Ellura Capsules

THR 46825/0001

UKPAR

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ELLURA CAPSULES

THR 46825/0001

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Laboratoire Pharmaceutique Pharmatoka S.A.S a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Ellura Capsules (Traditional Herbal Registration number: THR 46825/0001). Ellura Capsules are available without prescription and can be bought from pharmacies and other outlets.

The active ingredient in Ellura Capsules comes from the juice of the cranberry fruit (Vaccinium macrocarpon Ait. Fructus). Ellura Capsules is a traditional herbal medicinal product used to help prevent recurrent uncomplicated acute urinary tract infections (UTIs) such as cystitis in women only, based on traditional use only.

This registration is based exclusively upon the longstanding use of cranberry fruit as a traditional herbal medicine and not upon data generated from clinical trials. There is no requirement under the Traditional Herbal Registration Scheme to prove scientifically that a product works.

No new or unexpected safety concerns arose from this application and it was, therefore, decided that a Traditional Herbal Registration Certificate could be granted.

This lay summary was last updated in January 2019, following a variation to update the use of the product, granted 19 December 2018.
ELLURA CAPSULES

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Please note the content of this PAR is based on the original assessment, updates following the approval of the Traditional Herbal Registration Certificate are found in the annex(s) at the end of the report.

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Ellura Capsules to PlantaPhile Ltd (THR number: THR 32294/0021) on 22 September 2016. Following a change of ownership on 2 November 2016 the THR was transferred to Laboratoire Pharmaceutique Pharmatoka S.A.S (THR number: THR 46825/0001).

This application was submitted according to Article 16.c of Directive 2001/83 EC, as amended, as part of the Traditional Herbal Medicines Registration Scheme. Ellura Capsules is a traditional herbal medicinal product used to help relieve symptoms of minor lower urinary complaints associated with cystitis in women only, based on traditional use only.

There is sufficient evidence to demonstrate use of cranberry fruit for at least 30 years, of which at least 15 years have been in an EU Member State. A satisfactory review of the available safety data on cranberry fruit has also been provided, together with an Expert Safety Report supporting the proposed product.
HERBAL SUBSTANCE: CRANBERRY FRUIT

Scientific name of the plant: Vaccinium macrocarpon Aiton
Plant family: Ericaceae

Manufacture of Herbal Substance
The plants are cultivated in the USA and Chile. The fruit is harvested between mid-September and early December in the USA and between late March and early June in Chile.

The plants are cultivated in accordance with the principles of Good Agricultural and Collection Practice (GACP) guidelines. The plants are treated with pesticides but the cranberries have not been irradiated.

Control of Herbal Substance
An appropriate specification is applied taking account of current guidelines and pharmacopoeial requirements and is acceptable. The specification is supported by the batch data provided.

Container Closure System
Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability of Herbal Substance
A shelf-life for the herbal substance is not necessary because it is only a precursor of the active substance, the herbal preparation. The actual guideline requires stability testing data for the herbal preparation and the herbal product in the application documents and not for the herbal substance.

HERBAL PREPARATION: Cranberry Fruit Juice (Vaccinium macrocarpon Aiton. Fructus) dry extract

Extraction solvent: Ethanol 70% (v/v)

Manufacture of Herbal Preparation
A satisfactory description of the manufacturing process of the herbal preparation and flow diagram has been provided. The in-process controls are satisfactorily detailed. Certificates of Analysis for all materials used in the manufacture of the herbal preparation have been provided.
Control of Herbal Preparation
A satisfactory specification with appropriate tests and limits has been provided for the herbal preparation.

Satisfactory analytical procedures are used to control the quality of the herbal preparation. Analytical procedures have been validated, as appropriate.

Certificates of Analysis have been provided for batches of the herbal preparation, demonstrating satisfactory compliance with the proposed specifications.

Container Closure System
Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability of Herbal Preparation
Stability studies have been carried out under ICH conditions. The results support the proposed retest period of the herbal preparation.

HERBAL PRODUCT: ELLURA CAPSULES

Description and Composition of Herbal Product
Ellura Capsules are colourless capsules containing a dark purple powder. Each capsule contains 195-216 mg of dry refined extract from the juice of the cranberry fruit, corresponding to 36 mg of proanthocyanidins (PAC), calculated as PAC A2. The capsule excipients are mannitol, magnesium stearate, silica (colloidal anhydrous) and hypromellose (capsule shell).

The compatibility of the herbal preparation with the excipients is demonstrated by the stability testing results. The excipients are controlled in line with their respective Ph Eur monographs.

Satisfactory Certificates of Analysis are provided for all excipients.

None of the excipients are derived from animal material.

Manufacture of Herbal Product
A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. A commitment has been provided to conduct process validation on the first three commercial scale batches manufactured.
Control of Herbal Product
The finished product specifications are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate.

Container Closure System
The capsules are stored in either blister packs of 15 or 30 capsules (PVC/PE/PVDC film - aluminium foil with PVC/PVA copolymer, and butylmethacrylate coating) or HDPE containers of 90 capsules with internal layer moisture based of polypropylene as desiccant and polypropylene cap. Not all pack sizes may be marketed.

Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with EU Directive and food regulations.

Stability of Herbal Product
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 18 months is appropriate when the storage precaution ‘store in the original packaging’ is applied.

Pharmaceutical Expert
The Quality Overall Summary has been written by an expert with suitable experience.

Product Literature
All product literature is satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

CONCLUSION
There are no objections to granting of a Traditional Herbal Registration from a quality point of view.
NON-CLINICAL ASSESSMENT

NON-CLINICAL OVERVIEW
The applicant has submitted a literature review with this application. An Expert Safety Report was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by a suitably qualified professional.

The overview submitted in support of this application is satisfactory.

Due to a shortage of published data on cranberry fruit it is not possible to assess if the safety package for the phytochemical constituents of this active ingredient is acceptable to the standards of today’s GLP and safety testing requirements. However, the information supplied demonstrating traditional use is acceptable and thus the lack of provision of a complete standard safety package is acceptable and in compliance with guideline EMEA/HMPC/32116/05.

Assurance was provided that the results of genotoxicity testing will be provided before renewal of the registration.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The SmPC for this product is satisfactory from a non-clinical point of view.

ENVIRONMENTAL RISK ASSESSMENT
An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

CONCLUSION
There are no objections to granting of a Traditional Herbal Registration from a non-clinical point of view.
CLINICAL ASSESSMENT

The initial indication & posology have been updated following a variation application - see annex I and updated product information available on the MHRA website.

INDICATIONS
The applicant submitted the following therapeutic indications:

“A traditional herbal medicinal product used to help relieve symptoms of minor lower urinary complaints associated with cystitis in women only, based on traditional use only”

These indications are acceptable.

POSOLOGY AND METHOD OF ADMINISTRATION
The applicant has submitted the following:

“For oral use only.

Ellura capsules should always be taken with a large glass of water (at least 300 ml).

Adult women over 18 years including the elderly
At the first sign of any symptoms, take one capsule each day.

A doctor or qualified healthcare practitioner should be consulted if symptoms worsen, or persist after one week.

Children and adolescents under 18 years old:
This product is not recommended in children and adolescents under 18 years old (see section 4.4 ‘Special warnings and precautions for use’)

This is acceptable.

EFFICACY
No clinical efficacy data is required for registration of Traditional Herbal Medicinal Products.

EVIDENCE OF TRADITIONAL USE
Article 16 c 1 (c) requires the applicant to provide bibliographic or expert evidence showing that the medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years, including at least 15 years within the EU.
There is sufficient evidence to demonstrate use of cranberry fruit for at least 30 years, of which at least 15 years have been in an EU Member State. The requirements of the Directive are, therefore, addressed for this aspect.

SAFETY REVIEW
Article 16 c 1 (d) requires the applicant to provide a bibliographic review of the safety data together with an Expert Safety Report.

A safety review has been provided as well as an Expert Safety Report written by a suitably qualified professional. These are satisfactory.

ASSESSMENT OF SUITABILITY FOR GSL STATUS
Cranberry fruit was assessed for suitability for GSL status.

Section 51 of the Medicines Act 1968 states that “GSL may be appropriate for medicines which can, with reasonable safety, be sold or supplied otherwise than by or under the supervision of a pharmacist”. The term “reasonable safety” may usefully be defined as: “Where the hazard to health and the risk of misuse and the need for special precautions in handling are small, and where wider sale would be a convenience to the purchaser”.

Suitability of indication for GSL:

1. Hazard to health
There appears to be a minimal risk of hazard to health.

2. Risk of misuse
The indications are clear and easily understandable to the patient. Doses are also clearly stated. Moreover other GSL products are available for the proposed indication.
The risk of misuse of this product is considered to be low.

3. Need to take special precautions in handling
There are no special precautions in handling this product other than keeping it out of the reach and sight of children (as with any other GSL medicine).

4. Wider sales are convenient to the purchaser
This would apply.

In summary, it is considered that the four above criteria for GSL status have been met and this product should be suitable for GSL status.

PRODUCT LITERATURE
The SmPC, PIL and labelling for this product are medically satisfactory.

CONCLUSION
There are no objections to granting of a Traditional Herbal Registration from a clinical point of view.
OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY
The quality data submitted with this application are satisfactory.

NON-CLINICAL
No new non-clinical data were submitted with this application. However, assurance was provided that the results of genotoxicity testing will be provided before renewal of this registration. This is satisfactory.

EFFICACY AND SAFETY
No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products.

There is sufficient evidence to demonstrate use of cranberry fruit for at least 30 years, of which at least 15 years have been in an EU Member State, and a satisfactory review of the safety data has been provided.

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The risk: benefit balance is acceptable and a Traditional Herbal Registration may be granted.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
LABELLING

Bottle label and blister:

- **Ingredients:**
  - Each capsule contains 100 mg flavone glycosides (from cranberry, adjusted to the equivalent of cranberry fruit (Vaccinium macrocarpon L. (cranberry), corresponding to 65 mg of cranberry (Vaccinium macrocarpon L.) adjusted to the equivalent of cranberry fruit (Vaccinium macrocarpon L.)).
  - For oral use only.
  - Please read the enclosed package leaflet carefully before use.

- **How to take:** Adult women over 18 years old including the elderly:
  - Follow the instructions on the bottle label, taking one capsule (333 mg) per day for 14 days for 1 course (14 capsules).
  - The capsules may be swallowed whole or dissolved in a small cup of water before taking.

- **Warning:** Do not use if you:
  - are pregnant or breast feeding,
  - are allergic to any of the ingredients of the medicinal product,
  - are 18 years or over.

- **Legal and regulatory notices:**
  - This medicinal product is subject to the rules of the Medicines Act (law of 6 August 1971) and its successive amendments.

**Traditional herbal medicinal product used to help prevent recurrent, uncomplicated acute urinary tract infections (UTIs) such as cystitis in women only, based on traditional use only.**

Laboratoire Pharmaceutique Pharmacia S.A.S.
39-22 avenue de la République,
92000 Nanterre, France.
Traditional herbal medicinal product used to help prevent recurrent uncomplicated adult urinary tract infections (UTIs) such as cystitis in women only, based on traditional use only.
Our Reference: THR 46825/0001
Product: Ellura Capsules
Marketing Authorisation Holder: Laboratoire Pharmaceutique Pharmatoka S.A.S

Ingredient(s): Cranberry Fruit Juice (Vaccinium macrocarpon Aiton. Fructus) dry extract

Type of Procedure: National
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard

Reason:
To update the indication for use to “A traditional herbal medicinal product used to help prevent recurrent uncomplicated acute urinary tract infections (UTIs) such as cystitis in women only, based on traditional use only”" Consequential changes to SPC section 4.1, 4.2, 4.3, 4.4, 4.5 and additional updates to 4.8. The THR holders address (section 7) has also been updated. The label and leaflet mock ups have been updated accordingly.

Evaluation
The prophylactic use of cranberry juice extract in the prevention of UTIs has been approved in Spain (Ellura capsules) and in Denmark (Vitabutin). The prophylactic use of cranberry juice extract has also been accepted in other non-EU countries.

There is no safety concern with the use of cranberry formulations.

Conclusion
Based on the justifications provided by the applicant, and the good safety profile, it is considered that the proposed variation can be considered acceptable.

Decision: Approved, 19 December 2018
ANNEX II

Our Reference: THR 46825/0001
Product: Ellura Capsules
Marketing Authorisation Holder: Laboratoire Pharmaceutique
Pharmatoka S.A.S

Ingredient(s): Cranberry Fruit Juice (Vaccinium macrocarpon Aiton. Fructus) dry extract

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard

Reason:
To increase the shelf life of the finished product from 18 months to 36 months, based on real time data. As a consequence, section 6.3 of the SmPC has been updated.

Evaluation
The stability data provided support the proposed change in shelf life from 18 months to 36 months.

Conclusion
The extended shelf life of 36 months is acceptable.

Decision: Approved, 30 January 2019