IPAR

Public Assessment Report for a

Traditional Herbal Medicinal Product for Human Use

Dormeasan Sleep Valerian Hops Oral drops

Tinctures of valerian root and hop strobile

TR2309/005/001

A. Vogel Ireland Limited

Scientific Discussion

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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 Dormeasan Sleep Valerian-Hops oral drops, containing tinctures from valerian root and hop strobile.

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 Dormeasan Sleep Valerian-Hops oral drops. The active ingredients of Dormeasan Sleep Valerian-Hops Oral Drops are tinctures obtained from Valerian root (*Valeriana officinalis* L.) and Hop strobile (*Humulus lupulus* L.).

Every 30 drop dose contains 394 mg of tincture from Valerian root (*Valeriana officinalis* L.) (1:10-11), extraction solvent: ethanol 58 % v/v, and 394 mg of tincture from Hop strobile (*Humulus lupulus* L.) (1:12-13), extraction solvent: ethanol 65 % v/v. 1 ml is equivalent to 35 drops.

II.1 S.1 Herbal Substance

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

II.2 S.2 Herbal preparation

The herbal preparations are tinctures of Hop strobile (*Humulus lupulus* L.) and Valerian root (*Valeriana officinalis* L.) and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The herbal preparation specifications are considered adequate to control the quality. Batch analytical data demonstrating compliance with the specifications 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.

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 is standard and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All other ingredients comply with Ph. Eur.

P.5 Control of the Finished Product

The Finished Product Specification is satisfactory and the tests and control limits are described and adequately validated, as appropriate.

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. or 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 current 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 Dormeasan Sleep Valerian-Hops oral drops.

III. NON-CLINICAL ASPECTS

Dormeasan Sleep Valerian-Hops 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 package for the phytochemical constituents of Dormeasan Sleep Valerian-Hops 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. Appropriate testing carcinogenicity and reproductive toxicity has not been performed, however a discussion regarding these individual areas has been provided with respect to the current available literature data. The applicant has also confirmed that Dormeasan Sleep Valerian-Hops oral drops is not genotoxic by means of an Ames Mutagenicity Assay.
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 16a of Directive 2001/83/EC, as amended.

Dormeasan Sleep Valerian-Hops oral drops is a traditional herbal medicinal product used to aid sleep. This is 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 Dormeasan Sleep Valerian-Hops oral dropsas 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 Dormeasan Sleep Valerian-Hops 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.

It is recommended that if symptoms persist, worsen or do not improve after 2 weeks use of Dormeasan Sleep Valerian-Hops oral drops a qualified healthcare professional e.g. a doctor or pharmacist should be consulted.

The use of this product is not recommended in children or adolescents under 18years because data are not sufficient and medical advice should be sought.

This product contains 62% vol % ethanol (alcohol). This corresponds to 420mg alcohol per 30 drop dose which is the equivalent of 10.6ml of beer or 4.4 ml of wine. This may be harmful for those suffering from alcoholism. This should also be taken into account in pregnant, breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. This product should also be avoided in patients taking other medicines known to interact with alcohol.

This product should also be avoided in patients taking other medicines that can cause drowsiness.

The safety of this product during pregnancy and lactation has not been established. Due to the lack of data, use during pregnancy and lactation is not recommended.

This product may impair the ability to drive and use machines. If affected, patients should not drive or operate machinery.

This product may cause side effects such as stomach upset and cramping.

Overdose of this product may cause alcohol intoxication.

Valerian root at a dose of approximately 20g (equivalent to 93 doses of this product) caused symptoms such as tiredness, stomach cramps, chest tightness, light headedness, handshaking and dilation of the pupil of the eye which disappeared within 24 hours. If these symptoms arise, the treatment should be supportive.

After intake of very high doses of Valerian root over several years (daily consumption corresponding to approximately 30g of the drug), withdrawal symptoms (delirium) have been reported.

In testing for the detection of gene mutation by this product, Dormeasan Sleep Valerian-Hops oral drops did not demonstrate genotoxic activity.

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 Dormeasan Sleep Valerian-Hops oral drops.
The HPRA, on the basis of the data submitted, considered that Dormeasan Sleep Valerian-Hops 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 Dormeasan Sleep Valerian-Hops oral drops is granted.

VI. REVISION DATE

February 2019

VII. UPDATES

Scope
B.II.e.1.B.1 Change in immediate packaging of the finished product: Change in type of container or addition of a new container: Solid, semi-solid and non-sterile liquid pharmaceutical forms

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
CRN 2205601	SPC section 6.5 & IPAR	12/04/2018	11/05/2018	Approved