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IRISH MEDICINES BOARD
PUBLIC ASSESSMENT REPORT FOR A TRADITIONAL HERBAL MEDICINAL PRODUCT FOR HUMAN USE

Stress Relief Daytime Valerian-Hops Oral Drops

Tincture of
Valerian root (*Valeriana officinalis L.)*
and
Hop Strobile (*Humulus lupulus L.)*

TR0725/020/001
TR holder: Bioforce (UK) Ltd

Date: 02/05/14

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 IMB has established the Traditional Herbal Medicinal Products Registration Scheme.

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) 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 IMB 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 IMB 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 IMB has granted Bioforce (UK) Ltd a Certificate of Traditional Use Registration for Stress Relief Daytime Valerian-Hops oral drops containing tincture from Valerian root (*Valeriana officinalis* L.) and Hop strobile (*Humulus lupulus* L.).

This application was submitted as a standard application according to Article 16a 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 IMB's website.

II QUALITY ASPECTS

This application is for Stress Relief Daytime Valerian-Hops oral drops. The active ingredients of Stress Relief Daytime Valerian-Hops are tinctures obtained from Valerian root (*Valeriana officinalis* L.) and Hop strobile (*Humulus lupulus* L.).

Every 20 drop dose contains 0.28 ml (263 mg) of tincture from Valerian root (*Valeriana officinalis* L.) (1:10-11), extraction solvent: ethanol 58% v/v, and 0.28 ml (263 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 specifications for the herbal substances are considered adequate to control the quality and are based on current pharmacopoieal requirements. The specifications are supported by the batch data provided.

II.2 S.2 Herbal preparation

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

The specifications for the herbal preparations are considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The product is a green to brown, clear liquid containing tincture from Valerian root (*Valeriana officinalis* L.) and tincture from Hop strobile (*Humulus lupulus* L.). The product also contains the following inactive ingredients: ethanol (alcohol) and water.

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 good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process is standard and process validation has been carried out.

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

All other ingredients comply with Ph. Eur.

P.5 Control of 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(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 product is presented in Type III brown glass dropper bottles with a twist off polyolefine cap or a polyethylene child resistant cap. The product is available in pack sizes of 15 ml, 30 ml and 50 ml.

Evidence has been provided that components of primary packaging material comply with Ph. Eur. or EU legislation for use with foodstuffs, as appropriate.

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 demonstrating the stability of the product for 2 years with no special storage conditions.

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 Stress Relief Daytime Valerian-Hops oral drops.

III NON-CLINICAL ASPECTS

Stress Relief Daytime 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 Stress Relief Daytime 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 Stress Relief 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 Bioforce (UK) Ltd under Article 16a of Directive 2001/83/EC, as amended.

Stress Relief Daytime Valerian-Hops oral drops is a traditional herbal medicinal product used to relieve the symptoms of mild mental stress. 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 Stress Relief Daytime Valerian-Hops 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 Stress Relief 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 Stress Relief Daytime 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 18 years 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 20 g (equivalent to 93 doses of this product) caused symptoms such as tiredness, stomach cramps, chest tightness, lightheadedness, hand shaking 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 30 g of the drug), withdrawal symptoms (delirium) have been reported.

No cases of overdose have been reported for Hops.

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 Stress Relief Daytime Valerian-Hops oral drops.

The IMB, on the basis of the data submitted, considered that Stress Relief Day time Valerian-Hops oral drops 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 registration for Stress Relief Daytime Valerian-Hops oral drops is granted.