized aqueous extract of rhizomes of *Agropyron repens* (20 mg/kg) on lipid metabolism in normal and streptozotocin-induced diabetic rats was tested by Maghrani *et al.* (2004). In normal rats, the aqueous extract induced a significant decrease in the plasma triglycerides concentrations 4 days and 1 week after repeated oral administration. This reduction was abolished 2 weeks after once daily repeated oral administration. A significant decrease of plasma cholesterol levels was observed only 1 week after repeated oral administration. In diabetic rats, the treatment caused a significant decrease in plasma cholesterol after a single and repeated oral administration. A strong decrease in cholesterol levels was observed 6 hours after a single oral administration of the extract. Four days after the repeated oral administration of the extract, the plasma cholesterol level was significantly decreased and remained still diminished after 2 weeks. Repeated oral administration of the aqueous extract of *Agropyron repens* rhizome caused a significant decrease in body weight 2 weeks after oral treatment. In severely hyperglycaemic rats, *Agropyron repens* extract treatment induced reduction of lipid levels and body weight.

Antidiabetic effects

The hypoglycaemic effect of an aqueous extract of *Agropyron repens* was investigated in normal and streptozotocin-induced diabetic rats. After a single oral administration (20 mg/kg) of the daily prepared and lyophilized aqueous extract (1 g/100 ml of water), a significant decrease in blood glucose levels in diabetic rats was observed. The blood glucose levels normalised 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 traditionally an aqueous extract of *Agropyron repens* rhizome is used in Morocco as an antidiabetic treatment (Eddouks *et al.* 2005, Eddouks *et al.* 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 2 and 8 hours after administration of the tested solutions. Other groups of mice received equivalent doses of *Valerianae radix* or *Radix Helenii* 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 the plants tested. The unspecific sedative effects of assayed plants with an unknown mechanism of action are discussed by the authors (Kiesewetter & Müller 1958).

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

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

Interactions - No data available.

Due to lack of data on pharmacokinetics of couch grass rhizome constituents, no relevant conclusions can be drawn.

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

The allelopathic influence of *Agropyron repens* on higher plants is described in numerous publications (Hagin & Bobnick 1991, Henderson 2002, Friebe *et al.* 1995, Korhammer & Haslinger 1994, Sánchez–Moreiras *et al.* 2004 and Weston *et al.* 1987) but it is not relevant for the safety of therapeutic use of the herbal substance and herbal preparations.

The phenolic glycoside fraction extracted from the dried quack grass roots is responsible not only for the allelopathic effect on seedlings of forage legumes but also for molluscidal effects on two slug species: *Deroceras reticulatum* (Müller 1999) and *Deroceras laeve* (Müller 1999, Hagin & Bobnick 1991). The main allelopathic substances in rhizomes of *Agropyron repens* were found to be 5-hydroxyindole-3-acetic acid and 5-hydroxytryptophan (Hagin & Bobnick 1991, Powell & Petroski 1992).

Weston *et al.* (1987) described the phytotoxic compounds after sequential partitioning of the aqueous extract of the quack grass shoots; the ether extract exhibited the most activity. From two flavonoid inhibitors isolated from the ether extract, one was recognized as tricin (5,7,4'-trihydroxy-3',5'-dimethoxyflavone). Both tricin and compound 2 caused 50% inhibition of radicle elongation of curly cress (*Lepidium sativum* L.) at concentration of 123.3 and 59.3 μg/ml respectively. These compounds may be released by exudation or degradation from both living and dead *Agropyron repens* shoots and rhizomes (Toai & Linscott 1979). Similar effects were shown by Penn & Lynch (1981; 1982), who found phytotoxic activity of both living and decaying couch rhizomes against the growth of seedlings of barley. They have shown that the anaerobic decay can generate phytotoxic concentrations of acetic and butyric acid.

From shoots and root exudates of 10-day old couch grass seedlings, several other phytotoxins were isolated such as cyclic hydroxamic acids: 2,4-dihydroxy-7-methoxy-2H—1,4-benzoxazin-3-one (DIMBOA - 0.02 mg/g), 2,4-dihydroxy-2H—1,4-benzoxazin-3-one (DIBOA – 0.5 mg/g) and the lactam derivative 2-hydroxy-1,4-benzoxazin-3-one (HBOA). Besides maleic, aconitic and citric acids, were isolated from the living intact seedlings of *Agropyron repens* vanilic acid, ferulic acid and β-hydroxybutyric acid in the range of 10 nmol/l (Friebe *et al.* 1995, Macías *et al.* 2006).

In famine, couch grass was traditionally a natural source of food.
In the USA, *Agropyron repens* is listed as GRAS (Generally Recognized As Safe) and its juice is used in several food supplements.

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 with maximal dose tested of 200 μ/plate.

Carcinogenicity

No published data could be found on the carcinogenicity of the couch grass rhizome and couch grass rhizome preparations.

Acute toxicity

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

Repeated dose toxicity

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

Reproductive and developmental toxicity

No data available.

Assessor's overall conclusions on toxicology

Practically, no toxicity studies on couch grass rhizome and couch grass rhizome preparations are available in the literature.

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

3.4. Overall conclusions on non-clinical data

Pharmacological activities of the rhizome support the traditional use of preparations containing *Agropyron repens* rhizome in the proposed indication in minor urinary complaints.

Toxicological data on couch grass rhizome are very limited, but neither the European tradition nor known constituents suggest that there is potential risk associated with the couch grass use. Due to the lack of data, no Community list entry for *Agropyron repens* rhizome can be established.

Oral administration of preparations from *Agropyron repens* rhizome 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. Treatment should be avoided because of possible complications due to hypokalaemia.

4. Clinical Data

4.1. Clinical Pharmacology

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

There are no data on human pharmacodynamics.

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

There are no data on human pharmacokinetics.

4.2. Clinical Efficacy

See below.

4.2.1. Dose response studies

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

4.2.2. Clinical studies (case studies and clinical trials)

Observational studies

Effect of fluid extract of *Agropyron repens* in urinary tract infections and irritable bladder

In an open clinical trial in 99 patients with micturition disorders (12 female and 87 male), a 20% ethanol fluid extract of *Agropyron repens* was 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. In result, 96% of patients estimated results as 'good' or 'very good'. Adverse effects were not recorded (Barsom 1981).

The efficacy and tolerability of a fluid extract of couch grass in 313 patients with urinary tract infections or irritable bladder was analysed in a multicenter open post-marketing study. The patients with diagnosis of irritable bladder, urethritis, cystitis and prostatitis were included to the test. The patients were treated on average for 12 days with 50-60 drops of 20% fluid ethanolic extract of *Agropyron repens*. Primary efficacy criterion was the clinically relevant improvement and change of urologic symptoms during the course of therapy: urge incontinence, painful micturition, dysuria, pollakisuria, nycturia and tenesmus. Dependent on the underlying urologic diagnosis, between 32% and 53% of the patients were completely 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 & Scheithe 2000).

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

No information available.

4.3. Overall conclusions on clinical pharmacology and efficacy

On the basis of published data, the quality of the available studies cannot be evaluated. There are no data available from controlled clinical studies.

Overall, the medicinal use of couch grass rhizome has to be regarded as traditional.

Administration of preparations of couch grass rhizome can be regarded as safe, especially at the recommended therapeutic doses and strength and for a short duration of use.

5. Clinical Safety/Pharmacovigilance

There are no adverse effects reported in the Member States, attention should however be paid to hypersensitivity to the active substance(s) and to other members of the Poaceae family.

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

There are no data from clinical trials available.

5.2. Patient exposure

None reported.

5.3. Adverse events and serious adverse events and deaths

None reported.

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

Intrinsic (including elderly and children)/extrinsic factors

There are no reports on the use of couch grass rhizome in children. The use of couch grass rhizome in children and adolescents under 18 years of age has not been established and is not recommended due to lack of adequate data.

Use in pregnancy and lactation.

The couch grass rhizome should not be used during pregnancy and lactation.
No data available on fertility.

Overdose

None reported.

Drug interactions

None reported for couch grass rhizome preparations.

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

None reported.

5.6. Overall conclusions on clinical safety

There are no reports of adverse effects of *Agropyron repens* from Member States of the European Union.

6. Overall conclusions

Available data are sufficient to establish a Community 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).

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

Due to the lack of adequate genotoxicity testing and lack of data on acute and chronic toxicity, repeated dose toxicity, carcinogenicity, reproductive and developmental toxicity, a Community list entry for *Agropyron repens* (L.) P. Beauv., rhizoma cannot be recommended.

Annex

List of references