CBG MEB

Public Assessment Report
Herbal medicinal product

Scientific discussion

Lyngonia, film-coated tablets
Arctostaphylos uva-ursi (L.) Spreng., folium (bearberry leaf)

NL/H/3771/001/DC

Date: 23 October 2017

This module reflects the scientific discussion for the approval of Lyngonia, film-coated tablets. The procedure was finalised on 19 April 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lyngonia, film-coated tablets from Florealis ehf.

Lyngonia, a traditional herbal medicinal product, is indicated in adult and elderly women for the relief 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. The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 16(a) of Directive 2001/83/EC, a so-called traditional use application. This traditional use application complies with the existing Community herbal monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium (EMA/HMPC/573462/2009) published by The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA).

The data supplied by the MAH substantiates 30 years of medicinal use of *Arctostaphylos uva-ursi* (L.) Spreng., folium, including at least 15 years in the European Community.

The concerned member states (CMS) involved in this procedure were Cyprus, Denmark, Finland, Iceland, Malta, Norway and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Lyngonia is a red-brown oblong film-coated tablet. Each tablet contains 361–509 mg of extract (as dry extract) from *Arctostaphylos uva-ursi* (L.) Spreng., folium (bearberry leaf), corresponding to 105 mg of hydroquinone derivatives calculated as anhydrous arbutin. For the manufacture of one tablet, 903 – 2291 mg of dried bearberry leaves are used. The extraction solvent is water.

The film-coated tablets are packed in PVC/PE/PVDC-Aluminium blisters in an outer carton.

The excipients are:
tablet core – microcrystalline cellulose, lactose monohydrate, talc, sodium starch glycolate Type A, colloidal anhydrous silica, magnesium stearate
tablet coating – macrogol 3350, titanium dioxide (E171), poly(vinyl alcohol), red iron oxide (E172), yellow iron oxide (E172), black iron oxide (E172) and talc.
excipient of the herbal preparation – maltodextrin

II.2 Herbal Substance

The herbal substance is the dried leave of bearberry, *Arctostaphylos uva-ursi* (L.) Spreng., folium. The specification of the herbal substance is described in the European Pharmacopoeia (Ph. Eur.). The two manufacturers of the herbal preparation purchase the herbal substance from different suppliers.

Manufacturing process
manufacturer one - The harvesting of the plant material takes place between August and March from wild growing plants after blooming in Southern or Eastern Europe. After harvesting the bushes are manually cleaned and cut, followed by peeling off the leaves. The leaves are naturally dried with warm air at approximately 25-30°C. Since the material is from wild growing plants, no pesticides are used.
manufacturer two – The harvesting of the plant material takes place between August and March from wild plants by hand after blooming in Spain. After harvesting the bushes are naturally dried on grids

under a roof. The plant material is not washed. The supplier has confirmed that no pesticides or insecticides are used.

Quality control of herbal substance
The herbal substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. The testing also complies to the Ph. Eur. and appropriate routine tests for potential contaminants are supplemented. The testing schemes are sufficiently justified by batch results.

Stability of herbal substance
Normally, the warehouse stock (maximum one period of vegetation) will be used within the period of one year. If this period is exceeded, the batch will be reanalysed based on the valid specification (manufacturer one).
The plant material is packed in bags in a closed storage. After delivering from the supplier to the manufacturer, the herbal substance is stored in a cool and dry place, protected form light, rodents and insects (manufacturer two).

II.3 Herbal Preparation

The herbal preparation is the dry aqueous extract of dry leaves of *Arctostaphylos uva-ursi* (L.) Spreng. It is a light-brown fine hygroscopic powder with a bitter taste and soluble in water, insoluble in ethanol, diethylether and chloroform with a loss on drying ≤ 5 %. For manufacture of the herbal preparation, two manufacturers are involved, who employ a similar extraction process.

Manufacturing process
The manufacturing process has been described and consists of cutting the plant material, water extraction, evaporation, homogenisation and standardisation step (addition of maltodextrin) to adjust to the specified content of hydroquinones. The dry extract is then ground, mixed, sieved and packed.

Quality control of herbal preparation
The tests and specifications are adequate to control the quality of the herbal preparation. Acceptable additional test and limits are set for microbiological quality. It is agreed that other possible contaminants (pesticides, heavy metals and aflatoxins) are tested on the herbal substance. The batch data indicate that the obtained dry extract from each of the active substance manufacturers complies with its specification.

Stability of herbal preparation
Stability data on the active substance have been provided for a total of 5 batches (by both manufacturers) in accordance with applicable European guidelines. Based on the data submitted, a retest period of 36 months could be granted without special storage conditions.

II.4 Herbal Medicinal Product

Pharmaceutical development
The development of the product is adequately described, the choice of excipients is justified and their functions explained. Several changes in formulation development are addressed: change in strength and dosing regime, change of coating and new manufacturer added. Also clinical trials have been performed on bioavailability and compliance of TLC- and HPLC fingerprints from extract to the finished product was demonstrated to demonstrate that the manufacturing process of the film-coated tablets has no negative influence on the extract.
Data are presented to justify that the disintegration within 30 minutes correlates with a dissolution, which conforms to the specified limits of the specification for shelf life. Consequently the time-consuming and extensive determination of the dissolution may be omitted within the specification for batch release and the determination of disintegration is sufficient. Results of bioavailability study (2000) demonstrate that the film-coated tablets with bearberry leaf dry extract are comparable to an aqueous solution of this extract.
Dissolution testing and similarity of dissolution profiles was performed after introducing the new one-layer film-coat. The comparison of batches with the old and batches with the new film-coat, and the overlay of dissolution profiles show high similarity of the two formulations. The change in composition

of the film-coat has no impact on the dissolution profile and the dissolution rate of the film-coated tablet, this is also reasonable since the tablet core composition itself has not changed at all.
Dissolution profiles are similar and comparable, the MAH has adequately demonstrated that the new developed film-coat has no influence on the dissolution attributes of the film-coated tablet.

Manufacturing process
The manufacturing process is straightforward. It has been adequately described and validated. The process consists of blending, compressing, stirring, pre-warming, film-coating, weighing and packaging. Process validation data on the product have been presented for 3 industrial scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur. or in-house monographs. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass and uniformity of mass, disintegration, hardness, identification, purity and dissolution rate. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data for 4 full-scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 2 pilot scaled batches stored at 25°C/60% RH (36 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. All results comply with the specification. The product is not sensitive to light. On basis of the data submitted, a shelf life of 36 months has been granted. No specific storage conditions need to be included.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient which is affected by the "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy via Medicinal Products". Confirmations of the supplier are included, ensuring that risk of TSE contamination is unlikely and compliance to EU-guidance.

II.5 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lyngonia has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Bearberry leaf dry extract contains several active constituents, including arbutin (5-16%), methylarbutin (4%), polyphenols (tannins, 10-20%), flavonoids (0.8-1.5%), small amounts of triterpenes (0.4-0.8%), phenol acids (0.25%), and free hydroquinone (<0.3%). It is supposed that different constituents contribute to the proposed mechanism of action. Thus, the bearberry dry leaf extract as a whole has to be regarded as the active principle.
The anti-bacterial effect of the extract is ascribed to hydroquinone which is liberated from arbutin via glycoside cleavage by β-glucosidase. Hydroquinone and hydroquinone conjugates appear to be primarily eliminated in the urine, which is beneficial in the treatment of urinary tract infections. It has been suggested that the urinary tract bacteria themselves hydrolyse arbutin, and accumulate free hydroquinone in higher concentrations intracellularly compared to outside the bacteria. There is no

consensus in literature whether bearberry leaf extract requires an alkaline pH in the urine to facilitate degradation of arbutin into free hydroquinone to exert antibacterial effects.
Other constituents of the extract, like polyphenols, triterpenes and flavonoids, support the therapeutic effect by their anti-inflammatory and anti-oxidative properties. On the other hand, this could theoretically lead to interactions with NSAID's, such as prednisolone or dexamethasone, but such interactions have not been reported clinically.
There is mixed evidence as to whether bearberry leaf extract has a weak diuretic effect or none at all while preliminary evidence suggests that it does not increase urinary calcium. Safety pharmacology effects have been reported for hydroquinone. These effects included adverse effects on the central nervous system (tremor, convulsions, hyperexcitability, dyspnoea) in rats and mice, but these effects have only been seen in cases of acute overdose.

III.2 Pharmacokinetics

Limited human data show that arbutin is rapidly absorbed in the small intestine and metabolised in the liver to form hydroquinone conjugates. Up to 85% of the arbutin is eliminated in urine as (nontoxic) conjugates of glucuronide and sulfuric acid, and only 0.6% of the dose as free hydroquinone.
The ability of bearberry leaf extract to act against urinary infections is believed to be the result of the pharmacological action of free hydroquinone being cleaved from the arbutin molecule. It is not known in which tissue this cleavage occurs *in vivo* and what amount of hydroquinone is present in the microorganisms after treatment with arbutin. This process is dependent on β-glycosidase, an enzyme which is usually not produced by mammalian cells but by bacteria, including those responsible for urinary tract infections.
There is theoretically a risk on drug interactions by inhibitory effects of the extract on CYP P450 enzymes and P- glycoprotein, but the effect has not been reported clinically.

III.3 Toxicology

Single dose toxicity
No data are available on single dose toxicity of bearberry leaf extracts or arbutin. Hydroquinone has low acute toxicity in most species. Acute 50% lethal doses range from 70 mg/kg in the cat to 550 mg in guinea pig with most species exhibiting values at the upper end of this range. The effects of acute high-level exposure to hydroquinone are directed primary toward the central nervous system, and include tremor, salivation, convulsions, hyperexcitability, incoordination, respiratory failure, coma and death.

Repeated dose toxicity
No data on repeated dose toxicity have been reported for bearberry leaf extract but there are data for arbutin and hydroquinone, and for further active ingredients. These data show that the amount of free hydroquinone liberated from the metabolism of arbutin is relevant for the safety of the bearberry leaf extract. Hydroquinone has been reported to have hepatoxic, nephrotoxic and mutagenic potential.
However, there is no evidence that free hydroquinone liberated from a therapeutic exposure of bearberry leaf extract could exert adverse effects in human. The exposure of free hydroquinone produced by the use of Lyngonia tablet was estimated to be 5 mg per day. This is not a concern, since this exposure during the prescribed treatment period of maximally one week does not exceed the estimated permitted daily exposure of 6 mg (100 µg/kg/day) for hydroquinone in human.

Genotoxicity/carcinogenicity
The genotoxic potential of a dry aqueous bearberry leaf extract, that is relevant for the extract used in Lyngonia tablets, has been tested in a GLP-compliant mutagenicity test, using five Salmonella typhimurium strains, TA98, TA100, TA102, TA1535 and TA1537, in two independent experiments, each carried out without and with metabolic activation (a microsomal preparation derived from Aroclor 1254-induced rat liver). The first experiment was carried out as a plate incorporation test and the second as a preincubation test. The results showed no signs of mutagenic potential.
Available literature so far do not point to concern for a genotoxic effect. A recombination test of a dry aqueous extract of bearberry leaves in Bacillus subtilis showed no mutagenic activity. A mixture of extracts of bearberry leaves did not affect the level of micronuclei in cultured human lymphocytes. Reports of the NTP (1989, 2006) and WHO (2004) showed no evidence of carcinogenicity of an aqueous extract of the leaves in male B6C3F1 mice.

Reproduction toxicity
There is no information on possible reproductive or lactation effects of bearberry leaf extract. In the absence of data, Lyngonia tablet should not be used by pregnant women and during the lactation period. If pregnancy occurs during treatment, treatment must be stopped.

III.4 Ecotoxicity/environmental risk assessment (ERA)

An Environmental Risk Assessment has not been provided. Herbal medicinal products are exempted from an environmental risk assessment due to the nature of their constituents.

III.5 Discussion on the non-clinical aspects

The pharmacological, pharmacokinetic and toxicological characteristics of Lyngonia as presented in the non-clinical overview are considered appropriate. There are no issues relating to the pharmacology or toxicology and formulation of Lyngonia. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical data is required.

IV. CLINICAL ASPECTS

IV.1 Introduction

For this traditional herbal medicinal product, bibliographic data has been provided based on scientific literature. The application is based on:

- the evaluation of efficacy and safety on the product, in correspondence with the assessment report of the Community Herbal Monograph on *Arctostaphylos uva-ursi* (L.) Spreng., folium., dated January 2012 (EMA/HMPC/573462/2009 Rev.1; available on http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2011/07/WC500108750.pdf).
- the traditional use and the available bibliographic evidence relating to the identical herbal medicinal product Arctuvan Bärentraubenblätter Filmtabletten, approved for marketing in Germany since 11 March 2003 as a re-registration and a prolongation of the marketing authorisation according to § 105 of the German Drug Law.

IV.2 Pharmacodynamics

The MAH only briefly discussed some pharmacodynamic studies with bearberry leaf extract from literature. Most of these studies have also been discussed in the assessment report on *Arctostaphylos uva-ursi* (L.) Spreng., (EMA, 2012). The antiseptic and diuretic properties claimed for bearberry leaf extract are mostly attributed to the hydroquinone derivatives, especially arbutin, but according to the principle of phytotherapy it is feasible that the other substances like polyphenols, phenolic acids, flavonoids, iridoids and triterpenes have an influence on the absorption and efficacy of the hydrochinone derivatives.

IV.3 Clinical efficacy

According to the HMPC monograph AR, 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 antibacterial effect of bearberry leaf extract is ascribed to hydroquinone which is liberated from arbutin via glycoside cleavage (this hypothesis is reported to come from 1883, it is unclear whether there is any evidence to support or refute this hypothesis). Literature provides some support to the antimicrobial activity of arbutin and hydroquinone in alkaline urine. It has furthermore been reported that the pH value of urine was the most important factor determining the antibacterial activity. Hydroquinone is naturally contained in coffee, tea or wheat cereals.
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 (see section on Clinical Safety below), and the results of nonclinical *in vitro*

and *in vivo* experiments proving antimicrobial activity support the use as traditional herbal preparations.

IV.4 Clinical safety

Exact patient exposure data are not available for arbutin or bearberry leaf extracts in general. For the herbal medicinal product Arctuvan Bärentraubenblätter Filmtabletten which is identical to the product of this application, an estimated patient exposure of approximately 45 million treatment periods of 1 week is assumed. No serious adverse effects directly attributable to bearberry leaf extracts were reported. As also concluded in the HMPC monograph AR, 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.

IV.5 Risk Management Plan

The submission of a risk management plan is not required for an application for a traditional-use registration.

IV.6 Discussion on the clinical aspects

The long-standing 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 support the use as traditional herbal preparations. The indication and SmPC are in line with the HMPC monograph, which was accorded by all member states.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to an approved user testing data for a comparable authorised product on the Swedish market (Uvicur). This product contains the same active substance, and has a similar purpose of use. As the comparability between the both leaflets was sufficiently demonstrated, the bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lyngonia, film-coated tablets has a proven chemical-pharmaceutical quality and its traditional use has been demonstrated. The benefit/risk balance is considered positive for this herbal medicinal product.

The Board followed the advice of the assessors. The application meets the requirements for a traditional use application: 30 years of medicinal use, including at least 15 years in the European Community.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that traditional use has been demonstrated for Lyngonia, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 April 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached