EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 January 2012
EMA/HMPC/573462/2009 Rev.1
Committee on Herbal Medicinal Products (HMPC)

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

Final

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)	*Arctostaphylos uva-ursi* (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) containing 23.5 – 29.3% of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry) D) Dry extract (DER 2.5 – 4.5:1), extraction solvent water containing 20 – 28% of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry)
Pharmaceutical form(s)	Herbal preparations in solid dosage forms or as herbal tea for oral use.
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1. Introduction

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

- Herbal substance(s)

Bearberry leaf (Uvae ursi folium) consists of whole or cut, dried leaf of *Arctostaphylos uva-ursi* (L.) Spreng. It contains not less than 7% of anhydrous arbutin ($C_{12}H_{16}O_7$; M_r 272.3), calculated with reference to anhydrous drug (European Pharmacopoeia 6.5, 2009)

- Herbal preparation(s)

  A) Comminuted herbal substance as herbal tea
  B) Powdered herbal substance
  C) Dry extract (DER 3.5 – 5.5:1), extraction solvent ethanol 60% (V/V) containing 23.5 – 29.3% of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry)
  D) Dry extract (DER 2.5 – 4.5:1), extraction solvent water containing 20 – 28% of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry)

- 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 (Pharmacopoeia Helvetica V, 1953)
Species anticystiticae: Betulae folium 25 g, Liquiritiae radix 30 g, Uvae ursi folium 45 g (Pharmacopoeia 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)

Other herbal 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, Matricariae 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 radicis 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)

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 and Haslam 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 methyl arbutin 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, ellagictannine corilagin (1-*O*-galloyl-3.6-di-*O*-hexahydroxydiphenoyl-*B*-D-glucose), catechin; anthocyanidin derivatives including cyanidin and delphinidin

Phenolic acids: approximately 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)

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-βD-galactoside, 2 isomeric quercetin arabinosides, aglycones of these compounds, kaempherol

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

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

Powdered herbal substance in solid dosage forms

Marketing authorisation of coated tablets containing 500 mg of the 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 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.

The 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 2 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 as herbal tea

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 – 3 g of the comminuted herbal substance and 150 ml of boiling water should be used 3 to 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 antiseptic (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), extraction solvent ethanol 60% (V/V), corresponding to 70 mg of hydroquinone derivatives calculated as anhydrous hydroquinone has been granted (since at least 1976). 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 above mentioned products are indicated for the treatment of inflammatory diseases of the urinary tract collection system. They 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, are 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 extracts

In **Germany**, an oral liquid medicinal product 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.

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

Regulatory status overview

Member State	Regulatory Status				Comments
Austria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Belgium	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ combinations
Bulgaria	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Denmark	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Estonia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ combinations
Finland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
France	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Germany	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ combinations
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Hungary	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None – should not be classified as food supplement
Ireland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Latvia	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Norway	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only

Poland	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Romania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Combinations only
Slovenia	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Spain	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	
Sweden	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
United Kingdom	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	

MA: Marketing Authorisation
TRAD: Traditional Use Registration
Other TRAD: Other national Traditional systems of registration
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 "Uvae ursi", "*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 a 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 as hydrops, lithiasis, in diabetes, for the therapy of gonorrhoea, etc. Until now only the use as urinary tract antiseptic and diuretic remains. Bearberry leaf was used also in the "New World" by the North American Indians for the 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 DAB 6. Ausgabe (1926), Československý lékopis 1. vydání (1947), Hagers Handbuch der Pharmazeutischen Praxis (Frerichs et al. 1938), Pharmacopoeia Helvetica V (1953), Österreichisches Arzneibuch 9. Ausgabe (1960), Martindale, The Extra Pharmacopoeia (Wade 1977), Deutsches Arzneibuch DAB 9. Ausgabe (1986), The Complete German Commission E Monographs (Blumenthal et al. 1998), WHO monographs on selected medicinal plants 2002, ESCOP Monographs 2003 and 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 et al. 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

ESCOP 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 et al. (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 – 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.

ESCOP Monographs (2003)

Dosage	cold water infusions of the dried leaf corresponding to 400 – 800 mg of arbutin per day divided into 2 to 3 doses; equivalent preparations not recommended for children
	patients should be advised to consume plenty of liquid during the treatment alkalisation of the urine may be beneficial
Route of administration	oral use
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
Interactions with other drugs	concomitant acidification of the urine (by other remedies, for instance) may result in a reduction of efficacy

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

Dosage	3 to 4 times daily: dried leaf 1.5 – 2.5 g or as infusion or as 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 g as an infusion 3 times daily; liquid extract (1:1) ethanol 25% 1.5 – 4 ml 3 times daily
Route of administration	oral administration *Uva-ursi* requires alkaline urine 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 form of an infusion or cold a maceration up to 4 times a day or 400 – 840 mg hydroquinone derivatives calculated as water-free arbutin; 0.4 g of dry extract in single dose; liquid extract single dose 2 g.
Route of administration	Oral use 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 g daily dose: 12 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 as herbal tea	Single dose: 1.5 – 4 g as a herbal infusion or as macerate, as herbal tea 2 to 4 times daily corresponding to the maximum daily dose of 8 g

B) Powdered herbal substance	The amount corresponding to 100 – 210 mg of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry) 2 to 4 times daily
C) Dry extract (3.5 – 5.5:1), extraction solvent ethanol 60% (V/V), containing 23.5 - 29.3% of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry)	The amount corresponding to 100 – 210 mg of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry) 2 to 4 times daily
D) Dry extract (2.5 – 4.5:1), water, containing 20 – 28% of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry)	The amount corresponding to 100 – 210 mg of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry) 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)	
Zerkleinerungsform:	minutim concis	minutim concis	plv. gross.	minutim concis	plv. gross.	A) concis-Drogen	B) Ganzdrogen
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. ziehenlassen	15 Min. kochen	30 Min. kalt extrahieren (Schüttelmaschine)	15 Min. kochen	30 Min. kalt extrahieren (Schüttelmaschine)	mit kochendem Wasser übergießen; 10 Min. ziehenlassen	
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
Arbutinkonkonzentration	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

The content of tannins has not been taken into consideration by Frohne (1970).
During decoction high amount of tannins is extracted while cold maceration prevents tannins elution (Frohne 2004; Hänsel et al. 1993). 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 is recommended:
To make a herbal infusion, pour 150 ml of boiling water over 1.5 – 4 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 – 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

A. 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 effects

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).

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

A decoction of bearberry leaf (10 g/100 ml water) increased remarkably the hydrophobicity of both *E. coli* and *Acinetobacter baumanii* strains *in vitro*. 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). A bearberry leaf aqueous extract (decoction 1:10/30 min/100°C/pH 4.7) exhibited a similar effect on *Helicobacter pylori* (Annuk et al. 1999).

The antimicrobial activity of an ethanolic extract (ethanol 80%) of the aerial parts of *A. 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).

The antimicrobial activity of extracts depends on the extraction solvent used. There is some evidence that extracts prepared with ethanol of high concentration have less activity. An aqueous extract of bearberry leaves inhibited the growth of *Streptococcus mutans* OMZ176 *in vitro* (Namba et al. 1981). A 30% ethanol extract of Uvae ursi folium 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 et al. 2003).

Diuretic effect

An aqueous extract of bearberry leaves (no other information on the type of extract and DER) was administered intraperitoneally (i.p.) 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 body weight. The urine volume from rats treated with the extract was significantly higher ($p<0.001$ from the 4^{th} to 8^{th} hour after administration; $p<0.05$ over a 24-hour period) than that 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).

Contrary results to that in the above mentioned study were obtained in 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 substance 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 were tested on the 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 the results of other 20 antimicrobial compounds. Only arbutin (present in urine samples collected after administration of 1 g arbutin), gentamycin and nalidixic acid were active against all strains tested. An 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 et al. 1975).

The antimicrobial activity of arbutin towards bacteria implicated in urinary tract infections was 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 and Howard 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-sterilising properties that are attributed to bacteriostatic hydroquinones, conjugates of glucuronic acid and sulfuric acid (Gruenwald et al. 2004).

Despite various pharmacological investigations, it is still debated 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 hydrolysed 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 effects

Bearberry leaf extract

Anti-inflammatory activity
An 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 the immuno-inflammatory response was studied in contact dermatitis triggered 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. A 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 and Willuhn 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 a 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 the 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 did not show any uterotonic effect (Shipochliev 1981).

Arbutin
In mice orally or i.p. treated with arbutin (50-200 mg/kg body weight [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 behaviour, blood pressure, heart rate or electrical activity (Li et al. 1982; NTP 2006).

Male and female cats (none anaesthetised) were administered oral (p.o.) and i.p. doses of 50 and 100 mg/kg [0.18 or 0.367 mmol/kg] body weight arbutin in water and observed at 0.5-, 1-, 2-, and 5-hour intervals. Arbutin at 50 mg/kg body weight (i.p. and p.o.) caused a statistically significant decrease in the number, intensity and frequency of coughs. Similar results were recorded for the 100 mg/kg body weight i.p. and p.o. doses; no increase of the antitussive activity was observed at this dose (Strapkova et al. 1991).

Arbutin (in concentrations 90 μg/ml and 40 μg/ml) did not inhibit the growth of rat hepatoma cells (Assaf et al. 1987; Barnes et al. 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 carrageenan-induced paw oedema (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 carrageenan-induced oedema and adjuvant-induced arthritis (Matsuda et al. 1991 – abstract).

Arbutin exhibited potent inhibitory effects on rat platelet aggregation induced by adenosine diphosphate (IC_{50}=0.12 mM) and collagen (IC_{50}=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 the crude extract or its components is very poor and did not allow any relevant conclusions.

Arbutin, the major constituent of Uvae ursi folium extracts, is a phenolic glycoside, which splits into 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 the 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 (GI) tract or possibly in the urinary tract, when infected (Müller and Kasper 1996 - abstract).

After ingestion of the leaves, arbutin is absorbed from the GI tract, and is hydrolysed by intestinal flora to form the aglycone, hydroquinone (Paper et al. 1993). Hydroquinone is metabolised to glucuronide and sulfate esters that are excreted in the urine (Kedzia et al. 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). Their antibacterial action reaches a maximum approximately 3 – 4 hours after ingestion (Blumenthal et al. 1998; Paper et al. 1993).

The 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 6 healthy volunteers. The arbutin equivalent was determined in urine samples collected within 24 hours, using the DAB 10 spectrophotometric method. The release of arbutin from the tablet compared to the extract was retarded by at least 3 hours. However, the bioavailability showed comparable values. In the urine samples, no free hydroquinone was detected using HPLC analysis. In a pilot study, the coated tablets and extract were administered together with 10 g sodium hydrogen carbonate. 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 a therapeutic concentration in urine only if the pH was alkaline (pH 8). In other urine samples the hydroquinone concentrations were below detection limit (1 μg/ml – HPLC method) (Paper et al. 1993). These findings are in agreement to those by Frohne, who detected free hydroquinone only after adjusting samples to pH 8 (Frohne 1970).

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 Uvae 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 cytochrome P450 enzymes to a 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).

Inhibitory effect of aqueous and methanolic Uvae ursi extracts on CYP3A isoenzymes was proved in *in vitro* tests (Chauhan et al. 2007). Possible interaction with finasteride should be taken into consideration as *in vitro* evidence suggests that agents which inhibit CYP3A activity are likely to inhibit the metabolism of finasteride (Wilde and Goa 1999).

Arbutin

As arbutin is reported to hydrolyse easily in diluted acids to yield D-glucose and hydroquinone, it is expected that ingested arbutin would be hydrolysed 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. The level of free hydroquinone in the body (urine and plasma samples) is usually at or below total concentration of hydroquinone measured in the pre-exposure background samples (Deisinger et al. 1996).

Female Wistar rats were given an aqueous solution of chromatographically pure arbutin, isolated from *A. 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 at allowed pH values. As long as antimicrobial action of arbutin depends on the release of hydroquinone, exo-enzymatic 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 from 0.4 to 0.8%, in dependence on the species of the microorganism (Jahodář et al. 1985).

Oral administration of arbutin (500 mg/kg [1.84 mmol/kg]) to female rats which were overloaded with fluid resulted in a 4-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. The diuretic activity following treatment with 200 mg/kg hydroquinone was greater than that observed in arbutin-treated animals (NTP 2006).

Investigations were performed in animals to elucidate the absorption, metabolism and elimination of arbutin. Isolated segments of the 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 has been also investigated in human small intestine obtained from biopsies of 18 patients with minor abdominal complaints without obvious gastrointestinal disease. In 3 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 [^{14}C]hydroquinone either in the diet or by gavage to Sprague-Dawley rats results in almost complete absorption from the GI 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 [^{14}C]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-oxidises 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 aqueous 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).

The 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. The 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 8 g/kg [29.38 mmol/kg] administered i.p. for 2 weeks, no toxic effects were observed (Li et al. 1982 [Chinese]; 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] body weight), 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).

The ames test and the 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]) incubation for 4 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. Foetal toxicity (e.g. stunted foetus, 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 (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 caused by picryl chloride and sheep red cell delayed type hypersensitivity in mice within 24 hours (Matsuda et al. 1990, 1991 [Japanese, abstract]). 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 5 days. At 300 µg/ml [1.10 mM] arbutin treatment for 5 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 in 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 - abstract; 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 via the urine and (<1%) in feces. Most of the arbutin is therefore transformed in to HQ conjugates (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).

Acute toxicity data on hydroquinone were published. The oral LD_{50} 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 LD_{50} values of 310 to 1050 mg/kg in rats. Thus, food showed to decrease the rate and extent of free HQ absorption. LD_{50} 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 LD_{50} 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 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 oxidised 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 overemphasised, since it has been suggested that there is little difference in qualitative responses between these two strains and TA 100, 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 i.p. 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. 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. The dietary concentration (0.8% hydroquinone) was the same as that used for the induction of renal tumours in F344 rats and, with less clarity, hepatocellular adenomas in male B6C3F1 mice (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 summarised in IPCS Health and Safety Guide No. 101 (IPCS 1994; IPCS 1996; NTP 2006).

Although extracts of the leaves do not appear to be carcinogenic, there is some evidence that hydroquinone is carcinogenic. In a 2-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 leukaemia), 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 characterised 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 body weight 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 tumours 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 end stage 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 recognise 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 tumours 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 tumours diagnosed by NTP were similar to the high dose tumours 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 re-evaluation, 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.

Reproduction and developmental toxicity

There are no germ cell studies of hydroquinone mutagenicity in which routes other than i.p. 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 i.p. route because the inguinal canal remains open. The i.p. 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).

Cytotoxicity

Hydroquinone has been reported to show a concentration-dependent cytotoxic activity on cultured rat hepatoma cells (HTC line). A dose 33 μg/ml caused cellular mortality of 40% of cells after 24 hours of incubation and no cells remained viable after 72 hours. A higher concentration of 66 μg/ml killed all the cells after a 24-hour contact (Assaf et al. 1987; Barnes et al. 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 to treat 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 humans 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 2 instead of 5 recommended strains. Results of this study were negative; however, clear conclusion about genotoxicity of the extract could not be made. Bearberry leaf extract was also negative in the *in vitro* micronucleus test; however, this test was not performed according to ICH S2B standard. 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 that in 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. The chinese hamster V79 mutation test performed with arbutin gave negative results. Whilst after preincubation of arbutin with β-glycosidase causing its cleavage to hydroquinone positive results of the assay were found. Furthermore the *in vivo* mouse micronucleus test revealed no increase incidence of micronuclei formation after treatment with arbutin compared to hydroquinone, used as positive control, that gave clear positive results. Arbutin alone seems to be of no genotoxic concern in animal studies, however, combination of arbutin with β-glycosidase but also the observed difference between the whole bearberry leaf extract and pure arbutin should be carefully considered. The assessment of genotoxicity should be performed very cautiously.

Carcinogenicity studies have not been performed with arbutin.

Reproduction and developmental studies performed in rats dosed with arbutin showed that 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.

Hyroquinone

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 chromatide 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 as 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. Furthermore hydroquinone is a naturally occurring substance and the 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 the 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 amounts above the detection limit (1 μg /ml – HPLC method) was found only at pH 8. It should also be 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 neutralise the hydroquinone just after its formation.

The safety margin could be considered sufficient regarding toxicity and adverse effects.

Furthermore, 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.

No adverse toxic reactions have been reported in scientific literature and several types of bearberry leaf extract have been in medicinal use for many years. Therefore non-clinical data on bearberry leaf extract and its main components arbutin and hydroquinone can be considered sufficient to support the traditional use of 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

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). As information on sodium sparing effect is not supported by any published case report, this interaction is not included in the Community herbal monograph.

Arbutin
In a study without controls, urine samples from healthy volunteers were collected 3 hours after oral administration of 0.1 or 1 g arbutin. The urine samples (adjusted to pH 8) 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 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). The maximum effect was detected from 3 – 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 et al. 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 the alkaline environment against bacterial infection of the 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, hydrolysed 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 hydrolysed by bacterial enzymes (Frohne 2004).

Hydroquinone

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

It is still unknown which of the hydroquinone compounds are 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 to 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 et al. 1975).

Alkalisation of urine

Urine samples from healthy volunteers received arbutin-containing tea or pure arbutin showed after alkalinisation of the urine inhibition of growth of bacteria tested. Samples of normal urine with or without alkalisation and arbutin solutions (1 – 3 mg/ml) 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 (when compared to the urine sample at pH 6) (Kedzia et al. 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 a clear inhibitory effect of urine containing metabolic products of arbutin. This urine sample has to be alkaline. Alkalisation alone or addition of arbutin alone did not show any bacteriostatic effect in the sample of urine (Frohne 1977).

Whether the alkalising 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).

A problem is the way of making the urine environment more alkaline. The common daily dose of natrium hydrogencarbonate or dinatrium phosphate is able to alkalinise urine only for a short period of time. Kedzia et al. (1975) suggested using 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. Frohne stated that further investigation of how to alkalinise urine in a 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, several references included statements on patients being advised to avoid eating highly acidic foods, such as acidic fruits and their juices during treatment with Uvae ursi folium (WHO 2002; Barnes et al. 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 destabilisation of its membranes. Alkalisation of the urine by intake of sodium

bicarbonate is not necessary considering the effective bacterial deconjugation by *E. coli*, the principal agent in urinary infections (Siegers et al. 2003).

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

The main constituent of Uvae ursi folium extracts is arbutin, a phenolic glycoside splits in hydroquinone and glucose (Jahodář et al. 1985). Free hydroquinone is the recognised 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 the 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 of one volunteer, which represented approximately half of the administered arbutin dose (Glöckl et al. 2001).

In an open, randomised, two-way crossover study, 16 healthy volunteers (8 males, 8 females, mean age of 25.4-year 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 4 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).

Twelve 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 administrated 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 glusulase (mixture of β-glucuronidase, aryl-sulfatase and cellulase) or an *E. coli* suspension, and analysed 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 glusulase (Siegers et al. 1997, 2003).

Arbutin
Arbutin was found to be extensively absorbed from the GI tract and bioavailable as hydroquinone. Volunteers (2 males and 2 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 2 to 3 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).

Hydroquinone
Most studies of hydroquinone kinetics and metabolism following oral administration have used arbutin or another 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 g of arbutin. Lower dose provided lower antibacterial effect but, independently of the dose, the pH value of urine was the most important factor determining the antibacterial activity (Kedzia et al. 1975).

According to Frohne (1970), the effective concentration of arbutin should be higher than 0.3%.

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 substance/preparation is not available at the time of the preparation of this report.

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

In the first clinical trial, the effect of a combination product (oral solution containing liquid extracts from Uvae ursi folium, Betulae folium, Equiseti herba, Virgaureae herba, Juniperi pseudo-fructus and Coccus cacti) in the treatment of urinary tract infections (UTIs) and frequent/impaired micturition were evaluated. The herbal preparation was compared to a 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 in the treatment of urinary tract infection caused by a long-term implantation of a urinary catheter was evaluated at an open, controlled clinical study with 60 patients. An oral solution –a combination of liquid extracts from 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 and Kreyes 1988). The therapeutic efficacy of the herbal medicinal product was evaluated as very good when compared with trimethoprim-sulfamethoxazol therapy especially in cases of old people with permanent catheter. The product was considered to be an effective alternative to chemoprophylaxis in patients with permanent catheter.

The third clinical study assessed the prophylactic effect of another combination product (containing hydroalcoholic extract of bearberry leaves with a standardised content of arbutin and methyl arbutin, and of dandelion root and leaf) on recurrent cystitis. The product had a prophylactic effect on recurrent cystitis in a double-blind, prospective, randomised 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**	**Larsson et al. 1993**
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	Uvae ursi folium, Betulae folium, Equiseti herba, Virgaureae herba, Juniperi fructus, Coccus cacti	Uvae ursi folium, Betulae folium, Equiseti herba, Solidaginis virgaureae herba	Hydroalcoholic extract of: - Uvae ursi folium - Taraxacum officinalis, radix cum herba
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

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.

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. After 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 evaluation 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 were used in the examined working environment (McGregor 2007).

5.3. Adverse events and serious adverse events and deaths

The internal use of Uvae ursi folium may cause nausea and vomiting due to stomach irritation from the high tannin content (WHO 2002; Blumenthal et al. 1998; Gruenwald et al. 2004; British Herbal Pharmacopoeia 1996; ESCOP 2003; Bradley 1992). Stomach ache has also been reported as adverse effect (Gruenwald et al. 2004; Hänsel et al. 1993).
In 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 and increased heart rate (NTP 2006).

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

In a 56-year old female who drank tea containing bearberry leaf regularly for 3 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 within an open, randomised, two-way crossover study with 16 healthy volunteers who received a single oral dose of 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). The tests were performed before and after the treatment and 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 semi quantitative 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 the result of the treatment with bearberry leaf dry extract (Schindler et al. 2002).

5.5. Safety in special populations and situations

The 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.

Incidence of urinary tract infections in men
UTIs are the second most common form of infection, accounting for nearly 25% of all infections. Incidence of UTIs is significantly higher in women than in men. Incidence of UTIs in men is increasing with age. Asymptomatic bacteriuria is believed to affect up to 50% of geriatric women and 30% of geriatric men. Asymptomatic bacteriuria is prevalent in elderly population but it frequently resolves without treatment and has no long-term sequelae. However, symptomatic UTI among the elderly requires antimicrobiological therapy (Foxman 2002).

For males aged 17 – 79 years, the mean annual UTI incidence is 2.2 %, for males aged ≥ 80 years, the mean annual UTI incidence rises to 5.3 % and risk factors in this age include presence of an indwelling urinary catheter, hospitalization and anatomical abnormalities associated with aging or disease (e.g. benign or malignant prostatic hyperplasia). The incidence of UTIs in men is significantly lower than in women. In women aged 15 – 39 years, the mean annual UTI incidence is 15.2 % and with age falls to 11.4 % for women aged 40 – 59 years and to 9.7 % for women aged 60 – 79 years (Guay 2008). Guay (2008) also reports on a study describing epidemiology of UTIs in a non-selected population-at-large. In this study, laboratory surveillance was conducted for all community-acquired UTIs among residents of Calgary Health Region (population of 1.2 million) in Canada during 2004 and 2005. A total of 40,618 episodes of UTI occurred among 30,851 residents (overall annual incidence was 17.5/1000). The incidence was significantly higher in females than in males (30.0 vs. 5.0/1000). After the first year of life, UTI was rare in males until late middle age, at which point a significant increase occurred with each subsequent decade of life. In the very old age (80 – 89 years old), UTI was common (males 638, females 926, overall 851/1000/year) (Guay, 2008).

Much higher incidence of UTIs in females during adolescence and childbearing years (adult women are 30 times more likely than men to develop a UTI) is reported also by Brusch (2011). The frequency of UTI in men approaches that of women only in men older than 60 years; in men aged 65 years or older,

10% have been found to have bacteriuria, as compared with 20% of women in this age group. In the normal host, UTI in men may occur due to infection of other parts of the genitourinary tract, typically the prostate. Older males with prostatic hypertrophy have incomplete bladder empting, predisposing them to UTI on the basis of urinary stasis. However, in males aged 3 months to 50 years, the incidence of UTI is low; therefore, the possibility of anatomic abnormality must be considered. In males older than 50 years, prostatic hypertrophy with partial obstruction is the main contributor to the increase UTI (Brusch, 2011).

Among complications of benign prostatic hyperplasia (BPH) resulting from persistent failure of the bladder to empty or store urine recurrent urinary tract are mentioned (Lee, 2000). In patients with mild symptoms of BPH, whose symptoms do not cause unacceptable distress, no drug therapy with α-adrenergic antagonists or with finasteride is yet necessary, and watch-full waiting is indicated instead (Lee 2000; Clifford and Farmer 2000). For treatment of symptoms of mild recurrent lower UTIs short term use of Uvae ursi products can be recommended but only after consultation with a doctor.

Neisseria gonorrhoeae and Chlamydia trachomatis are clinically important infectious causes of urethritis (Workowski and Berman 2006).

Assessor´s conclusion:
According to reports on the traditional use no differentiation between the genders was done. While recurrent mild infections of the lower urinary tract are usually uncomplicated in women, a delayed consultation of a medical doctor may imply serious risks for men. Incidence of UTIs in men is significantly lower than in women. Incidence of UTis in young men is very low and risk of anatomical abnormalities, acute inflammations of lower urinary tract such as acute prostatitis or acute epididymitis, as well as sexually transmitted diseases such as gonorrhoea and Chlamydia infections should be taken in consideration by a medical doctor. In men over 50 years, incidence of UTIs is increasing due to prostatic hyperplasia (benign or malignant) and presence of an indwelling catheter. Both, prostatic hyperplasia and indwelling catheter require medical supervision.

The criterion of the Article 16 a) of Directive 2001/83/EC for traditional herbal medicinal products "they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment" is not fulfilled for use in men. Therefore, the use in men is excluded from the traditional use and traditional use can be recommended for females only.

Paediatric population
A posology for children and adolescents was published in Kinderdosierungen von Phytopharmaka (Dorsch et al. 1998) for bearberry leaf:

Dosage in children:

0 – 1 year	>1 – 4 years	>4 – 10 years	>10 – 16 years
		5 – 10 g	10 g

Corresponding amount of arbutin:

0 – 1 year	>1 – 4 years	>4 – 10 years	>10 – 16 years
			400 – 700 mg

However, posology data for children is not supported by any clinical data (clinical studies, post marketing reports). The data published by Dorsch et al. (1998) are derived from calculations only.

Furthermore, the use in children and adolescents cannot be recommended for traditional use because infections of the urinary tract, even in their early stage, in children and adolescents should be treated under medical supervision.

Overdose

An overdosing with bearberry leaf extract can lead to inflammatory irritation of the bladder and urinary tract mucosa accompanied with dysuria and hematuria, or later with blood excreta. Finally, overdosing 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 et al. 2002).

Hydroquinone is reported to be toxic if ingested in large quantities: 1 g (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).

Although the symptoms of overdose and long-term use are described in the literature, they are not supported by case reports. Taking into consideration information from the literature the patients are advised to follow the recommended dose and duration of use.

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 anaemia, emaciation, steatosis and de-pigmentation 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 et al. 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 hepatic impairment, especially in children after long-term use (Hänsel et al. 1993).

Although consequences of long-term use are described in the literature, they are not supported by case reports. Taking into consideration information from the literature, patients are advised to follow the recommended duration of use found in products' package leaflet. The Community herbal monograph provides recommended duration of use for those herbal preparations included in the monograph.

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 800 mg of hydroquinone derivatives calculated as arbutin per day used for one week can be considered as safe for human use.

Patients using bearberry leaf extract should strictly follow recommendation on dose and duration 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 and extracts.

Non-clinical data available from the published literature could be considered sufficient to support traditional use for treatment of symptoms of mild recurrent lower urinary tract infections such as burning sensation during urination and/or frequent urination, after serious conditions have been excluded by a medical doctor.

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 benefit/risk ratio can be considered positive. The long-standing of use of bearberry leaf extracts in the treatment of uncomplicated bacterial infection of the lower urinary tract, the absence of reported serious adverse effects directly attributable to bearberry leaf extracts, and the results of non-clinical *in vitro* and *in vivo* experiments proving antimicrobial activity supporting the use as traditional herbal preparations. However, the use in men requires always medical supervision. The criterion of the Article 16 a) of Directive 2001/83/EC for traditional herbal medicinal products "they have indications exclusively appropriate to traditional herbal medicinal products which, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment" is not fulfilled for use in men. Therefore, the use in men is excluded from the traditional use and traditional use can be recommended for women only.

The only risk apparent from the available literature is the toxicity of hydroquinone. This substance when used in large amount has been reported to be 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 benefit/risk 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[1] value and together with a limited period of administration, the benefit/risk 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

[1] Threshold of Toxicological Concern – see EMA/HMPC/107079/2007

level of β-glycosidase in the organism. β-glycosidase is an enzyme causing decomposition of arbutin to hydroquinone as 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. The use in children and adolescents is not recommended as medical advice should be sought in this age group.

Due to inadequate data on genotoxicity, 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