IPAR

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

Eucarbon Herbal Tablets

Cassia senna L. (*C. acutifolia* Delile) and/or *Cassia angustifolia* Vahl, folium (Senna leaf) Rhei radix (Rhubarb root) Vegetable Charcoal.
TR 1743/1/1

TR holder F. Trenka Chem.-pharm. Fabrik Ges.m.b.H.,

29th May 2015

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 HPRA has established the Traditional Herbal Medicinal Products Registration Scheme.

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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 F. Trenka chem. Pharm. Fabrik Gesmbh a Certificate of Traditional Use Registration for Eucarbon herbal Tablets, containing powdered Senna Leaf, Rhubarb Dry Extract and Vegetable Charcoal.

This application was submitted as a standard application according to Article 16c of Directive 2001/83/EC, as amended, 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.

II QUALITY ASPECTS

This application is for Eucarbon herbal Tablets. The active ingredients of Eucarbon herbal Tablets are anthraquinone derivatives (present in both powdered Senna Leaf and Dry Extract of Rhubarb Root) and Vegetable Charcoal.
Each tablet contains 105 mg of *Cassia senna* L. (*C. acutifolia* Delile) and/or *Cassia angustifolia* Vahl, folium (Senna leaf), and 25 mg of extract (as dry extract) from *Rheum palmatum* L. or *Rheum officinale* Baillon, or hybrids of these two species or a mixture, Rhei radix (Rhubarb root) (3- 5: 1), (Extraction solvent : Ethanol 70% v/v), corresponding to a total amount of anthraquinone derivatives of 3.3 mg, and 180 mg of Vegetable Charcoal.

II.1 S.1 Herbal Substance

The herbal substance specifications meet current pharmacopoeial requirements and are considered adequate to control the quality of Senna Leaf, Rhubarb Root and Vegetable Charcoal. Batch analytical data demonstrating compliance with these specifications have been provided.

II.2 S.2 Herbal preparation

The herbal preparation Powdered Senna Leaf is described in the European Pharmacopoeia (Ph. Eur.) and is manufactured in accordance with the principles of good manufacturing practice (GMP).

The herbal preparation Rhubarb Dry Extract is described in the German Pharmacopoeia (DAB) and is manufactured in accordance with the principles of good manufacturing practice (GMP).

The herbal preparation Vegetable Charcoal is controlled to an internal specification and is manufactured in accordance with the principles of good manufacturing practice (GMP).

The herbal preparation specifications meet current pharmacopoeial requirements and are considered adequate to control the quality. Batch analytical data demonstrating compliance with these specifications have been provided.

II.3 Medicinal product

P.1 Composition

Eucarbon herbal Tablets are grey-black, cylindrical, biconvex tablets.

Each tablet contains 105 mg of *Cassia senna* L. (*C. acutifolia* Delile) and/or *Cassia angustifolia* Vahl, folium (Senna leaf), and 25 mg of extract (as dry extract) from *Rheum palmatum* L. or *Rheum officinale* Baillon, or hybrids of these two species or a mixture, Rhei radix (Rhubarb root) (3- 5: 1), (Extraction solvent : Ethanol 60% v/v), corresponding to a total amount of anthraquinone derivatives of 3.3 mg, and 180 mg of Vegetable Charcoal.

The tablets also contain the following excipients: Sucrose, Maize starch, Talc, Kaolin Heavy, Acacia, Peppermint oil, Bitter Fennel Fruit Oil.

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.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer’s specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Tablets and 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 have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented as blister packs made of PVC/PVdC-Aluminium.

Evidence has been provided that packaging material complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

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 demonstrating the stability of the product for 3 years when stored below 30°C and in the original container in order to protect from light.

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 Eucarbon herbal Tablets.

III NON-CLINICAL ASPECTS

Eucarbon herbal Tablets is a traditional herbal medicinal product as defined by Article 16a (1) of Directive 2001/83/EC as amended.

No new preclinical studies have been submitted. Given the type of application and limited data available, it is not possible to assess if the safety package for the phytochemical constituents of Eucarbon herbal Tablets are acceptable to the standards of today's GLP and safety testing requirements.

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

IV CLINICAL ASPECTS

This is a national application submitted by F. Trenka Chem. pharm. Fabrik Gesmbh under Article 16c of Directive 2001/83/EC, as amended.

The active ingredients of Eucarbon herbal Tablets are anthraquinone derivatives (present in both powdered Senna leaf and dry extract of Rhubarb root) in addition to Vegetable Charcoal which is a non - activated charcoal (Carbo Ligni)

Eucarbon herbal Tablets contain 105 mg of *Cassia senna* L. (*C. acutifolia* Delile) and/or *Cassia angustifolia* Vahl, folium (Senna leaf), and 25 mg of extract (as dry extract) from *Rheum palmatum* L. or *Rheum officinale* Baillon, or hybrids of these two species or a mixture, Rhei radix (Rhubarb root) (3- 5: 1), (Extraction solvent : Ethanol 70% v/v), corresponding to a total amount of anthraquinone derivatives of 3.3 mg, in addition to 180 mg of Vegetable Charcoal.

Eucarbon herbal Tablets is a traditional herbal medicinal product used *for the short term relief of occasional constipation exclusively based on longstanding 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 Eucarbon herbal Tablets 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 Eucarbon herbal Tablets 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 16 c 1(d) the applicant has provided a bibliographic review of the safety data together with an expert report.

Adolescents over 12 years of age , adults, elderly
1-2 tablets with or after meals with liquid up to 3 times daily to obtain a mild laxative and purgative effect. If a stronger laxative effect is desired, the evening dose can be increased to 3 – 4 Eucarbon herbal tablets.

Herbal substance/preparation equivalent to 2.65 to 3.95 mg of hydroxyanthracene derivatives in one tablet, calculated as rhein (an anthranoid active metabolite).

The maximum daily dose of hydroxyanthracene glycosides is 30 mg.
This is equivalent to 8 tablets. The correct individual dose is the smallest dose required to produce a comfortable soft-formed motion.

Do not use Eucarbon herbal Tablets

- in cases of known hypersensitivity to any of the active ingredients of senna leaves, rhubarb extract, charcoal or to any of the excipients.
- in cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis);
- if you have abdominal pain of unknown origin or a suspected gastric or intestinal ulcer
- if you have sudden change in bowel habit that persists for more than 2 weeks, undiagnosed rectal bleeding and failure to defaecate following the use of a laxative
- in a severe dehydration state with water and electrolyte depletion
- in children under 12 years of age
- during pregnancy or lactation

Special warnings and precautions for use:

- If there is no bowel movement after three days consult a doctor.
- Prolonged continuous use is not recommended.
- This THMP is recommended for oral short term use only.
- If the condition worsens during use or symptoms do not improve after 1 week of Eucarbon herbal Tablets, a doctor should be consulted.

Full details of all special warnings and pre cautions for use along with potential interactions of Eucarbon herbal Tablets can be found in the Summary of Product Characteristics (SmPC) and Package Leaflet (PL)

Undesirable effects

Hypersensitivity reactions (pruritus, urticaria, local or generalised exanthema) may occur.
Meteorism (accumulation of gas in the abdomen or the intestine, usually with distension) may occur commonly.

Eucarbon herbal Tablets may produce abdominal pain and spasm and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary.

Chronic use may lead to disorders in water equilibrium and electrolyte metabolism and may result in albuminuria and haematuria.

Furthermore, chronic use may cause pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation.

Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.

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.

Method of Sale and Supply:
Other such laxatives which have been authorised by the HPRA are restricted to Pharmacy only. In view of the known risks of anthranoid containing laxatives and the contraindications and warnings required to ensure the safe use of this THMP the method and sale of supply of Eucarbon herbal Tablets will be OTC Pharmacy sale.

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 Eucarbon herbal Tablets.

The HPRA, on the basis of the data submitted, considered that Eucarbon herbal Tablets demonstrated adequate evidence of traditional use for the approved indication and no new preclinical or clinical safety concerns have been identified.

A certificate of traditional use for Eucarbon herbal Tablets is granted.

DATE OF APPROVAL: 29th May 2015