30 January 2018
EMA/HMPC/589805/2017
Committee on Herbal Medicinal Products (HMPC)

Overview of comments received on European Union herbal monograph on *Arctostaphylos uva-ursi (L.)* Spreng., folium (EMA/HMPC/750269/2016)

Final

Table 1: Organisations and/or individuals that commented on the draft European Union herbal monographon *Arctostaphylos uva-ursi* (L.) Spreng., folium as released for public consultation on 12/04/2017 until 15/07/2017.

	Organisations and/or individuals
1	AESGP (Association of the European Self-Medication Industry)

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Table 2: Discussion of comments

General comments to draft document

Interested party	Comment and Rationale	Outcome

Specific comments on text

Section number and heading	Interested party	Comment and Rationale	Outcome
4.1 Therapeutic indications	AESGP	In the current draft monograph, the use of Uvae ursi folium in men is generally excluded because of concerns requiring medical supervision. This exclusion is based on the rationale that in men, UTIs (urinary tract infections) are mainly contracted as a result of anatomical abnormalities, acute inflammations of the lower urinary tract (acute prostatitis or acute epididymitis), STDs (sexually transmitted diseases) or in older males by prostatic hyperplasia or an indwelling catheter, all of which should require medical supervision (draft assessment report, P 42 and 43). While the need for medical supervision is considered an exclusion criterion for traditional use, the use in females is recommended after serious conditions have been excluded by a medical doctor. We consider that the general exclusion of the use of Uvae ursi folium in men is unjustified and think that the use in men is appropriate, once serious conditions have been excluded by a medical doctor. Our opinion is based on the following rationale: - Anatomical abnormalities of the urogenital system can contribute to the contraction of UTIs in younger men, but not all UTIs in younger men are caused by anatomical abnormalities. UTIs can also be contracted from working in cold, wet environments, from protracted immersion in cold water, unsanitary conditions etc. Anatomical abnormalities are a serious condition that can obviously be present in women too	Not endorsed. Recurrent mild infections of the lower urinary tract are usually uncomplicated in women. In men, due to the anatomical disposition of the lower urinary tract, a risk of severe inflammations of lower urinary tract of various origin exists and therefore urinary tract infection always requires medical examination. A delayed consultation of a medical doctor may imply serious risks for men. In men over 50 years the incidence of UTIs is increasing due to increased incidence of prostatic hyperplasia (benign or malignant) and potential 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

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		and has to be excluded by a medical doctor. We propose that anatomical abnormalities that require medical supervision should be included in the contraindications, irrespective of gender. - STDs occur in both women and men, some of them, such as Chlamydia, being especially harmful to women. They need to be treated by a medical doctor and the risk of misinterpreting their symptoms for that of UTIs is present in both genders. Since UTIs are far more common in women of childbearing age (who are usually more at risk to contract STDs than older women) than in men of similar age and thus better known as a relatively common type of infection to women, we consider the risk of misinterpreting the symptoms of an STD for those of an UTI not to be higher in men. Thus, STDs as a serious condition need to be excluded by a medical doctor for both sexes and are not considered to be a reason for the general exclusion of the use of Uvae ursi folium in men. - Acute prostatitis or acute epididymitis are serious conditions that need to be treated by a medical doctor. They are usually not mild in their symptoms and are as such not to be treated with Uvae ursi folium. Since only a fraction of UTIs in men is caused by this kind of serious infections, we consider a warning that serious conditions need to be excluded by a medical doctor (such as the current draft monograph recommends for the use in women) more appropriate than the general exclusion of the use in men. - Indwelling catheters always require the supervision of medically trained doctors of staff, irrespective of the sex of the patient. This does not mean however that Uvae ursi folium cannot be used as long as the medical supervision of the catheter itself is ensured. In case the risk of using a traditional medicinal product in men with indwelling catheters is considered unacceptable, indwelling catheters in men could be included in the contraindications without eliminating the use in men altogether. - Prostatic hyperplasia is a non-infective condition that only	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. Although men are excluded from the traditional use, Uvae ursi folium or preparations thereof can be used when advised by a medical doctor.

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		occurs in men and is more common in older men than in younger ones. It can affect the frequency of UTIs in men. While the prostatic hyperplasia itself is not to be treated with Uvae ursi folium and requires supervision of a medical doctor, there is apparently no reason why mild UTIs themselves should not be treated with Uvae ursi folium as long as the prostatic hyperplasia itself is under medical surveillance. Certainly, if serious medical conditions like prostatic hyperplasia have been excluded by a medical doctor, a general exclusion of the use of Uvae ursi folium in men is not justified. **In case a general use in men cannot be recommended by the HMPC monograph, we propose to replace the sentences:** - "***The use in men is not recommended***", given in section 4.2 Posology and method of administration, and - "***The use in men is not recommended because of concerns requiring medical advice***", given in Section 4.4 Special warnings and precautions for use by the following wording: "***The use in men - especially over 50 years - is not recommended without medical advice.***" The reasons are explained as follows: • Indeed, symptoms of urinary frequency and burning sensation during urination occurred at very low incidence in adult males younger than age 50 years (approximately 5-8 per year per 10,000) (Foxman 2002). These symptoms are due to uncomplicated urinary tract infections that may have diverse causes (e.g. sexually transmitted disease-related infections of the urethra, homosexual behaviour with anal intercourse or anatomic anomalies) (Workowski et al. 2006). *E. coli* is the main causative agent of the symptoms (80%) (Guay 2008). For the treatment of these recurrent mild symptoms, Uvae ursi folium-containing products are a help, particularly when antibiotics are still not required. Therefore, an exclusion of men seems	

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		unreasonable. • In men older than 50 years, however, the incidence of urinary frequency and burning sensation during urination rises dramatically (range, 20-50% prevalence) because of prostate enlargement, 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 that most men suffering from these disorders are already under medical advice. In order to prevent the overlooking of these illnesses, however, men and especially the subgroup of men over 50 years should be advised to consult a doctor before using any Uvae ursi folium-containing preparations. • 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). Uvae ursi folium-containing products do not interfere with such medications because they do not affect the activity of the CYP450 (Chauhan et al. 2007; HMPC monograph and Assessment Report 2011 and 2017). Therefore, there are not safety concerns regarding interactions among Uvae ursi folium-containing products and agents for treating BPH. There are *a priori* no pharmacological reasons to prevent the use of Uvae ursi folium-containing products with other prostate therapies.	
4.4. Special warnings and precautions for	AESGP	In the current draft monograph, the use of Uvae ursi folium in children and adolescents under 18 years of age is generally not recommended because of concerns requiring medical supervision. This exclusion is based on the rationale that in children, infections	Not endorsed. HMPC is of the opinion that the use of bearberry leaves and preparations thereof in children and

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use		of the urinary tract, even in their early stage, should be treated under medical supervision. While the need for medical supervision is considered an exclusion criterion for traditional use, the use in females is recommended after serious conditions have been excluded by a medical doctor.Like in men, we think it is justified to allow use in adolescents from 12 years of age onwards as long as serious conditions have been excluded by a medical doctor.	adolescents 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.
5.3. Preclinical safety data (reproductive toxicity)	AESGP	The monograph on Arctostaphylos uva-ursi states: *"Arbutin, the main component of Uvae ursi folium, displayed some **maternal** and **fetal** toxicity in rats after subcutaneous administration of 400 mg/kg per day. No effect on reproduction has been observed at doses of 100 mg/kg per day."* Accordingly, the Assessment Report (AR) concretizes these maternal and fetal effects. Here, fetal toxicity is exemplarily specified by "stunted foetus and reduced body weight", maternal effects are described as "(not specified) in the ovaries and the fallopian tubes". The source of these findings seems to be the study by Itabashi et al. 1988, which is also referred by WHO (2002) and NTP (to male and female rats and 2006). We assume that false conclusions have been drawn from the literature within the monograph and the AR, which are in contrast to the original data provided by Itabashi *et al.* (1988). Itabashi et al. (1988) is often cited indirectly only, instead of considering the primary source, which is available in Japanese language only. • Therefore, we propose the following wording for the monograph on Arctostaphylos uva-ursi in Section 5.3, third paragraph: *"Arbutin, the main component of Uvae ursi folium, was administered subcutaneously at 25, 100 or 400 mg/kg body weight/ day to male Sprague-Dawley rats before mating and to female rats during pregnancy and lactation. A significantly reduced body weight of female fetuses was observed only at doses of 400 mg/kg body weight. No effect on reproduction has been observed (Itabashi et al. ,1988)."*	Partly endorsed. The text in the Assessment report has been changed accordingly. However, as the study do not reveal any concerns regarding reproduction and developmental toxicity of arbutin, there is no reason to keep this information in the European Union monograph.

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		Explanations: The original publication of Itabashi *et al.* (1988) is found to be a very detailed, precise and well-designed study on reproduction effects on arbutin in rats, although GLP and OCD guidelines on reproduction and developmental toxicity had before already been established in Europe. Viability, fertility and mortality; musculoskeletal system growth; sex ratio; behaviour and psychologic processes; multigenerational reproductive toxicity; paternal and maternal weight changes were measured (NTP 2006). However, regarding the **foetal** toxicity effects of arbutin, as mentioned in the monograph, the only findings in the highest treatment group (400 mg/kg bw) by Itabashi et al. (1988) are I) reduced weight of the **left ovary** in the fetus, and II) reduced body weight of only **female foetuses**. The authors of the study distinguished that: I) the weight of the right, and of both ovaries together is not significantly different from the controls; moreover, "there is no treatment-related change in the reproductive performance of the F_1 rats", and II) the body weight of the male foetuses showed only a tendency to reduction. However, "no treatment-related change was seen in the implantation rate, mortalities of embryos and fetuses, placental weight, sex ratio, incidences of external and internal anomalies, degree of ossification of skeletal system, incidences of skeletal variations or anomalies in any of the treated fetal groups" (Itabashi *et al.,* 1988). It can be concluded that the monograph and the AR point to foetal toxicity, which is observed in the highest treatment group by a reduced body weight of the female foetuses only. However, the mode of expression of "stunted foetus" in the AR is scientifically inappropriate as "reduced weight of left ovaries" and "stunted foetus" are in their meanings very far apart from each other. • Thus, we propose to revise this passage in the AR.	

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		Regarding "**maternal** effects" – referred in the monograph, Itabashi et al. (1988) observed in the 100 and 400 mg/kg bw arbutin groups III) reduced food consumption in the **male** parents. It should be mentioned that "no significant difference was observed in body weight or reproductive performance between control and treated" parent rats which include female and male rats. Fertility and autopsies revealed no treatment effects in the parents. Thus, there is no **maternal** effect, and neither an effect on reproduction, but probably a metabolic effect in the males. The primary source of this statement in the AR and the monograph regarding **maternal** toxicity cannot be based on the study by Itabashi *et al.* (1988). There are no hints on maternal effects in the meaning of reproductive toxicity. • Thus, we propose to eliminate the "maternal toxicity" within the monograph and to revise the passages in the AR, respectively. Moreover, the AR refers to Itabashi et. al. (1988) and the NTP (2006) in conjunction with **oral** administration of arbutin, which is incorrect because Itabashi administered arbutin **subcutaneously** only. Unfortunately, the AR does not reflect the whole NTP statement, where a clarification occurs: "The RTECS (1997) record states the following regarding the Itabashi et al. (1988) study: Oral (route of administration appears to be **incorrectly** annotated in RTECS record) administration of arbutin (lowest published toxic dose = 13,600 mg/kg [49.954 mmol/kg]) for 14 days prior to copulation and 20 days of pregnancy produced maternal effects (not specified) in the ovaries and fallopian tubes. Fetotoxicity (e.g., stunted fetus) but no deaths was reported" (NTP 2006, p 9). Not only does the route of administration seem to be recorded incorrectly in the RTECS database, but the lowest published toxic	

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		dose, maternal effects and fetotoxicity are also not in accordance with the study of Itabashi et al. (1988). Therefore, it is difficult to identify which study is listed in this RTECS record. Anyway, it is better to refer to the original publication. • Thus, we propose to revise this passage in the AR. An assessment of the reproductive and developmental toxicity of Bearberry leaf extract and its main components or metabolites should also consider the following aspects supporting our proposal for revision of the third paragraph in Section 5.3 of the monograph: A) The administration route of arbutin in the study of Itabashi et al. (1988) was **subcutaneous** and not oral. This means amongst others that the first path effect of arbutin is circumvented including the formation of non-toxic type II metabolites of hydroquinone. Thus, even if minor toxic effects may have been shown in this reproductive and developmental toxicity study, it cannot be concluded whether this may have been elicited by *in vivo* **oral** application too. • Thus, we propose to revise this passage in the AR as well as to consider the different route of application within the safety (risk) assessment analyses. B) Itabashi et al. (1988) administered arbutin to the rats over a very long period of time. Female rats received arbutin two weeks prior to copulation, 20 days of pregnancy, and partly additionally during the lactation period; male parents received arbutin nine weeks prior to pairing and until the positive conception of the females was achieved. This period is mentioned **incorrectly** in the AR, here also males are putatively treated two weeks only. Thus, the arbutin effects noticed in this study may be overestimated in the AR, as the intake of Uva-ursi extracts according to the monograph is limited to one week only. In addition, an amount of 400 mg arbutin/kg bw in rats correlates to 9.2 times the recommended human daily dose. • The safety assessment of Uva-ursi should consider these safety	

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		factors. C) Studies regarding the reproductive and developmental toxicity of **hydroquinone (HQ)**, which is generated from arbutin, revealed neither a teratogenic nor a reproductive effect, even perorally administered in high doses (review: DeCaprio 1999, conclusion: Hagers Enzyklopädie der Drogen und Arzneistoffe, **2015**). Unfortunately, the review of DeCaprio (1999), as well as the recent edition of Hagers Enzyklopädie (2015) and there mentioned original publications, respectively, are not considered in the chapter "Reproductive and developmental toxicity" of the AR of Arctostaphylos uva-ursi. Instead, the AR discusses the publication of McGregor (2007). Obviously, this reference is wrong, since McGregor (2007) evaluates possible risks of hydroquinone due to carcinogenic and mutagenic properties. In contrast, DeCaprio (1999) reviews reproductive and developmental toxicity of hydroquinone in detail. The author concluded: "Fetotoxicity (growth retardation) accompanies repeated administration of HQ at maternally toxic dose levels in animal studies. HQ exposure has not been associated with other reproductive and developmental effects using current USEPA test guidelines." This review and its cited original publications should additionally be discussed in the AR. • We propose to revise the chapter "Reproductive and developmental toxicity" of the AR and to take additional studies conducted with HQ into account. In summary, based on the facts given in the original publication of Itabashi et al. (1988) and the additional information/safety data mentioned under A) B) and C) above, we conclude that no reproductive safety concerns arise from Uva ursi-containing HMPs providing that they are applied in accordance with the monograph. • Considering all these facts, we propose the following wording for the monograph on Arctostaphylos uva-ursi: *"Arbutin, the main component of Uvae ursi folium, was administered subcutaneously at 25, 100 or 400 mg/kg body weight/ day to male Sprague-Dawley rats before mating and to*	

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		female rats during pregnancy and lactation. A significantly reduced body weight of female fetuses was observed only at doses of 400 mg/kg body weight. No effect on reproduction has been observed (Itabashi et al. 1988).”	