IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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 Irish Botanica a Certificate of Traditional Use Registration for Peace & Calm Oral Liquid, containing an ethanolic tincture of valerian root.
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 Peace & Calm Oral Liquid. The active ingredient of Peace & Calm Oral Liquid is an extract obtained from *Valeriana officinalis* L., radix (valerian root).
Each 5 ml of oral liquid contains 2 ml of tincture from dried valerian root (*Valeriana officinalis* L., radix) (1:2). Extraction solvent: Ethanol 60% v/v
In addition, 5 ml of oral liquid contains approximately 1.78 g of ethanol (alcohol), equivalent to 45 ml of beer or 18.8 ml of wine, and 734 mg of sucrose.

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 a valerian ethanolic 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)
All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of the Finished Product
The Finished Product Specification is based on the pharmacopoeial monograph for oral liquids 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(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 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 Peace & Calm Oral Liquid.

III. NON-CLINICAL ASPECTS

Peace & Calm Oral Liquid is a traditional herbal medicinal product as defined by Article 16a(1) of Directive 2001/83/EC as amended. Given the type of application and limited data available, it is not possible to assess if the safety standards for the phytochemical constituents of Valerian root extract are acceptable to the standards of today's GLP and safety testing requirements.

While no new non-clinical studies have been submitted, an expert report on safety has been provided. Appropriate testing for genotoxicity, carcinogenicity and reproductive toxicity has not been performed. In view of the absence of genotoxicity data the applicant is required to submit this data within two years of the granting of a certificate of registration.

Overall, the information presented demonstrating traditional use is acceptable and thus the lack of provision of a complete standard safety package is acceptable and 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

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 Peace & Calm Oral Liquid 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 Peace & Calm Oral Liquid 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.

All relevant safety warnings have been recorded in the SmPC and patient information.

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 traditional use 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 Peace & Calm Oral Liquid.
The HPRA, on the basis of the data submitted, considered that Peace & Calm Oral Liquid demonstrated adequate evidence of traditional use for the approved indication(s) and no new non-clinical or clinical safety concerns have been identified.
A Certificate of Traditional Use Registration for Peace & Calm Oral Liquid is granted.