SleepEezy Valerian tablets

THR 33336/0006

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Natures Aid Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal product SleepEezy Valerian tablets (Traditional Herbal Registration number: THR 33336/0006). SleepEezy Valerian tablets are available without prescription and can be bought from pharmacies and other outlets.

The active ingredient in SleepEezy Valerian tablets comes from the roots of the Valerian plant, which is also known as *Valeriana officinalis* L. Valerian root is a traditional herbal medicinal product used for the temporary relief of sleep disturbances due to symptoms of mild anxiety.

This registration is based exclusively upon the longstanding 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 a 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.
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The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal medicinal product SleepEezy Valerian tablets on 12 January 2012. 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. SleepEezy Valerian tablets is a traditional herbal medicinal product used for the temporary relief of sleep disturbances due to symptoms of mild anxiety 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
The plant is cultivated in Ukraine, Bulgaria, Poland, France, the Netherlands, Germany and Hungary. The roots are collected from autumn to winter and are harvested manually or mechanically, cut, washed and oven-dried before being stored.

The supplier of the Valerian root 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 plant material is not treated with chemicals or irradiation following harvesting.

Control of Herbal Substance
The specifications for the herbal substance are in line with the Ph Eur monograph for Valerian root and are satisfactory.

Container Closure System
Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability
Confirmation is given that the herbal substance will be tested prior to being used to make the herbal preparation. A shelf-life for the herbal substance is not necessary because it is only a precursor of the active substance, the herbal preparation. The actual guideline requires stability testing data for the herbal preparation and the herbal product in the application documents and not for the herbal substance.

HERBAL PREPARATION: VALERIAN ROOT DRY EXTRACT

Extract solvent: Ethanol 70%v/v
Drug extract ratio (native): 5-6:1

Manufacture
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 specifications.

Container Closure System
Satisfactory details of the container closure system are provided and confirmation has been given that all components of the container closure system comply with current legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

Stability
Stability studies have been carried out under ICH conditions. The results support the proposed retest period of the herbal preparation.

HERBAL PRODUCT: SLEEPEEZY VALERIAN TABLETS

Description and Composition of the Herbal Product
SleepEezy Valerian tablets are brown, circular, convex, film-coated tablets containing 150 mg of dry extract from Valerian root. The tablets also contain the excipients maltodextrin and silica colloidal anhydrous (from the herbal preparation), calcium hydrogen phosphate anhydrous, cellulose microcrystalline, silica colloidal hydrated, croscarmellose sodium and magnesium stearate (which form the tablet core) and croscarmellose sodium, lecithin, dextrose monohydrate (glucose), sodium citrate and dextrin (which form the tablet coating).

The compatibility of the herbal preparation with the excipients is demonstrated by the stability testing results. The excipients are controlled in line with their respective Ph Eur monograph and representative Certificates of Analysis are provided to demonstrate full compliance with the Ph Eur.

The magnesium stearate used in the product is confirmed to be of vegetable origin.

Manufacture
A description and flow-chart of the manufacturing method has been provided. The manufacturing procedure is a standard procedure and is satisfactory for the product.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on production scale batches and the results are satisfactory.

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 come in Ph Eur type III glass bottles with a polypropylene closure incorporating an induction heat seal liner. The tablets may be available in packs of 30, 60 or 90, 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 legislation relating to plastic materials and articles intended to come into contact with foodstuffs.

**Stability**
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 chemist with suitable experience.

**Product Literature**
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**
The applicant has submitted a literature review with this application. 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.

The overview submitted in support of this application is satisfactory.

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 this active ingredient 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.

**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 from a non-clinical point of view.
CLINICAL ASSESSMENT

INDICATION
The applicant has proposed the following indication:

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

This indication is acceptable.

POSOLOGY AND METHOD OF ADMINISTRATION
The applicant has submitted the following:

“For oral use only.
Adults and the elderly: take 1 – 2 tablets half an hour before bedtime. If necessary, an additional tablet can be taken earlier in the evening.
Not for children or adolescents under 18 years (see Section 4.4 Special warnings and precautions for use).
As treatment effects may not be apparent immediately, the tablets should be taken continuously for 2 – 4 weeks.
Duration of use:
If symptoms worsen or do not improve after 4 weeks a doctor or qualified healthcare practitioner should be consulted.”

This is acceptable.

EFFICACY
No clinical efficacy data are 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 showing 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 European Community.

The applicant has provided a bibliographic review as evidence for the use of Valerian root within the European Community for a period exceeding 30 years. In addition, the published Committee on Herbal Medicinal Products (HMPC) assessment report and community monograph for Valerian root adopted by the HMPC adequately cover the evidence for traditional use of the herbal preparation in the product under assessment in the European Community for at least 30 years. The requirements of the Directive are 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. The SmPC is in line with the HMPC monograph.

PRODUCT LITERATURE
The SmPC, PIL and labelling for this product are medically satisfactory.

RECOMMENDATION
A Traditional Herbal Registration may be granted.
OVERALL CONCLUSION AND 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 provides ample evidence of the use of Valerian root within the European Community for a period exceeding 30 years and a satisfactory review of the safety data has been provided.

Furthermore, the published assessment report and monograph for Valerian root adopted by the HMPC 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.

BENEFIT-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 may be granted.
SLEEPEEZY VALERIAN TABLETS

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STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the Traditional Herbal Registration application on 8 February 2011
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 22 February 2011
3. Following assessment of the application the MHRA requested further information relating to the clinical dossier on 29 July 2011
4. The applicant responded to the MHRA’s request, providing further information on the clinical dossier on 10 August 2011
5. Following assessment of the application the MHRA requested further information relating to the quality dossier on 25 August 2011
6. The applicant responded to the MHRA’s request, providing further information on the quality dossier on 24 October 2011
7. Following assessment of the response the MHRA requested further information relating to the quality dossier on 23 November 2011
8. The applicant responded to the MHRA’s request, providing further information on the clinical dossier on 19 December 2011
9. A THR was granted on 12 January 2012
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
SleepEezy Valerian tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One tablet contains 150mg of extract (as dry extract) from Valerian root
(Valeriana officinalis L). Equivalent to 750mg - 900mg of Valerian root.)

Extraction solvent: ethanol 70%v/v.
DER (native) 5-6:1

Each tablet contains dextrose (glucose) 1.8mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet, film-coated.
A brown circular convex coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
A traditional herbal medicinal product used for the temporary relief of sleep
disturbances due to symptoms of mild anxiety based on traditional use only.

4.2 Posology and method of administration
For oral use only.
Adults and the elderly: take 1 – 2 tablets half an hour before bedtime. If
necessary, an additional tablet can be taken earlier in the evening.
Not for children or adolescents under 18 years (see Section 4.4 Special
warnings and precautions for use).
As treatment effects may not be apparent immediately, the tablets should be
taken continuously for 2 – 4 weeks.
Duration of use:
If symptoms worsen or do not improve after 4 weeks a doctor or qualified
healthcare practitioner should be consulted.

4.3 Contraindications
Hypersensitivity to Valerian or any of the excipients.

4.4 Special warnings and precautions for use
Do not exceed the stated dose.
The use of this product is not recommended in children and adolescents below
the age of 18 years because data are not sufficient and medical advice should
be sought.
If symptoms worsen, or do not improve after 4 weeks, a doctor or qualified healthcare practitioner should be consulted.

Each tablet contains dextrose (glucose) 1.8mg (see section 6.1); Patients with rare hereditary problems of glucose-galactose malabsorption should not take this medicine.

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 this product may be potentiated by alcohol. Excessive concomitant consumption of alcohol should therefore be avoided.

4.6 **Fertility, pregnancy and lactation**

The safety of the product during pregnancy has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended.

Studies on the effect on fertility have not been performed.

4.7 **Effects on ability to drive and use machines**

May impair the ability to drive and use machines. 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 20g (equivalent to 22 – 27 tablets) caused benign symptoms (fatigue, abdominal cramp, chest tightness, light-headedness, 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 10g of the drug) withdrawal symptoms (delirium) have been reported.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

Not required as per Article 16c (1) (a) (iii) of Directive 2001/83/EC as amended.
5.2 Pharmacokinetic properties
Not required as per Article 16c (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
- Maltodextrin
- Silica colloidal anhydrous
- Tablet core
- Calcium hydrogen phosphate anhydrous
- Cellulose microcrystalline
- Silica colloidal hydrated
- Croscarmellose sodium
- Magnesium stearate
- Tablet coating
- Croscarmellose sodium
- Lecithin
- Dextrose monohydrate (glucose)
- Sodium citrate
- Dextrin

6.2 Incompatibilities
Not applicable

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C
Store in the original package.

6.5 Nature and contents of container
Ph Eur type III glass bottles with polypropylene closure incorporating an induction heat seal liner. Printed outer carton containing Patient Information Leaflet.
Pack sizes: 30, 60, 90 tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Natures Aid Ltd
St Georges Park
Kirkham
Preston
Lancashire PR4 2DQ
Tel: 01772 686231
Fax: 01772 671688
email: sales@naturesaid.co.uk

8 MARKETING AUTHORISATION NUMBER(S)
THR 33336/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
12/01/2012

10 DATE OF REVISION OF THE TEXT
12/01/2012
PATIENT INFORMATION LEAFLET

SleepEezy®
Valerian tablets
Valerian root extract 150mg

Read all of this leaflet because it contains important information for you.
This medicine is available without prescription. However, you still need to use this product carefully to get the best results from it.
Keep this leaflet. You may need to read it again.
Ask your doctor, pharmacist, or qualified healthcare practitioner if you need more information or advice.
You must contact a doctor if your symptoms worsen, or do not improve after four weeks.
If any side effect gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

In this leaflet:
1. What the product is and what it is used for.
2. Before you take this product.
3. How to take this product.
4. Possible side effects.
5. How to store this product.
6. Further information.

1. WHAT THE PRODUCT IS AND WHAT IT IS USED FOR

This product is a traditional herbal medicinal product used for the temporary relief of sleep disturbances due to symptoms of mild anxiety based on traditional use only.
Each film-coated tablet contains 150mg of extract (as dry extract) from Valerian (Valeriana officinalis L) root, equivalent to 750 – 900mg of Valerian root.
Extraction solvent: ethanol 70% v/v

2. BEFORE YOU TAKE THIS PRODUCT

This product is not suitable for patients under 18 years of age.
Do not take this product if:
• you are allergic to Valerian or any of the other ingredients (see section 6 for more information)

Take special care with this product:
○ Do not exceed the recommended dose.
○ The effect of this product may be increased by alcohol. Excessive use of alcohol should be avoided.
○ This product contains glucose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product.

Taking other medicines.
Do not take this product if you are already taking a medicine for sleep or anxiety.

Pregnancy and breast-feeding.
Do not take this product if you are pregnant of breastfeeding, because there is no evidence that it is safe to do so.

Driving and using machines.
This product may cause drowsiness. If you are affected, do not drive or operate machines.
3. **HOW TO TAKE THIS PRODUCT**

**Adults and the elderly:** swallow one to two tablets half an hour before bedtime. If necessary, an additional tablet can be taken earlier in the evening.

The effects of this product may not occur immediately. The tablets should therefore be taken continuously for 2 - 4 weeks.

**Do not** take if you are under 18 years of age.

Do not exceed stated dose.

**If you take too much of this product (overdose).**
If you take more than the recommended dose, speak to a doctor, pharmacist or qualified healthcare practitioner. Take this leaflet with you.

**If you forget to take this product.**
Do not take a double dose to make up for a forgotten dose. Take the next dose when it becomes due.

**If you stop taking this product.**
There are no reported adverse effects associated with stopping this product, but if you feel unwell talk to your doctor or qualified healthcare practitioner.

4. **POSSIBLE SIDE EFFECTS**

Like all medicines, this product can cause side effects, although not everybody gets them. The frequency of side effects is not known. Possible, minor, side effects include:

- abdominal cramps
- nausea

If you find these effects troublesome, stop using the product. Speak to your doctor or pharmacist if you are at all concerned, if a side effect becomes serious, or you notice an effect not mentioned in this leaflet.

5. **HOW TO STORE THIS PRODUCT**

Keep out of the reach and sight of children.

Do not store the tablets in a place where the temperature goes above 25°C. Store in the original packaging.

Do not use this product after the expiry date which is stated on the side of the label after EXP. The expiry date refers to the last day of that month.

Do not use this product if you notice any discoloring or softening of the tablets, as this means they may have deteriorated.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. **FURTHER INFORMATION**

Each tablet contains 150mg of dry ethanolic extract equivalent to 750 – 900mg of Valerian root.

It also contains other, non-active, ingredients. These ingredients are: calcium hydrogen phosphate; microcrystalline cellulose; colloidal silicon dioxide; croscarmellose sodium; magnesium stearate; lecithin; dextrose monohydrate; sodium citrate; dextrin.

The product is available in packs of 30, 60 and 90 tablets (not all sizes may be marketed).

Registration number: THR 33336/0006

Traditional Herbal Registration Holder and Manufacturer:
Natures Aid Ltd., St Georges Park, Preston, Lancs, PR4 2DQ.
Tel 01772 686231; Fax 01772 681088; Email: sales@naturesaid.co.uk

You can also 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 from your GP’s surgery or pharmacy, or call free phone 0808 100 3352 (available 10am – 2pm Monday – Friday).

This leaflet was last revised on 01/09/2011

For a large print, braille or audio version of this leaflet please call 01772 686231
LABELLING
Label:

Directions: Read package leaflet before use.

Dosage: For one use only.
Adults and the elderly, take 1-2 tablets half an hour before bedtime. If necessary, an additional tablet can be taken earlier in the evening. Take continuously for 2–4 weeks.

Warning: Do not exceed the stated dose.
Do not use if you are allergic to Valerian, or any of the other ingredients.
Not suitable for children and adolescents under 18 years of age.
Do not take if you are taking other medication for sleep or anxiety.

SleepEezy® may make you drowsy. If affected do not drive or operate machinery.
The effects of SleepEezy® may be increased by alcohol.
Excessive alcohol consumption should be avoided.
See your doctor if symptoms worsen, or do not improve after four weeks.

Active Ingredients:
Each film-coated tablet contains 150mg of extract (as dry extract) from Valerian root (Valeriana officinalis L.) equivalent to 750mg - 900mg of Valerian root.

Extraction Solvent:
Ethanol 70% v/v.
Also contains glucose.

Registration holder/manufacturer:
Natures Aid Ltd, 50 Georges Park, Preston, Lancs, PR4 2DO.
Tel: 01772 686231 Fax: 01772 671658
email: sales@naturesaid.co.uk

ThE 33336/0006; BNJEXP: See side of label.
Do not store above 25°C. Store in original packaging.
Keep out of reach and sight of children.
Carton: