IPAR

Public Assessment Report for a
Traditional Herbal Medicinal Product
for Human Use

Ellura hard capsules
Cranberry fruit juice, refined dry extract

TR 22953/001/001
TR Holder: Laboratoire Pharmaceutique Pharmatoka SAS

CONTENTS

I. INTRODUCTION

Specific provisions were introduced for traditional herbal medicinal products (THMPs) in accordance with the Traditional Herbal Medicinal Products Directive (2004/24/EC). The national regulations, the Medicinal Products (Control of Placing on the Market) Regulations 2007 (S.I. No. 540 of 2007) which implement this Directive came into force on 23rd July 2007. Consequently, the Health Products Regulatory Authority (HPRA) has established the Traditional Herbal Medicinal Products Registration Scheme.

The Public Assessment Report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of a Certificate of Traditional Use Registration for a specific traditional herbal medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of EC Directive 2001/83/EC, as amended by Directive 2004/27/EC and Directive 2004/24/EC. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the traditional herbal medicinal product for marketing in Ireland.

Based on the review of the data on quality, safety and traditional use, the HPRA has granted Laboratoire Pharmaceutique Pharmatoka SAS a Certificate of Traditional Use Registration for Ellura hard capsules, containing a refined dry extract obtained from the juice of cranberry fruit (*Vaccinium macrocarpon* Aiton, fructus).

This application is for a traditional herbal medicinal product as defined by Article 16a(1) of Directive 2001/83/EC as amended and was submitted as part of the Traditional Herbal Medicinal Product Registration Scheme.

The Summary of Product Characteristics (SmPC) for this traditional herbal medicinal product is available on the HPRA's website.

Name of the product	Ellura
Name(s) of the active substance(s) (INN)	Cranberry fruit juice refined dry extract
Pharmacotherapeutic classification (ATC Code)	G04BX
Pharmaceutical form and strength(s)	Hard capsules
Marketing Authorisation Number(s) in Ireland (PA)	TR22953/001/001
Marketing Authorisation Holder	Laboratoire Pharmaceutique Pharmatoka SAS 20-22 Avenue de la République Rueil Malmaison 92500 France

II. QUALITY ASPECTS

This application is for Ellura hard capsules. The active ingredient of Ellura hard capsules is a refined dry extract obtained from the juice of cranberry fruit (*Vaccinium macrocarpon* Aiton, fructus).

II.1 S.1 Herbal Substance

The herbal substance is cranberry fruit and consists of the fresh or frozen, whole, crushed, or powdered, mature fruits of *Vaccinium macrocarpon* Aiton. The herbal substance is produced in accordance with the principles of good agricultural and collection practice (GACP).

The specification of the cranberry juice is adequate to control the quality and meets current requirements for fruit juice intended for human consumption. Batch analytical data demonstrating compliance with this specification have been provided.

II.2 S.2 Herbal preparation

The herbal preparation is a refined dry extract from the juice of cranberry fruit and is manufactured in accordance with the principles of good manufacturing practice (GMP).

The herbal preparation specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification have been provided.

II.3 Medicinal product

P.1 Composition

The composition of the medicinal product is stated in sections 2 and 6.1 of the SmPC. A description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of GMP at suitably qualified manufacturing sites.

The manufacturing process involves standard operations only and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All of the excipients comply with monographs of the European Pharmacopoeia. No ingredients of animal origin are used.

P.5 Control of the Finished Product

The finished product specification is based on the pharmacopoeial monograph for capsules and reflects the requirements of the European guideline on specifications for herbal medicinal products (EMA/HMPC/162241/2005). The tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging materials comply with Ph. Eur. and/or EU legislation on materials intended for use with foodstuffs.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Conclusion on quality

The important quality characteristics of the product are well-defined and controlled. Satisfactory pharmaceutical documentation has been provided, assuring consistent quality of Ellura hard capsules.

III. NON-CLINICAL ASPECTS

The HPRA has been assured that good laboratory practice (GLP) standards were followed in an appropriate manner in the studies conducted.

An expert report on safety has been provided which includes an appropriate review of the available literature. Overall, the information presented demonstrating traditional use is considered to be acceptable and the lack of provision of a complete standard safety package is in line with the EMA 'Guideline on Non-clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (bibliographical and mixed applications) and in Applications for Simplified Registration' (EMEA/HMPC/32116/05).

An Ames test was performed, in which mutagenic effects were detected in 3 strains of *Salmonella typhimurium* without metabolic activation, and in 4 strains with metabolic activation. However, the active substance, cranberry refined dry extract, contains acknowledged genotoxic compounds (quercetin and kaempferol) not known to be carcinogenic. The applicant has argued that the presence of these flavonoid compounds likely explains the positive results obtained in the Ames test and this argument is accepted. Based on a risk assessment carried out in accordance with the Guideline on the Assessment of Genotoxicity in Herbal Substances/Preparations (EMEA/HMPC/107079/2007), it was concluded that cranberry refined dry extract is not associated with any safety concerns.

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

IV. CLINICAL ASPECTS

Ellura hard capsules is a traditional herbal medicinal product *used to prevent recurrent uncomplicated acute urinary tract infections (UTIs) such as cystitis in adult women over the age of 18 years exclusively based on long standing use.*

IV.1 Clinical Efficacy

There is no requirement under the Traditional Herbal Registration Scheme to prove scientifically that the product is efficacious, the registration is based exclusively upon the longstanding use of Ellura hard capsules as a traditional herbal medicine and not upon data generated from clinical trials.

Article 16c1(c) of Directive 2001/83/EC requires the applicant to provide bibliographic or expert evidence to show 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 Community. With regard to this traditional use data, the requirements of Article 16c1(c) have been met.

The efficacy of this traditional herbal medicinal product is plausible on the basis of long-standing use and experience.

The indication proposed for Ellura hard capsules is in line with traditional indications recorded and hence, compatible with the requirements of the Traditional Herbal Medicinal Products Directive 2004/24/EC.

IV.2 Clinical Safety

In accordance with Article 16c1(d) the applicant has provided a bibliographic review of the safety data together with an expert report.

Ellura is to be used if you suffer from recurrent uncomplicated acute UTIs, meaning that you have had at least 3 or more episodes in the past 12 months or 2 or more episodes in the past 6 months. If these UTIs recur more often, a doctor should be consulted for advice including advice on how often you should take Ellura.

One capsule of Ellura per day should be taken to prevent uncomplicated acute UTIs from recurring. The capsule should be taken with a large glass of water. Do not take more than the recommended dose.

This preventative treatment should be taken for at least 15 days after your last UTI.
Ellura should not be taken for longer than 6 months.

If symptoms of a urinary tract infection arise during the use of Ellura, a doctor should be consulted.

If any of the following symptoms develop: high temperature (fever), difficulty passing urine or bladder spasms, pain when urinating, blood in your urine, abdominal pain, back pain or you become incontinent you should consult a doctor and seek medical advice immediately.

This product is not suitable for use in men, urinary symptoms in men should be treated by a doctor.

Ellura should not be taken, if you are a man, if you are allergic (hypersensitive) to the active substance or any of the other ingredients of this medicine, if you are under 18 years old or if you are pregnant or breastfeeding.

Ellura should not be taken If you suffer from: fluid retention caused by a kidney or heart problem or if you have current or previous kidney problems including kidney stones.

Ellura should not be taken If you are taking any anticoagulant medicine used to help prevent blood clots or if you are taking any immunosuppressant medicines such as tacrolimus or having chemotherapy.

Please see the SmPC and package leaflet for full details on the safe use of this product including warnings and contraindications to use of Ellura.

In conclusion, this product proves not to be harmful in the specified conditions of use based on the review of safety data, expert report and additional data provided.

IV.3 Pharmacovigilance

It should be noted that in accordance with Article 16g of Directive 2001/83/EC, as amended, the pharmacovigilance requirements described in Articles 101- 108 of Directive 2001/83/EC, as amended, also apply in respect of traditional herbal medicinal products.

V. OVERALL CONCLUSIONS

The important quality characteristics of the product are well-defined and controlled. Satisfactory pharmaceutical documentation has been provided, assuring consistent quality of Ellura hard capsules.

The HPRA, on the basis of the data submitted, considered that Ellura hard capsules demonstrated adequate evidence of traditional use for the approved indication and no new non-clinical or clinical safety concerns have been identified.

A Certificate of Traditional Use Registration for Ellura hard capsules is granted.