EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 January 2012
EMA/HMPC/46410/2011Rev.1[1]
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on Community herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium (EMA/HMPC/573460/2009)

Table 1: Organisations and/or individuals that commented on the final Community herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium published on 19 April 2011.

	Organisations and/or individuals
1	European Scientific Cooperative on Phytotherapy (ESCOP)
2	Association of the European Self-Medication Industry (AESGP)

[1] Rev.1: following assessment of the comments received in July 2011 regarding the changes in the monograph on Uvae ursi folium concerning the gender-specific indication, the monograph and supporting documents have been revised.

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Table 2: Discussion of comments

GENERAL COMMENTS		
Interested party	**Comment and Rationale**	**Outcome**
AESGP	We have noted the publication of the final community monograph on *Arctostaphylos uva-ursi* (L.) Spreng, folium on 19 April 2011. Although the finalisation of the monograph is in principle positive, we have noted the following important changes compared to the draft version. In the absence of publication of the companion documents, i.e. overview of comments and the final assessment report, the reason as to why the indication has been made gender specific remains unclear. Given the importance of this change, we feel that in **terms of process**, this should have given rise to a new consultation on this specific point. Given the potential repercussion for products on the market and on new registrations, it is of paramount importance that stakeholders be made aware and be consulted on a modification of this level before a monograph is finalised. We would ask this is taken into account in the future before monographs become final and are published.	The comment will be taken in consideration in all future monographs. When significant changes in a monograph are made after public consultation, these changes will be subject of a new consultation.
ESCOP	ESCOP had principally welcomed the draft Community herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium, prepared by the Committee on Herbal Medicinal Products (HMPC). Nevertheless, the severe amendment of the final Community herbal monograph (exclusion of men as users of the herbal tea and herbal preparations) without any further discussion has changed this point of view. Thus, ESCOP considers the following changes necessary.	See above

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Section number and heading	**Interested party**	**Comment and Rationale**	**Outcome**
4.1 Therapeutic indications	AESGP	**Comments:** The indication has been modified to read: *"Traditional herbal medicinal product used for treatment of ~~early~~ symptoms of mild **recurrent lower** urinary tract infections such as burning sensation during urination and/or frequent urination **in women, after serious conditions have been excluded by a medical doctor**."* We propose to delete "in women" from section 4.1 'therapeutic indications'. **Rationale**: in terms of the **nature of the change and scientific justification**, we have the following detailed remarks: The exclusion of men in the final HMPC monograph occurred without previous announcement in the draft monograph or discussion into the accompanying assessment report, leading to the conclusion that this unexpected decision was based on *serious safety concerns*. • Indeed, symptoms of urinary frequency and burning sensation during urination occurred at very low incidence in adult males under 50 years of age (approximately 5-8 per year per 10,000) (Foxman 2002). These symptoms are due to uncomplicated urinary tract infections of various causes (Workowski et al. 2006). *E. coli* is the main causative agent	Not endorsed. According to reports on the traditional use no differentiation between the genders was done. However, 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

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		of the symptoms (80%) (Guay 2008). *Uva ursi*-containing products are a help for the treatment of these recurrent mild symptoms, particularly when antibiotics are still not required. Therefore, an exclusion of men seems unreasonable. • In men over 50 years of age, however, the incidence of urinary frequency and burning sensation during urination rises dramatically (range, 20-50% prevalence) because of the enlargement of the prostate, difficulties for complete bladder emptying and use of urinary catheters (Foxman 2002). In this group of men, the spectrum of causative agents is broader and the most important risk factor includes urinary tract obstruction due to stones, tumours, strictures or enlarged prostate. It is reasonable to assume that most men suffering from these disorders are already under medical advice. In order to prevent the overlooking of these illnesses men, and especially the subgroup of men over 50 years, should be advised to consult a doctor before using any *Uva ursi*-containing preparations.	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.
		• Benign prostatic hyperplasia (BPH) is the non-malignant enlargement of the prostate and clinically occurs predominantly in men aged over 50 years (Clifford et al. 2000). This enlargement of the prostate gland is associated with a 3-fold increase in the risk of having moderate to severe symptoms of urinary frequency and burning sensation during urination. Pharmacotherapy for symptomatic BPH in men reduces the prostate volume with agents, such as finasteride, or decrease smooth muscle tone in the prostate with agents, such as tamsulosin (Lee 2000; Wilde and Goa 1999). *Uva ursi*-containing products do not	The Chauhan article states the following: "Of 3 izoenzmes studied within CYP3A subfamily, the degree of inhibition, from most to least, was in the order CYP3A5 ≥ CYP3A7 > 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." The last sentence was already included in the AR with the following note: "From the pharmacology point of view the interaction of bearberry leaf extract with CYP isozymes should be

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		interfere with such medications because they do not affect the activity of the CYP450 (Chauhan et al. 2007; HMPC monograph 2011). Therefore, there are no safety concerns regarding interactions among *Uva ursi*-containing products and agents for treating BPH. There are *a priori* no pharmacological reasons to prevent the use of *Uva ursi*-containing products with other prostate therapies. • Many men with BPH and lower urinary tract symptoms (LUTS) do not require treatment because their symptoms are not significantly interfering with their quality of life (QoL). Moreover, progression of symptoms or deterioration of QoL occurs only in a fraction of men and treatment intervention is still effective, even when delayed. In these cases the Guideline of the Management of BPH 2011 of the American Urological Association (AUA) recommends "watchful waiting". In case of mild urinary tract infections, doctors may recommend phytotherapeutic agents like *Uva ursi*. If, however, the use of this plant extracts "is not recommended in men", doctors will not have this treatment option and may prescribe antibiotics. • For years, the EU and the EMA have been promoting a "rational use of antibiotics", which advise against the indiscriminate use of wide-spectrum antibiotics especially in older people (Cars et al. 2011; ECDC/EMEA joint technical report 2009; Council Recommendation 2002). For this reason, the use of *Uva ursi*-containing products in mild recurrent uncomplicated lower urinary tract infections in man could positively reduce the use of antibiotics. References:	carefully considered." Moreover, in Wilde and Goa article which was also provided by AESGP the following sentence has been found: "recent in vitro evidence suggests that agents which inhibits CAP3A activity are likely to inhibit the metabolism of finasteride." Interaction of Uvae ursi products with finasteride has not been confirmed by clinical data and therefore it was not included in the Community Monograph; however, its possibility should be kept in mind. Information on in-vitro evidence that agents which inhibit CYP3A activity are likely to inhibit the metabolism of finasteride has been added to section 3.2 of the Assessment Report.

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		Cars O, Hedin A, Heddini A. The global need for effective antibiotics-Moving towards concerted action. Drug Resist Updat. 2011 Apr;14(2):68-9. Epub 2011 Apr 1. Chauhan B, Yu C, Krantis A, Scott I, Arnason JT, Marles RJ, Foster BC. In vitro activity of uva-ursi against cytochrome P450 isoenzymes and P-glycoprotein. Canadian Journal of Physiology and Pharmacology 2007, 85(11):1099-107. Clifford GM, Farmer RD. Medical therapy for benign prostatic hyperplasia: a review of the literature. Eur Urol 2000; 38:2-19 ECDC/EMEA JOINT TECHNICAL REPORT. The bacterial challenge: time to react A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf 01.09.2009 Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med. Jul 8 2002;113 Suppl 1A:5S-13S. Guay DR. Contemporary management of uncomplicated urinary tract infections. Drugs. 2008;68(9):1169-205. Guideline of the Management of BPH 2011 of the American Urological Association (AUA) http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bph-management/chap_3_ResultsTreatmentOutcomesAnalyses.pdf Lee M Tamsulosin for the treatment of benign prostatic hypertrophy. Ann Pharmacother 2000; 34 :188-199. Report from the Commission to the Council on the Basis of Member States' Reports on the Implementation of the Council Recommendation (2002/77/Ec) on the prudent use of antimicrobial agents in human medicine http://europa.eu/legislation_summaries/public_health/threats_to_health/c11569_en.htm Wilde MI, Goa KL. Finasteride: an update of its use in the	

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		management of symptomatic benign prostatic hyperplasia. Drugs 1999; 57: 557-581 Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. MMWR Recomm Rep. Aug 4 2006; 55:1-94.	
4.2 Posology and method of admini-stration	AESGP	It is now specified that the posology is for *"Female adults and elderly"*. We propose to delete "Female" from the sentence "Female adults and elderly" in section 4.2 Rationale: see above	Not endorsed. See explanation above
4.4 Special warnings and precautions for use	AESGP	We propose to replace 'The use in men is not recommended because of concerns requiring medical advice' by 'The use in men - especially over 50 years - is not recommended without medical advice' Rationale: see above	Not endorsed. See explanation above
4.2. Posology **and** **4.4. Special warnings and precautions for use**	ESCOP	**<u>Comment</u>** The rationale for the unforeseen restriction "The use in men is not recommended" and "The use in men is not recommended because of concerns requiring medical advice" in the assessment report is given without any proof from literature and only based on the concern to underdiagnose a severe affection of the urogenital tract in elderly men due to a	Not endorsed. See explanation above

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		delayed consultation of medical advice. This does not seem adequate for the restriction of the use of bearberry leaf to women only. As a compromise ESCOP proposes the following wording in both paragraphs: "The use in elderly men is only recommended after serious conditions have been excluded by medical doctor" In consequence, "in women" and "female adults" in 4.1. and 4.2. has to be changed accordingly. **Rationale** A restriction of the use of bearberry in men has not been published in reputated handbooks of phytotherapy until now (1-4) despite a very well-documented traditional use. Additionally, no respective concerns can be deduced from clinical studies. **References** 1) Schilcher H, Kammerer S, Wegener T. Leitfaden Phytotherapie 4th ed. München: Elsevier, 2010; 70. 2) Mills S, Bone K. Principles and Practice of Phytotherapy. Edinburgh, London, New York: Churchill Livingstone, 2000; 280-5. 3) Jänicke C, Grünwald J, Brendler T. Handbuch Phytotherapie. Stuttgart: Wissenschaftliche Verlagsgesellschaft, 2003;39-41. 4) Barnes J, Anderson LA, Phillipson JD. Herbal Medicines 2nd edition. London, Chicago: Pharmaceutical Press, 2002:465-67.	

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Overview of comments received on Community herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium (EMA/HMPC/573460/2009)

Published on 14 July 2011

Table 1: Organisations and/or individuals that commented on the draft Community herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium as released for public consultation on 18 August 2010 until 15 December 2010.

	Organisations and/or individuals
1	European Scientific Cooperative on Phytotherapy (ESCOP)
2	The European Botanical Forum (EBF)
3	Association of the European Self-Medication Industry (AESGP)

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Table 2: Discussion of comments

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Interested party	**Comment and Rationale**	**Outcome**
ESCOP	ESCOP appreciates the draft for a Community Herbal Monograph on "bearberry leaf" prepared by the Committee on Herbal Medicinal Products (HMPC). However, we consider the following modification necessary.	
EBF	Policy of precautionary principle to exclude all children/adolescents bellow age of 18 years of age in Posology by the wording: „The use in children and adolescents under 18 years of age is not recommended because data are not sufficient and medical advice should be sought." without any justification by only "not sufficient data" substantiation is inappropriate and the real impact is practical exclusion of the whole category of population of benefits of phytotherapy selfmedication with drive to more toxic chemotherapy even in early symptoms of mild infections (dysmicrobias).	The therapeutic use of traditional herbal medicinal products in specific age groups should be based on the long term experience in these groups. Unless this experience is documented, the safe use is considered not demonstrated and, therefore, cannot be recommended in the Community herbal monograph. The opinion of HMPC members is that infections of the urinary tract in children and adolescents should be treated under medical supervision even at early stage. See also section 4.2 and 4.4 below
AESGP	AESGP in principle welcomes the development of the above-mentioned Community herbal monograph which, by providing harmonised assessment criteria for Uvae ursi-containing products, should facilitate mutual recognition in Europe.	

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2. Qualitative and quantitative composition	AESGP	**Comments:** We propose to classify the dry extracts as standardised extracts instead of "quantified" as mentioned for the dry extracts C and D in the draft monograph. In Germany these herbal preparations are usually standardised, e.g. to a content of 70 mg hydroquinone derivatives, calculated as anhydrous arbutin (see example below). This means that these medicinal products are manufactured by adjusting the given content of e.g. 70 mg hydroquinone derivatives by adding excipients, in contrast to "quantified" extracts in which a defined range of constituents has to be adjusted by blending batches only (see also below). **Proposed change:** For preparation C the text should therefore read: *"Dry extract (DER 3.5-5.5:1), extraction solvent ethanol 60 % (V/V) standardised to a given content within the range from 23.5 to 29.3% of hydroquinone derivatives calculated as anhydrous arbutin determined by spectrophotometry or corresponding amount of arbutin determined by HPLC".* A preparation currently marketed in Germany might serve as an example: one tablet contains 238.7 – 297.5 mg dry extract from bearberry leaf (3.5 – 5.5:1) corresponding to 70 mg hydroquinone derivatives calculated as anhydrous arbutin. This	Partly endorsed. Standardisation is only acceptable when constituents with therapeutic activity are known. Because the efficacy of bearberry preparations was not supported by the clinical studies, standardisation of the extracts cannot be accepted. However, section 2 is changed as follows: c) Dry extract (DER 3.5-5.5:1), extraction solvent ethanol 60 % (V/V) containing 23.5 to 29.3% of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry). d) Dry extract (DER 2.5-4.5:1), extraction solvent water containing 20 to 28% of hydroquinone derivatives calculated as anhydrous arbutin (spectrophotometry).

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		extract has also been described in Section 1.2 of the Assessment Report under “dry extracts”. According to the declaration which is in line with the respective HMPC Guideline, this extract unequivocally is a standardised extract. A second example is Arctuvan® containing an aqueous standardised extract of Arctostaphylos uva-ursi (2.5 – 4.5:1), 425.25 – 519.75 mg (corresponding to 105 mg hydroquinone derivates, calculated as anhydrous arbutin). The need for standardisation is also in line with the Assessment Report which recognises (Section 3.2) hydroquinone as the active metabolite, the amount of hydroquinone being crucial for the therapeutic activity. Section 4.1.1 clearly states that the antiseptic and diuretic properties claimed for bearberry leaf extract can be attributed to the hydroquinone derivatives, especially arbutin. Moreover, section 4.3 explains that while sufficient clinical data is lacking from the rapporteur’s viewpoint, a traditional use can be accepted based on the given *in vitro* data of bearberry leaf preparations containing arbutin as the main active compound. From our point of view there is no contradiction between a plausible traditional use and the standardisation of the respective preparation. Even though no proof of efficacy is required for the registration of a traditional medicinal product, according to Directive 2004/24/EC *“the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience”*. This means that for a traditional registration possible pharmacological effects or	

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		efficacy can be assumed which can be attributed to certain constituents. For this reason standardisation to these constituents is possible. For this reason standardisation of bearberry leaf extract to a defined amount of hydroquinone derivatives calculated as arbutin is justified taking into account that the pharmacological effects of the extracts – as explained in the Assessment Report – can be clearly attributed to the hydroquinone derivatives, especially arbutin. In addition the production of a quantified extract requires the adjustment of the amount of active markers by blending batches. Any adjustment with inert excipients is in principle not possible according to the definition of quantified extract in the European Pharmacopoeia. Taking into account the minimum level of 7% of arbutin (anhydrous) required for the herbal drug, which corresponds to a level of about 8.75% hydroquinone derivates (photometric), this could yield extracts with higher contents of hydroquinone derivates. E.g., a transition rate for the aqueous extract of 80% for hydroquinone derivates and a DER of 4:1, a herbal drug containing 8.75% (calculated from the minimum value of 7% arbutin determined by HPLC with a conversion factor of 1.25) would lead to an extract containing 28% hydroquinone derivates. For the aqueous extract this is the permitted maximum level. In case of a higher content in the herbal starting material or a better transition rate the maximum level would be exceeded. An adjustment in the meaning of quantification would require extracts with lower contents of	

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		hydroquinone derivates, but in this case the herbal starting material would not meet the Ph. Eur. requirement concerning the minimum arbutin content. Therefore standardisation with inert excipients is appropriate and necessary.	
4.1. Therapeutic indications	EBF	**Comments:** Therapeutic indications: "Traditional herbal medicinal product used for treatment of early symptoms of mild urinary tract infections such* as burning sensation during urination and/or frequent urination „ should be ammended by more pregnant *"such as prodromal cystitis signalised as…" according to ESCOP Monograph Uvae Ursi Folium. (E/S/C/O/P Monographs. The scientific foundation for herbal medicinal products. 2nd ed. Thieme, 2003, 536-538.) There is no doubt that Uvae Ursi Folium is containing substantial amount of tannins present to the extent of 6 to 7 per cent. This class of constituents is having strong interaction with mucous membranes by binding to proteins. This way is Uvae Ursi Folium acting as adstringens with supporting anti-inflammatory efficacy in cystitis. (Ozarowski, A.:Ziololecznictwo, PZWL Warsaw 1980, 71-72) **Proposed change :** Therapeutic indications: "Traditional herbal medicinal product used for treatment of early symptoms of mild urinary tract infections such as prodromal cystitis signalised as burning sensation during urination and/or frequent urination . Herbal constituents are having additional synergic anti-inflammatory efficacy in urinary tract infections "	Partly endorsed. We agree with the EBF that it should be clearly stated in the monograph that the early symptoms of mild urinary tract infections are related to the lower part of the urinary tract i.e. bladder and/or urethra. However we do not agree to add information on the activity of the constituents to the therapeutic indication. Only indications can be stated in section 4.1. Section 4.1 has been changed to the following: Traditional herbal medicinal product used for the treatment of symptoms of mild recurrent lower urinary tract infections such as burning sensation during urination and/or frequent urination in women, after serious conditions have been excluded by a medical doctor.

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4.2. and 4.4.	*ESCOP*	**Comments:** The restrictions of use in adolescents are not justified [1]. Proposed change (if any): 4.2. The use in children under 12 years of age is not recommended. 4.4. The use in children under 12 years of age is not recommended because data are not sufficient and medical advice should be sought.	Not endorsed. The posology for bearberry leaf in 'Kinderdosierungen' from Phytopharmaka is not supported by any clinical data (clinical studies, post marketing reports). Use in children and adolecsents cannot be recommended for traditional use as infections of the urinary tract even at early stage in children and adolescents should be treated under medical supervision.
4.2. Posology and method of administration	EBF	**Comments:** In accordance with the « Assessment report on Arctostaphylos uva-ursi », the current posology corresponds to an intake of 400 à 840 mg per day of hydroquinone derivatives expressed as arbutin brought by herbal tea or herbal preparations (extracts). As described in the EP monograph for bearberry leaves (n°1054), the leaves contain a minimum of 7% arbutin (HPLC) which corresponds to approx.7.5 – 9.5% hydroquinonic derivatives expressed as arbutin (UV-VIS) with an average of 8%. Given that, the posology for drug product and herbal tea should be equivalent to suggested modification and the following precision could be added for herbal preparation.	Partly endorsed. Limitation of the daily dose to maximum 8 g of the comminuted herbal substance for tea/macerate preparation is meaningful taking in consideration the Ph.Eur. requirement for a minimum content of arbutin 7 % determined by HPLC (or hydroquinone derivatives calculated as arbutin 8 % determined by spectrophotometry in previous versions oh Ph.Eur.) and the fact that according to the information provided by the company producing herbal teas, the average content of hydroquinone derivatives calculated as arbutin in bearberry leaf batches is about 10 % determined by spectrophotometry. The inclusion of a corresponding amount of hydroquinone derivatives is not endorsed as no standardisation is expected for the comminuted herbal substance.

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		Proposed change : • herbal tea : 1,5 - 4 g of the comminuted herbal substance (120 mg à 320 mg of hydroquinone derivatives expressed as arbutin) 2 to 4 times daily (equivalent to 6 to 8 g of herbal substance/day) Herbal preparations b), c),d) : The amount corresponding to 100 – 210 mg of hydroquinone derivatives calculated as anhydrous arbutin (photometric)) or corresponding amount of arbutin (HPLC) 2 to 4 times daily, equivalent to 400 to 840 mg of hydroquinone derivatives expressed as arbutin per day .	Section 4.2 is changed as follows: Female adults, elderly a) Herbal tea: 1.5 – 4 g of the comminuted herbal substance in 150 ml of boiling water as an infusion, 2 to 4 times daily corresponding to the maximum daily dose of 8 g b) 1.5 – 4 g of the comminuted herbal substance in 150 ml of water as a macerate, 2 to 4 times daily corresponding to the maximum daily dose of 8 g. The macerate should be used immediately after preparation. Proposed change in posology of herbal preparations b), c), d) was not endorsed. It is not necessary to add the daily dose as it is easy to calculate it from the single dose. The following text has been added after discussion in MLWP: The use in men is not recommended (see section 4.4 ‘Special warnings and precautions for use’).

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4.2 Posology and method of admini-stration **Duration of use**	AESGP	**Proposed change:** We suggest to replace the sentence: "If the symptoms **persist for more than 2 days** during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted" by the following wording: "***If symptoms persist longer than 1 week during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted".*** **Comments:** The reasons are explained as follows: • From our point of view, there are no pharmacological, pharmacodynamic or toxicological reasons to restrict the use to only 2 days. Furthermore, there is no clinical data available supporting the efficacy of bearberry leaf on the relief of symptoms after only 2 days of treatment. • According to the study of Schnitker (1993) quoted in the Assessment Report, clinical experience of 75 physicians in the treatment of urinary tract infections (UTI) showed that the mean time to observe efficacy of preparations was at least 3 to 4 days. • Patients who immediately received antibiotic treatment for their uncomplicated UTI, experienced an improvement of symptoms after 3.5 days [1]. For some patient groups (e.g. patients with delayed start of treatment, with resistant infections, with frequent somatic symptoms, without antibiotic prescription or with urethral syndrome)	Partly endorsed. The references AESGP[1,2,3] concern the relations between symptoms and antibiotic treatment in urinary tract infection; however, bearberry leaf should be used and indicated only in case of the very first symptoms of urinary tract infection and if these symptoms progress or do not improve, the standard antibiotic therapy should be prescribed by a doctor or qualified healthcare professional. Taking in consideration AESGPs arguments we could agree to prolong the period before consultation of a doctor or a qualified healthcare professional in case that the symptoms are not improving to 4 days. Reference to the duration of use of Solidago virgaurea, Taraxacum officinale and Juniperus communis cannot be accepted as the main therapeutic effect of these plants consist in increase of urine volume and in case of Solidago and Taraxacum also in their anti-inflammatory activity in contrary to Uvae ursi leaf where the main therapeutic effect consists in its antibacterial activity. Reference to Thymus vulgaris is not relevant as this plant is used in a different indication - Thyme herb is traditionally used as an expectorant in cough associated with cold. Proposed change in section 4.2.

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		the time required for relief of the symptoms was even longer (4 to 5 days) [2]. • The duration of antibacterial treatment for uncomplicated UTIs in general has also been systematically reviewed: three days of antibacterial treatment of uncomplicated UTI were adequate to achieve symptomatic relief for most patients, but it appears that longer therapy would be better in terms of bacteria elimination from the urine, no matter which antibiotic is used [3]. • Other monographs on bearberry leaf (e.g. ESCOP) have recommended that "treatment should be continued until complete disappearance of symptoms (up to a maximum of 2 weeks), but if symptoms worsen during the first week of treatment, medical advice should be sought". The WHO monograph recommends consulting a doctor if the symptoms persist, without a limitation of time. • For these reasons, the efficacy of bearberry leaf preparations traditionally used for self-medication should not be assessed after a short period of two days. This is neither done in case of systemically acting antibiotics. • Further HMPC draft monographs describing traditional herbal preparations with antimicrobial activity recommend taking the respective preparation for longer periods of time before the efficacy is put into question. - *Solidago virgaurea*, indicated as adjuvant in the treatment of minor urinary complaints, recommends "If the symptoms persist during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted." - *Taraxacum officinale*, indicated as an adjuvant in minor	**Duration of use** The duration of use should not exceed one week. If the symptoms persist for more than 4 days or worsen during the use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.

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		urinary complaints, recommends “if symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor should be consulted.” - *Juniperus communis* recommends “if symptoms persist longer than 2 weeks during the use of the medicinal product, a doctor should be consulted.” - *Thymus vulgaris* recommends “if symptoms persist longer than 1 week during the use of the medicinal product, a doctor should be consulted.” This restriction could be understood as an implementation of the Guidelines on the prudent use of antimicrobial agents for human medicine [4,5] including the recommendations published by the Working Party of the British Society for Antimicrobial Chemotherapy with regard to self-medication of antibacterial agents without medical prescription (OTC) [6]. Most recent publication [7] reports about self-medication with antibiotics in Europe and its most important consequences. However, none of these documents recommends reducing the duration of treatment to 2 days if symptoms do not improve. It is certainly implicit in all discussions that the self-medication of antimicrobial agents should be as short as possible. However, it should be taken into account that the most important reason for restricting the free use of antibiotics is to prevent the development of “bacterial resistances”. In this respect, however, bearberry leaf has an unspecific mechanism of antimicrobial activity and therefore does not induce any type of “bacterial resistance”. For this reason, bearberry leaf products do not present a risk for the development of “bacterial resistances” and so far resistances to bearberry leaf have not	

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		been recorded (e.g. in the database of the European Antimicrobial Resistance Surveillance System).	
4.4 Special warnings and precautions for use	AESGP	**Comments:** In a daily life situation, the possible change of coloration of urine on exposure to air cannot be observed. **Proposed change:** We propose to shorten the last sentence to: *"Use of Uvae ursi folium may cause a greenish-brown coloration of the urine".*	Endorsed. Proposed change in section 4.4 Use of Uvae ursi folium may cause a greenish-brown coloration of the urine. The following text has been added after discussion in MLWP: The use in men is not recommended because this condition requires medical supervision.
HMPC Draft list of references	AESGP	**Comments:** With regard to the HMPC reference list, we propose to replace the internal Report Schnitker (1993) cited on page 28 of the Assessment Report by the publication of Stammwitz (1998) [8]. The internal report is a document of the Schaper & Brümmer Company which has only been utilised within a marketing authorisation procedure and thus should not be quoted in the Assessment Report. As data of this report has meanwhile been published we suggest quoting the publication instead of the internal report.	Partly endorsed. Due to the potentially confidential content of the internal report by Schnitker (1993) this reference is deleted in the AR and List of references. The brief information in the article by Stammwitz cannot replace the detailed Schnitker report and does not provide additional information. This reference is therefore not added to the AR and List of references.

References:

ESCOP

[1] Anonymus In: Kooperation Phytopharmaka, editors. Kinderdosierungen von Phytopharmaka. 3rd edition. 2002.

AESGP

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