IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

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 marketing authorisation for a specific 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 Directive 2001/83/EC, as amended. 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 medicinal product for marketing in Ireland.

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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 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 grantedGR Lane Health Products Ltd a Certificate of Traditional Use Registration for Kalms Day Film-coated Tablets containing Valerian root extract (*Valeriana officinalis L,. radix*) and Hops strobile extract (*Humulus lupulus L., strobiles*).

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 IMB's website.

II. QUALITY ASPECTS

This application is for Kalms Day film-coated tablet. The active ingredients of Kalms Day film-coated tabletare extracts obtained from the root of *Valeriana officinalis L*

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 has been provided.

II.2 S.2 Herbal preparation

The herbal preparation is Valerian root dry extract 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 has 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 a suitably qualified manufacturing site.

The manufacturing process has been validated and the process provides a product of satisfactory quality and consistency.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or U.S.P. specifications 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 approved packaging for this product is described in section 6.5 of the SmPC.
Evidence has been provided that the bottle complies with the requirements of the Ph. Eur. and that the blister complies with the requirements of EU directive 2008/39/EC for plastic materials and articles intended to come in contact with foodstuffs.

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 Kalms Day film-coated tablets.

III. NON-CLINICAL ASPECTS

Kalms Day 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 Kalms Day 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 GR Lane Health products limited under Article 16c of Directive 2001/83/EC, as amended.

The proposed indication for this product is 'a traditional herbal medicinal product for the relief of symptoms of mild mental stress 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 Kalms Day 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 Kalms Day 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.

Patients with known hypersensitivity to Valerian Root or Hop Strobiles should not use Kalms Day film-coated tablets.

This THMP is recommended for oral short term use only.

It is not recommended for children or adolescents under 18 years.

As a general precaution co-medication with hypnotics and other sedatives is not recommended as additive effects cannot be excluded.

Kalms Day film-coated tablets may impair ability to drive and use machines. Patients who are affected should not drive or operate machinery.

The effect of Kalms Day maybe increased by alcohol. Excessive use of alcohol should therefore be avoided.

The safety of Kalms Day during pregnancy and lactation has not been established therefore use during pregnancy and lactation is not recommended.

The possible side effects that may occur after ingesting Kalms Day including gastro-intestinal symptoms such as nausea and abdominal cramps. The frequency is not known.

Overdose :

Valerian root at a dose of approximately 20 g (equivalent to 77 to 96 tablets) caused benign symptoms (fatigue, abdominal cramp, chest tightness, lightheadedness, hand tremor and mydriasis), which disappeared within 24 hours. If symptoms arise, treatment should be supportive.
After intake of very high doses of valerian root over several years (daily consumption corresponding to approximately 10 g of the drug) withdrawal symptoms (delirium) have been reported.

No case of overdose has 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 chemical and pharmaceutical documentation has been provided, assuring consistent quality of Kalms Day film-coated tablet.

The IMB, on the basis of the data submitted, considered that Kalms Day 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 Kalms Day film-coated tablet is granted.