LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2015-02-05

Public Assessment Report
Scientific discussion

Canephron, coated tablet
(*Centaurium erythraea* Rafn (herba), pulverised, *Levisticum officinale* Koch (radix), pulverised, *Rosmarinus officinalis* L. (folium), pulverised)

Asp no: 2013-0723

This module reflects the scientific discussion for the approval of Canephron, coated tablet. The procedure was finalised at 18 December 2014. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted Bionorica SE, Germany, a traditional-use registration for the herbal medicinal product Canephron, coated tablet. This product is available without prescription and can be bought from pharmacies and other outlets.

Canephron was approved with the following therapeutic indication:
Traditional herbal medicinal product used together with generous fluid intake for
a) prevention of recurrent formation of kidney stones
b) relief of symptoms (such as burning sensation during urination and/or frequent urination) of recurrent mild lower urinary tract infections in women.
To be used 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.
(Traditionellt växtbaserat läkemedel använt tillsammans med rikligt vätskeintag för att
a) förebygga återkommande bildning av njursten
b) lindra symtom (såsom miktionssveda och/eller ökad miktionsfrekvens) vid återkommande lindriga nedre urinvägsinfektioner hos kvinnor.
Används sedan läkare konstaterat att annan, allvarlig sjukdom inte föreligger.
Indikationerna för ett traditionellt växtbaserat läkemedel grundar sig uteslutande på erfarenhet av långvarig användning.)

The active ingredients are dried and pulverised herb, root and leaf from *Centaurium erythraea* (Centaury)*, Levisticum officinale* (Lovage) and *Rosmarinus officinalis* (Rosemary) respectively. This registration is based exclusively upon evidence of traditional use of the above mentioned drugs 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 Canephron could be registered as a traditional herbal medicinal product.

I. INTRODUCTION

Bionorica SE, Germany has applied for a traditional-use registration for Canephron, coated tablet. The application was submitted under Article 16a traditional use registration for herbal medicinal product of the Directive 2001/83 EC, as amended.
The application is a national application for Sweden.

The active substances are:

- *Centaurium erythraea* (centaury) dried herb, powder
- *Levisticum officinale* (lovage) dried root, powder
- *Rosmarinus officinalis* (rosemary) dried leaf, powder

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Canephron is presented in the form of coated tablet containing 18 mg of pulverised herb from centaury, 18 mg of pulverised root from lovage and 18 mg of pulverised leaf from rosemary.

The excipients are: sucrose, talc, lactose monohydrate, maize starch, calcium carbonate, povidone, colloidal anhydrous silica, dextrin, magnesium stearate, liquid spraydried glucose, titanium dioxide, shellac, riboflavin, montan glucol wax, red iron oxide and virgin castor oil.

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

II.2 Drug Substance

The herbal substances *Centaurium erythraea* Rafn*,* herba*, Levisticum officinale* Koch*,* radix and *Rosmarinus officinalis* L.*,* folium comply with their respective monograph in the European Pharmacopoeia and the general monograph for herbal drugs.

The plants used are collected in Europe (Albania, Austria, Germany, Hungary, France and Poland), North Africa and West Asia, both form cultivations and the wild. 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 preparations consist of pulverised herbal substances. The manufacturing process is a simple milling of the dried herbal substances.

The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials (herbal substance) and excipients/solvents. The tests and limits in the specifications are considered appropriate to control the quality in relation to the intended purpose.

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

Stability studies under ICH conditions have been conducted.

II.3 Medicinal Product

Canephron, coated tablet are formulated using excipients described in the current European Pharmacopoeia except for red iron oxide which is controlled according to USP (United States' Pharmacopoeia), and montan glycol wax which is controlled according to DAB (German Pharmacopoeia).

Lactose monohydrate is derived from milk but the milk is sourced from healthy animals in the same conditions as milk is collected for human consumption. Hence, 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 SPC.

III. NON-CLINICAL AND CLINICAL ASPECTS

III.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has not elaborated any Community monograph on the fixed combination of lovage root [*Levisticum officinale* Koch (radix)], rosemary leaf [*Rosmarinus officinalis* L. (folium)] and centaury herb [*Centaurium erythraea* Rafn (herba)] in Canephron, but there are individual Community monographs on all three herbal substances.

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 active substances contained in Canephron in relation to its traditional medicinal use cannot be considered clarified.

Product specific studies on mutagenic activity have been performed. No mutagenic effects were observed in Ames' test (with or without metabolic activation) or in the micronucleus assay in the rat.

Based on the non-clinical information, both from the literature and product specific studies, no objections are raised to the approval of centaury herb, lovage root and rosemary leaf as active ingredients in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Canephron 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 applicant has provided a bibliographic review which shows sufficient evidence for the medicinal use of *Centaurium erythraea* Rafn*,* herba*, Levisticum officinale* Koch*,* radix and *Rosmarinus officinalis* L.*,* folium throughout a period of at least 30 years, including at least 15 years within the Community. The product has traditionally been used together with generous fluid intake for prevention of recurrent formation of kidney stones and for relief of symptoms (such as burning sensation during urination and/or frequent urination) of recurrent mild lower urinary tract infections in women.

III.6 Clinical safety

Conventional clinical safety data are virtually absent. However, longstanding medicinal use and experience of *Centaurium erythraea* Rafn*,* herba*, Levisticum officinale* Koch*,* radix and *Rosmarinus officinalis* L.*,* folium, has been documented. During this time, no clinical signals that *Centaurium erythraea* Rafn*,* herba*, Levisticum officinale* Koch*,* radix and *Rosmarinus officinalis* L.*,* folium is harmful under normal conditions of use have been identified.

Due to the risk of developing complications that require treatment by a physician Canephron *cannot* be recommended for use in children below the age of 18 years with urinary tract symptoms. Furthermore the product *cannot* be recommended for men with symptoms of urinary tract infection due to the risk of developing complications that require treatment by a physician.

Due to lack of safety data, the use of products containing *Centaurium erythraea* Rafn*,* herba*, Levisticum officinale* Koch*,* radix and *Rosmarinus officinalis* L.*,* folium during pregnancy and lactation is not recommended.

Based on the clinical safety information available, no objections are raised to the approval of Canephron 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 (PL) 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 PL was Spanish.

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 Canephron 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 Committee on Herbal Medicinal Products (HMPC) has not elaborated any Community monograph on the fixed combination of lovage root, rosemary leaf and centaury herb in Canephron, but there are individual Community monographs on all three herbal substances. The applicant has provided evidence that Canephron has had a medicinal use for at least 30 years, including at least 15 years within the Community.

No signals of preclinical or clinical safety concern have been identified under normal conditions of use.

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

VI. APPROVAL

Canephron, coated tablet was approved in the national procedure on 2014-12-18.

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Läkemedelsverket 2015-02-05

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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se