



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Arctostaphylos uva-ursi* (L.) Spreng, folium

Draft

Based on Article 10a of Directive 2001/83/EC as amended (well-established use)

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<i>Arctostaphylos uva-ursi</i> (L.) Spreng, folium (bearberry leaf)
Herbal preparation(s)	A) Comminuted herbal substance B) Powdered herbal substance C) Dry extract (DER 3.5-5.5:1), extraction solvent ethanol 60% (V/V) D) Dry extract (DER 2.5-4.5:1), extraction solvent water
Pharmaceutical forms	Comminuted herbal substance as herbal tea or herbal preparations in solid dosage forms for oral use

Note: This draft Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng, folium. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this draft assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft monograph.



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1. Introduction

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

- Herbal substance(s)

Bearberry leaf (*Uvae ursi folium*) consists of whole or cut, dried leaf of *Arctostaphylos uva-ursi* (L.) Spreng. It contains not less than 7.0% of anhydrous arbutin ($C_{12}H_{16}O_7$; M_r 272.3), calculated with reference to anhydrous drug (European Pharmacopoeia)

- Herbal preparation(s)

A) Comminuted herbal substance for herbal tea preparation

B) Powdered herbal substance

C) Dry extract (DER 3.5-5.5:1), extraction solvent ethanol 60% (V/V)

D) Dry extract (DER 2.5-4.5:1), extraction solvent water

- 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.

Herbal teas

Species anticystiticae: *Betulae folium* 20 parts, *Uvae ursi folium* 20 parts, *Maydis stylus* 20 parts, *Liquiritiae radix* 20 parts, *Graminis rhizoma* 20 parts (Pharmacopoea Helvetica V, 1953)

Species anticystiticae: *Betulae folium* 25 g, *Liquiritiae radix* 30 g, *Uvae ursi folium* 45 g (Pharmacopoea Helvetica VII (1993))

Species urologicae: *Uvae ursi folium* 35 parts, *Herniariae herba* 35 parts, *Betulae folium* 30 parts (Österreichisches Arzneibuch 9, 1960)

Blasen- und Nierentee II: *Uvae ursi folium* 35 – 50%, *Betulae folium* 10 – 20%, *Phaseoli fructus sine semine* 10 – 20%, *Equiseti herba* 10 – 30% (Standard Zulassungen, 1996)

Blasen- und Nierentee IV: *Uvae ursi folium* 35 – 50%, *Ononidis radix* 10 – 25%, *Orthosiphonis folium* 15 – 30%, *Equiseti herba* 10 – 30% (Standard Zulassungen, 1996)

Blasen- und Nierentee V: *Uvae ursi folium* 35 – 50%, *Phaseoli fructus sine semine* 10 – 20%, *Solidaginis or Solidaginis virgaureae herba* 10 – 25%, *Orthosiphonis folium* 15 – 30% (Standard Zulassungen, 1996)

Blasen- und Nierentee VII: *Uvae ursi folium* 35 – 50%, *Betulae folium* 15 – 25%, *Graminis rhizoma* 15 – 25% (Standard Zulassungen, 1996)

Urologicae species: *Betulae folium* 30 g, *Uvae ursi folium* 30 g, *Herniariae herba* 5 g, *Menthae piperitae herba* 15 g, *Ononidis radix* 10 g, *Petroselini radix* 10 g (Slovenský farmaceutický kódex 1, 1997)

Combination teas reported by the Member States:

- *Uvae ursi folium*, *Juniperi fructus*, *Betulae folium*, *Equiseti herba*, *Solidaginis herba*, *Orthosiphonis folium* (DK)
- *Uvae ursi folium*, *Equiseti herba*, *Myrtilli herba*, *Chamomillae flos*, *Sambuci flos*, *Solidaginis herba*, *Thymi herba* (SK, CZ)
- *Urticae folium*, *Uvae ursi folium*, *Betulae folium*, *Juniperi pseudo-fructus pulvis* (HU)
- *Betulae folium*, *Uvae ursi folium*, *Ononidis radix*, *Petroselini radix*, *Polygoni avicularis herba*, *Sambuci nigrae flos*, *Urticae herba*, *Millefolii herba* (CZ)
- *Betulae folium*, *Uvae ursi folium*, *Herniariae herba*, *Menthae piperitae herba*, *Ononidis radix*, *Petroselini radix* (CZ)

Other combination products reported by the Member States

- Uvae ursi folii extractum 5:1, Taraxaci radices cum herba extractum 5:1 - tablets (DK, NO)
- Uvae ursi extractum, Solidaginis giganteae herbae extractum, Orthosiphonis folii extractum - tablets (DK)
- Extract of Solidaginis herba, Betulae folium, Cerasi stipites, Equiseti herba, Uvae ursi folium, extraction solvent ethanol 45% V/V – oral liquid (HU)
- Extract of Uvae ursi folium, Urticae radix, Salviae officinalis folium, Betulae folium, Salicis cortex, Millefolii herba, Urticae folium, extraction solvent ethanol 24% V/V – oral liquid (HU)
- Extract of Urticae radix, Salviae folium, Uvae ursi folium, Cucurbitae semen, Betulae folium, Salicis cortex, Millefolii herba, Urticae folium, extraction solvent 20% ethanol (DER 1:4.2) – oral liquid (HU)
- Extract of Uvae ursi folium, Millefolii herba, Agrimoniae herba, Urticae folium, Equiseti herba, Betulae folium, extraction solvent 20% ethanol (DER 1:4) - tincture (HU)

Vitamin(s)¹

Mineral(s)

Short overview on main active compounds (Bradley 1992, ESCOP 2003, British Herbal Pharmacopoeia 1996, Gruenwald et al. 2004, Barnes et al. 2002, Frohne 2004, Hänsel et al. 1993, Britton et al. 1965, Frohne 1977, Jahodář et al. 1978)

Hydroquinone derivatives: arbutin (hydroquinone-*O*- β -D-glucoside) 5 - 16%; the arbutin content is seasonally variable, leaf content over 17% has been reported; methyl arbutin (*O*-methyl hydroquinone-*O*- β -D-glucoside) up to 4% according to origin of the drug; galloyl derivatives of arbutin 0.05% (*O*-galloyl hydroquinone-*O*- β -D-glucoside, 2'-*O*-galloyl arbutin, 6'-*O*-galloyl arbutin); free hydroquinone usually less than 0.3% and methylhydroquinone

The amount of arbutin and methylarbutin is related to the photometric method with 4-aminoantipyrin-Emerson reaction, while the currently used HPLC method can give different results.

Polyphenols (tannins): 10 – 20%, gallotannins including penta-*O*-galloyl- β -D-glucose and hexa-*O*-galloyl- β -D-glucose, ellagictannin corilagin (1-*O*-galloyl-3,6-di-*O*-hexahydroxydiphenyl-*B*-D-glucose), catechin; anthocyanidin derivatives including cyanidin and delphinidin

Phenolic acids: approx. 0.25% in free form, mainly gallic, *p*-coumaric and syringic acids, but also salicylic acid, *p*-hydroxybenzoic acid, ferrulic acid, caffeic acid and lithospermic acid (dimeric caffeic acid) are mentioned in the literature

Piceoside: (4-hydroxyacetophenone-*O*- β -D-glucopyranoside)

Flavonoids: hyperoside (0.8 – 1.5%), quercitrin-3- β -D-O-6'-galloyl galactoside, quercitrin, isoquercitrin, myricitrin, myricetin-3-*O*- β -D-galactoside, 2 isomeric quercetin arabinosides, aglycones of these compounds, kaempferol

Iridoid glucoside: monoterpein (0.025%)

Triterpenes: 0.4 – 0.8%, including ursolic acid, uvaol, α -amyrin, α -amyrin acetate, β -amyrin, lupeol, mixture of mono- and di-ketonic α -amyrin derivatives

Enzymes: β -glucosidase (arbutase)

Other constituents: allantoin, resin (e.g. ursone), volatile oil (trace) and wax

¹ Only applicable to traditional use

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

Powdered herbal drug in solid dosage forms

Marketing authorisation of coated tablets containing 500 mg of powdered herbal substance in one tablet is reported from **Germany** (authorised at least since 1976). The posology for adults and adolescents over 12 years is 6 tablets (500 mg of powdered herbal substance/1 tbl) 4 times daily. The product is used for treatment of inflammatory diseases of the urinary tract collection system. The product should not be used longer than one week and not more than 5 times a year without medical advice.

Powdered herbal substance in a form of capsules (1 capsule contains 270 mg of the powdered herbal substance) is registered in **Spain** (since 1991). The dosage is 1 capsule 3 times daily. The product is used as a diuretic. The use in children is not recommended.

There are hard capsules containing 350 mg of powdered herbal substance registered in **France** (since 1982). The posology is 2 capsules two times daily (up to 5 capsules per day). The product is "traditionally used to promote the renal elimination of water and as an adjuvant to diuretic treatments in benign urinary tract conditions".

Comminuted herbal substance for tea preparation

Comminuted herbal substance in a form of herbal tea is registered/authorised in **Germany, Poland, Spain** and **Lithuania** for more than 30 years, in **Slovenia** since 1996 and in **Estonia** since 2005. The tea prepared from 1.5 to 3 g of the comminuted herbal substance and 150 ml of boiling water should be used 3 – 6 times daily. The teas are recommended for the treatment of uncomplicated, mild infections of the lower urinary tract (Poland, Slovenia), for treatment of inflammatory diseases of the urinary tract collection system (Germany, Lithuania) or as a diuretic and urinary tract disinfectant (Spain, Estonia).

Dry extracts

Marketing authorisation for tablets containing 500 mg of dry extract (2.5:1), extraction solvent ethanol 50% (V/V) has been reported from **Belgium** (authorised since 2006). The dosage recommended for adults and adolescents is 2 tablets 4 times daily. The duration of use is limited to 5 days. The product is used as urinary antiseptic in cases of cystitis in adult women not having other health problems and not pregnant.

In **Germany**, a marketing authorisation for coated tablets containing 238.7 – 297.5 mg of dry extract (3.5-5.5:1) (since at least 1976), extraction solvent ethanol 60% (V/V), corresponding to 70 mg of hydroquinone derivatives calculated as anhydrous hydroquinone has been granted. The posology is 2 tablets 3 times daily. Other marketing authorisations have been approved (since at least 1976) for 2 products – coated tablets - with a dry extract (3-4:1), extraction solvent water. One of them contains 114 - 143 mg of the dry extract corresponding to 31.5 mg of hydroquinone derivatives calculated as anhydrous arbutin and the other 228 – 315 mg of the dry extract corresponding to 63 mg of hydroquinone derivatives. The dosage is 4 times 4 to 5 tablets respectively 4 times 2 – 3 tablets daily. Additionally marketing authorisation for film coated tablets containing 425.25 – 519.75 mg of dry extract (2.5-4.5:1), extraction solvent water corresponding to 105 mg of hydroquinone derivatives has been reported (authorised since at least 1976). The dosage recommended is 2 tablets 2 to 4 times daily.

All the above mentioned products are indicated for the treatment of inflammatory diseases of the urinary tract collection system. All products are intended for adults and adolescents over 12 years and should be used no longer than one week and not more than 5 times a year without medical advice.

In **Poland**, film coated tablets containing 215 mg of dry extract 2.5-4.5:1, extraction solvent water, corresponding to 40 mg of arbutin are registered (since 2000). The dosage for adults and adolescents

over 12 years is 4 tablets 3 times daily. The tablets are used in uncomplicated infections of the lower urinary tract, when antibiotic treatment is not considered essential.

In **France** hard capsules containing 200 mg of dry extract 3.5–6.0:1, extraction solvent water is registered (since 1992). The posology is 1 capsule twice daily. The product is “traditionally used to promote the renal elimination of water and as an adjuvant to diuretic treatments in benign urinary tract conditions”.

Liquid extract

In **Germany**, oral liquid containing an extract (1:0.54-0.99), extraction solvent water: calcium oxide (44:1) is authorised (since 2006). The dosage is 1.8 – 3.6 ml of the product (corresponding to 101 – 207 mg of anhydrous arbutin) 4 times daily. The product is used for supportive treatment of inflammatory diseases of the urinary tract in adults and adolescents over 12 years. The product should be used no longer than one week and not more than 5 times a year without medical advice.

In **Iceland**, *Uvae ursi folium* would not be classified as food supplement.

For information on combination products marketed in the MS see section 1.1.

Regulatory status overview

Member State	Regulatory Status				Comments (not mandatory field)
Austria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations only
Belgium	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	+ combinations
Bulgaria	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
Cyprus	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Czech Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations only
Denmark	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations only
Estonia	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	+ combinations
Finland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
France	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Germany	<input checked="" type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	+ combinations
Greece	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
Hungary	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations only
Iceland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None – should not be classified as food supplement
Ireland	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
Italy	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
Latvia	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Liechtenstein	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Lithuania	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Luxemburg	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Malta	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
The Netherlands	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None

Norway	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations only
Poland	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Portugal	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	None
Romania	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Slovak Republic	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	Combinations only
Slovenia	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Spain	<input type="checkbox"/> MA	<input checked="" type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
Sweden	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	
United Kingdom	<input type="checkbox"/> MA	<input type="checkbox"/> TRAD	<input type="checkbox"/> Other TRAD	<input type="checkbox"/> Other Specify:	

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

- Databases assessed (date, search terms) and other sources used

Data bases PubMed (June 2009) and HSDB were searched using the terms "uva ursi", "bearberry leaf", "arbutin" and "hydroquinone". Handbooks and textbooks on the topic were also used.

Articles and data that were found to be relevant for assessment are included in the List of references.

2. Historical data on medicinal use

2.1. Information on period of medicinal use in the Community

Bearberry leaves use is for the first time literally documented in the Middle Ages in the Welsh "Physicians of Nyddfai" from the 13th century. It seems that bearberry leaf was used in Northern areas as a folk remedy long before it came to the Central Europe. In Renaissance herbaria bearberry was only mentioned occasionally without any link to specified medicinal use. Bearberry is mentioned for example in "Historia Rariorum Plantarum" by Carolus Clusius (Antwerp, 1601) and also by Linné in his "Materia Medica" from 1749. In Germany, bearberry was used in larger scale since the middle of 18th century. From the beginning of 19th century bearberry is in official use. It was used for treatment of different diseases such hydrops, lithiasis, in diabetes, for therapy of gonorrhoea, etc. Until now only use as urinary tract disinfectant and diuretic remains. Bearberry leaf was used also in the "New World" by the North American Indians for treatment of urinary tract diseases (Frohne, 1977).

The medicinal use has been documented continuously in many pharmacopoeias, pharmacognostical texts and handbooks dating e.g. from 1926, 1938, 1947, 1953, 1960, 1977, 1986, 1998, 2002, 2003 and 2009 - Deutsches Arzneibuch 6. Ausgabe (1926), Československý lékopis 1. vydání (1947); Hagers Handbuch der Pharmazeutischen Praxis (Frerichs et al. 1938), Pharmacopoea Helvetica V (1953), Österreichisches Arzneibuch 9. Ausgabe (1960), Martindale, The Extra Pharmacopoeia (Wade 1977), Deutsches Arzneibuch 9. Ausgabe (1986), The Complete German Commission E Monographs (Blumenthal et al. 1998), WHO monographs on selected medicinal plants 2002, ESCOP Monographs 2003 European Pharmacopoeia 6.5 (2009). Bearberry leaf is traditionally used for the treatment of urinary tract disorders.

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

The following traditional uses have been recorded for bearberry leaf:

The Complete German Commission E Monographs (Blumenthal, 1998)

Uses: inflammatory disorders of the efferent urinary tract

WHO Monographs on Selected Medicinal Plants (Volume 2, 2002)

Uses: described in pharmacopoeias and in traditional systems of medicine: as a mild urinary antiseptic for moderate inflammatory conditions of the urinary tract and bladder, such as cystitis, urethritis and dysuria

Uses: described in folk medicine: as a diuretic, to stimulate uterine contractions, and to treat diabetes, poor eyesight, renal or urinary calculi, rheumatism and venereal disease, topically for skin depigmentation

ESCOMP Monographs (2003)

Therapeutic indications: uncomplicated infections of the lower urinary tract such as cystitis, when antibiotic treatment is not considered essential

British Herbal Compendium (Bradley, 1992)

Bearberry leaf is used as a urinary antiseptic and astringent in mild infections of the urinary tract.

Herbal Medicines. A guide for healthcare professionals (Barnes et al. 2002)

Martindale Extra Pharmacopoeia (Wade, 1977)

Barberry is a diuretic and astringent and has been stated to exert an antiseptic effect on the urinary tract. It has been employed in urethritis and cystitis.

British Herbal Pharmacopoeia (1996)

Indications: mild infections of the urinary tract

PDR for Herbal Medicines (Gruenwald et al. 2004)

Indications: infections of the urinary tract - for inflammatory disorders of the efferent urinary tract

Standard Zulassungen (1996)

Used as an adjuvant in therapy of bladder and renal pelvis catarrhs

Martindale, The Extra Pharmacopoeia (2004)

Bearberry has been reported to be a diuretic, bacteriostatic, and astringent and has been used in the treatment of urinary-tract disorders.

www.associatedcontent.com/article/19953/effects_of_bearberry_uva_ursi_for_urinary_infections.htm

(Bartleby, 2006)

Uva-ursi is used by both Native Americans and the Chinese for centuries for urinary tract infections and sexually transmitted diseases that affect urination

Schindler (2002)

Bearberry is traditionally used in the treatment of the urinary tract infections (i.e., acute cystitis) with bacteriuria below 10^5 ml^{-1} without risk factors and in symptomatic bacteriuria that does not necessarily need treatment with antibiotics.

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

The following posologies have been recorded for bearberry leaf:

The Complete German Commission E Monographs (Blumenthal et al. 1998)

Dosage: 3 g drug to 150 ml water as an infusion or cold maceration or 100 – 210 mg hydroquinone derivatives, calculated as water free arbutin up to 4 times daily

Route of administration: oral administration

Duration of use: not to be taken for longer than a week or more than five times a year without consulting a physician

Interactions with other drugs: Preparations of bearberry leaf should not be taken together with drugs that cause acidic urine since this reduces the antibacterial action

WHO Monographs on Selected Medicinal Plants (Volume 2 2002)

Dosage: 3 g of the drug/150 ml as an infusion or cold macerate 3 to 4 times daily; 400 to 840 mg hydroquinone derivatives; other preparations accordingly calculated as arbutin

Route of administration: oral administration, patients have been advised to avoid eating highly acidic foods and to drink plenty of fluids

Duration of use: not to be used for prolonged period

ESCOMP Monographs (2003)

Dosage: adults – cold water infusions of the dried leaf corresponding to 400 – 800 mg of arbutin per day, divided into 2 – 3 doses; equivalent preparations, not recommended for children

Route of administration: oral use. Patients should be advised to consume plenty of liquid during the treatment. Alkalinization of the urine may be beneficial

Duration of use: treatment could be continued until complete disappearance of symptoms (up to maximum of 2 weeks), if symptoms worsen during the first week of treatment medical advice should be sought

British Herbal Compendium (Bradley 1992), *British Herbal Pharmacopoeia* (1996)

Dosage: three to four times daily: dried leaf – 1.5 – 2.5 g or in infusion or cold aqueous extract; liquid extract (1:1), ethanol 25% 1.5 – 2.5 ml; tincture (1:5), ethanol 25% 2 – 4 ml

Route of administration: oral use

Duration of use: maximum 7 days

an “alkaline” diet should be taken during treatment

Herbal Medicines. A guide for healthcare professionals (Barnes et al.. 2002)

Dosage: dried leaves 1.5 – 4.0 g as an infusion three times daily, liquid extract (1:1), ethanol 25% 1.5 – 4.0 ml three times daily

Route of administration: oral administration, uva-ursi requires alkaline urine for it to be effective, patients are advised to avoid eating highly acidic foods

Duration of use: prolonged use is not advisable; patients in whom symptoms persist for longer than 48 hours should consult a doctor

Martindale Extra Pharmacopoeia (Wade 1977)

Dosage: fresh infusion 1:20 - 15 – 30 ml; concentrated infusion 1:2.5 - 2 – 4 ml; liquid extract 1:1 – 2 ml

PDR for Herbal Medicines (Gruenwald et al. 2004)

Dosage: a daily dose of finely cut or powdered drug 10 g (corresponding to 400 – 840 mg of arbutin) or 3 g of the drug/150 ml in a form of infusion or cold maceration up to 4 times a day or 400 to 840

mg hydroquinone derivatives calculated as water-free arbutin; 0.4 g of dry extract in single dose; liquid extract single dose 2 g; the urine should be alkaline

Standard Zulassungen (1996)

Dosage: 1 cap of a decoct prepared from 1 teaspoon (approx. 2 g) of pulverised drug boiled with 150 ml of water for 15 minutes or a macerate prepared with cold water (after several hours maceration) 3 to 4 times daily

Route of administration: oral administration, vegetable diet is recommended to achieve alkaline urine; additionally sodium hydrogen carbonate can be used

Duration of use: not to be used for long time without consultation with a doctor

Český lékopis (2005)

Dosage: single dose 3.0 g, daily dose: 12.0 g

Duration of use: maximum 2 weeks

Proposed posology for the specified preparations based on the literature data and information received from the Member States:

Specified preparation	Dosage
A) Comminuted herbal substance for tea preparation	Single dose: 1.5 – 4.0 g for tea or macerate preparation up to 4 times daily
B) Powdered herbal substance	The amount corresponding to 100 – 210 mg of hydroquinone derivatives calculated as anhydrous arbutin (photometric) or corresponding amount of arbutin (HPLC) 2 to 4 times daily
C) Dry extract (3.5-5.5:1), ethanol 6% (V/V)	The amount corresponding to 100 – 210 mg of hydroquinone derivatives calculated as anhydrous arbutin (photometric) or corresponding amount of arbutin (HPLC) 2 to 4 times daily
D) Dry extract (2.5-4.5:1), water	The amount corresponding to 100 – 210 mg of hydroquinone derivatives calculated as anhydrous arbutin (photometric) or corresponding amount of arbutin (HPLC) 2 to 4 times daily

There is different information on tea preparation in different literature sources. Herbal tea could be prepared by decoction from the powdered herbal substance (DAB 9, Blumenthal et al. 1998; Standard Zulassungen, 1996; Weiss, 1985) or as an infusion from cut or powdered herbal substance (Blumenthal et al. 1998; Gruenwald et al. 2004) or by maceration for several hours (Standard Zulassungen, 1996; Gruenwald et al. 2004). Results of the research done by Frohne (1970) are summarised in the following table:

Droge	Folia uvae ursi, Handelsdroge					Teemischungen (species urologicae)	
	minutim concis	minutim concis	plv. gross.	minutim concis	plv. gross.	A) concis-Drogen	B) Ganzdrogen
Zerkleinerungsform:							
Ansatzverhältnis- (Droge/Wasser)	10 g/150 ml	10 g/150 ml	10 g/150 ml	2 g/150 ml	2 g/150 ml	6 g/150 ml*	6 g/150 ml*
Zubereitung:	mit kochendem Wasser übergießen, 10 Min. ziehen lassen	15 Min. kochen	30 Min. kalt extrahieren (Schüttelmaschine)	15 Min. kochen	30 Min. kalt extrahieren (Schüttelmaschine)	mit kochendem Wasser übergießen; 10 Min. ziehen lassen	
Extraktmenge:	1) 131,5 ml 2) 129 ml	1) 107 ml 2) 122 ml	1) 112 ml 2) 120 ml	1) 142 ml 2) 146 ml	1) 141 ml 2) 141 ml	1) 120 ml 2) 115 ml	1) 127 ml 2) 120 ml
Arbutinkonzentration	1) 0,32% 2) 0,35%	1) 0,59% 2) 0,56%	1) 0,71% 2) 0,72%	1) 0,11% 2) 0,12%	1) 0,13% 2) 0,13%	1) 0,033% 2) 0,056%	1) 0,005% 2) 0,009%
Arbutinmenge pro Tasse	1) 422 mg 2) 447 mg	1) 634 mg 2) 683 mg	1) 800 mg 2) 864 mg	1) 162 mg 2) 168 mg	1) 189 mg 2) 189 mg	1) 38 mg 2) 60 mg	1) 4 mg 2) 7,6 mg

Alle Bestimmungen kolorimetrisch mit 4-Aminoantipyrin

* = 1 Eßlöffel pro Tasse Wasser

No content of tannins had been taken into consideration by Frohne.

During decoction high amount of tannins is extracted while cold maceration prevents tannins elution. Taking in consideration that in most literature sources there is a recommendation to use the comminuted herbal substance in a form of cold macerate or infusion, the following instruction for use should be included in the Community monograph:

To make a tea, pour 150 ml of boiling water over 1.5 to 4.0 g of comminuted herbal substance and steep for 10 to 15 minutes. To make a macerate, pour 150 ml of cold water over 1.5 to 4 g of the comminuted herbal substance and steep for minimum 30 minutes stirring frequently. The macerate should be used immediately after preparation.

3. Non-Clinical Data

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

Arctostaphylos uva-ursi and its leaf preparations are generally considered to have antibacterial activity and are traditionally used for treatment of the lower urinary tract infections. Published literature provides information on antibacterial activity of bearberry leaf preparations together with several other activities. Publicly available is also information on arbutin and hydroquinone which are the components generally considered to be responsible for the antibacterial activity of the extract.

3.1.1. Primary pharmacodynamic

Bearberry leaf extract Antimicrobial effect

Oral administration of 800 mg of arbutin or an infusion of the leaves containing an equivalent amount of arbutin to healthy volunteers had strong antibacterial activity against *Staphylococcus aureus* SG 511

and *Escherichia coli*, as measured in urine samples after adjustment of the urine pH to 8.0. Urine of pH 6 was ineffective (Frohne, 1970).

Bearberry leaf extract (fluid extract 1:5, extracted with ethanol 70%) has exhibited antimicrobial activity towards a variety of organisms including *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Mycobacterium smegmatis*, *Shigella sonnei* and *Shigella flexeneri* (Moskalenko, 1986).

The decoctions of bearberry (10 g/100 ml water) increased remarkably the hydrophobicity of both *E. coli* and *Acinetobacter baumannii* strains *in vitro*. The leaves of bearberry possessed the antimicrobial activity, there was no growth registered after the exposure of 20 different *E. coli* strains to the undiluted decoction of bearberry and in case of two-fold dilution only one strain showed growth afterwards in peptone broth. This antimicrobial activity could be connected to the ability of bearberry leaf aqueous extract to increase aggregation of Gram-negative bacteria mainly caused by increased hydrophobicity of their cell surface. (Türi et al. 1997). Similar effect possessed bearberry leaf aqueous extract (decoction 1:10/30 min/100°C/pH 4.7) on *Helicobacter pylori* (Annuk et al. 1999).

Antimicrobial activity of the ethanolic extract (ethanol 80%) of the aerial parts of *Arctostaphylos uva ursi* and its ethyl acetate fraction was tested *in vitro* against *Escherichia coli*, *Proteus vulgaris*, *Streptococcus faecalis* and *Enterobacter aerogenes*. Bearberry extract showed antimicrobial activity against all the microorganisms tested. The inhibitory activity was compared to the antimicrobial activity of streptomycin. The highest activity found in the experiment was approximately 1/100 of the activity of streptomycin against *E. coli* and 1/300 against *P. vulgaris*. In case of *S. faecalis* the activity corresponded to the activity of streptomycin; however, streptomycin is known to be less active against these bacteria (Holopainen et al. 1988).

Antimicrobial activity of the extracts depends on the extraction solvent used. There is some evidence that extracts prepared with ethanol of high concentration lose antibacterial activity. An aqueous extract of the leaves inhibited the growth of *Streptococcus mutans* OMZ176 *in vitro* (Namba et al. 1981). A 30% ethanol extract of *Folium Uvae Ursi* inhibited the growth *in vitro* of *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *Serratia marcescens* and *Staphylococcus aureus* (WHO, 2002). However, 95% ethanol or chloroform extracts had no antibacterial activity (Ríos et al. 1987; Gottshall et al. 1949; WHO, 2002).

The bearberry leaf extract (95 % ethanolic extract – 15:100 material to solvent ratio) alone displayed no antimicrobial activity against any of the 25 bacteria tested (Dykes, 2003).

Diuretic effect

An aqueous extract of bearberry leaves (no other information on the type of extract and DER) was administered intraperitoneally to 10 male rats as a single dose of 50 mg/kg body weight; a control group of 10 rats received hypotonic saline solution and another group of 10 rats received the diuretic compound hydrochlorothiazide at 10 mg/kg bw. The urine volume from rats treated with the extract was significantly higher ($p < 0.001$ from the 4th to 8th hour after administration; $p < 0.05$ over a 24-hours period) than from the controls and was comparable to the volume after hydrochlorothiazide treatment. No increase in sodium and potassium excretion was observed after administration of bearberry leaf extract (Beaux et al. 1999).

In contrary to the above mentioned study there is another experimental study in which diuretic effect of several flavonoid drugs including *Uvae ursi folium* was investigated. The following preparations were administered to dogs: the flavonoid fraction isolated from the crude drug, a dry methanolic extract, a dry aqueous extract, a decoction and an aqueous suspension of the pulverised drug. The starting herbal drug contained 1.5% of total flavonoids. Preparations of *uvae ursi folium* inhibited diuresis (Borkowski, 1960 – abstract).

Additionally, no diuretic effect of uva-ursi tea is reported by Weiss, 1985. However, the author did not provide any references supporting this statement.

Arbutin

Antimicrobial effect

In a study in humans, urine samples collected after administration of 0.1 or 1 g of arbutin with or without additional use of 0.250 g of Diuramid (acetazolamide) to achieve alkaline urine have been tested on antibacterial activity against 74 strains of bacteria including *Escherichia coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus rettegeri*, *Klebsiella*, *Enterobacter*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. The results were compared with results of other 20 antimicrobial compounds. Only arbutin (present in urine samples collected after administration of 1.0 g arbutin), gentamycin and nalidixic acid were active against all the strains tested. Antimicrobial effect was apparent even after administration of 0.1 g of arbutin. The effect of arbutin was higher in alkaline urine in comparison to urine with pH 6. In this study arbutin or free hydroquinone were not detected in urine samples (Kedzia, 1975).

The antimicrobial activity of arbutin towards bacteria implicated in producing urinary tract infections has been found to be directly dependent on the β -glucosidase activity of the infective organism. The highest enzymatic activity was shown by *Streptococcus faecalis*, *Klebsiella* and *Enterobacter* genera and by *Proteus vulgaris* and the lowest by *Escherichia coli*. The minimum inhibitory concentration of arbutin is reported to be 0.4 – 0.8% depending on the microorganism (Jahodář et al. 1985). In summary, it has been suggested that a direct relationship exists between the antibacterial action of arbutin and the degree of enzymatic activity of the microorganism.

Arbutin and its metabolite hydroquinone showed inhibition of the growth of *Ureaplasma urealyticum* and *Mycoplasma hominis in vitro* (WHO, 2002; Robertson et al. 1987).

Hydroquinone

Other sources associate the antimicrobial effect of uva-ursi leaf extract with the aglycon hydroquinone released from arbutin (transport form) or arbutin metabolites in the alkaline urine. The drug has urine-sterilizing properties that are attributed to bacteriostatic hydroquinones, conjugates of glucuronic acid and sulfuric acid (Gruenwald et al. 2004).

Despite various pharmacological investigations, it remains open to debate whether the antibacterial effect in the urine is caused by hydroquinone esters, especially the sulphate ester, or by free hydroquinone liberated from them in alkaline urine (Kedzia et al. 1975).

It has even been suggested that arbutin could be hydrolyzed directly to hydroquinone in the urinary tract by β -glucosidase activity of pathogenic bacteria causing the infection (Jahodář et al. 1978).

Tannins

Tannic acid seems to be a component of bearberry aqueous extract with the highest activity to decrease cell surface hydrophobicity as well as antibacterial activity against *H. pylori* (Annuk et al. 1999).

3.1.2. Secondary pharmacodynamic

Bearberry leaf extract

Anti-inflammatory activity

Anti-inflammatory activity (rat paw oedema tests) has been documented for *A. uva-ursi* against a variety of chemical inducers such as carrageenan, histamine and prostaglandins (Herbal Medicines, 2008).

The effect of 50% methanolic extract from bearberry leaf on immuno-inflammation was studied by contact dermatitis caused by picryl chloride in mice. When given orally immediately before and 16 hours after the application of picryl chloride an inhibitory effect on the swelling was observed. Significant therapeutic effect at a dose of 100 mg/kg or more has been demonstrated 24 hours after application (Kubo et al. 1990 – abstract).

Other activities

An aqueous extract of the leaves (prepared from 1 part of the herbal substance and 10 parts of water) had antiviral activity *in vitro* against *Herpes simplex* virus type 2, influenza virus A2 (Mannheim 57) and vaccinia virus at a concentration of 10% (May et al. 1978; WHO, 2002).

Addition of an infusion of the leaves to the drinking-water (3 g/L) of rats fed a standard diet fortified with calcium (8 g/kg body weight) had no effect on urinary calcium excretion and diuresis (Grases et al. 1994; WHO, 2002).

The effect of 50% methanolic extract from bearberry leaf on melanin synthesis was investigated *in vitro*. Bearberry leaf extract as well as arbutin isolated from bearberry leaves had an inhibitory effect on tyrosinase activity. Furthermore bearberry leaf extract inhibited the production of melanin from dopa by tyrosinase and from dopachrome by autoxidation (Matsuda et al. 1992a – abstract).

Water extracts (infusions) from a group of medicinal plants were studied in terms of their activity enhancing the uterine tonus in a series of experiments with a preparation of an isolated rabbit and guinea pig uterine horn. Infusion of bearberry leaves (*Arctostaphylos uva-ursi* L.) did not show any uterotonic effect (Shipochliev, 1981).

Arbutin

In mice orally or intraperitoneally (i.p.) treated with arbutin (50-200 mg/kg [0.18-0.735 mmol/kg]), a dose-dependent antitussive effect to ammonia-induced cough was observed. The antitussive effect of arbutin (200 mg/kg [0.735 mmol/kg]) was as potent as that of codeine phosphate (30 mg/kg), but arbutin had no analgesic or anesthetic effects. Additionally, arbutin had no effect on tracheal smooth muscle contraction, respiratory activity, spontaneous behavior, blood pressure, heart rate or electrical activity (Li et al. 1982 – Chin; NTP, 2006).

Unanaesthetized male and female cats were administered oral (p.o.) and intraperitoneal (i.p.) doses of 50 and 100 mg/kg [0.18 or 0.367 mmol/kg] of body weight arbutin in water and observed at 0.5-, 1-, 2-, and 5-hour intervals. Arbutin at 50 mg/kg bw (i.p. and p.o.) elicited a statistically significant decrease in the number, intensity, and frequency of coughs. Similar results were recorded for the 100 mg/kg bw i.p. and p.o. doses; an increase in antitussive activity was not observed at this dose (Strapkova et al. 1991).

Arbutin (in concentrations 90 µg/ml and 40 µg/ml) was not found to inhibit growth of the rat hepatoma cells (Assaf et al. 1987; Barnes, 2002; Herbal Medicines, 2008).

3.1.3. Pharmacodynamic drug interactions

Bearberry leaf extract

In mice, *A. uva-ursi* extract or arbutin in combination with prednisolone or dexamethasone inhibited swelling of contact dermatitis induced by picryl chloride (PC-CD) and sheep red blood cell delayed type hypersensitivity (SRBC-DTH) response to a greater extent than either of the two chemicals alone (Kubo et al. 1990 – abstract; Matsuda et al. 1990 – abstract; Matsuda et al. 1991 – abstract).

Water extracts from the leaf of *A. uva-ursi* increased the inhibitory effect of dexamethasone ointment on PC-CD- and carrageenin-induced paw edema (Matsuda et al. 1992 b– abstract).

An *A. uva-ursi* extract (95% ethanolic extract), enhanced the antimicrobial activity of nisin; bearberry extract alone had no effect (Dykes et al. 2003).

Arbutin

Aloesin (an anti-inflammatory drug) and arbutin synergistically inhibit tyrosinase activity. In a study of their effects on UV-induced pigmentation in human skin *in vivo*, co-treatment with both chemicals (100 mg/g each) produced an additive effect; 63.3% suppression of pigmentation versus 34% with aloesin and 43.5% with arbutin alone (Choi et al. 2002). Additionally, arbutin inhibited UV-induced nuclear factor-kappaB activation in human keratinocytes (Ahn et al. 2003).

Arbutin plus indomethacin showed a stronger inhibitory effect than indomethacin alone in carrageenin-induced edema and adjuvant-induced arthritis (Matsuda et al. 1991 – abstract).

Arbutin exhibited potent inhibitory effects on rat platelet aggregation induced by adenosine diphosphate (ADP; IC₅₀=0.12 mM) and collagen (IC₅₀=0.039 mM) and displayed the same inhibitory activities as the positive control, tetramethylene glutaric acid, on rat lens aldose reductase (Lim et al. 2003 [Korean with English summary]; NTP, 2006).

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

In general, non-clinical pharmacokinetic information regarding crude extract or its components is very poor and did not allow any relevant conclusion being made.

Arbutin, major constituent of *Uvae ursi* folium extracts, is a phenolic glycoside, which is broken down to yield hydroquinone (HQ) and glucose (Jahodář et al. 1985). HQ is the recognised active substance at the site of drug action, which is the lower urine tract. The total amount of HQ (free HQ and HQ-conjugates) in urine is crucial for the therapeutic activity of the herbal preparation. Therefore, human pharmacokinetic studies have been focused on the availability of total HQ in urine and the use of HQ and arbutin as pharmacokinetic markers is plausible (Paper et al. 1993; Schindler et al. 2002; Quintus et al. 2005).

Bearberry leaf extract

The ability of bearberry leaf to act against urinary infections is believed to be the result of action of free hydroquinone cleaved from arbutin molecule in the urinary tract. It is not known in which tissue this cleavage occurs *in vivo* and what amount of hydroquinone is present in the organisms after treatment with arbutin. The cleavage is mediated via β -glycosidase, an enzyme which is usually not present in mammalian cells but is present in microorganisms which occur in the gastrointestinal tract or possibly in the urinary tract, when infected (Müller and Kasper, 1996 - abstract).

After ingestion of the leaves, arbutin is absorbed from the gastrointestinal tract, and is hydrolysed by intestinal flora to form the aglycone, hydroquinone (Paper, 1993). Hydroquinone is metabolized to glucuronide and sulfate esters that are excreted in the urine (Kedzia, 1975; Frohne, 1970). These active hydroquinone derivatives exert an antiseptic and astringent effect on the urinary mucous membranes when the urine is alkaline (pH 8.0). Their antibacterial action reaches a maximum approximately 3-4 hours after ingestion (Blumenthal et al. 1998; Paper et al. 1993).

Bioavailability of gastro resistant coated tablets containing aqueous extract of *Uvae ursi* folium in comparison to the genuine extract was studied in a crossover design with six healthy volunteers. Arbutin equivalent has been determined in urine samples collected within 24 hours using the DAB 10 spectrophotometric method. Release of arbutin from the tablet compared to the extract was retarded at least three hours. However, bioavailability showed comparable values. In the urine samples no free hydroquinone was detected by HPLC method. In a pilot study the coated tablets and extract were

administered together with 10 g sodium hydrogencarbonate. The pH of the urine changed from 6.5 to 7.4 and in one case to pH 8 for one hour. Free hydroquinone was found in therapeutic concentration in urine only if the pH was alkaline (pH 8), in other urine samples hydroquinone concentrations were below detection limit (1 µg/ml – HPLC method). These findings are in agreement to Frohne, who detected free hydroquinone only after adjusting samples to pH =8 (Frohne, 1970; Paper et al. 1993).

Arbutin

As arbutin is reported to hydrolyze easily in diluted acids to yield D-glucose and hydroquinone, it is expected that ingested arbutin would be hydrolyzed to free hydroquinone by stomach acids. However, a set of experiments suggested that absorbed hydroquinone is rapidly conjugated since it is not detectable as free hydroquinone. Level of free hydroquinone in the body (urine and plasma samples) is usually at or below total concentration of hydroquinone measured in the preexposure background samples (Deisinger et al. 1996).

Female Wistar rats were given an aqueous solution of chromatographically pure arbutin, isolated from *Arctostaphylos uva-ursi*, and their excreted urine was evaluated by TLC, HPLC and spectral analysis. Unchanged arbutin was excreted at 82% and 100% after 16 and 30 hours post-treatment, respectively, corresponding to 90.7% of the total arbutin dose administered orally. Arbutin is not changed in urine even in changed pH. As long as antimicrobial action of arbutin depends on the release of hydroquinone, exoenzymatic β-glucosidase activity of some microorganisms producing inflammatory processes in the urinary tract must be taken into account (Jahodář et al. 1983).

The highest β-glucosidase extracellular enzymatic activity was found in the genera *Streptococcus faecalis* (100%), *Klebsiella* (95%), and *Enterobacter* (72%), the lowest in *Escherichia coli* (11.6%). A direct dependence of the antimicrobial effect of arbutin on the level of the enzymatic activity of microorganisms was found. The presumption of the autocidal action of some bacteria on arbutin was confirmed. The minimal bactericidal concentration of arbutin ranges, in dependence on the species of the microorganism, from 0.4 to 0.8% (Jahodář, 1985).

Oral administration of arbutin (500 mg/kg [1.84 mmol/kg]) to female rats which were overloaded with fluid resulted in a four-fold excess of excreted urine during the second hour of dosing and a total increase of 61% in the first day. No free hydroquinone was detected in the urine samples. Diuretic activity from treatment with 200 mg/kg hydroquinone was greater than that observed in arbutin-treated animals (NTP, 2006).

Investigations have been performed in animals to elucidate the absorption, metabolism and elimination of arbutin. Isolated segments of intestine from the distal part of the duodenum and the caecum of hamster and chicken were used in an *in vitro* model to study in detail the absorption process of arbutin. Experimental data *in vitro* indicate that arbutin is absorbed via the Na⁺/glucose carrier in the small intestine. The transport of arbutin in the small intestine was a freely reversible process, also used by glucose and its analogues (Alvarado 1965, Alvarado and Monreal 1967).

Arbutin uptake (a model of an actively absorbed sugar) has been also investigated in human small intestine obtained from biopsies of 18 patients with minor abdominal complaints without obvious gastrointestinal disease. In three patients non-tropical sprue was diagnosed. The specimens were differentiated in 4 morphological groups. A significant difference in arbutin uptake between the morphological groups was found. Arbutin uptake was clearly reduced in the case with histological evidence of jejunitis and in cases of non-tropical sprue (Semenza et al. 1969).

Hydroquinone

Oral administration of [¹⁴C]hydroquinone either in the diet or by gavage to Sprague-Dawley rats results in almost complete absorption from the gastrointestinal tract, with only 4% being recovered from feces. Of the absorbed material, about 99% of the radioactivity was recovered from urine. In a

comparison of the kinetics of hydroquinone administered orally and dermally, it was reported that dermal absorption was poor. However, pulmonary absorption, after intratracheal instillation, was very rapid in male Sprague-Dawley rats, with [¹⁴C]hydroquinone being detectable in arterial blood within 5–10 s. Later blood sampling (45–720 s) indicated rapid metabolism to glucuronides and elimination of the parent compound.

Following oral administration to rats, by far the major proportions of metabolites are conjugates of glucuronic (up to 67%) and sulfuric (up to 33%) acids. The remaining urinary metabolites consist of 0–5 % mercapturates, 0–3% unconjugated hydroquinone, and <1% unconjugated 1.4-benzoquinone. The oxidation of hydroquinone to the very reactive 1.4-benzoquinone, which can occur both enzymatically and non-enzymatically could be of toxicological significance. Hydroquinone auto-oxidizes at neutral pH to form 1.4-benzosemiquinone, which can undergo a disproportionation reaction to 1.4-benzoquinone (McGregor, 2007).

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

Bearberry leaf extract

No data on single or repeated dose toxicity have been reported for bearberry leaf extract. There are no data on reproduction toxicity or drug interaction available.

Genotoxicity

Uvae Ursi folium (dry water extract) has not been mutagenic in the *Salmonella*/microsome assay with *S. typhimurium* strains TA98 or TA100 as well as in the *Bacillus subtilis* rec-assay (Morimoto et al. 1982; WHO, 2002).

Cytogenetic effect of ethanolic extracts of Uvae ursi folium on irradiated human blood lymphocytes was assessed. Micronucleus formation in unirradiated and irradiated samples of cultured blood lymphocytes using the cytochalasin block micronucleus test was examined. Treatment of cells with bearberry leaf extract did not affect the level of micronuclei in any of the concentration studied (0.025, 0.05, 0.1, or 0.2 mg/ml) (Joksic et al. 2003; NTP, 2006).

Carcinogenicity

There was no evidence of carcinogenic activity of an aqueous extract of the uvae-ursi leaves in male B6C3F1 mice (treated by gavage with 50-100 mg extract/kg body weight) (NTP, 1989, 2006; WHO, 2002).

Arbutin

Repeated dose toxicity of arbutin has been investigated in mice. At a dose of 8000 mg/kg [29.38 mmol/kg] administered i.p. for two weeks, no toxic effects were observed (Li et al. 1982 [Chin.]; NTP, 2006).

Genotoxicity

Arbutin (up to 10⁻² M [2.73 mg/ml]) did not induce mutations in hamster V79 cells; however, after preincubation of arbutin (≥1 mM [0.3 mg/ml]) with β-glycosidase, it did have a mutagenic effect. An increase in mutation frequency was observed with concentrations of 10⁻³ M arbutin and higher. Hydroquinone which was used as positive control exhibited clear effects with a LOEC of about 10⁻⁵ M. In mice orally treated with arbutin (0.5-2 g/kg [2-7 mmol/kg] bw), there was no induction of bone marrow micronuclei. Hydroquinone which was used as a positive control (50 and 100 mg/kg i.p.) induced clearly elevated micronucleus incidence (Müller and Kasper, 1996 – abstract).

Ames test and micronucleus test have been performed with urine containing arbutin. Results have shown no indication of genotoxicity related to arbutin (Siegers et al. 1997).

Carcinogenicity

There are study results providing information that arbutin (2.5, 12.5, or 50 µg/ml [9.2, 45.9, 180 µM]) incubated for four days weakly inhibited the growth of human colon carcinoma HCT-15 cells (Kamei et al. 1998; NTP, 2006).

Reproduction and developmental toxicity

Arbutin was administered subcutaneously at 25, 100 or 400 mg/kg of body weight daily to male Sprague-Dawley rats 14 days before mating and to female rats for 20 days during pregnancy and lactation. No effect on reproduction of male and female rats, or the development of the offspring was observed at doses of up to 100 mg/kg body weight. Fetal toxicity (e.g. stunted fetus, reduced body weight) but no deaths together with maternal effects (not specified) in the ovaries and fallopian tubes were observed at doses of 400 mg/kg body weight. However, based on the fact that the dose is 33 times higher than the maximal dose recommended for oral use (840 mg/day, i.e 12 mg/kg/day) there are no safety concerns in humans (WHO, 2002; Hänsel et al. 1993).

Immunotoxicity

Oral application of arbutin (10 or 50 mg/kg [0.037 or 0.18 mmol/kg]) quickly reduced the swelling of PC-CD and SRBC-DTH within 24 hours (Matsuda et al. 1990, 1991 [Jpn.]). Arbutin (1 mg/ml [4 mM]) inhibited the binding of mouse monoclonal anti-dinitrophenyl immunoglobulin E (IgE[aDNP]) to DNP by 65% (Varga et al. 1991).

In macrophage cells from male Swiss mice, arbutin (2 mg/ml 7 mM]) failed to induce the release of hydrogen peroxide (Moreira et al. 2001; NTP, 2006).

Cytotoxicity

Growth of human melanoma cells and normal human melanocytes was not inhibited by exposure to 100 µg/ml [0.367 mM] arbutin for five days. At 300 µg/ml [1.10 mM] arbutin treatment for five days, cell toxicity and detachment of cells from the dishes were observed within 48 hours (NTP, 2006).

Arbutin (5-50 µM [1-14 µg/ml]) inhibited the growth of the roots of *Allium sativum* L. and produced anti-mitotic effects. At 10 µM, the anti-mitotic effect was already visible within 24 hours and ended at 48 hours. At 20 µM [5.4 µg/ml], arbutin was very toxic, completely stopping root growth after day 1. The effects were similar to those seen with hydroquinone at 5 µM (Deysson and Truhaut, 1957; NTP, 2006).

Hydroquinone

The toxicology of free hydroquinone (HQ) has been reconsidered on several published reviews and it was concluded that there is no evidence to suggest that the toxicology of free HQ is of human relevance (Deisinger et al. 1996; DeCaprio 1999; McGregor 2007).

In previous sections, it has been addressed that the active component of bearberry leaf extract, arbutin is converted to free HQ to exert its antibacterial effect. Based on the pharmacokinetic profile of arbutin, it has been shown that free HQ has an irrelevant accumulation risk since arbutin is very fast conjugated and transformed in innocuous metabolites.

Only in a very low percentage (0.6% of the given dose) free HQ is eliminated in urine and (<1%) in feces. Most of the arbutin is therefore transformed in HQ conjugated (70%) (Siegers et al. 1997; 2003). Free HQ is not accumulated in the animal or human organism and its potential accumulation is

not justified by any pharmacodynamic/pharmacokinetic reason (English and Deisinger 2005; Siegers 1996).

Acute toxicity data on hydroquinone were published. The oral LD₅₀ of hydroquinone in 2% aqueous solution has been determined as 320 mg/kg in rats, 400 mg/kg in mice 550 mg/kg in guinea pigs, 300 mg/kg in pigeons, 70 mg/kg in cats and 200 mg/kg in dogs (Woodard et al., 1949).

Acute exposure of rats to high doses of hydroquinone (over 1300 mg/kg body weight) caused severe effects on the central nervous system, including hyperexcitability, tremor, convulsions, coma and death (IPCS 1994).

The presence of food may increase oral LD50 values of 310 to 1050 mg/kg in rats. Thus, food showed to decrease the rate and extent of free HQ absorption. LD50 values for free HQ by parenteral administration have been reported as 115-160 mg/kg in the rat and 190 mg/kg in the mouse (DeCaprio 1999-abstract). In the course of toxicological animal experiments, free HQ demonstrated a very low toxicity since LD50 values were very high. In addition, the presence of food importantly improves its safety.

Genotoxicity

Hydroquinone was negative for mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 in the presence and absence of metabolic activation (S9). In Chinese hamster ovary (CHO) cells, it induced sister chromatid exchanges (with and without S9) and chromosomal aberrations (with S9). Hydroquinone also induced trifluorothymidine resistance in mouse L5178Y/TK lymphoma cells and was mutagenic in the micronucleus test. Inconclusive results, however, were obtained in *Drosophila* (NTP, 1989, NTP, 2006). However, hydroquinone was found to be mildly myeloclastogenic in the micronucleus test in SPF mice after oral administration of a toxic dose (200 mg/kg) (Gad-El-Karim et al. 1985).

The DNA reactivity of hydroquinone has been documented in animals and this enhanced activity is presumably due to the oxidized forms of hydroquinone, 1.4-benzosemiquinone and/or 1.4-benzoquinone, which can react with sulfhydryl groups and isolated calf thymus DNA and therefore have the potential to contribute to the toxicity of hydroquinone (McGregor, 2007).

Hydroquinone is generally not active in bacterial tests for mutation, but it has been reported to cause base-pair changes in the oxidant-sensitive strains *Salmonella typhimurium* TA 104 and TA 102, which is consistent with the mutagenicity of 1.4-benzoquinone in several strains of *S. typhimurium*. This result from a single study should not be overemphasized, since it has been suggested that there is little difference in qualitative responses between these two strains and TA100, against which hydroquinone has been tested to a 13-fold higher dose without any significant response. In other submammalian genetic toxicity assays, hydroquinone induced forward mutations but not mitotic recombination or gene conversion in *Saccharomyces cerevisiae*, and it did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* when delivered either in the feed or by injection – (McGregor, 2007).

Hydroquinone induced micronuclei and chromosomal aberrations in several studies in bone-marrow cells of mice treated *in vivo*, but not sister chromatid exchanges in a single study. Hyperploidy and chromosome loss (as demonstrated by centromere-positive micronuclei) but not polyploidy were also found in mouse bone marrow. In mouse spermatocytes, chromosomal aberrations and hyperploidy have been observed. In all of these studies *in vivo* dosing was by ip. injection; however, other dose routes have been used in a small number of other studies. In the exceptions, subcutaneous injection was used in one study finding a significant response and oral dosing was used in the other two, with a significant but weak response being found in one gavage administration study and no effect resulting from dietary administration for 6 days at the same dietary concentration (0.8% hydroquinone) as used

by for the induction of renal tumors in F344 rats and, with less clarity, hepatocellular adenomas in male B6C3F1 mice.

The administration route difference is probably significant and it is unfortunate that there has been such a heavy emphasis on the ip. injection mode of administration. There are no germ cell studies of hydroquinone mutagenicity in which routes other than ip. have been used. Unlike the adult human anatomy, the testes of adult rats are likely to receive direct exposure to a chemical that is delivered by the ip. route because the inguinal canal remains open. The ip. route would seem to largely destroy any rationale for testing *in vivo* because exposure of many *in vivo* target cells in animals dosed by this method differs little from that achieved *in vitro*. Although it is not clear that dominant lethal assays are truly germ-cell mutation assays, they are usually assumed to be so. The only one conducted with hydroquinone did not produce any significant response after dosing of male Sprague-Dawley rats with up to 300 mg/kg body weight per day, 5 days per week, for 10 weeks – (McGregor, 2007).

Hydroquinone is mutagenic *in vitro* and *in vivo*, but the administration route used to demonstrate the *in vivo* activity is inappropriate and exposure by more appropriate routes, methods and doses allow protective mechanisms to contain the potentially damaging effect of the oxidative properties of hydroquinone (McGregor, 2007).

Carcinogenicity

Relatively more information on carcinogenicity is available for hydroquinone and its derivatives. The health effects of hydroquinone have been extensively reviewed in IPCS Environmental Health Criteria No. 157 and summarized in IPCS Health and Safety Guide No. 101 (IPCS, 1994, 1996; NTP, 2006).

Although extracts of the leaves do not appear to be carcinogenic, there is some evidence that hydroquinone is carcinogenic. In a two-year carcinogenesis bioassay, hydroquinone (25 or 50, or 100 mg/kg) administered by gavage gave some evidence of carcinogenicity in male F344/N rats (kidney tubular cell adenoma), female F344/N rats (mononuclear cell leukemia), and female B6C3F1 mice (liver adenoma or carcinoma). Additionally, the incidence of thyroid follicular cell hyperplasia was increased in female and male mice (WHO, 2002; NTP, 2006).

In a U.S. National Toxicology Program study, groups of 55 male and 55 female Fischer 344/N rats, 7 to 9 weeks of age, were administered 0, 25, or 50 mg/kg body weight hydroquinone (purity >99%) by gavage on 5 days per week for 103 weeks. Survival was reduced in exposed rats. Also, the mean body weight of exposed males was reduced and the relative kidney weights for high-dose males were greater than those for vehicle controls (NTP, 1989).

Nephropathy was observed in nearly all male and most female rats of all dosed groups and vehicle controls. The nephropathy was characterized by degeneration and regeneration of tubule epithelium, atrophy and dilatation of some tubules, hyaline casts in the tubule lamina, glomerulosclerosis, interstitial fibrosis, and chronic inflammation. In males, the nephropathy was more severe in the high-dose (50 mg/kg bw per day) group, while in females no dose dependence was observed. Nephropathy had also been observed in males in earlier 13-week studies. The presence of hyaline droplets was not reported.

In exposed males, renal tubule-cell adenomas developed in 4/55 low-dose group rats ($p = 0.069$) and 8/55 high-dose group rats ($p = 0.003$), compared with 0/55 in control group rats. A low, non-significant incidence of renal tubule hyperplasia also was reported in the high dose group of male rats (2/55) compared with none in the other groups. There were no renal tumors found in female rats of any group (NTP, 1989).

A reanalysis of the histology of the NTP study, in addition to demonstrating a low incidence of foci of atypical tubule hyperplasia and small adenomas at both doses, also found substantial exacerbation of chronic progressive nephropathy (CPN) to endstage grades of severity at the high dose (Hard et al. 1997).

Briefly, CPN begins at about 2 months of age, when some rats develop basophilic renal tubules with a thickened basement membrane. Progression involves an increase in number of tubules affected, tubule degeneration and atrophy, and an ongoing tubule-cell proliferation in which mitotic figures may be frequent (Hard and Seely, 2005). By the time that end stage (grade 8) is reached, there are virtually no normal tubules remaining and death from renal failure is highly probable. It is important to recognize that this degenerative and regenerative disease is not the result of any chemical treatment, and it is necessary to distinguish its regenerative aspects from preneoplasia (atypical hyperplasia), from which adenomas develop. These are usually small (≤ 0.5 mm). In general, the overall low incidence of both atypical hyperplasia and tubule-cell adenomas may be increased by examining additional step-sections of the kidney rather than relying exclusively on the more usual single, cross and longitudinal section.

The histopathological reanalysis of the hydroquinone study (Hard et al. 1997) found that of the 8 tumors identified by NTP in the high dose, 4 were definite adenomas (one being a cystadenoma), 3 were very early adenomas (incipient adenomas), and 1 was a focus of atypical hyperplasia. In the low dose, 3 of the 4 tumors diagnosed by NTP were similar to the high dose tumors diagnosed by Hard et al. (1997), 2 being definite adenomas and 1 a very early adenoma; the fourth was considered to be a metastasis from a mesothelioma that was present in the peritoneal cavity and certain lymph nodes in this rat, which died at 56 weeks. Besides the 1 focus of atypical hyperplasia already mentioned, Hard et al. (1997) found 13 other foci of atypical hyperplasia in 11 of the 51 rats examined, whereas only 2 were mentioned in the NTP report. Only one of these was confirmed in the reevaluation, with the other probably representing an inflammatory lesion unrelated to neoplasia. In the high-dose group, 40% of males showed exacerbation of CPN to end stage, compared with 5% in the control group males.

Cytotoxicity

Hydroquinone has been reported to show a concentration-dependent cytotoxic activity on cultured rat hepatoma cells (HTC line). A dose 33 $\mu\text{g/ml}$ caused cellular mortality of 40% of cells after 24 h of incubation and no cells remained viable after 72 h. A higher concentration of 66 $\mu\text{g/ml}$ killed all the cells after a 24 h contact (Assaf et al. 1987; Barnes, 2002).

3.4. Overall conclusions on non-clinical data

Available pharmacodynamic data regarding antibacterial activity of bearberry leaf extract together with experiments performed with arbutin or hydroquinone provide solid ground for bearberry leaf extract to be assessed as useful antibacterial agent for treatment early symptoms of mild infections of the lower urinary tract.

There are no data on safety pharmacology of bearberry leaf extract or its component arbutin and metabolite hydroquinone available at present. It is not possible to conclude any information on drug effect on central nervous system, cardiovascular system or respiratory system. Taking into account the difference in metabolism of arbutin in human and animals, and metabolism ambiguity of arbutin to hydroquinone together with the fact that bearberry extract seems to be more active in patients compared to the healthy subjects further non-clinical evaluation is not considered necessary. Relevant safety data can be obtained mainly from clinical trials.

Bearberry leaf extract

There is almost no information available on the toxicity of crude extract of bearberry leaves. Bearberry crude extract was evaluated in Ames test using only two instead of five recommended strains. Results of this study were negative; however, clear conclusion about genotoxicity of the extract could not be made. Further bearberry leaf extract was negative in *in vitro* micronucleus test; however, this test was

not performed according to ICH S2B. Studies in mice revealed there is no carcinogenic potential of bearberry leaf extract.

Arbutin

Single dose toxicity study has not been performed with arbutin but repeat administration of doses much higher compared to clinical practice revealed no toxic effects in mice.

Arbutin has been evaluated *in vitro* in Ames assay and micronucleus test showing no indication of genotoxic potential. Chinese hamster V79 mutation test performed with arbutin gave negative results but after preincubation of arbutin with β -glycosidase causing its cleavage to hydroquinone positive results of the assay were found. Further *in vivo* mouse micronucleus test revealed no increase incidence of micronuclei formation after treatment with arbutin compared to the hydroquinone, used as positive control, providing clear positive results. Arbutin alone seems to be of no genotoxic concern in animal studies, however, combination of arbutin with β -glycosidase together with the observed difference between whole bearberry leaf extract and pure arbutin should be carefully considered. The assessment of genotoxicity should be performed very carefully.

Carcinogenicity studies have not been performed with arbutin.

Reproduction and developmental studies performed in rats dosed with arbutin showed there is no risk on male and female fertility and no deaths were observed in offsprings. The results of the study are considered irrelevant to clinical practice since low doses of arbutin were used.

Hydroquinone

Acute toxicity of hydroquinone has been evaluated and lethal doses were established in several animal species. High exposure of rats to hydroquinone led to severe toxic effect on the central nervous system.

Genotoxicity and mutagenicity of hydroquinone has been extensively studied but clear conclusion could not be made. While the standard Ames assay was negative, sister chromatid exchange, chromosomal aberrations, mouse lymphoma assay and micronucleus test were positive after treatment with hydroquinone. Unambiguous conclusion based on these results could not be made. Firstly, doses of the hydroquinone used in the studies are much higher than is expected clinical dose after administration of bearberry leaf extract. Secondly, in the *in vivo* studies hydroquinone was mainly administered intraperitoneally. In case of oral administration results were often negative and toxic effects described as mild. Further hydroquinone is naturally occurring substance and human body is commonly exposed to this substance. Hydroquinone is present in coffee, tea or pears and low parts-per-million levels are detectable in human body. Finally, after administration of bearberry leaf extract or arbutin hydroquinone has been detected in human urine only in several studies and in very small amount. After administration of bearberry leaf extract free hydroquinone in amount exceeding the detection limit (1 $\mu\text{g}/\text{ml}$ – HPLC method) was found only at pH = 8. It should be also considered that administration of bearberry leaf to humans is limited to very short period and the time of exposure of human body to hydroquinone is also very short since it is rapidly transformed to its inactive and nontoxic metabolites that are excreted via urine.

Free hydroquinone showed no mutagenetic risk in several *in vitro* and *in vivo* assays. The potential mutagenicity of free hydroquinone occurred only at concentrations that excess more than 20 times the maximal theoretical concentration reached in an animal or human organism (2.4 mg/kg; when all arbutin was transformed in free hydroquinone). As a response to this possibility the organism has a potent conjugation metabolism to neutralize the hydroquinone just after its formation.

Safety margin could be considered sufficient regarding toxicity and adverse effects.

Further it should be considered that available data did not report any serious adverse and toxicity effects in animals after administration of arbutin or hydroquinone doses relevant for human use and assessment of human safety.

Provided that no adverse toxic reactions have been reported in scientific literature together with the fact that several types of bearberry leaf extract are used for long period of time, non-clinical data on bearberry leaf extract and its main components arbutin and hydroquinone can be considered sufficient to support traditional use of herbal preparation bearberry leaf extract in the short term treatment of mild lower urinary tract infections.

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

Bearberry leaf extract

The antiseptic and diuretic properties claimed for bearberry leaf extract can be attributed to the hydroquinone derivatives, especially arbutin. Arbutin is absorbed from the GI tract virtually unchanged and during renal excretion is hydrolysed to yield the active principle, hydroquinone, which exerts antiseptic and astringent action on the urinary mucous membranes (Frohne, 1970).

The crude extract of bearberry leaf is reported to be more effective as an astringent and antiseptic than isolated arbutin. This may be due to the other hydroquinone derivatives, in addition to arbutin, that are present in the crude extract and which will also yield hydroquinone. It has been stated that the presence of gallic acid in the crude extract may prevent β -glucosidase cleavage of arbutin in the GI tract before absorption, thereby increasing the amount of hydroquinone released during renal excretion (Herbal Medicines, 2008).

Pharmacodynamic drug interactions

Bearberry leaf extract

There were no drug interactions documented for bearberry leaf extract (Herbal Medicines, 2008). However, it was observed that the sodium sparing effect of bearberry leaf extract may offset the diuretic effect of thiazide and loop diuretics (Gruenwald et al. 2004).

Five bearberry leaf products were tested to determine their influence on CYP 3A4, 3A5, 3A7, 2C19 and CYP19-mediated metabolism *in vitro*, as well as on p-glycoprotein efflux activity within human THP-1 and Caco-2 cells. There was difference in the range of inhibition of 3 isozymes of CYP3A family caused by water extract of *uva-ursi*. The degree of inhibition, from most to least, was in the order CYP3A5 > CYP 3A7 > CYP3A4. Although CYP3A4 was inhibited to a lesser degree than CYP3A5 or CYP3A7, such an inhibitory effect would likely have a greater influence on the elimination of xenobiotics as a result of its biological importance. Methanolic extract inhibited P450 enzymes to lesser extent compared to the water extract. From the pharmacology point of view the interaction of bearberry leaf extract with CYP isozymes should be carefully considered (Chauhan et al. 2007).

Arbutin

In a study without controls, urine samples from healthy volunteers were collected 3 hours after oral administration of 0.1 or 1.0 g arbutin. The urine samples (adjusted to pH 8.0) and 20 antibacterial compounds (at their usual urine concentration) were tested *in vitro* using 74 strains of bacteria, including *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Only arbutin (present in urine samples collected after administration of 1.0 g arbutin), gentamicin and

nalidixic acid were active against all the strains tested. Antibacterial effect was observed also at 10-fold lower doses of arbutin (0.1 g). Maximum effect was detected from 3 to 4 hours post-dose. Sample of alkaline urine alone did not show any antibacterial effect. It could be concluded that metabolic products of arbutin are responsible for antibacterial effect of uva-ursi leaves but these substances are active only in alkaline urine (Kedzia, 1975; Frohne, 1977; WHO, 2002).

Oral administration of arbutin (800 mg) or an infusion of the leaves containing an equivalent amount of arbutin to healthy volunteers had strong antibacterial activity, as measured in urine samples after adjustment of the urine pH to 8.0 (Frohne, 1970). With respect to the slight toxicity of arbutin its metabolic product could be used as an effective antibacterial substance in alkaline environment against bacterial infection of urinary tract (Frohne, 1977).

The antibacterial effect of bearberry leaf extract according to the hypothesis formulated already in 1883 is ascribed to hydroquinone which is liberated from arbutin via glycoside cleavage. Therefore, arbutin is the prodrug of the relatively toxic active principle hydroquinone. In the case of arbutin, hydrolyzed by β -glucosidase, the formed aglycone hydroquinone may possibly be absorbed already in the intestine or in the liver and detoxified through conjugation with glucuronic acid or sulfuric acid, these conjugates do not have antibacterial activity, but they can be hydrolyzed by bacterial enzymes (Frohne, 2004).

Hydroquinone

In urine hydroquinone exists in form of glucuronide and after alkalization of the urine it splits to free form having antibacterial activity (ESCOP, 2003).

It is still unknown which of the hydroquinone compound is responsible for the antibacterial effect. Investigation data revealed that hydroquinone glucuronide could not be responsible for antibacterial activity since its maximum in urine was detected 2 hours after administration of arbutin and maximum antibacterial activity of urine was observed at 3-4 hours post-dose. This led to the conclusion that the most probable compound responsible for the antimicrobial activity could be hydroquinone sulphate instead of hydroquinone glucuronide (Kedzia, 1975).

Alkalization of urine

Urine samples from patients received arbutin-containing tea or pure arbutin showed after alkalization of the urine inhibition of growth of bacteria tested. Samples of normal urine and arbutin-containing samples with or without alkalization did not show any antibacterial activity (Frohne, 1970). It has been experimentally proven that pH value of the urine sample is very important for its antibacterial activity. Antibacterial effect of arbutin was increased and prolonged in alkaline urine pH 8.0 (when compared to the urine sample at pH 6) (Kedzia, 1975).

Urine with high content of metabolic products of arbutin leaving on the air clearly showed low potency for bacterial infections compared to the control urine sample. Bacterial culture incubation (*E. coli* and *Staphylococcus aureus*) showed clear inhibition effect of urine containing metabolic products of arbutin. This urine sample has to be alkaline. Alkalization alone or addition of arbutin alone did not show any bacteriostatic effect in the sample of urine (Frohne, 1977).

Whether the alkalizing of the urine – which, through the administration of sodium hydrogen carbonate, can be attained only short-term – also has the same effect *in vivo*, is doubtful. In any case, measurable levels of hydroquinone have not been detected in the urine (Paper et al. 1993; Frohne, 2004).

Concerning this the only problem is the way of making urine environment more alkaline. The common daily dose of natrium hydrogencarbonate or dinatrium phosphate is able to alkalize urine only for a short period of time. Kedzia et al. (1975) suggested using of diuramid which is able to make urine

alkaline for longer period; however, due to its toxicity it could be administered only for 3 or 4 days. Further investigation of how to alkalinize urine in much more effective manner is necessary (Frohne, 1977).

Since concomitant acidification of the urine (by other remedies) may result in a reduction of its antibacterial efficacy; patients have been advised to avoid eating highly acidic foods, such as acidic fruits and their juices during treatment with *Uvae Ursi folium* (WHO, 2002; Barnes, 2002; ESCOP, 2003; Gruenwald et al. 2004).

However, a study from 2003 demonstrated that bacteria causing urinary tract infections participate in the deconjugation of arbutin and liberate the toxic free hydroquinone. The free hydroquinone then can damage the cell by destabilization of its membranes. Alkalinization of the urine by intake of bicarbonate is not necessary considering the effective bacterial deconjugation by *E. coli*, the principal agent in urinary infections (Siegers, 2003).

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

Major constituent of *Uvae ursi folium* extracts is arbutin, a phenolic glycoside which is broken down to yield hydroquinone and glucose (Jahodář et al. 1985). Free hydroquinone is the recognized active substance at the site of drug action that is the lower urine tract. The total amount of hydroquinone (free hydroquinone and conjugated hydroquinone) in urine is considered crucial for the therapeutic activity of the herbal extract. Therefore, pharmacokinetic studies have been mainly focused on the availability of total hydroquinone in urine. The use of hydroquinone and arbutin as pharmacokinetic markers is reasonable and justified (Paper et al. 1993; Schindler et al. 2002; Quintus et al. 2005).

Bearberry leaf extract

Four hours after ingestion of a single dose of a preparation containing bearberry leaf extract (945 mg corresponding to 210 mg arbutin), 224.5 µmol/L hydroquinone glucuronide and 182 µmol/L hydroquinone sulfate were recovered in the urine, which represented approximately half of the administered arbutin dose (Glöckl et al. 2001).

In an open, randomized, two-way crossover study, 16 healthy volunteers (8 males, 8 females, mean age of 25.4-years-old) received a single oral dose of bearberry leaf dry extract (BLDE) as film-coated tablets (2 tablets containing 472.5 mg BLDE, corresponding to 105 mg arbutin) or as an aqueous solution (945 mg BLDE, corresponding to 210 mg arbutin). Hydroquinone glucuronide and hydroquinone sulfate were recovered in the urine during the first four hours but no metabolites were detected after 24 hours. The rate of metabolism was faster in the group given BLDE in an aqueous solution. The total metabolite concentration represented 66.7% of the administered dose in the tablets and 64.8% in the solution. Hydroquinone glucuronide accounted for 67.3% and 70.3% of the total arbutin metabolites recovered in each group, respectively (Schindler et al. 2002).

12 human volunteers (6 males and 6 females) received 3 x 2 dragees containing 238.7 – 297.5 mg of bearberry leaf dry extract (DER 3.5 – 5.5:1, extraction solvent ethanol 60% V/V corresponding to 70 mg of arbutin) in one tablet. The urine was sampled for 36 hours and fractionated in periods of 6 hours. Free and conjugated hydroquinone was measured in the samples. Only 0.6% of the administered arbutin dose (420 mg) was excreted as free hydroquinone and in 6 out of 12 volunteers no free hydroquinone was detected in urine (detection limit 0.3 µg/ml), 70% of the arbutin dose was found as hydroquinone conjugated to glucuronic and sulfuric acid.

Urine samples collected in this study were assayed with or without added glucosylase (mixture of β-glucuronidase, aryl-sulfatase and cellulase) or an *E. coli* suspension, and analyzed by HPLC for hydroquinone content. Incubation of the urine with *E.coli* proved the ability of bacteria to deconjugate

the hydroquinone glucuronide and sulphate to free hydroquinone. Deconjugation was 2.3-fold higher than after incubation with glucosylase (Seigers et al. 1997, 2003).

Arbutin

Arbutin was found to be extensively absorbed from the gastrointestinal (GI) tract and bioavailable as hydroquinone. Volunteers (two males and two females, 36-45 years old) receiving a diet containing high levels of arbutin and hydroquinone (coffee or tea, wheat cereal, whole wheat bread, wheat germ, and Bosc pears) had significant increases in mean total hydroquinone (i.e., hydroquinone and its conjugated metabolites) plasma levels. After 2 hours, it was 5-times the background concentration (at 0.15 µg/g [0.55 nmol/g]). Urinary total hydroquinone excretion rates were also significantly increased; after two-three hours, levels were 12 times background levels. A low- hydroquinone diet (corn cereal, 2 % milk, cantaloupe, black cherry yogurt, and soft drink) resulted in a slight decrease in the mean levels of hydroquinone in human plasma and urine (Deisinger et al. 1996).

Arbutin is a stable glucoside that is not hydrolyzed at pH 3.5 or 9.0. It has been investigated that arbutin could be hydrolyzed enzymatically by virtue of β-D-glycosidase yielding to hydroquinone and other phenol derivatives (Kedzia, 1975).

Hydroquinone

Most studies of hydroquinone kinetics and metabolism following oral administration have used arbutin or other form of bearberry leaf extract. For information on hydroquinone kinetics see sections above.

4.2. Clinical Efficacy

4.2.1. Dose response studies

Dose response has been investigated in healthy volunteers. Antibacterial effect has been observed after administration of 0.1 or 1.0 g of arbutin. Lower dose provides lower antibacterial effect but independently of the dose the pH value of urine was the most important factor determining the antibacterial activity (Kedzia, 1975).

A study was performed of β-glucosidase extracellular activity of 225 strains of various species of bacteria producing infections of the urinary tract as a condition of the antimicrobial action of arbutin. The highest enzymatic activity was found in *Streptococcus*, *Klebsiella* and *Enterobacter*, and the lowest activity in *Escherichia coli*. Direct dependence of the antimicrobial effect of arbutin on the level of the enzymatic activity of microorganisms was found. The minimal bactericidal concentration of arbutin ranges, in dependence of the microorganism species, from 0.4 to 0.8% (Jahodář et al. 1985). According to Frohne (1970) effective concentration of arbutin should be higher than 0.3%.

Continuous long term use is not recommended in some sources (Blumenthal et al. 1998; Barnes et al. 2002; Bradley, 1992; ESCOP, 2003).

Recommended duration of use varies in the available literature sources from maximum 48 hours (Barnes et al. 2002) to two weeks (ESCOP, 2003). It should not be used more than five times a year without medical advice (Blumenthal et al. 1998).

4.2.2. Clinical studies (case studies and clinical trials)

Bearberry leaf extract

Clinical research assessing the effects of bearberry leaf extract as a single drug/preparation is not available at this time.

Results of three controlled clinical trials with bearberry leaf extract in combination with other herbal extracts are available.

In the first clinical trial effect of the combination product (combination of *uva-ursi folium*, *Betulae folium*, *Equiseti herba*, *Virgauree herba*, *Juniperi fructus* and *Coccus cacti*) in the treatment of urinary tract infections and frequent /impaired micturition was evaluated. Herbal preparation was compared to the sulfonamide combination. Forty six patients suffering from acute urinary tract infection were included in the trial. Both monitored symptoms were improved in the herbal treatment group. Authors concluded that the treatment with the herbal combination demonstrated an improvement in micturition and cured urinary tract infection in selected patients in a period of 3 weeks (Beeko et al. 1983). It should be noted that the amount of bearberry leaf was relatively small in the tested preparation.

The effect on the treatment of urinary tract infection caused by a long term implantation of a urinary catheter was evaluated in the open, controlled clinical study with 60 patients. Tested product - combination of *Uvae-ursi folium*, *Betulae folium*, *Equiseti herba* and *Solidaginis virgaureae herba*- was compared to trimethoprim-sulfamethoxazol. The effect of the product on the evaluated symptoms was observed after 8 and 12 weeks of treatment compared to the antibiotic treatment with trimethoprim-sulfamethoxazol (Albrecht J. and Kreyes G., 1988).

The third clinical study assessed prophylactic effect of another combination product (containing hydroalcoholic extract of bearberry leaves with a standardized content of arbutin and methylarbutin, and Dandelion root and leaves) on recurrent cystitis. The product had a prophylactic effect on recurrent cystitis in a double-blind, prospective, randomized study of 57 women. The experiment led to the conclusion that bearberry leaf extract is not the treatment of choice for acute cystitis but it could have a possible prophylactic role in the treatment of recurrent urinary tract infections. However, this conclusion cannot be made with certainty (Larsson et al. 1993).

Table 1 Overview of clinical studies with *Uvae ursi folium* preparations (combination products) in urological indications:

Reference/Study Number	Beeko et al. 1983	Albrecht and Kreyes 1988	Albrecht and Kreyes 1988
Study design	open, controlled compared to a sulphonamide combination	open, controlled compared to trimethoprim-Sulfamethoxazol	controlled, prospective, randomised double-blind
Number of Patients	46	60	57
Specific diagnosis	UTI disorders of micturition	UTI >10 ⁴ bacteria in urine symptoms: burning, pain and pressure feeling in the bladder	cystitis
Preparation used	<i>Uvae ursi folium</i> , <i>Betulae folium</i> , <i>Equiseti herba</i> , <i>Virgauree herba</i> , <i>Juniperi fructus</i> , <i>Coccus cacti</i>	<i>Betulae folium</i> , <i>Equiseti herba</i> , <i>Solidaginis virgaureae herba</i> , <i>Uvae ursi folium</i>	Hydroalcoholic extract of : - <i>Uvae ursi folium</i> - <i>Taraxacum officinalis, radix cum herba</i>
Dosage (daily)	3 teaspoons (15 ml)	3 x 5 ml	3 x 3 tablets
Duration of administration	3 weeks	12 weeks	4 weeks
Criteria of evaluation/ results	improved micturate disorders UTI	improved symptoms (burning, pain and pressure feeling in the bladder) and bacteriuria	prevent the recurrence of cystitis and symptoms

Except for these controlled clinical trials there exist a final report summarizing clinical experience of 75 registered physicians in private practice with bearberry leaf extract preparations (both, mono and combination products) in the treatment of urinary tract infections. The reported information was obtained from a total of 186,122 patients during a period of 10 years (Schnitker, 1993). Treatment effect of bearberry leaf medication on uncomplicated cystitis and urinary tract infections was evaluated as very good or good by both patients and physicians. The mean time required to observe the efficacy of the medication was 3 or 4 days for the group with uncomplicated cystitis or patients with urinary tract infections, respectively. Mean treatment duration of 9 or 10 days for patients with uncomplicated cystitis or urinary tract infections, respectively, complied with recommendation in existing monographs.

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

There are no clinical studies in special population available for bearberry leaf extract or for arbutin.

4.3. Overall conclusions on clinical pharmacology and efficacy

Available controlled clinical trials evaluated the effect of bearberry leaf extract in combination with other herbal substances. There are no clinical studies evaluating the efficacy of bearberry leaf extract alone that would be suitable to support the well established use of this extract.

A report on the long-term clinical experience with bearberry leaf extract in the treatment of uncomplicated cystitis or urinary tract infections provide a compact data set supporting efficacy of the bearberry leaf extract in the real clinical practise. However, although many patients were involved in the report, the study is not acceptable to support WEU of bearberry leaf preparations as no real clinical data (no results of laboratory findings, no description on inclusion criteria etc.) are included.

Based on results of *in vitro* tests on antimicrobial activity of bearberry leaf preparations containing arbutin as a main active component and long standing use of bearberry leaf extract for treatment of uncomplicated infections of the lower urinary tract, the traditional use of bearberry leaf extract in the short-term treatment of uncomplicated lower urinary tract infections can be considered plausible.

Clinical significance of bearberry leaf extract administration with respect to the hydroquinone exposure should be considered taking into account that even without administration of bearberry leaf extract hydroquinone can be naturally found in the human body. Hydroquinone is naturally contained in coffee, tea or wheat cereals.

5. Clinical Safety/Pharmacovigilance

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

There is a lack of clinical safety and toxicity data for bearberry leaf extract and further investigation of these aspects should be performed.

Bearberry leaf extract in combination with dandelion root and leaf extract, used in a treatment study of 57 women with recurrent cystitis, produced no side effects. At the end of one year of treatment, 5/27 women in the placebo group had a recurrence compared to 0/30 women in the treatment group. Neither group reported side effects (Larsson et al. 1993).

5.2. Patient exposure

There are no special data on patient exposure to bearberry leaf extract or arbutin available.

Several cohort studies were performed with workers getting in daily contact with hydroquinone. Workers were engaged in colour printing and processing, in a plant where hydroquinone was manufactured, as lithographers or in motion picture film processing. Results of the study led to the conclusion that adverse effect could not be directly attributed to the hydroquinone exposure the studies were mostly of poor quality. Some other substantial parameters were not followed and evaluated such as cigarette smoking habits. Finally it should be considered that many other chemicals are used in the examined working environment (McGregor, 2007).

5.3. Adverse events and serious adverse events and deaths

Internal use of *Uvae ursi folium* may cause nausea and vomiting due to stomach irritation from the high tannin content (WHO monograph, 2002; Blumental et al. 1998; Gruenwald et al. 2004; British Herbal Pharmacopoeia, 1996; ESCOP, 2003; Bradley, 1992). Stomachache has also been reported as adverse effect (Gruenwald et al. 2004; Hänsel et al. 1993).

In a view of the high tannin content and toxicity of hydroquinone, prolonged use of bearberry leaf extract may cause chronic liver impairment (Barnes et al. 2002; Herbal Medicines, 2008; Gruenwald et al. 2004).

In persons with sensitive stomachs, nausea and vomiting are possible side effects after ingestion of dried bearberry leaves (as low as 15 g). Other symptoms that have been reported in association with bearberry leaf extract are irritability, insomnia, an increased heart rate (NTP, 2006).

Uvae ursi leaf extract use has also been linked to albuminuria, hematuria, and urine cast (Adesunloye, 2003; NTP, 2006).

In a 56-year-old female who drank tea containing bearberry leaf regularly for three years to prevent recurrent urinary tract infection, bull's eye maculopathy, paracentral scotomas, reduction in electroretinography amplitude, and retinal thinning on optical coherence tomography were observed. The maculopathy was suspected to result from bearberry leaf because of its ability to inhibit melanin synthesis (NTP, 2006).

Due to the high tannin content of the leaves, the tea infusion tastes bitter and astringent which can lead to nausea and vomiting in patients with sensitive stomachs. Hydroquinone appears to be non-toxic with the administration of bearberry leaf tea; however, hydroquinone must remain in suspicion with regard to having mutagenic and possibly carcinogenic effects (Frohne, 2004).

Uvae ursi folium should not be used for prolonged periods. Patients with persistent symptoms of a urinary tract infection should consult a physician. Use of *Uvae ursi folium* may cause a greenish-brown coloration of the urine that darkens on exposure to air due to the oxidation of hydroquinone (WHO, 2002).

5.4. Laboratory findings

Laboratory screening tests were performed before and after the treatment with bearberry leaf dry extract as film-coated tablets (2 tablets containing 472.5 mg dry extract, corresponding to 105 mg arbutin) or as an aqueous solution (945 mg dry extract, corresponding to 210 mg arbutin). These included a differential blood count, prothrombin time (PT), partial thromboplastin time (PTT), electrolytes (potassium, sodium, calcium, magnesium), blood glucose, urea, creatinine, bilirubin, aspartate-amino-transferase, alanin-amino-transferase, gamma- glutamyl-transferase, alkaline phosphatase, alpha-amylase, total protein, albumin, C reactive protein, triglycerides, cholesterol, and semiquantitative urinalysis. After the treatment period, the laboratory parameters were screened again except for PT, PTT, triglycerides, and cholesterol. There were no unexplained pathologic laboratory

results that were suspected to be result of the treatment with bearberry leaf dry extract (Schindler, 2002).

5.5. Safety in special populations and situations

Safety of bearberry leaf extract in human is mainly based on the traditional use. There are only several clinically reliable data regarding safety of the extract after administration in human.

Pediatric population

No data available. Use in children and adolescents is not recommended because data are not sufficient and medical advice should be sought.

Overdose

An overdosing with bearberry leaf extract can lead to inflammatory irritation of bladder and urinary tract mucosa accompanied with disuria and hematuria, or later with blood excreta. Finally overdosing with the drug could lead to liver damage (hepatic impairment) (Gruenwald et al. 2004; Hänsel et al. 1993).

Extremely high doses of bearberry leaf extract (i.e., ten times the recommended amount) can cause ringing in the ears, shortness of breath, convulsions, collapse, delirium, and vomiting. Liver damage is a risk with long-term use (NTP, 2006).

Large doses of bearberry leaf extract are reported to be oxytocic, although *in vitro* studies have reported a lack of utero-activity. In view of the potential toxicity of hydroquinone, the use of bearberry leaf extract during pregnancy and lactation should be avoided (Herbal Medicines, 2008; Barnes, 2002).

Hydroquinone is reported to be toxic if ingested in large quantities: 1g (equivalent to 6-20 g of plant material) has caused tinnitus, nausea and vomiting, sense of suffocation, shortness of breath, cyanosis, convulsions, delirium and collapse. A dose of 5 g (equivalent to 30-100 g of plant material) has been proved to be fatal (Herbal Medicines, 2008).

Long-term use

A. *Uva-ursi* is not for unsupervised prolonged use (Gruenwald et al. 2004).

Long-term use of higher doses of bearberry leaf or its extracts could lead to the chronic poisoning with following adverse effects: haemolytic anemia, emaciation, steatosis and depigmentation of hair (Hänsel et al., 1993).

Prolonged use of *Uvae ursi folium* to treat urinary tract infection is not advisable since it may lead to liver damage. Patients in whom symptoms persist for longer than 48 hours should consult their doctor (Barnes, 2002).

Uvae ursi folium should not be used for prolonged periods. Patients with persistent symptoms of a urinary tract infection should consult a physician (WHO, 2002).

Free hydroquinone could lead to the hepatic impairment especially in children after long-term use (Hänsel et al. 1993).

Contraindications

Individuals with kidney disorders (WHO, 2002; British Herbal Pharmacopoeia, 1996; ESCOP, 2003), with irritated digestive disorders and acidic urine should not take bearberry leaf extract (Gruenwald et al. 2004).

5.6. Overall conclusions on clinical safety

Available information leads to the conclusion that bearberry leaf extract corresponding to the 800 mg of hydroquinone derivatives calculated as arbutin per day used for one week can be considered safe for human use.

Patients using bearberry leaf extract should strictly follow recommendation on dose and length of use since there is still the possibility of mutagenic effect of hydroquinone especially on the urinary tract.

6. Overall conclusions

Bearberry leaf extract has been documented to be used for a long period of time which supports the traditional use of the herbal substance. Scientific evidence of its efficacy and safety in human is very poor and considered insufficient to support well established use of the herbal substance extract.

Non-clinical data available from the published literature could be considered sufficient to support traditional use for treatment of early symptoms of mild urinary tract infections such as burning sensation during urination and/or frequent urination.

Clinical data describing pharmacology, efficacy and safety of any bearberry leaf extract or its main component arbutin are very limited and provide only basic grounds for scientific evaluation of safety and efficacy in humans.

The risk-benefit ratio can be considered positive. Long tradition of use of bearberry leaf extracts in the treatment of uncomplicated bacterial infection of lower urinary tract, absence of serious adverse effects directly attributable to bearberry leaf extracts and results of non-clinical *in vitro* and *in vivo* experiments proving antimicrobial activity are benefits supporting the use of bearberry leaf extracts as traditional herbal preparation.

The only risk apparent from the available literature is the toxicity of hydroquinone. This substance when used in large amount has been reported toxic to animals and also mutagenic in some *in vitro* and *in vivo* tests. However, the amount of hydroquinone corresponding to the recommended dose of bearberry leaf extract is considered to be safe in short-term use.

In conclusion, the following points should not be omitted in the risk/benefit assessment.

Hydroquinone could be naturally present in the human body. It occurs in coffee, tea or wheat cereals. In any of the presented studies hydroquinone above 1 mg/ml was not detected in the samples. This amount is very close to the most conservative TTC value and together with limited period of administration the risk benefit ratio can be considered positive.

Most of the animal experiments were performed in healthy animals. This is important because there is no or a very low level of pathological bacteria in urinary tract of healthy animals resulting in very low level of β -glycosidase in the organism. β -glycosidase is an enzyme causing decomposition of arbutin to hydroquinone as was described in several *in vitro* studies.

Administration of bearberry leaf to humans is limited to very short period and the time of exposure of human body to hydroquinone is also very limited since it is rapidly transformed to its nontoxic metabolites that are excreted via the urine.

Nevertheless, as a precautionary measure, use in pregnancy and during lactation should be avoided. Use in children and adolescents is not recommended as medical advice should be sought in this age group.

Due to inadequate data on genotoxicity and unclear pharmacokinetic properties of arbutin an inclusion in the Community list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products cannot be recommended.

Annex

List of references