EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Betula pendula* Roth and/or *Betula pubescens* Ehrh. as well as hybrids of both species, folium

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)		*Betula pendula* Roth and/or *Betula pubescens* Ehrh. as well as hybrids of both species, folium
Herbal preparation(s)		a) Comminuted herbal substance b) Powdered herbal substance c) Dry extract (DER 3-8:1), extraction solvent water d) Liquid extract prepared from fresh leaves (DER 1:2-2.4), extraction solvent water e) Liquid extract prepared from fresh leaves stabilised by 96% ethanol vapours (DER 1:1), extraction solvent ethanol 50-60% (V/V)
Pharmaceutical form(s)		Comminuted herbal substance as herbal tea for oral use. Herbal preparations in solid or liquid dosage forms for oral use.
First assessment	Rapporteur(s)	A. Raal
	Peer-reviewer	H. Pittner
Revision	Rapporteur(s)	R. Länger
	Peer-reviewer	M. Heroutovà

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Introduction

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

- Herbal substance(s)

Definition according to the European Pharmacopoeia (2014): Whole or fragmented dried leaves of *Betula pendula* Roth and/or *Betula pubescens* Ehrh. as well as hybrids of both species. They contain no less than 1.5% of flavonoids, expressed as hyperoside ($C_{21}H_{20}O_{12}$ = 464.4), with reference to the dried drug.

Birch leaves contain 1-3.5% of flavonol glycosides, basically hyperoside and other quercetin glycosides (e.g. quercetin-3-O-glucuronide, quercetin-3-O-rhamnoside) together with glycosides of kaempferol and myricetin (Keinänen & Julkunen-Tiitto 1996; Ossipov *et al*. 1996; Dallenbach-Tölke *et al*. 1987a; Dallenbach-Tölke *et al*. 1987b; Dallenbach-Tölke *et al.* 1986; Pokhilo *et al.* 1983; Hänsel & Sticher 2010).

Carnat *et al.* (1996) analysed the content of flavonoids in the dried leaves of *Betula pendula* (14 batches of commercial origin) and *Betula pubescens* (3 batches). They found in both species respectively: total flavonoids 3.29 and 2.77%, hyperoside 0.80 and 0.77%, avicularin 0.57 and 0.26%, galactosyl-3 myricetol 0.37 and 0.18%, glucuronyl-3 quercetol 0.25 and 0.36%, quercitrin 0.14 and 0.12%. The flavonoid levels were higher in young leaves compared to old leaves of *Betula pendula.*

Flavonoid aglycons found on the surfaces of *Betula* spp. leaves may constitute up to 10% of the dry weight of the leaf. Birch species with diploid chromosome sets did not contain any of the flavanones that were present in the leaves of other species (Lahtinen *et al.* 2006).

Among other phenolic compounds 3,4'-dihydroxypropiophenone 3-glucoside, caffeic acid and chlorogenic acid (Keinänen & Julkunen-Tiitto 1996; Ossipov *et al.* 1996), lignans, diarylheptanoids (Wang & Pei 2000), triterpene alcohols and malonyl esters of the dammarene type (Pokhilo *et al.* 1983; Fischer & Seiler 1959; Fischer & Seiler 1961; Baranov *et al.* 1983; Pokhilo *et al.* 1986; Rickling 1992; Hilpisch *et al.* 1997, Hänsel & Sticher 2010) are present.

Seasonal dynamics of water-soluble phenols in *Betula pendula* leaves in mosaic urban environment and in different weather conditions during vegetation period was studied. The maximum content of phenols was observed in the beginning of May with a transition to a lower level in the middle of July and rising in late summer and autumn. The tendency of a decrease in the phenols content during drought years was observed (Kavelenova *et al.* 2001).

The birch leaves contain polymeric proanthocyanidins; their total content (expressed as dry weight) was 39 mg/g in *Betula pendula* (Karonen *et al.* 2006).

The content of lipids and fatty acids in the leaves of *Betula pendula* and *Betula pubescens* change during their development. During leaf development a decrease of linoleic acid relative content and an increase of linolenic acid were observed. In yellowed leaves there was a high level of linolenic acid in all tested lipid fractions (neutral, glyco- and phospholipid) and the part of saturated fatty acids was large in the neutral and phospholipid fractions (Shulyakovskaya *et al.* 2004).

The birch leaves contain 0.05-0.1% of essential oil consisting primarily of sesquiterpene oxides (Blaschek *et al.* 2013).

Thirty-three components were identified from a carbon dioxide extract of *Betula pendula* leaves, the major ones being α-pinene (2.22%), bornyl acetate (2.736%), lambertianic acid (2.448%), and n-tricosan (2.50%) (Demina *et al.* 2006).

The concentration of potassium in Betulae folium (*Betula pendula*) is 8045 µg/g dry matter, in a decoction 4725 µg/g were detected. Only 40 µg/g of sodium were found in the dried leaves (Szentmihályi *et al.* 1998).

Further constituents: vitamins (up to 2-8%, among them 0.5% ascorbic acid, nicotinic acid), carotenes, coumarins (0.44%), tannins (5-9%) and sterols (Turova *et al.* 1987; Lavrjonov & Lavrjonova, 1999).

- Herbal preparation(s)

  a) Comminuted herbal substance

  b) Powdered herbal substance

  c) Dry extract (DER 3-8:1), extraction solvent water

  d) Liquid extract prepared from fresh leaves (DER 1:2-2.4), extraction solvent water

  e) Liquid extract prepared from fresh leaves stabilised by 96% ethanol vapours (DER 1:1), extraction solvent ethanol 50-60% (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.

Not applicable.

1.2. Search and assessment methodology

Databases assessed: PubMed, Scopus

Search terms: Betula pendula, Betula pubescens

Exclusion criteria: allergy to birch pollen

Inclusion criteria: constituents, clinical trial, pharmacology, safety

Other resources: University library of the University of Vienna

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 Posology Duration of use	Regulatory status (date, member state)
1. Comminuted herbal substance	Traditional herbal medicinal product used additionally as a mild diuretic in the minor ailments of the urinary tract.	Herbal tea (infusion) Single dose: 1.9 g Max. daily dose: 12 g	Poland Since more than 30 years
2. Dry extract from Betulae folium (4-8:1), extraction solvent: water	To increase the amount of urine to achieve flushing of the urinary tract in case of bacterial and inflammatory diseases of the lower urinary tract. Adjuvant treatment of rheumatic complaints.	Coated tablet 300 mg Adults: 1 coated tablet 3-4 times daily	Germany At least since 1976 WEU
3. Liquid extract prepared from fresh leaves (DER 1:2-2.4), extraction solvent water (often referred as 'expressed juice')	Adjuvant treatment of rheumatic complaints. To increase the amount of urine to achieve flushing of the urinary tract in case of inflammatory diseases of the lower urinary tract and in case of renal gravel.	>12 years: 15 ml expressed juice 2-3 times daily	Germany At least since 1976 WEU

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory status (date, member state)
4. Dry extract from Betulae folium (4-8:1), extraction solvent: water	To increase the amount of urine to achieve flushing of the urinary tract in case of bacterial and inflammatory diseases of the lower urinary tract and in case of renal gravel.	Effervescent tablet 500 mg >12 years: 1 effervescent tablet 3 times daily	Germany Since 1997 WEU
5. Dry extract from Betulae folium (4-8:1), extraction solvent: water	To increase the amount of urine to achieve flushing of the urinary tract in case of bacterial and inflammatory diseases of the lower urinary tract.	Coated tablet 300 mg Adults: 1 coated tablet 3-4 times daily	Germany Since 1998 WEU
6. Dry extract from Betulae folium (4-8:1), extraction solvent: water	To increase the amount of urine to achieve flushing of the lower urinary tract as prophylaxis.	Coated tablet 182.7 mg >12 years: 2 coated tablets 3 times daily	Germany At least since 1976 WEU
7. Dry extract from Betulae folium (3-5.5:1), extraction solvent: water	To increase the amount of urine to achieve flushing of the urinary tract in case of bacterial and inflammatory diseases of the lower urinary tract and in case of renal gravel.	Capsule, soft 277.5 mg >12 years: 2 capsules, soft 3 times daily	Germany At least since 1976 WEU
8. Dry extract from Betulae folium (4-8:1), extraction solvent: water	To increase the amount of urine to achieve flushing of the urinary tract in case of bacterial and inflammatory diseases of the lower urinary tract and in case of renal gravel.	Coated tablet 450 mg >12 years: 1 coated tablet 3 times daily	Germany Since 2005 WEU
9. Powdered herbal substance	Traditionally used to promote urinary and digestive elimination functions. Traditionally used to promote the renal elimination of water.	Hard capsule containing 325 mg powdered herbal substance. 2 capsules 2 times daily	France 1981–2011

Active substance	Indication	Pharmaceutical form Posology Duration of use	Regulatory status (date, member state)
10. Liquid extract prepared from fresh leaves stabilised by 96% ethanol vapours (DER 1:1), extraction solvent ethanol 50-60% (V/V)	Chronic urinary tract symptoms with reduced excretion of urine. As an adjuvant in urolithiasis, rheumatic disease and gout.	Single dose: 2.5 ml 3 times daily.	Poland Since 1956 See details below.

Stabilised juices (#10 in table 1) are obtained from fresh herbal crude drugs, usually after preliminary inactivation of the enzymes, differently from expressed juices. They exist as a pharmaceutical form of herbal medicinal products in Poland for several dozen years. The technology of stabilised juice was described in 1973 by Lutomski in "Technology of Herbal Drug" PZWL Warsaw (Lutomski & Małek 1973) and then in consecutive edition of "Farmacja stosowana" by Janicki *et al.* in 1996, 1998, 2000, 2001 and 2006 (Janicki & Fiebieg, 1996). Fresh leaves, previously cleaned and comminuted, are subjected to stabilisation with 96% ethanol vapours in autoclaves under 0.2 MPa for 2-4 hours. Thus, stabilised juice is obtained by maceration of prepared fresh leaves with a solvent, consisting of the ethanolic extract fluid after stabilisation, water and 96% ethanol, in a ratio ensuring that the content of the ethanol in the finished product is 50-60% (Janicki & Fiebieg 1996).

Stabilised juice of Succus Betulae folii recens for oral use, is presented on the Polish pharmaceutical market since 1956 (Lutomski & Małek 1973; Janicki & Fiebieg 1996). In the European Union herbal monograph on Betulae folium the stabilised juice prepared from fresh birch leaves is mentioned as the liquid extract from fresh leaves stabilised by 96% ethanol vapours (1:1, extraction solvent ethanol 50-60% (V/V)).

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

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

Birch leaf is a standard component in combination herbal teas used for increasing the amount of urine.

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

As mentioned by Pliny, the therapeutic use of birch probably goes back to the ancient Greeks and Romans. It was used by Teutonic tribes in potions to promote strength and beauty. The opinions however differ with respect to the etymology of the name Betula. Probably it derives from the ancient Sanskrit word 'burga' which means, 'a tree whose bark is for writing on'. Another opinion derives it from the Gallic word 'betu', which translates as 'heart' from the Latin 'betula', 'betulla' (bitumen). As written by Pliny, the Gauls produced a form of bitumen from the juice of the birch tree. The English

word birch appears in a similar form in all Germanic languages, and is thought to be related to the Sanskrit root, 'bharg' (to shine, to be bright) (Herb CD 2001; 2003). The Anglo-Saxon name for birch was beorc or birce. It probably derived from a word for 'white' or 'shining' (Bunney 1993). From its uses in boat-building and roofing it is also connected with the word 'beorgan' (to protect or shelter) (Grieve 1998).

Hildegard von Bingen (1098-1179) was familiar with the use of the bark of birch for wound healing (Herb CD 2001).

The English doctor, apothecary and astrologer Nicolas Culpeper (1616-1654) wrote his book 'Culpeper's Complete Herbal and English Physician Enlarged' where he offers remedies for all ills known to 17th century society. About birch Culpeper mentioned: "The juice of the leaves, while they are young, or the distilled water of them, or the water that comes from the tree being bored with an auger, and distilled afterwards; any of these being drank for some days together, is available to break the stone in the kidneys and bladder, and is good also to wash sore mouths" (Culpeper 1995).

Albrecht von Haller (1708-1777) described a diaphoretic and diuretic action of the juice and recommended it for "complaints connected with heaviness of the humours and blockages of the arteries" (Herb CD 2001; 2003).

Generally, in folk medicine, the leaves are used as a blood purifier and for gout and rheumatism. Externally, preparations of the leaves are used for hair loss and dandruff (Gruenwald *et al*. 2004).

In Russian folk medicine birch is a popular remedy for a wide range of complaints (Herb CD 2001). For example, the bath of leaves was in use for rheumatism, arthritis, gout and other pains (Lavrjonov & Lavrjonova 1999; 2003). The usage of *Betula pendula* and *Betula pubescens* is similar (Yakovlev & Blinova 1999).

In Estonian ethnomedicine birch leaves are a popular remedy for increasing diuresis (Tammeorg *et al*. 1984).

According to The Dispensatory of the United States of America (Remington *et al*. 1918), birch leaves have been employed in the form of infusion in gout, rheumatism and dropsy.

Nowadays birch leaves are used for bacterial and inflammatory diseases of the urinary tract and for kidney gravel. They are also used for increasing the amount of urine and for rheumatic ailments. Birch leaf is also employed as an astringent and it is used as a mouthwash. Due to the complex composition, it is understandable why birch leaves are more accurately described as an antidyscratic agent rather than a mere aquaretic (Gruenwald *et al*. 2004; Muravjova *et al.* 2002; Herb CD 2000; Muravjova 1991; Ladynina & Morozova 1987; Evans 2000; Chevallier 1996; Sokolov & Zamotaev 1988; Gehrmann *et al.* 2005; Turova 1974; Yakovlev & Blinova 1996; ESCOP 2003).

Usually daily doses of 2-3 g leaves are used for making a tea. One teaspoon of comminuted herbal substance corresponds approximately to 1 g dried leaves. Preparation of the herbal tea: 150 ml of boiled water are added to 1 teaspoon of drug, allowed to stand for 10-15 minutes and strained (Wichtl 2009).

The German Commission E attributes a diuretic effect to birch leaf; it is used in inflammation and infection of the urinary tract, in urolithiasis and for the supportive treatment of rheumatic ailments (Blumenthal 1998).

Table 2: Overview of historical data

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
Comminuted herbal substance as herbal tea		2-3 g as herbal tea Several times daily	German Commission E 1986 (according to Blumenthal 1998)

2.3. Overall conclusions on medicinal use

The herbal preparations mentioned below (table 3) fulfil all criteria for traditional herbal medicinal products and are therefore proposed for inclusion into the European Union Monograph.

Table 3: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
Comminuted herbal substance as herbal tea	Traditional herbal medicinal product used additionally as a mild diuretic in the minor ailments of the urinary tract.	Single dose 1.9 g Max. daily dose 12 g Single dose 2-3 g Several times daily Single dose 2 g Several times daily	Poland, more than 30 years Germany, more than 30 years German Standard Marketing Authorization
Powdered herbal substance	Traditionally used to promote urinary and digestive elimination functions. Traditionally used to promote the renal elimination of water.	Hard capsule containing 325 mg powdered herbal substance. 2 capsules 2 times daily	France, 1981-2011
Dry extract (DER 3-8:1), extraction solvent water	To increase the amount of urine to achieve flushing of the lower urinary tract as prophylaxis.	Single dose 300 – 560 mg Daily dose 900 – 1665 mg As the dry extract can be considered as a dried herbal tea the posology for the monograph is widened to a single dose of 0.25 – 1000 mg up to 4 times daily.	Germany, at least since 1976
Liquid extract (fresh leaves)	Adjuvant treatment of rheumatic complaints. To increase the amount of urine to achieve flushing of	Single dose 15 ml Daily dose 30-45 ml	Germany, at least since 1976

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	the urinary tract in case of inflammatory diseases of the lower urinary tract and in case of renal gravel.		
Liquid extract (stabilised)	Traditional herbal medicinal product used additionally as a mild diuretic in the minor ailments of the urinary tract.	Single dose 2.5 ml Daily dose 7.5 ml	Poland, since 1956

The proposed indication is: Traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

3. Non-Clinical Data

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

3.1.1. Primary pharmacodynamics

Herbal preparations:

After oral administration of a birch leaf tea (infusion) to rabbits, urine volume and chloride excretion increased dose dependently up to about 19% and 41%, respectively (concrete dosing not clearly stated). In mice urine volume increased up to 42% and chloride excretion up to 128% (Vollmer 1937). In rats an infusion of Betulae folium failed to increase the volume of urine volume. However the excretion of urea and chloride increased (Vollmer & Hübner 1937).

Young birch leaves administered orally to rats and mice did not produce these above mentioned effects (Elbanowska & Kaczmarek 1966). However, the oral administration of powdered birch leaves to dogs at 240 mg/kg body weight increased the urine volume by 13.8% after 2 hours; a flavonoid fraction extracted from dried leaves at 14 mg/kg increased the urine volume by 2.8% (Borkowski 1960).

More recent studies in rats showed an increased excretion of urine after the oral administration of aqueous (148 mg% flavonoid content) and alcoholic (48 and 70 mg% flavonoid content) extracts rich in flavonoids. Best results were achieved with the aqueous extract. From a dose of 2.66 ml/kg up the amount of excreted urine increased significantly. With a dose of 5.32 ml/kg BW (corresponding to approximately 7.5 mg total flavonoids/kg BW) an increase in urine excretion of 54% was observed after 3 hours. The excretion of sodium, potassium or chloride was only slightly affected. The authors concluded that the diuretic effect of Betulae folium was partly, but not entirely, due to flavonoids and estimated that in humans at least 50 mg of flavonoids per day would be necessary to produce a diuretic effect (Schilcher 1984; Schilcher 1987; Schilcher & Rau 1988; Schilcher *et al.* 1989a; Schilcher *et al.* 1989b).

An ethanolic extract from Betulae folium (extraction solvent ethanol 70%) was fractionated (butanol, water). The oral administration to rats (ethanolic extract corresponding to 43 mg total flavonoids/kg BW; butanol extract corresponding to 192 mg total flavonoids/kg BW; water extract corresponding to 0.7 mg total flavonoids/kg BW) did neither change the amount of excreted urine nor the amount of excreted ions (Rickling & Glombitza 1992).

Wojnicz *et al.* (2012) investigated extracts of several herbal substances regarding their effect on virulence factor expression and biofilm formation by uropathogenic *E. coli*. A hot water extract of Betulae folium reduced the motility of *E. coli* in a dose-dependent manner (concentrations between 5 and 20 mg/ml). Compared to extracts of other medicinal plants the inhibition of biofilm formation by *E. coli* was very weak.

Rafsanjany *et al.* (2013) investigated an ethanolic extract of Betulae folium (ethanol 50% V/V) regarding the adhesion of uropathogenic *E. coli* on the human bladder cell line T24. The extract showed a significant inhibition of adhesion with an IC_{50} of 415 µg/ml.

Isolated constituents:

Various flavonoids were investigated for their inhibitory activity on specific neuropeptide hydrolases which regulate the formation of urine through excretion of sodium ions (Borman & Melzig 2000). Quercetin inhibited *in vitro* in a concentration of 300 µM the neutral endopeptidase NEP up to 73%.

A fraction containing a mixture of dammarane esters, isolated from leaves of *Betula pendula*, did not exhibit diuretic activity when tested *p.o.* in male Wistar rats. Rickling & Glombitza (1993) also concluded that former reports on the presence of saponins in birch leaf extracts could not be confirmed and that the haemolytic activity of the extracts, which was earlier ascribed to saponins, is caused by the dammarane esters.

3.1.2. Secondary pharmacodynamics

A water extract from birch leaves has been reported to have virostatic and cytostatic properties *in vitro* (Petkov 1988).

A carbon dioxide extract of *Betula pendula* leaves showed antibacterial activity against *Staphylococcus aureus* but not antiviral activity against monkey pox virus. The authors recommended the extract for use as an antibacterial preservative for cosmetic uses at a concentration of 0.045% in combination with fungicides (Demina *et al.* 2006).

Fever induced by baker's yeast in rats can be positively influenced by an aqueous extract from birch leaves (25% Betulae folium, 75% water, no more details available) in a dose of 4 ml/100 g BW. This effect was rather weak and short lasting as compared to the effect of acetylsalicylic acid. The extract was ineffective in the carrageenin edema model of the rats paw (Klinger *et al.* 1989).

Rauha *et al.* (2000) investigated the antimicrobial effects of an extract of Betulae folium prepared with 70% acetone. 500 µg of the total extract exhibited a significant activity against *Staphylococcus aureus* (strain DSM 20231) but not against other bacteria of fungi.

3.1.3. Safety pharmacology

Duric *et al.* (2008) investigated the potential of dermal irritation or sensibilization of a decoction of birch leaves in a cream base (information on strenght is missing) in mice, rats and rabbits. No signs of dermal irritation or sensibilsation could be detected.

3.1.4. Pharmacodynamic interactions

No data available.

3.1.5. Conclusions

Aqueous infusions and decoctions, as well as the leaves and aqueous-ethanolic, butanolic and carbon dioxide extracts from Betulae folium as well as fractions and isolated individual substances and their groups have been investigated in several pharmacological animal models for their diuretic and saluretic properties. Unfortunately, in many publications the correct specifications of solvent and/or drug-extract ratio are missing. The findings are inconclusive. However, the results support the plausibility of the traditional use of Betulae folium as a mild aquaretic.

The aquaretic effect correlated with the amount of flavonoids, however the effects achieved with isolated flavonoids are weaker compared to the entire extract.

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

No data available.

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

3.3.1. Single dose toxicity

No data available.

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

A commercial extract of birch leaf (preparation not clearly stated) showed a very weak mutagenic response in the AMES test in *Salmonella typhimurium* strains TA 98 and TA 100 with and without metabolic activation by the S9 mix (Göggelmann & Schimmer 1986). The authors assume that quercetin may be responsible for the observed effects. Most investigations showed a lack of carcinogenicity of quercetin (Bertram 1989).

3.3.4. Carcinogenicity

No data available.

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 available.

3.3.8. Conclusions

The available toxicological data are poor. However, constituents which might bear a risk are not known for birch leaves. A birch leaf extract showed weak mutagenic effects which may be ascribed to flavonols such as quercetin. Quercetin is known to give positive results in *in vitro* tests on genotoxicity, while *in vivo,* no such signs could be found. Due to the lack of adequate data on genotoxicity a list entry cannot be proposed.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on Betulae folium to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.

Specific data on pharmacokinetics and interactions are not available.

Non-clinical information on the safety of Betulae folium is scarce.

Adequate tests on genotoxicity have not been performed.

Tests on reproductive toxicity carcinogenicity have not been performed.

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

The oral administration can be regarded as safe for traditionally used doses with the exception of patients with severe renal or cardiac disease e.g. renal and heart failure.

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 data available.

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

No data available.

4.2. Clinical efficacy

4.2.1. Dose response studies

As mentioned by Schilcher & Wülkner (1992), a minimum of 50 mg of the total flavonoids per day (2-3 g of drug as tea several times in day) is necessary for increasing the amount of urine. A sufficient dose of flavonoids is principally available also by using dry extracts rich in flavonoids in capsules, sugar-coated tablets and tablets (Schilcher & Wülkner 1992; Schilcher & Emmrich 1992).

4.2.2. Clinical studies (case studies and clinical trials)

Early studies in few healthy adults did not show a significant increase in diuresis after administration of an infusion (1:10) of birch leaf compared to the effect of pure water (Marx & Büchmann 1937; Braun 1941).

In a randomised, double-blind, placebo-controlled pilot study, 15 patients with infections of the lower urinary tract were treated with 4 cups of birch leaf tea or placebo tea daily for 20 days. Microbial counts in the urine of the birch leaf tea group decreased by 39% compared to 18% in the placebo group. At the end of the study, 3 out of 7 patients in the verum group and 1 out of 6 in the control group no longer suffered from a urinary tract infection (Engesser *et al.* 1998).

Müller & Schneider (1999) reported a non-interventional study: 1066 patients were classified into four groups: 73.8% suffered from urinary tract infections, cystitis or other inflammatory complaints, 14.2% from irritable bladder, 9.3% from stones and 2.7% from miscellaneous complaints. 56% of patients in the first group also received antibiotic therapy. All patients received a dry aqueous extract of birch leaf (4-8:1) at various daily doses (from 180 to 1080 mg or more) for irrigation of the urinary tract. In most cases the treatment period was 2-4 week. After this period the symptoms disappeared in 78% of patients in the first group, in 65% in the second group and in 65% in the third group. The symptoms disappeared in 80% of patients treated with, and in 75% of those going without antibiotics. Both physicians and patients considered the efficacy to be very good (39% and 48% respectively) or good (52% and 44% respectively).

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

No data available.

4.4. Overall conclusions on clinical pharmacology and efficacy

Only few clinical trials were performed. The data are not sufficient for accepting a well-established use of herbal preparations of birch leaf. No information is available on dose-response relationship and on clinical studies in special populations, such as elderly and children. Based on the documented experience a duration of use of 2-4 weeks is proposed.

5. Clinical Safety/Pharmacovigilance

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

No data available.

5.2. Patient exposure

Limited data from controlled clinical trials (15 patients) and from non-interventional studies (1066 patients) are available. No special risks have been identified.

If patients with known intolerance to birch leaves are excluded, a traditional use is possible if administration follows the instructions as specified in the monograph.

5.3. Adverse events, serious adverse events and deaths

After the use of a dry extract from birch leaves some adverse reactions, but non-serious, such as skin disorders (itching, rash), gastro-intestinal system disorders (diarrhoea, nausea, stomach upset, etc), metabolic and nutritional disorders (oedema of the legs), and general disorders (allergic reaction with dizziness, nausea, swelling of nasal mucous membrane, peripheral oedema) have been reported (Dr. Willmar Schwabe Arzneimittel 1998).

In an open post-marketing study, mild adverse effects were reported in only 8 out of 1066 patients who received a dry aqueous extract of birch leaf (4-8:1) at daily doses of up to 1080 mg for 2-4 weeks (Müller & Schneider 1999).

Fresh birch sap and crushed leaf of birch were tested with the scratch chamber method in 117 atopic persons, 74 of whom were allergic and 43 were non-allergic to birch pollen, and also in 33 control patients. The positive reactions to birch sap were seen in 39% and to leaf in 28% of the allergic patients, but in none of the control patients. The authors conclude that birch leaves may cause contact urticaria (Lahti & Hannuksela 1980).

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

No data available. As for other monographs for the same indication the use in children under 12 years of age is not recommended.

5.5.2. Contraindications

No data available.

For safety reasons the use in persons with hypersensitivity to birch pollen as well as in conditions where a reduced fluid intake is recommended is contraindicated.

5.5.3. Special Warnings and precautions for use

No data available.

The following standard sentence is proposed for the monograph: If complaints or 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

No data available.

5.5.5. Fertility, pregnancy and lactation

No data available.

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

No studies have been performed.

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

No serious adverse effects have been reported from human studies with birch leaf. There are no data available about serious adverse events and deaths, drug interactions, use in pregnancy and lactation, overdose, drug abuse, withdrawal and rebound, effects on ability to drive or operate machinery or impairment of mental ability.

The long standing medicinal use does not indicate a special risk for patients taking herbal preparations of birch leaf.

6. Overall conclusions (benefit-risk assessment)

The therapeutic use of birch leaves goes back to the ethnomedicine of ancient times. The positive effects of Betulae folium, to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints, have long been recognised empirically.

The herbal preparations comminuted herbal substance, powdered herbal substance, dry extract (DER 3-8:1, extraction solvent water), liquid extract prepared from fresh leaves (DER 1:2-2.4, extraction solvent water) and liquid extract prepared from fresh leaves (stabilised by 96% ethanol vapours, DER 1:1, extraction solvent ethanol 50-60% V/V) fulfil the requirement for at least 30 years of medicinal use at a specified strength and specified posology, according to Directive 2001/83/EC as amended.

The efficacy is plausible on the basis of long-standing use and experience for use as a traditional herbal medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints.

Only two clinical trials which included herbal preparations of Betulae folium are published. The design of the clinical studies where patients with urinary tract infections were included was insufficient in order to support well-established use for this indication. No clinical trials supporting the indication ‘medicinal product to increase the amount of urine to achieve flushing of the urinary tract as an adjuvant in minor urinary complaints’ are published. Therefore the clinical data are not sufficient to support a well-established use.

Due to the lack of sufficient safety data the use of birch leaf cannot be recommended during pregnancy and breast-feeding. As no safety data from the use in children are available, the use of Betulae folium is not recommended in children under 12 years of age. However, based on the long-standing medicinal use, the absence of constituents with toxicological concern, as well as the absence of reports of serious adverse events, a sufficient degree of safety as necessary for traditional herbal medicinal products can be assumed.

In conclusion, preparations from Betulae folium can be regarded as traditional herbal medicinal products.

Neither constituents with known therapeutic activity nor active markers contributing to the therapeutic activity can be recognised by the HMPC.

A European Union list entry is not supported due to lack of adequate data on genotoxicity.

Annex

List of references