IPAR

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

Agnus castus oral drops
Tincture of Agnus castus fruit

TR2309/017/001

A. Vogel Ireland Limited

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 A. Vogel Ireland Limited a Certificate of Traditional Use Registration for Agnus castus oral drops, containing Agnus castus tincture.

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.

II. QUALITY ASPECTS

This application is for Agnus castus oral drops.
The active ingredient of Agnus castus oral drops is a tincture obtained from the berries of the *Vitex agnus-castus* L. plant.
Each dose (15 – 20 drops) contains 407 mg – 542 mg of tincture from *Vitex agnus-castus* L., fructus DER (1:10). Extraction solvent: ethanol 69.5 % v/v.

II.1 S.1 Herbal Substance

The herbal substance 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.2 S.2 Herbal preparation

The herbal preparation is agnus castus tincture 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 has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

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

All ingredients comply with Ph. Eur.

P.5 Control of the Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for 'Liquid Preparations for Oral use' 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 approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging components comply with Ph. Eur. and EU food contact legislation 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 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 Agnus castus oral drops.

III. NON-CLINICAL ASPECTS

Agnus castus oral drops 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 Agnus castus oral drops 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 A. Vogel Ireland Limited under Article 16c of Directive 2001/83/EC, as amended.

Agnus castus oral drops is a traditional herbal medicinal product used for the relief of minor symptoms of premenstrual syndrome, exclusively based upon 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 Agnus castus oral drops 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 Agnus castus oral drops 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.

<u>Contraindications to use:</u>
Agnus castus oral drops should not be used by those with:

- Known hypersensitivity to Agnus castus fruit or to any of the excipients
- A current pituitary disorder
- Or if pregnant or breastfeeding.

Special warnings and precautions for use:

- Patients who suffer or suffered from an oestrogen-sensitive cancer or those with a history of pituitary disorder or those using dopamine agonists, dopamine antagonists, oestrogens and antioestrogens should consult their doctor before using Agnus castus.
- In cases of prolactin secreting tumours of the pituitary gland the intake of Agnus castus fruits can mask symptoms of the tumour.
- The use in children and adolescents under 18 years of age has not been established due to lack of adequate data.
- If symptoms worsen during use or do not improve after a continued use over 3 months a qualified healthcare professional, e.g. a doctor or pharmacist should be consulted.
- This product contains 69.5 V/V% ethanol (alcohol).

Please see the HPRA website for the SmPC for Agnus castus oral drops for full product information details such as contraindications, warnings for use, possible interactions and possible adverse events for this THMP.

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 Agnus castus oral drops.

The HPRA, on the basis of the data submitted, considered that Agnus castus oral drops 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 Agnus castus oral drops is granted.

VI. REVISION DATE

November 2018

VII. UPDATES

Scope
B.II.e.7.B - Change in supplier of packaging components or devices (when mentioned in the dossier): Replacement or addition of a supplier

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
CRN 2206944	SPC section 6.5	16/05/2018	05/07/2018	Approved