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Betula pendula Roth; *Betula pubescens* Ehrh., folium

**ASSESSMENT REPORT FOR THE DEVELOPMENT OF COMMUNITY MONOGRAPHS
AND FOR INCLUSION OF HERBAL SUBSTANCE(S), PREPARATION(S) OR
COMBINATIONS THEREOF IN THE LIST**

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ASSESSMENT REPORT

FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH TRADITIONAL USE

Betula pendula Roth; *Betula pubescens* Ehrh., folium

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Betula pendula</i> Roth and/or <i>Betula pubescens</i> Ehrh. as well as hybrids of both species, folium (birch leaf)
Herbal preparation(s)	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) Liquid extract from fresh leaves stabilised by 96% ethanol vapours (1:1, 50-60 % (V/V) ethanol)
Pharmaceutical forms	Herbal substance or herbal preparations in solid or liquid dosage forms for oral use
Rapporteur	Dr A. Raal

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I. REGULATORY STATUS OVERVIEW

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'

Member State	Regulatory Status				Comments
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Belgium	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
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II.1. INTRODUCTION

This assessment report reviews the scientific data available for herbal preparations of *Betula pendula* Roth and *Betula pubescens* Ehrh. as well as hybrids of both species, folium (birch leaf).

The report focuses on findings with aqueous and aqueous - ethanolic extracts and tea since clinical experience has been collected mainly with these types of preparations, and they were used in most preclinical and clinical trials.

Other preparations used for a long period like the bugs, tar and fresh plant juice are discussed in section II.4. 'Traditional use'.

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

- Herbal substance(s)

The whole or fragmented dried leaves of *Betula pendula* and/or *B. pubescens* as well as hybrids of both species. They contain not less than 1.5% of flavonoids, calculated as hyperoside ($C_{21}H_{20}O_{12} = 464.4$), with reference to the dried drug (European Pharmacopoeia, 2005).
- Herbal preparation(s)
 - 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)
 - liquid extract from fresh leaves stabilised by 96% ethanol (1:1, 50-60 % (V/V) ethanol)

Stabilised juices 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 Warszawa (Lutomski and Małek, 1973) and then in consecutive edition of "Farmacja stosowana" by Janicki et al. in 1996, 1998, 2000, 2001 and 2006 (Janicki and 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. Stabilised juice is obtained from thus prepared fresh leaves by their maceration with the solvent prepared from ethanolic extract fluid obtained after stabilisation, 96% ethanol and water, in a ration ensuring that the content of ethanol is in finished product is 50-60% (Janicki and Fiebieg, 1996).

Stabilised juice of *Succus Betulae folii recens* for oral use, is presented on the Polish pharmaceutical market since 1956 (Lutomski and Małek, 1973; Janicki and Fiebieg, 1996). In the Community 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, 50-60% (V/V) ethanol).

II.1.2. Chemical composition of herbal substance

II.1.2.1. Flavonoids and other phenolic compounds

The birch leaves contain 1-3% of flavonol glycosides, basically hyperoside and other quercetin glycosides together with glycosides of kaempferol and myricetin (Keinänen and 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; Pawlowska, 1982; Steinegger and Hänsel, 1992; Schier et al, 1994; Brühl 1984; Robbers and Tyler, 2000, Bradley, 2006); among other phenolic compounds 3,4'-dihydroxypropiophenone 3-glucoside, caffeic acid and chlorogenic acid (Keinänen and Julkunen-

Tiitto, 1996; Ossipov et al, 1996), lignans, diarylheptanoids (Wang and Pei, 2000b; Wang and Pei, 2001; Hänsel and Sticher, 2007); also triterpene alcohols and malonyl esters of the dimmarenene type (Pokhilo et al, 1983; Fischer and Seiler, 1959; Fischer and Seiler, 1961; Baranov et al, 1983; Pokhilo et al, 1988; Pokhilo et al, 1986; Rickling, 1992; Hilpisch et al, 1997; Pokhilo and Uvarova, 1998), and saponins (Kroeber, 1924; Kofler and Steidl, 1934; Tamas et al, 1978) are present.

The content of flavonoids in the samples of birch leaves ranges 2.3-3.5%, as calculated with reference to hyperoside (Kurkin and Stenyaeva, 2004). 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).

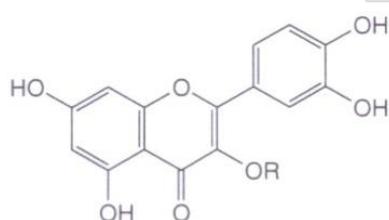
In (Hänsel and Sticher, 2007) the following flavonoids are mentioned in the leaves of birch: Quercetin-3-O-galactoside (=hyperoside), quercetin-3-O-glucuronide, myricetin-3-O-galactoside, quercetin-3-O-rhamnoside (=quercitrin), as well as other quercetine glycosides.

Seasonal dynamics of water-soluble phenols in *B. pendula* leaves in mosaic urban environment and in different weather conditions during vegetation period was studied. The maximum of phenol content was observed in the first and second decades 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 phenol content during drought years was observed (Kavelenova et al, 2001).

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

Carnat et al (1996) analyzed the content of flavonoids in the dried leaves of *B. pendula* (14 batches of commercial origin) and *B. 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 and lower in old leaves of *B. pendula*.

The chemical structures of quercetin and hyperoside as main flavonoids are as follows (Evans, 2000)



Quercetin; R = H

Hyperoside; R = galactosyl

II.1.2.2. Other constituents

The content of the lipids and the fatty acid compound of their fractions in the leaves of *B. pendula* and *B. pubescens* change according to the phase of their development. The growth of a leaf blade is accompanied by a change of the lipid fractions' fatty acid compound. There is a decrease of linoleic acid relative content (18:2) and an increase of linolenic acid (18:3).

In yellowed leaves in all lipids fractions there is a high level of linolenic acid and in neutral and phospholipids the part of saturate fatty acids is large (Shulyakovskaya et al, 2004).

Thirty-three components were identified from the carbon dioxide extract of *B. 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).

Four diarylheptanoids were isolated from leaves of *B. platyphylla* and identified as acerogenin E, (3R)-3,5'-dihydroxy-4'-methoxy-3',4''-oxo-1,7-diphenyl-1-heptene, 15-methoxy-17-O-methyl-7-oxoacerogenin E, and acerogenin K (Wang and Pei, 2001). Also a new monoterpene glucoside, (2E,6Z)-2,6-dimethyl-8- β -D-glucosyloxy-2,6-octadienoic acid (Wang et al, 2001a), and a new caffeoylquinic lactone, named neochlorogenic lactone (Wang et al, 2001b) were isolated from the leaves of *B. platyphylla*.

A series of phenols and acids were isolated from the leaves of *Betula platyphylla* Suk: 1,2-dihydroxybenzene, 4-hydroxybenzaldehyde, 1,4-dihydroxybenzene, 3,4-dihydroxybenzoic acid, 4-hydroxy-3-methoxybenzoic acid, 2-furoic acid, gallic acid, succinic acid and β -sitosterol (Wang and Pei, 2000a).

The accumulation of the metals such as Cu, Ca, Mn, Fe, Pb, Cd, and Sr in the leaves and branches of the birch trees was investigated as well as in different parts of the crown, and also in soil samples. The planting of *Betula pendula* Roth birch trees is recommended to reduce the environmental pollution with metals (Ginijatullin and Kulagin, 2004).

There are also essential oil (0.04-0.05%), vitamins (up to 2-8%) of ascorbic acid, nicotinic acid, carotenes, etc), coumarins (0.44%), tannins (5-9%), saponins (up to 3.2%), sterols, etc in the leaves of *B. pedula* (Turova et al, 1987; Lavrjonov and Lavrjonova, 1999). The content of ascorbic acid mentioned in Robbers and Tyler (2000) seems to be more realistic (0.5%).

The content of essential oil of leaves is similar to the content of essential oil of buds (3,5-6% of essential oil): Betulol, betulenic acid, naphthalin, sesquiterpenes (Lavrjonov and Lavrjonova, 1999).

II.1.2.3. Assessor's conclusions on chemical composition

The chemical composition of birch leaves has been investigated quite extensively. The characteristic components of *Betulae folium* are flavonoids: Hyperoside and other quercetin glycosides together with glycosides of kaempferol and myricetin. The chemical composition of other constituents of birch leaves is ~~not~~ less well documented.

II.1.3. Information on the period of medicinal use in the Community regarding the specified indication

See Section II.4. Traditional use

II.2. NON-CLINICAL DATA

II.2.1. Pharmacology

II.2.1.1. Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

Depending on the extraction technique birch leaf extracts contain differing amounts of flavonoids (such as quercetin), flavonol glycosides (principally hyperoside and other quercetin glycosides together with glycosides of myricetin and kaempferol), and other phenolic compounds (ESCOP monographs, 2003). Unfortunately information concerning the quantitative composition of the preparation is not available.

Among the components listed above, quercetin is mentioned as the main active ingredient of birch leaves. A possible synergistic action of several flavonoids and phenolic components is assumed. Therefore the whole extract of *Betula* spp. leaves must be considered as the active ingredient.

II.2.1.1.1. Isolated substances

II.2.1.1.1.1. Flavonoids

Various flavonoids were investigated for their inhibitory activity on specific neuropeptide hydrolases which regulate the formation of urine through excretion of sodium ions (Borman and Melzig, 2000). The certain flavonoids, principally quercetin, and other phenolic compounds present in birch may contribute to the accelerated formation of urine (Melzig and Major, 2000). Usually the activities of whole flavonoid complex, extracted with water, ethanol (70%) or butanol, were investigated. The aquaretic effect correlated with the amount of flavonoids, but no saluretic effect could be demonstrated (Rickling, 1992; Schilcher, 1987, 1990; Schilcher and Rau, 1988; Schilcher et al, 1989). Potassium nitrate containing in leaves may increase an action of the flavonoids (Petkov, 1988).

Plant phenolics, especially dietary flavonoids of birch, are effective against gram-positive *Staphylococcus aureus* as much as flavonoids of pine (*Pinus sylvestris* L.) and potato (*Solanum tuberosum* L.) (Rauha et al, 2000).

As mentioned by Schilcher and 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 of 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 and Wülkner, 1992; Schilcher and Emmrich, 1992).

II.2.1.1.1.2. Triterpenoids

A fraction containing a mixture of dammarane esters, isolated from leaves of *B. pendula*, did not exhibit diuretic activity when tested *p.o.* in male Wistar rats. Rickling and 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.

II.2.1.1.1.3. Minerals

High potassium-sodium ratios were determined in dried birch leaf (189:1) and in a 1% decoction (168:1) (Szentmihalyi et al, 1998). The potassium content of birch leaf may contribute to the diuretic effect (Schilcher, 1987; Schilcher, 1990; Schilcher and Rau, 1988; Schilcher et al, 1989). Birch leaves

are rich in potassium so they do not cause the potassium-depleting problem associated with conventional diuretic drugs (Conway, 2002).

The concentration of potassium in *Betulae folium* (*Betula pendula*) is 8045 µg/g dry matter (4725 µg/g refer to the drug in decoctions), in some other herbal substances: *Uvae ursi folium* – 5985 (2115 µg/g), *Equiseti herba* – 29820 (24810 µg/g), *Sambuci flos* – 22090 (19120 µg/g), *Tiliae flos* – 10652 (849 µg/g), *Millefolii herba* – 18220 (10175 µg/g) (Szentmihályi et al 1998).

II.2.1.1.1.4. Other constituents

Methyl salicylate containing in the essential oil of birch leaves or buds has counter-irritant and analgesic properties (Kowalchik and Hylton, 1998). As it was already mentioned above, the content of essential oil in leaves of birch is extremely low (0.04-0.05%, 3,5-6% in buds).

II.2.1.1.1. Infusion, powder, sap, aqueous, aqueous-ethanolic and methanolic birch leaf extracts

After oral administration of a birch leaf tea (infusion) to rabbits, urine volume increased by 30% and chloride excretion by 48%. In mice urine volume increased by 42% and chloride excretion by 128% (Vollmer 1937), and in rats, urine volume did not increase but excretion of urea and chloride increased (Vollmer and Hübner, 1937).

Young birch leaves administered orally to rats and mice did not produce these mentioned above effects (Elbanowska and 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% (Borowski, 1960).

More recent studies in rats showed an increased excretion of urine after the oral administration of aqueous and alcoholic extracts rich in flavonoids (48, 76 and 148 mg/100 ml). The excretion of sodium, potassium or chloride was unaffected. 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, 1987; Schilcher and Rau, 1988; Schilcher et al, 1989, Bradley, 2006).

Various extracts from birch leaf were administered orally to rats: An extract prepared with ethanol 70% (43 mg flavonoids/kg body weight), a butanol fraction of this extract (192 mg flavonoids/kg body weight) and the aqueous residue from the described separation process (0.7 mg flavonoids/kg body weight). An increase in diuresis or saluresis could not be demonstrated for any of these preparations (Rickling, 1992).

The water extract from birch leaves has virostatic and cytostatic properties in vitro (Petkov, 1988).

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

The birch sap exhibited after administration of high doses (1 or 2 ml/100 g b.m.) to rats a weak anti-inflammatory activity for a short period, but the birch leaves extract was ineffective (Klinger et al, 1989).

Fever induced by baker's yeast can be inhibited by the extract from birch leaves, but not by birch sap. This effect was rather weak and short lasting as compared with the effect of acetylsalicylic acid. Also

the experiments on carrageenin edema and yeast-induced fever have been reproduced with the same results (Klinger et al, 1989).

An antimicrobial activity of birch sap against *Staphylococcus aureus* could be observed only with undiluted sap the agar-diffusion test, this effect was evidently caused by penicillium grown in the sap. The birch leaves extract was sterile, there was no antimicrobial activity (Klinger et al, 1989).

The water extracts of herbs from *Solidago virgaurea*, *S. gigantea* and *S. canadensis*, as well as water and ethanol extracts from *B. pendula* leaves ~~are~~ have shown significant aquaretic properties in Wistar SBF rats. The effect was apparent using birch extracts containing 76 mg% (50% ethanol), 48 mg% (water extract) and 148 mg% (water) of total flavonoids. However the isolated fraction of flavonoids was ineffective, and probably the other constituents are also important in the aquaretic action of birch leaf. A weak diuretic effect of all investigated drugs is justifying their use only for irrigation therapy as mentioned also in the Commission E Monographs (Schilcher et al, 1989; Schilcher and Rau, 1988).

The in-vivo and in-vitro models have shown that the pharmacological actions and the use of birch leaf mentioned in ESCOP Monographs (2003) are scientifically evidence-based (Melzig and Schmidt, 2001).

The constituents of birch leaf extracts decelerate the formation of atrial natriuretic peptide (ANP), therefore they have aquaretic, but not diuretic effects (Melzig and Schmidt, 2001).

II.1.2. Assessor's overall conclusions on pharmacology

Aqueous infusions and decoctions, as well as the leaves and aqueous-ethanolic, butanolic and carbon dioxide extracts and sap from *Betulae folium* as well as fractions and isolated individual substances and their groups have been investigated in several pharmacological animal models. Unfortunately, in many publications the correct specifications of solvent and/or drug-extract ratio are missing. In these cases no details can be given, if the extract could not be identified otherwise. Neither a total extract of birch leaf nor various fractions produced any significant increase in diuretic or saluretic effects after oral administration to rats. In vivo studies on the diuretic effect of birch leaf have shown weakly positive results on rabbits and dogs but contradictory results in rodents.

Diuretic effects do not appear to be due entirely to flavonoids since weaker effects were achieved with isolated flavonoid fractions. The aquaretic effect correlated with the amount of flavonoids.

No remarkable antimicrobial effects, but some antiphagocytotic activity could be demonstrated; furthermore a weak anti-inflammatory and antipyretic effect could be shown by the birch sap and leaf extract. In comparison with anti-inflammatory drugs, antipyretics, analgesics and antibiotics the mentioned birch products have a very weak anti-inflammatory activity.

II.2.2. Pharmacokinetics

II.2.2.1. Overview of available data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

No information available.

II.2.2.2. Assessor's overall conclusions on pharmacokinetics

No information on absorption, distribution, metabolism, elimination, pharmacokinetic interactions with other medicinal products is available.

II.2.3. Toxicology

II.2.3.1. Overview of available data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

Experimental data on the toxicological properties of birch leaf extract and other preparations and its single compounds are limited.

II.2.3.1.1. Mutagenicity and carcinogenicity

An extract of birch leaf showed a very weak mutagenic response in the Ames test (Göggelmann and Schimmer, 1986). No other studies have been performed to confirm this. Adequate tests on genotoxicity have not been performed. As it was concluded by Göggelmann and Schimmer (1986), these results indicate that more information is required on the potential mutagenicity and moreover on the potential carcinogenicity of medicinal plants to decide which drugs can be used in therapy without hazard to human health. Most investigations showed a lack of carcinogenicity of quercetin (Bertram, 1989).

II.2.3.2. Assessor's overall conclusions on toxicology

There are only some data about mutagenic activity of birch leaf extract. The birch leaf extract showed mutagenic effects which may be ascribed to flavonols such as quercetin and kaempferol. Moreover it must be taken into consideration that different components in a drug can influence each other.

For birch leaves there are no data available about single/repeat dose toxicity, reproductive and developmental toxicity, carcinogenicity, local tolerance, and other special studies.

II.3 CLINICAL DATA

II.3.1. Clinical Pharmacology

Early studies in humans did not show a significant increase in diuresis after administration of an infusion of birch leaf compared to the effect of pure water (Marx and Büchmann, 1937; Braun, 1941).

II.3.1.1. Pharmacodynamics

II.3.1.1.1. Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

Aqueous birch leaf extracts were found to be more effective than alcoholic extracts (Weiss and Fintelmann, 2000). Special investigations would be necessary in the future.

II.3.1.1.2. Assessor's overall conclusions on pharmacodynamics

Only minimal data about pharmacodynamics are available.

II.3.1.2. Pharmacokinetics

II.3.1.2.1. Overview of available data regarding the herbal substance(s)/herbal preparation(s) including data on constituents with known therapeutic activity.

No information available.

II.3.1.2.2. Assessor's overall conclusions on pharmacokinetics

No information available.

II.3.2. Clinical Efficacy

II.3.2.1. Dose response studies

No information available.

II.3.2.2. Clinical studies (case studies and clinical trials)

In an abstract by Müller and Schneider (1999), 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) (Müller and Schneider, 1999).

In a randomized, 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).

II.3.2.3. Clinical studies in special populations (e.g. elderly and children)

No information available.

II.3.2.4. Assessor's overall conclusions on clinical efficacy

Only few clinical trials were performed. There is a lack of a control group, and the period of observation is too short. The existing clinical trials are not sufficient for accepting a well-established use of birch leaf. No information is available on dose-response relationship and on clinical studies in special populations, such as elderly and children.

II.3.3. Clinical Safety/Pharmacovigilance

II.3.3.1. Patient exposure

No information available.

II.3.3.2. Adverse events

After the use of the effervescent tablets Urorenal (500 mg dry extract from birch leaves) some adverse reactions, but non-serious, such as skin and appendages 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 and 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. Birch leaves may cause contact urticaria in the Finnish sauna, where bath whisks are traditionally used (Lahti and Hannuksela, 1980).

II.3.3.3. Serious adverse events and deaths

No information available.

II.3.3.4. Laboratory findings

No information available.

II.3.3.5. Safety in special populations and situations

No information available.

II.3.3.5.1. Intrinsic (including elderly and children) /extrinsic factors

No information available.

II.3.3.5.2. Drug interactions

No information available.

II.3.3.5.3. Use in pregnancy and lactation

No information available.

II.3.3.5.4. Overdose

No information available.

II.3.3.5.5. Drug abuse

No information available.

II.3.3.5.6. Withdrawal and rebound

No information available.

II.3.3.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

No information available.

II.3.3.6. Assessor's 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.

II. 4. TRADITIONAL USE

II. 4.1. Traditional use in pharmacy and medicine

II.4.1.1. Traditional use in Ancient Times

The therapeutic use of birch probably goes back to the ancient Greeks and Romans when Pliny is mentioning it briefly. It was used by Teutonic tribes in potions to promote strength and beauty. With respect to the etymology of the name ,Betula' the opinions differ. 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' via 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 the birch was beorc or birce, it was 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 *beorgan* (to protect or shelter) (Grieve, 1998).

The birch formed a part of traditional May Day celebrations in Germany and was thought to have the power to ward off witches. Among the Druids birch branches were in use for the initiation of ceremonies (Herb CD, 2001).

II.4.1.2. Traditional use in Middle Ages and later

Hildegard von Bingen (1098-1179) was familiar with the bark for wounds (Herb CD, 2001).

Petrus Andreas Matthiolus (1501-1577) recommended fresh birch juice extracted from the bark for healing of wounds and baths of the same for treating mange (Herb CD, 2001). The sap taken fresh or preserved with alcohol is a diuretic and anti-inflammatory (Conway, 2002). In ethnomedicine it is popular for treatment of renal and bladder diseases, rheumatism, gout, etc (Hoppe, 1975). Nowadays the sap is used for example in the following preparations: Kneipp pressed juice, Schöneberger pressed juice, Uro-Fink®-teabag, Renal Tea 2000 powder, Nieron®-tee N powder, and Cystinol (Schilcher and Wülkner, 1992).

Adam(us) Lonicerus (1528-1586) and Bock mentioned the good effect of the birch bark for stones, jaundice, stomachache and also skin blotches (Herb CD, 2001; 2003).

The famous 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.'

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).

Georg Dragendorff who worked in 1864-1894 at the University of Tartu (Estonia) says the bark is given in malarial fevers, in dropsy, gout, disease of the lungs; also in abscesses, and in skin diseases and itch, and where there is excessive sweating of the feet. The juice or sap from the tree is used in kidney and bladder trouble (The American Materia Medica, 1919).

II.4.1.3. Traditional use in ethnomedicine

In traditional herbal medicine of China the birch is used for headaches, rheumatic pain and inflammation (Li, 2002).

The shamans of Chippewa Indians used the enema to promote a laxative effect in people suffering from constipation or to stop watery stools in their patients suffering from diarrhoea. 1-1/2 tablespoons of birch bark were boiled in 1-1/2 pints of water for 15 minutes; the lukewarm liquid was administered through the rectum to promote active bowel movement (Heinerman, 1996). The American Indians steeped the leaves of the black birch in hot water and drank the tea to relieve headaches and ease rheumatism. Some tribes of Indians used the tea from birch leaves and dried bark for fevers, kidney stones, and abdominal cramps caused by gas in the digestive system. Poultices of boiled bark helped to treat burns, wounds, and bruises. Indians also gargled with birch tea to freshen their mouths and drunk it to stimulate urination, sometimes the birch tea was used by women during painful menstruation (Kowalchik and Hylton, 1998).

Generally, in folk medicine, the leaves are used as a blood purifier and for gout and rheumatism. Externally the leaves are used for hair loss and dandruff (PDR, 1998).

In Russian folk medicine the 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 and Lavrjonov, 1999; 2003). The usage of *B. pendula* and *B. pubescens* is similar (Yakovlev and Blinova, 1999).

In Estonian ethnomedicine the birch leaves are a popular remedy for increasing diuresis. Birch tar was skin irritant and is used externally for skin diseases, such as scabies. The water-ethanolic extract of buds is used externally as an antiarthritic remedy and internally as antispasmodic and for improving digestive disorders. Birch juice and sometimes also some other parts of tree were quite popular as home cosmetics mainly for improving beauty as a product for hair care and against dandruff (Tammeorg et al 1984; Herba 2006).

II.4.1.4. Traditional use in Modern Times

Today traditionally the **young shoots** and **leaves** secrete a resinous substance having acid properties, which, combined with alkalies, is said to be a tonic laxative. The **leaves** have been employed in the form of infusion (Birch Tea) in gout, rheumatism and dropsy, and recommended as a reliable solvent of stone in the kidneys. With the **bark** they resolve and resist putrefaction. A decoction of them is good for bathing skin eruptions, and is serviceable in dropsy. The **oil** is adstringent and is mainly employed for its curative effects in skin affections, especially eczema, but is also used for some internal diseases. The **inner bark** is bitter and adstringent and has been used in intermittent fevers.

The **vernal sap** is diuretic. **Moxa** is made from the yellow, fungous excrescences of the wood, which sometimes swell out from the fissures (Grieve, 1998).

King's American Dispensatory (1898) gives the following description of the Black birch (*Betula lenta*): Gently stimulant, diaphoretic, and astringent. Used in warm infusion wherever a stimulating diaphoretic is required; also in diarrhoea, dysentery, cholera infantum, etc. In decoction or syrup it forms an excellent tonic to restore the tone of the bowels after an attack of dysentery. Said to have been used in gravel and female obstructions. Oil of birch will produce a drunken stupor, vomiting, and death. It has been used in gonorrhoea, rheumatism, and chronic skin diseases. Dose, 5 to 10 drops.

As written in The British Pharmaceutical Codex (1911), the birch tar oil resembles oil of cade in its properties, and is used for external application in the form of ointment (10 per cent.) or soap (10 per cent) for eczema, psoriasis, and other skin affections. Mixed with essential oils it is used to keep away mosquitoes.

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

Nowadays the birch leaves are used for bacterial and inflammatory diseases of the urinary tract and for kidney gravel. They are also used in adjunct therapy for increasing the amount of urine and for rheumatic ailments. Leaves are used externally for hair loss, dandruff, etc. Birch leaf is also employed as an astringent and it is used as a mouthwash. The bark can be macerated in oil and applied to rheumatic joints. Due to the complex composition, it is understandable why birch leaves are more accurately described as an antidyscratic agent rather than a mere aquaretic (PDR, Muravjova et al, 2002; Herb CD, 2000; Bown, 1996; Muravjova, 1991; Ladygina and Morozova, 1987; Kuznetsova and Pybatshuk 1984; Weiss and Fintelmann, 2000; Evans, 2000; Chevallier, 1996; Bruneton 1999; Sokolov and Zamotaev 1988; Gehrmann et al, 2005; Hammermann et al, 1983; Turova, 1974; Yakovlev and Blinova, 1996).

Usually daily doses of 2-3 g leaves are used for making of a tea. One teaspoons of drug corresponds to 1.3 g dried leaves (Braun and Frohne, 1987). As mentioned in DAB 10, 150 ml of boiled water are added to 1 teaspoon of drug, allowed to stand for at least 10 minutes and strained (Braun and Frohne, 1987).

Often birch leaves are used in combinations with other drugs, for example in mixtures as follows:

Rp. *Fol. Betulae*
 Herb. Equiseti
 Rad. Ononidis
 Fol. Orthosiphonis
 Fol. Uvae ursi (minutim conc.) ana ad 100,0

M.f. species

D.S. 1 tablespoon for 1 cup of hot water, allowed to stand some hours and strained (Braun and Frohne, 1987)

In the absence or lack of pharmacological or clinical data, in France the drug is traditionally used orally to enhance urinary and digestive elimination functions, and to enhance the renal elimination of water. 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 adjunctive treatment of rheumatic pain (Bruneton, 1999).

The monograph of *Betulae folium* has been published in European Pharmacopoeia (2005). Birch leaf is used in herbal medicine, particularly for urinary tract disorders. Birch leaf oil has also been used. Birch tar oil and Sweet birch oil is also known in several pharmacopoeias (Martindale, 2007).

II. 4.1.6. Traditional use of other herbal drugs of birch

The bark contains mainly 4-5% tannins and essential oil, it is known as an antipyretic (Hoppe, 1975). Also betulin as the triterpene similar to lupeol, and the glycoside betuloside with aglycone betuligenol are found from bark (Gessner, 1974). The content of betulin in the bark is between 10-14%, there are also glycoside gaulterine, saponins, some essential oil (the principal component is methyl ester of salicylic acid), etc (Lavrjonov and Lavrjonova, 1999).

Winternitz and Jenicke (both 20th Century) recommended the bark (containing betulin, a resinous substance, and betulalbin) as a remedy for its diuretic effect and for its influence in dissolving kidney stones. Winternitz made an infusion of the dried leaves in the preparation of one part to six or eight parts of water by weight. This infusion is recommended for albuminuria. The quantity of the urine would increase from six to ten times of its bulk. Jenicke used it in nephrolithiasis. In one case, a stone had been discovered in the kidney by an X-ray. The urine was concentrated, sometimes bloody, contained pus cells, and uric acid in large quantities with three and one-half per cent of albumin. This tea reduced the quantity of albumin, relieved the pain, improved the general health of the patient so that in twelve weeks' time he was entirely cured with the urine being normal. From time to time tiny pieces of stone have passed from the kidney with the water (The American Materia Medica, 1919).

Scientists attribute the bark's cancer-fighting properties to betulinic acid. As it was shown at the 86th Annual Meeting of the American Association of Cancer Research in Toronto, the activity of the betulinic acid against cancer is very remarkable. It was the most promising discovery among more than 2,500 plant extracts studied by Pezzuto and his colleagues. Based on that evidence, birch bark tea may be one of the more reasonable alternatives in treating existing melanoma (Heinerman, 1996).

The buds contain 4-6% of essential oil (Gessner, 1974), and as the drug of USSR. XI Pharmacopoeia (Gemmae Betulae) they are used as diuretic (USSR Pharmacopoeia, 1986).

Oleum Betulae empyreumaticum rectificatum is **the oil** obtained by the dry distillation of the bark and wood of *Betula alba* and rectified by steam distillation. It is used mainly as an external remedy in cutaneous diseases. (A Manual of Organic Materia Medica and Pharmacognosy, 1917). The external application of pix betulina is recommended in parasitic infestation of the skin with subsequent hair loss, rheumatism and gout, dry eczema and dermatoses, psoriasis and other chronic skin diseases (Muravjova et al, 2002; Ladygina and Morozova, 1987; Kuznetsova and Pybatshuk 1984; Sokolov and Zamotaev 1988; Turova, 1974). The dry distillation of birch wood yields about 6% phenols (cresole, quajacole, xylene, coesole). In veterinary medicine the *Oleum Betulae empyreumaticum rectificatum* is known as fermifuge (Gessner, 1974). Pix betulina (earlier Oleum Rusci) was used as an antiparasitic against scabies (Gessner, 1974).

The tar belongs to the content of Unguentum contra scabiem and Unguentum Wilkinsonii. Tinctura Cellichnol also contains the birch tar (Braun and Frohne, 1987).

A very interesting birch object is **the chaga** (*Inonotus obliquus*) – a fungal growth (*Fungus betulinus*) that appears on the outer bark of birch. It was used traditionally in the folk medicines of many nations (Tammeorg et al, 1984; Heinerman, 1996; Lavrjonov and Lavrjonov, 1999). The famous Russian author Aleksandr Solzhenitsyn popularized the chaga in his novel *Cancer Ward*. Some clinical investigations into chaga in Poland, former U.S.S.R. and U.S.A. showed that the decoction of chaga made hard tumours softer, smaller and less painful, with patients sleeping, eating and feeling a lot better than they did before (Heinerman, 1996).

Betula alba is used also in homeopathy, basically as a natural diuretic as well as against gastric complaints, etc (Mihailov, 2002).

II. 4.2. Traditional use without pharmacy and medicine

The birch is also a very important tree without medicine and pharmacy. Its wood is soft and not very durable but cheap, and the tree is able to thrive in any situation and soil, growing all over Europe. In country districts the birch has very many uses. The lighter twigs are used for thatching and wattles. The birch twigs are used in broom making and in the manufacture of cloth. The birch has been one of the sources from which asphyxiating gases have been manufactured, and its charcoal is much used for gunpowder. The white epidermis of the bark is separable into thin layers, which may be employed as a substitute for oiled paper and applied to various economical uses.

It yields oil of Birch Tar, and the well-known odour of Russian leather is due to the use of this oil in the process of dressing. The production of Birch Tar oil is a Russian industry of considerable importance. It is also distilled in the Netherlands and Germany, but these oils are appreciably different from the Russian oil. It has the property of keeping away insects and preventing gnatbites when smeared on the hands. It is likewise employed in photography.

When the stem of the tree is wounded, a saccharine juice flows out. A beer, wine, spirit and vinegar are prepared from it in some parts of Europe (Grieve, 1998).

The leaves are used to make a yellow dye for fabric and wood (Vermeulen, 1999).

The shampoo containing birch extract is useful for treatment of dandruff and pruritus caused by dry scalp (Miyamoto, 2006). The sap can be tapped and used for mainly cosmetic purposes, such as against greasy hair, stem hair loss or to get rid of dandruff (Vermeulen, 1999).

An infusion of the leaves or a decoction of the bark is a skin-freshening lotion; an infusion of birch acts as a tonic and refreshes the skin when added to the bath. In some areas of the south-eastern U.S. people chew the twigs of *B. lenta* to clean their teeth. Persons who want to stop smoking should consider chewing on a birch branch to relieve the oral fixation (Kowalchik and Hylton, 1998).

II.4.3. ASSESSOR'S OVERALL CONCLUSIONS ON TRADITIONAL USE

The therapeutic use of birch goes back to the ethnomedicine of many nations and to the ancient times. Several organs and products of birch such as leaves, buds, bark, juice, chaga, distilled oil, etc. have been used throughout the centuries in different regions of the world. In former Soviet Union the most popular herbal substance was *Betulae gemma* which was the official herbal drug in the U.S.S.R Pharmacopeia. In other European regions mainly leaves were used traditionally as well as in modern times.

II.5. ASSESSOR'S OVERALL CONCLUSIONS

The therapeutic use of birch leaves as well as of the other parts and products of the birch tree goes back to the ethnomedicine of the 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 use is made plausible by pharmacological data.

The chemical composition of flavonoids as main constituents of birch leaves has been investigated quite extensively.

Neither a total extract of birch leaf nor various fractions produced any significant increase in diuretic or saluretic effects after oral administration to rats. In vivo studies on the diuretic effect of birch leaf have shown weakly positive results on rabbits and dogs but contradictory results in rodents. The aquaretic effect of birch leaf extracts correlates with the amount of flavonoids.

There are only some clinical trials published about clinical efficacy of birch leaf; there is a lack of control groups, and the period of observation is too short. The clinical data are not sufficient to support a well established use.

Due to the lack of toxicity data the use of birch leaf cannot be recommended during pregnancy, breast-feeding or in children younger than 12 years of age.

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