LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2014-08-25

Public Assessment Report
Scientific discussion

Uvicur, coated tablet
Arctostaphylos uva-ursi (L.) Spreng., folium, dry extract

Asp. No: 2013-0742

This module reflects the scientific discussion for the approval of Uvicur, coated tablet. The procedure was finalised at 27 June 2014. For information on changes after this date please refer to the module 'Update'.

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LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted Schaper & Brümmer GmbH & Co. KG, Germany, a traditional-use registration for the herbal medicinal product Uvicur, coated tablet. This product is available without prescription and can be bought from pharmacies and other outlets.

Uvicur is traditionally used 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 active ingredient is a dry extract from leaves of *Arctostaphylos uva-ursi* (L.) Spreng., i.e. bearberry leaves (mjölonblad in Swedish). This registration is based exclusively upon evidence of traditional use of bearberry leaves as a herbal medicinal product and not upon data generated from clinical trials. For traditional herbal medicinal products there is no requirement to scientifically prove the effect; adequate evidence of traditional use is sufficient.

The chemical/pharmaceutical quality of the product is acceptable and no new or unexpected safety concerns have been identified during the assessment. It was therefore decided that Uvicur could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Schaper & Brümmer GmbH & Co. KG has applied for a traditional-use registration for Uvicur, coated tablet. The application was submitted under Article 16a traditional use registration for herbal medicinal products of the Directive 2001/83 EC, as amended.
The application is a national application for Sweden.

The active substance is a dry extract from leaves of *Arctostaphylos uva-ursi* (L.) Spreng.
For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Uvicur is presented in the form of coated tablets, each containing 265 mg of the active substance dry extract of *Arctostaphylos uva-ursi* (L.) Spreng., folium, (3.5-5.5:1), corresponding to 62.3-77.7 mg hydroquinone derivates, calculated as arbutin anhydrous. This amount of dry extract corresponds to approximately 1.2 g dried bearberry leaves.

The excipients are: microcrystalline cellulose, lactose monohydrate, hypromellose, anhydrous colloidal silica, magnesium stearate, macrogol, titanium dioxide (E171), O-laquer green (colorant which consists of hydrated aluminium oxide, kinolin yellow (E104) and indigo carmine (E132)) and long-chain partial glycerides.

All manufacturers involved in the production operate in accordance with EU-GMP, or where relevant, GACP (Good Manufacturing Practise, Good Agricultural and Collection Practice, respectively).

II.2 Drug Substance

The herbal substance *Arctostaphylos uva-ursi* (L.) Spreng., folium, complies with the monograph “Bearberry leaf” in the European Pharmacopoeia and the general pharmacopoeial requirements for herbal drugs.

The plants used are collected from the wild in Spain and Russia. Relevant information on growing conditions and controls of the herbal substance (such as residues of heavy metals and pesticides as well as microbiological quality) has been provided.

The herbal substance is dried, cut and extracted with ethanol. For manufacturing reasons, the genuine extract is mixed with excipients; thereafter the solvent is evaporated to obtain a dry extract.

The manufacturing process has been adequately described and satisfactory specifications have been provided for the herbal substance, extraction solvent and excipients. The tests and limits in the specifications are considered appropriate to control the quality of the starting materials, in relation to their intended purpose.

The specification of the active substance (herbal preparation) includes relevant tests, and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

The stability of the active substance has been confirmed by stability studies under ICH conditions.

II.3 Medicinal Product

All excipients used in Uvicur, apart from the long chain partial glycerides and the colorant O-laquer green, are controlled for compliance with their respective Ph. Eur. monographs. Since there are no Ph. Eur. monographs for long chain partial glycerides and O-laquer green, these substances are controlled via in-house specifications, which are considered acceptable.
All raw materials used in the product are safe with view to possible TSE/BSE risk.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SmPC.

III. NON-CLINICAL AND CLINICAL ASPECTS

III.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued a Community monograph on *Arctostaphylos uva-ursi*, folium.
The reader is referred to the Community monograph and the pertinent assessment report for details.

III.2 Non-clinical aspects

The applicant has collected available information from the literature in the areas of non-clinical pharmacology and toxicology. This information has been assessed by the MPA and no signals of non-clinical safety concern have been identified. The exact mechanism of action of the bearberry leaf extract, in relation to its traditional medicinal use, cannot be considered clarified.

A product/extract specific study on mutagenic activity has been performed. The extract has been shown not to be mutagenic in Ames test.

Based on the non-clinical information, both from the literature and the product specific study, no objections are raised to the approval of the bearberry leaf extract as active ingredient in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Uvicur is a traditional herbal medicinal product. According to "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00), (traditional) herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

III.4 Clinical aspects

Results of clinical trials concerning clinical efficacy and safety are not required for the registration of a traditional herbal medicinal product.

III.5 Traditional use

The Committee (HMPC) concluded in the Community monograph that herbal preparations of *Arctostaphylos uva-ursi*, folium, in solid dosage forms, or as herbal tea, for oral use have a traditional use 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 proposed indication, dosage and administration of Uvicur comply with the Community monograph.

The applicant has provided a bibliographic review which shows sufficient evidence for the medicinal use of *Arctostaphylos uva-ursi* (L.) Spreng., throughout a period of at least 30 years, including at least 15 years within the Community.

III.6 Clinical safety

Conventional clinical safety data are virtually absent. However, longstanding medicinal use and experience of *Arctostaphylos uva-ursi* (L.) Spreng., folium, has been documented within the Community. During this time, no clinical signals that *Arctostaphylos uva-ursi* (L.) Spreng., folium, is harmful under normal conditions of use have been identified.

However, as there is a risk of complications related to urinary tract infections in children/adolescents below the age of 18 years, as well as in men, self-medicating with Uvicur *cannot* be recommended for these patient categories.

In harmonisation with the Community monograph, pregnant women are excluded from treatment with Uvicur. Furthermore, due to lack of safety data, the use of products containing *Arctostaphylos uva-ursi* (L.) Spreng., folium, during lactation is not recommended.

Based on the clinical safety information available, no objections are raised to the approval of Uvicur as a traditional herbal medicinal product.

IV. PRODUCT INFORMATION

The product information (Summary of Product Characteristics, Package Leaflet and labelling) has been assessed and accepted by the Medical Products Agency.

User consultation
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the package leaflet was German.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

V. OVERALL CONCLUSION, RISK ASSESSMENT AND RECOMMENDATION

For Uvicur, coated tablet, the handling, manufacture and quality control of raw materials, active substance and finished product are in line with GMP and pharmacopoeial requirements. The applicant has shown that the chemical/pharmaceutical quality is acceptable and can confirm that the process is under control and ensures both batch reproducibility and compliance with the product specification.

The bearberry leaf extract in Uvicur is covered by the Community monograph on *Arctostaphylos uva-ursi*, folium, and the proposed dosage, administration and traditional indication of Uvicur comply with this monograph.

The medicinal use of the bearberry leaf extract for at least 30 years, including at least 15 years within the Community, is adequately documented. No signals of preclinical or clinical safety concern have been identified under normal conditions of use.

Uvicur, coated tablet, can be recommended for registration as a traditional herbal medicinal product.

VI. APPROVAL

Uvicur, coated tablet, was registered via the national procedure on 2014/06/27.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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