

KALMS NIGHT

THR 01074/0229

UKPAR

TABLE OF CONTENTS

Lay summary	Page 2
Scientific discussion	Page 3
Steps taken for assessment	Page 12
Summary of Product Characteristics	Page 13
Product Information Leaflet	Page 17
Labelling	Page 19

KALMS NIGHT

THR 01074/0229

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted G. R. Lane Health Products Limited a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Kalms Night (Traditional Herbal Registration number: THR 01074/0229) on 15 July 2013. Kalms Night is available without prescription and can be bought from pharmacies and other outlets.

Kalms Night is a traditional herbal medicinal product used for the temporary relief of sleep disturbances based on traditional use only. The active ingredient in Kalms Night comes from the roots of the Valerian plant (*Valeriana officinalis* L.)

This registration is based exclusively upon evidence of the use of Valerian root as a traditional herbal medicine and not upon data generated from clinical trials. There is no requirement under the Traditional Herbal Registration Scheme to prove scientifically that the product works.

No new or unexpected safety concerns arose from this application and it was, therefore, decided that a Traditional Herbal Registration Certificate could be granted.

KALMS NIGHT

THR 01074/0229

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction	Page 4
Pharmaceutical assessment	Page 5
Preclinical assessment	Page 8
Clinical assessment	Page 9
Overall conclusions and risk assessment	Page 11

INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicinal product Kalms Night (THR 01074/0229) to G. R. Lane Health Products Limited on 15 July 2013. This product is on the general sales list (GSL).

This application was submitted according to Article 16.c of Directive 2001/83 EC, as amended, as part of the Traditional Herbal Medicines Registration Scheme. The product is used for the temporary relief of sleep disturbances based on traditional use only.

The data supplied by the applicant demonstrate 30 years of traditional use of Valerian root in the European Community. A satisfactory review of the available safety data on Valerian root has also been provided, together with an Expert Safety Report supporting the proposed product.

PHARMACEUTICAL ASSESSMENT

HERBAL SUBSTANCE: VALERIAN ROOT

Scientific name of the plant: *Valeriana officinalis* L.

Plant family: Valerianaceae

Manufacture of Herbal Substance

The Valerian plants from which the herbal substance is obtained are cultivated in Eastern Europe. The roots are harvested in early autumn (before the blooming phase), washed and artificially dried in a building, protected from direct sunlight. The roots are stored in a dry warehouse.

The plant is treated before and during harvesting with a herbicide. The supplier of the herbal substance has provided confirmation that the herbal substance is produced in accordance with the principles of Good Agricultural and Collection Practice (GACP) (EMEA/HMPC/246816/20050) and that the herbal substance is not treated with ethylene oxide or irradiation following harvesting.

Control of Herbal Substance

An appropriate specification based on the Ph Eur monograph is applied and is acceptable. The specification is supported by the batch data provided.

Container Closure System

The herbal substance is stored in a suitable container.

Stability of Herbal Substance

No stability data have been provided and none are needed as a shelf-life for the herbal substance is not appropriate because it is only a precursor of the active substance, the herbal preparation. The guideline requires stability testing data for the herbal preparation and the herbal product in the application documents and not for the herbal substance. Confirmation is given that the herbal substance will be tested prior to being used to make the herbal preparation.

HERBAL PREPARATION: VALERIAN ROOT DRY EXTRACT

Drug extract ratio (DER): 3-5:1

Extraction solvent: Ethanol 60% v/v

Manufacture of Herbal Preparation

A satisfactory description of the manufacturing process of the herbal preparation and flow diagram has been provided. The in-process controls are satisfactorily detailed. The manufacture of the herbal preparation is considered a standard procedure.

Certificates of Analysis for all materials used in the manufacture of the herbal preparation have been provided.

Control of Herbal Preparation

A satisfactory specification with appropriate tests and limits has been provided for the herbal preparation.

Satisfactory analytical procedures are used to control the quality of the herbal preparation. Analytical procedures have been validated, as appropriate.

Certificates of Analysis have been provided for production batches of the herbal preparation, demonstrating satisfactory compliance with the proposed specification.

Container Closure System

An appropriate container closure system is used to store the herbal preparation.

Stability of Herbal Preparation

Stability studies have been performed in accordance with current guidelines. The proposed re-test period for the herbal preparation is acceptable.

HERBAL PRODUCT: KALMS NIGHT

Description and Composition of the Herbal Product

The herbal product is a white, circular, film-coated tablet. Each tablet contains 96 mg of dry extract from Valerian root. The tablets also contain the pharmaceutical excipients maltodextrin and colloidal anhydrous silica (from the herbal preparation), croscarmellose sodium, magnesium stearate, Prosolv SMCC50 (silicified microcrystalline cellulose), talc and silicon dioxide (which make up the tablet core) and Opadry™ White 07F28588 (hypromellose, titanium dioxide, polyethylene glycol (PEG) 3350, saccharin sodium; which makes up the tablet coating).

The compatibility of the herbal preparation with the excipients is demonstrated by the stability testing results. The excipients croscarmellose sodium, magnesium stearate and talc are controlled in line with their respective Ph Eur monograph. Prosolv SMCC50 and Opadry™ White 07F28588 are controlled in line with suitable in-house specifications and silicon dioxide is controlled in line with USP and NF specifications; in the absence of Ph Eur monographs for these excipients this is acceptable. Satisfactory Certificates of Analysis are provided for all excipients.

Manufacture of Herbal Product

A flow diagram outlining the various stages of the manufacturing process and the in-process controls is provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. No process validation data are given for the product formulation, however, data are provided for a product with the same core formulation coated with different excipients and the results are satisfactory. A commitment to conduct process validation on the first production batches of the approved formulation has been given.

Control of Herbal Product

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification.

Container Closure System

The tablets are stored in amber glass or white HDPE bottles with white HDPE tamper-evident caps. Pack sizes of 50, 100 or 200 tablets have been authorised, although not all pack sizes may be marketed. Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with current regulations.

Stability of Herbal Product

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 2 years is appropriate when the storage precautions "Do not store above 25°C" and "Store in the original package" are applied.

Pharmaceutical Expert

The Quality Overall Summary has been written by a professional with suitable experience.

Summary of Product Characteristics, product labels and Patient Information Leaflet

All product literature is satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Conclusion

There are no objections to granting of a Traditional Herbal Registration from a quality point of view.

NON-CLINICAL ASSESSMENT

NON-CLINICAL OVERVIEW

An Expert Safety Report was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by a suitably qualified professional.

Due to a shortage of published data on Valerian root, it is not possible to assess if the safety package for the phytochemical constituents of Valerian root is acceptable to the standards of today's GLP and safety testing requirements. However, the information supplied demonstrating traditional use is acceptable and thus the lack of provision of a complete standard safety package is acceptable and in compliance with guideline EMEA/HMPC/32116/05.

In view of the absence of results of genotoxicity testing the applicant has provided assurance that results will be provided before the renewal of the registration.

The overview submitted in support of this application is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

The SmPC for this product is satisfactory from a non-clinical point of view.

ENVIRONMENTAL RISK ASSESSMENT

An environmental risk assessment is not required for herbal medicinal products according to guidance CPMP/SWP/4447/00.

CONCLUSION

There are no objections to granting of a Traditional Herbal Registration Certificate from a non-clinical point of view.

CLINICAL ASSESSMENT

PROPOSED INDICATION

The applicant has proposed the following:

“A traditional herbal medicinal product used for the temporary relief of sleep disturbances based on traditional use only.”

The indication is acceptable.

POSOLOGY AND METHOD OF ADMINISTRATION

The applicant has proposed the following:

“For oral use.

Adults and the elderly: Swallow 4 tablets 30-60 minutes before bedtime. If necessary, on subsequent evenings, swallow 4 additional tablets earlier during the evening.

As treatment effects may not be apparent immediately, Kalms Night should be taken for 2-4 weeks continuously.

Duration of use:

If symptoms worsen or do not improve after 4 weeks, a doctor or qualified healthcare practitioner should be consulted.

The use in children or adolescents under 18 years of age is not recommended (see Section 4.4. Special warnings and precautions of use).”

This is acceptable.

EFFICACY

No clinical efficacy data is required for registration of Traditional Herbal Medicinal Products.

EVIDENCE OF TRADITIONAL USE

Article 16 c 1 (c) 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 EU.

The applicant has provided a bibliographic review as evidence for the use of Valerian root within the EU for a period exceeding 30 years. In addition, the Committee on Herbal Medicinal Products (HMPC) assessment report and community monograph for Valerian root adequately cover the evidence for traditional use of the herbal preparation in the product under assessment in the EU for at least 30 years. The requirements of the Directive are, therefore, considered to be met.

SAFETY REVIEW

Article 16 c 1 (d) requires the applicant to provide a bibliographic review of the safety

data together with an Expert Safety Report.

The safety review and Expert Safety Report are satisfactory and the Expert Safety Report is written by a suitably qualified professional. In addition, the HMPC assessment report for Valerian root covers the bibliographic safety data available.

PRODUCT LITERATURE

The product literature (Summary of Product Characteristics, Patient Information Leaflet and labelling) for this product is medically satisfactory.

CONCLUSION

There are no objections to granting of a Traditional Herbal Registration Certificate from a clinical point of view.

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The quality data submitted with this application are satisfactory.

NON-CLINICAL

No new non-clinical data were submitted with this application. However, assurance was provided that the results of genotoxicity testing will be provided before renewal of this registration. This is satisfactory.

EFFICACY AND SAFETY

No clinical efficacy data are required for registration of Traditional Herbal Medicinal Products.

The applicant has provided a bibliographic review which shows ample evidence for the use of Valerian root within the EU for a period exceeding 30 years and a satisfactory review of the safety data has been provided.

Furthermore, the HMPC assessment report and monograph for Valerian root adequately cover the evidence for traditional use of the extract in the product under assessment for at least 30 years and the safety issues associated with Valerian root.

The SmPC, PIL and labelling are satisfactory.

RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The risk: benefit balance is acceptable and a Traditional Herbal Registration Certificate may be granted.

KALMS NIGHT

THR 01074/0229

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Traditional Herbal Registration application on 26 July 2012
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 2 August 2012
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 31 October 2012 and the quality dossier on 12 December 2012
- 4 The applicant responded to the MHRA's requests, providing further information on the dossier on 6 February 2013
- 5 Following assessment of the response the MHRA requested further information relating to the quality dossier on 18 March 2013
- 6 The applicant responded to the MHRA's requests, providing further information on the quality dossier on 15 July 2013
- 7 A THR was granted on 15 July 2013

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Kalms Night

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 96mg of extract (as dry extract) from Valerian root (*Valeriana officinalis* L.)(equivalent to 384 – 480mg of Valerian root)

Extraction solvent: Ethanol 60% V/V

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet

White, circular

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A traditional herbal medicinal product used for the temporary relief of sleep disturbances based on traditional use only.

4.2 Posology and method of administration

For oral use.

Adults and the elderly: Swallow 4 tablets 30-60 minutes before bedtime. If necessary, on subsequent evenings, swallow 4 additional tablets earlier during the evening.

As treatment effects may not be apparent immediately, Kalms Night should be taken for 2-4 weeks continuously.

Duration of use:

If symptoms worsen or do not improve after 4 weeks, a doctor or qualified healthcare practitioner should be consulted.

The use in children or adolescents under 18 years of age is not recommended (see Section 4.4. Special warnings and precautions of use).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Do not exceed stated dose

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

If symptoms persist or worsen after 4 weeks of using the medicinal product, a doctor or qualified healthcare practitioner should be consulted.

4.5 Interaction with other medicinal products and other forms of interaction

Only limited data on pharmacological interactions with other medicinal products are available. Clinically relevant interactions with drugs metabolised by the CYP 2D6, CYP 3A4/5, CYP 1A2 or CYP 2E1 pathway have not been observed.

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

The effect of Kalms Night may be potentiated by alcohol. Excessive concomitant consumption of alcohol should therefore be avoided.

4.6 Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established. As a precautionary measure, because of lack of data, use during pregnancy and lactation is not recommended.

Studies on the effects on fertility have not been performed.

4.7 Effects on ability to drive and use machines

May impair ability to drive and use machines. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Gastrointestinal symptoms (e.g. nausea, abdominal cramps) may occur. The frequency is not known.

If other adverse reactions not mentioned above occur, a doctor or qualified healthcare practitioner should be consulted.

4.9 Overdose

Valerian root at a dose of approximately 20 g (equivalent to 42 to 51 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not required as per Article 16 c (1) (a) (iii) of Directive 2001/83/EC as amended.

5.2 Pharmacokinetic properties

Not required as per Article 16 c (1) (a) (iii) of Directive 2001/83/EC as amended.

5.3 Preclinical safety data

Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Extract excipients

Maltodextrin

Colloidal anhydrous silica

Tablet Core

Croscarmellose Sodium

Magnesium Stearate

Prosolv SMCC50 (Silicified Microcrystalline Cellulose)

Talc

Silicon Dioxide

Tablet Coating

Opadry TM White 07F28588 (Hypromellose, Titanium Dioxide, Polyethylene Glycol (PEG) 3350, Saccharin Sodium)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25°C.

Store in the original package.

6.5 Nature and contents of container

50, 100 or 200 tablets stored in amber glass or white HDPE bottles with white HDPE tamper-evident caps.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

G. R. Lane Health Products Limited

Sisson Road

Gloucester

GL2 0GR
United Kingdom
Tel: +44 (0)1452 524012
Fax: +44 (0)1452 507930
Email: info@laneshealth.com

8 MARKETING AUTHORISATION NUMBER(S)
THR 01074/0229

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**
15/07/2013

10 DATE OF REVISION OF THE TEXT
15/07/2013

PRODUCT INFORMATION LEAFLET

5. How to store Kalms Night

Keep out of the reach and sight of children.

Do not take Kalms Night after the expiry date which is stated on the packaging.

Do not store above 25°C.

Store in the original package.

6. Further Information

What Kalms Night contains

The active substance per tablet is:

Dry extract from Valerian root..... 96 mg
(*Valeriana officinalis* L.) (equivalent to 384 - 480mg of Valerian root) Extraction solvent: Ethanol 60%v/v
Excipients: Maltodextrin, Colloidal Anhydrous Silica.

The other ingredients are:

Core: Croscarmellose Sodium, Magnesium Stearate, Silicified Microcrystalline Cellulose, Talc and Silicon Dioxide.

Coating: Hypromellose, Talc, Titanium Dioxide, Macrogol, Saccharine Sodium.

What Kalms Night looks like and contents of the pack

Kalms Night tablets are white circular film coated tablets. They are available in bottles containing 50, 100 and 200 tablets. Not all pack sizes may be marketed.

Traditional Herbal Registration holder and Manufacturer

G. R. Lane Health Products Limited,
Sisson Road, Gloucester; GL2 0GR,
United Kingdom.
Tel: +44 (0) 1452 524012
Email: kalmsnight@laneshealth.com



This leaflet was last revised June 2013

613030 THR 01074/0229

Kalms Night

Valerian Root Extract 96 mg

For a large print, Braille or audio version of this leaflet please telephone 01 452 524012

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription. However you still need to take Kalms Night carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after 4 weeks.
- If any of the side effects become serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Kalms Night is and what it is used for
2. Before you take Kalms Night
3. How to take Kalms Night
4. Possible side effects
5. How to store Kalms Night
6. Further information

1. What Kalms Night is and what it is used for

Kalms Night is a traditional herbal medicinal product containing valerian root extract, used for the temporary relief of sleep disturbances, based on traditional use only.

2. Before you take Kalms Night

Do not take Kalms Night if you:

- are allergic to any of the ingredients (see Section 6 for a complete list of ingredients).

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including:

- medicines which make you drowsy
- medicines obtained without a prescription.

Taking Kalms Night with food and drink

Alcohol may increase the sedative effect of Kalms Night. Therefore, excessive alcohol consumption should be avoided whilst you are taking Kalms Night.

Pregnancy and breast-feeding

Kalms Night is not recommended for use during pregnancy or when breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Kalms Night is designed to make you feel sleepy. This could affect your ability to drive or operate machinery. If affected:

- do not drive because Kalms Night could stop you driving safely
- do not operate any tools or machinery.

3. How to take Kalms Night

Swallow 4 tablets 30 to 60 minutes before bedtime. If necessary, on subsequent evenings, swallow 4 additional tablets earlier during the evening.

Not recommended for anyone under 18 years old.

As the effects of this product may not occur immediately, the tablets should be taken continuously for 2-4 weeks.

If you take more Kalms Night than you should

Seek medical advice in the event of an overdose.

If you forget to take Kalms Night

Do not take a double dose to make up for a missed dose.

4. Possible side effects

Like all medicines, Kalms Night can cause side effects, although not everybody gets them.

Tell your doctor if you notice any of the following mild side effects:

- nausea
- abdominal cramps.

If any of the side effects become serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or pharmacist.

You can help to make medicines safer by reporting any side-effects to the Yellow Card Scheme at www.mhra.gov.uk/yellowcard. Alternatively you can get a paper Yellow Card form from your surgery or pharmacy, or call freephone 0808 100 3352 (available 10am-2pm Monday – Friday).

LABELLING

Label:

<p>Directions: Swallow 4 tablets 30-60 minutes before bedtime. If necessary, on subsequent evenings, swallow 4 additional tablets earlier during the evening. Not recommended for anyone under 18 years old. Do not take if you are allergic to any of the ingredients. Do not take if you are taking any other medicine for sleep. Kalm's Night is not recommended for use during pregnancy or when breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine. You must contact a doctor if symptoms worsen or do not improve after 4 weeks. Kalm's Night is designed to make you feel sleepy. This could affect your ability to drive or operate machinery. Alcohol may increase the sedative effect. Excessive alcohol consumption should be avoided. Keep out of the reach and sight of children. Do not store above 25°C. Do not use if cap seal is broken. Store in the original package. Read the package leaflet before use.</p>	 <p>Kalm's Night Valerian Root Extract 96mg A traditional herbal medicinal product used for the temporary relief of sleep disturbances, based on traditional use only.</p> <p>50 TABLETS</p>	<p>Active ingredient per film coated tablet: Dry extract from Valerian root (<i>Valeriana officinalis</i> L.) (equivalent to 384 - 480mg of Valerian root) Extraction solvent: Ethanol 60% v/v.....96 mg</p>  <p>Traditional Herbal Registration holder: G. R. Lane Health Products Ltd., Sisson Road, Gloucester, GL2 0GR, UK.</p> <p>612033 THR 01074/0229  Certification Mark</p> <p>Exp: BN:</p>
--	---	--

Carton:

