

NITEHERB TABLETS

THR 23056/0006

UKPAR

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NITEHERB TABLETS

THR 23056/0006

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted M H Pharma (UK) Ltd a Traditional Herbal Registration Certificate for the traditional herbal medicinal product NiteHerb Tablets (Traditional Herbal Registration number: THR 23056/0006). This product is available without prescription and can be bought from pharmacies and other outlets.

The active ingredient of NiteHerb Tablets comes from the roots of the plant *Valeriana officinalis* L., also known as Valerian. Valerian is a traditional herbal medicine 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 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.

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal remedy NiteHerb Tablets to M H Pharma (UK) Ltd on 19 December 2007. This product is available without prescription and can be bought from pharmacies and other outlets.

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

PHARMACEUTICAL ASSESSMENT

INTRODUCTION

This is a national application submitted by M H Pharma (UK) Ltd, trading as Medic Herb, under the Traditional Herbal Medicines Registration Scheme.

Valerian products are currently widely available in the UK as herbal remedies exempt from licensing under Section 12(2) of the Medicines Act 1968. Valerian is used as an ingredient in a number licensed product; in six products as the sole active ingredient and in 70 combination products.

A General Sales List status has been granted to this product.

HERBAL SUBSTANCE: VALERIAN ROOT

General information

Scientific name of the plant: *Valeriana officinalis* L.
Family: Valerianaceae
Synonyms of the herbal substance: Valerian
Parts of the plant used: root

Manufacture

The plant source of the herbal substance Valerian root is *Valeriana officinalis* L., belonging to the Valerianaceae family. The plant is cultivated in Europe (Germany, Poland, Netherlands, Bulgaria). The roots are collected in late autumn. The roots are harvested mechanically, washed and dried before being stored protected from light, heat and moisture.

The supplier of the Valerian root has provided confirmation that the herbal substance is cultivated under GACP controlled conditions and that storage is in dry, well ventilated warehouses protected from pests. Chemical treatments during cultivation include herbicides and fertilisers. Assurance has been provided from the supplier of the Valerian root that fumigant treatments/irradiation have not been used.

Control of Herbal Substance

The specifications of the herbal substance are in line with the European Pharmacopoeia monograph and are satisfactory.

Certificates of analysis are presented for batches of the herbal drug giving full results for test parameters to support the proposed specification.

Container Closure System

A suitable container closure system is used to store the herbal substance. The primary packaging materials comply with Directive 2002/72/EC.

Stability

A confirmation is given that the herbal substance is tested prior to making the herbal preparation.

A shelf-life for the herbal drug based on real time stability data is not necessary because it is a precursor of the active substance, the herbal preparation.

HERBAL PREPARATION

General information

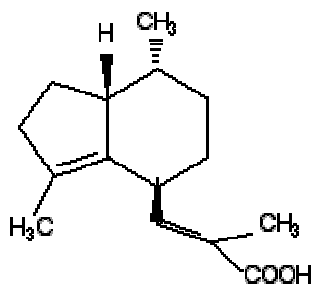
Herbal preparation: Valerian root dry extract

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

Parts of the plant used: dried roots

Extraction solvent: ethanol 70 % v/v

Valerenic acid



The dry extract preparation is a reddish brown powder with a characteristic odour.

Manufacture

Manufacture of the extract is a standard procedure. A satisfactory description of the manufacturing process of the herbal substance and flow diagram has been provided.

The in-process controls (IPC) and specifications are satisfactorily detailed. There are no critical steps identified as the manufacture of the herbal preparation is considered a standard procedure.

The dry extract is stored in tightly closed containers, protected from light, heat and moisture.

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

Control of herbal preparation

The specification for Valerian root dry extract is satisfactory.

Satisfactory details of the analytical methods are provided.

Certificates of analysis (CoA) are provided for batches of the dry extract to support the proposed specification.

Container Closure System

The extract is stored in an appropriate container closure system. Specifications have been provided by the supplier together with the declaration of compliance with Directive 90/128 EC, as amended. Assurances have been provided from the suppliers that the packs and their contents/labels etc are suitable for food use.

Stability

Stability studies have been carried out on batches of the herbal preparation under ICH conditions. The results support the proposed retest period for the dry extract of 24 months, when stored below 25°C and protected from heat, light and moisture.

HERBAL PRODUCT

Description and Composition of the Herbal Product

NiteHerb Tablets contain liquid glucose (spray dried), colloidal anhydrous silica, powdered cellulose, croscarmellose sodium, stearic acid, talc, sucrose, calcium carbonate E170, acacia, tragacanth, titanium dioxide E 171 and capol 600 T.S. (containing white beeswax, carnauba wax and shellac).

The choice of excipients is based on experience and compatibility of the chosen excipients with the drug substance is confirmed by stability testing. All excipients used comply with their respective European Pharmacopoeial monograph. The colouring agent, titanium dioxide E171, is stated to comply with Directive 95/45/EC. Certificates of analysis of the excipients have been provided by the suppliers. Water used in the manufacture of the finished product is purified water corresponding to the standards of the Ph Eur

The applicant has confirmed that the stearic acid used in this product is of vegetable origin. There are no excipients of animal or human origin in this product.

Manufacture

A description and flow-chart of the manufacturing method has been provided. The manufacturing method is a standard procedure for direct tableting, coating and blistering.

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

Finished product specification

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. Certificates of analysis have been provided for any working standards used.

Container Closure System

The tablets are presented in packs of 30 or 60 sealed into binary blisters made of PVC/PVDC and aluminium with 10 tablets each.

Suitable specifications have been provided by the packaging suppliers and it has been confirmed that all primary packaging materials comply with Directive 2002/72/EC.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a product shelf-life of 3 years is appropriate.

Pharmaceutical Expert

The Quality Overall Summary has been written by a pharmacist with extensive experience with herbal products.

Assessor's comments on the Summary of Product Characteristics, label and Patient Information Leaflet

All product literature is satisfactory.

The 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.

Assessor's overall conclusions on quality

The grant of a Traditional Herbal Registration is acceptable.

PRECLINICAL ASSESSMENT

PRECLINICAL SAFETY DATA

The Safety Expert Report submitted by the applicant lists relevant references to published work studying the acute toxicity, subacute toxicity and chronic toxicity of Valerian root.

NONCLINICAL OVERVIEW

The applicant has submitted an adequate literature review with this application. An Expert Safety Report was also provided, which included reviews of some nonclinical data. The Expert Safety Report was written by a pharmacist with suitable expertise in herbal medicines.

The Nonclinical Overview contains a short review of the nonclinical data for Valerian. Some of the studies in the literature review were conducted and published before GLP was a regulatory requirement. Moreover, it is not possible to ascertain if the data assessed in the review would comply with today's regulatory safety testing requirements with regards to design, conduct and analysis.

Due to a shortage of published data on Valerian it is not possible to assess if the safety package for the phytochemical constituents of Valerian meets current standards of 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/32116/0.

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

The Summary of Product Characteristics for this product is satisfactory.

ENVIRONMENTAL RISK ASSESSMENT

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

CONCLUSION

The information supplied demonstrating traditional use of Valerian is acceptable. An adequate literature review for Valerian has been carried out by the applicant and no new nonclinical data was submitted for assessment with this application. Granting of a THR is acceptable.

CLINICAL ASSESSMENT

LEGAL STATUS

General Sales List status is requested for the product. Valerian is currently on the GSL Order so this is acceptable.

PROPOSED 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.”

Assessor’s comment: This indication is satisfactory.

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 Community.

The Applicant has provided a bibliographic review which shows evidence for the use of *Valeriana officinalis* within the EU for a period exceeding 30 years.

SAFETY REVIEW

Article 16 c 1 (d) requires the Applicant to provide bibliographic review of the available safety data together with an expert report.

The Applicant has provided satisfactory information supporting the safety of valerian root.

SUMMARY OF PRODUCT CHARACTERISTICS

The SPC for this product is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL for this product is satisfactory.

LABELLING

All product labelling is satisfactory.

RECOMMENDATIONS

A Traditional Registration may be granted.

OVERALL CONCLUSION AND RISK ASSESSMENT

QUALITY

The quality data submitted with this application are satisfactory.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY

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

The Applicant has provided a bibliographic review which shows ample evidence for the use of Valerian within the EU for a period exceeding 30 years.

A satisfactory review of the safety data has also been provided.

The SPC, PIL and labelling are satisfactory.

RISK ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

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STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the Traditional Herbal Registration application on 31 May 2006
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 28 December 2006
- 4 Following assessment of the application the MHRA requested further information relating to the quality dossier on 2 May 2007 and the clinical dossier on 10 May 2007
- 5 The applicant responded to the MHRA's requests, providing further information on the dossier on 14 December 2007
- 6 A THR was granted on 19 December 2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

NiteHerb® Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains:

150 mg of extract (as dry extract) from Valerian root (*Valeriana officinalis* L.)(equivalent to 450-900 mg of Valerian root).

Extraction solvent: Ethanol 70% v/v.

One coated tablet contains 35 mg of glucose and 136 mg of sucrose.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Coated tablet.

White, glossy, round, biconvex.

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 short term use only.

For adults and the elderly take 1 to 2 tablets half an hour before bedtime. If necessary, an additional tablet can be taken earlier in the evening. The tablets should not be chewed.

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

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

Not for children or adolescents under 18 years.

4.3 Contraindications

Hypersensitivity to Valerian or any of the constituents in this product

The product should not be used in children or adolescents under 18 years of age.

4.4 Special warnings and precautions for use

This product contains glucose.

1 coated tablet contains max. 35mg of glucose.

This product contains sucrose.

1 coated tablet contains max. 136mg of sucrose or 0,21 carbohydrate units.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase

deficiency or 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. Additive effects with hypnotics and other sedative drugs cannot be excluded and therefore co-medication is not recommended as a general precaution.
The effect of Valerian may be potentiated by alcohol. Excessive concomitant consumption of alcohol should therefore be avoided.
- 4.6 Pregnancy and lactation**
Safety during pregnancy and lactation has not been established. Due to the lack of data, use during pregnancy and lactation is not recommended.
- 4.7 Effects on ability to drive and use machines**
May impair the ability to drive and use machines. If affected, patients should not drive or operate machinery.
- 4.8 Undesirable effects**
Gastrointestinal symptoms, such as 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 10 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 30 g of the drug) withdrawal symptoms (delirium) have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Not applicable

5.2 Pharmacokinetic properties

Not applicable

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid glucose, spray dried

Silica, colloidal anhydrous

Cellulose, powdered

Croscarmellose sodium

Stearic acid

Talc

Sucrose

Calcium carbonate E170

Acacia

Tragacanth

Titanium dioxide E 171

Capol 600 T.S. containing:

Beeswax, white

Carnauba wax

Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Original packages contain 30 or 60 coated tablets

NiteHerb tablets are packed in PVC/ PVDC- aluminium blisters and inserted into a carton.

6.6 Special precautions for disposal

No special requirements

7 REGISTRATION HOLDER

M H Pharma (UK) Ltd

t/a MedicHerb

PO Box 2835

Brewery Courtyard

Draymans Lane

Marlow

Buckinghamshire

SL7 2XG

8 REGISTRATION NUMBER

THR 23056/0006

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**
19/12/2007

10 DATE OF REVISION OF THE TEXT
19/12/2007

PATIENT INFORMATION LEAFLET

Valerian root extract 150mg

Please read this leaflet carefully before you start taking these tablets.
It contains some important information about NiteHerb.

Keep this leaflet with the tablets.
You may want to read it again or show it to your doctor, pharmacist or healthcare practitioner.

What is in this leaflet

| | |
|--|--------|
| 1: What this product is and what it is used for..... | page 1 |
| 2: Before you take this product | page 2 |
| 3: How to take this product | page 2 |
| 4: Side-effects | page 3 |
| 5: After taking this product | page 3 |
| 6: Product description | page 4 |

1: What this product is and what it is used for

This product is a traditional herbal medicinal product containing Valerian root. Each coated tablet of this product contains 150mg of extract (as dry extract) from Valerian root (*Valeriana officinalis* L.) (equivalent to 450-900mg of Valerian root. Extraction solvent: ethanol 70%v/v.

1

NiteHerb is a traditional herbal medicinal product used for the temporary relief of sleep disturbances due to symptoms of mild anxiety. This usage is based on traditional use only.

2: Before you take this product

DO NOT TAKE this product if you are:

- pregnant or breastfeeding
- allergic to any of the ingredients (see section 6)
- under 18 years of age
- already taking a medicine which makes you drowsy

Tell your doctor before taking this product if you have an intolerance to some sugars (see section 6)

The effects of this product may be increased by alcohol. Excessive use of alcohol should therefore be avoided.

3: How to take this product

Adults and the elderly

Take 1 to 2 tablets half an hour before bedtime. If necessary, an additional tablet can be taken earlier in the evening. Swallow the tablets whole with some water or other liquid. Do not chew the tablets.

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

Do not exceed the 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 healthcare practitioner and take this leaflet with you.

If you forget to take this product

Continue to take your usual dose at the usual time; it does not matter if you have missed a dose.

2

If you have any questions, or are unsure about anything, please ask your doctor, pharmacist or healthcare practitioner.

4: Side-effects

Like all medicines, this product can have side-effects. These are listed below.

| Side-effects | |
|---|---|
| <ul style="list-style-type: none">● abdominal cramps● nausea | If these persist for more than a few days, or become troublesome, stop taking this product. |
| Other side-effects | |
| Tell your doctor or pharmacist if you notice any other side-effect. | |
| This product may cause drowsiness. If you are affected do not drive or operate machines. | |

5: After taking this product

You must speak to a healthcare practitioner if your symptoms worsen, if they do not improve after four weeks, or if side-effects not mentioned in this leaflet occur.

Do not use your tablets after the expiry date.

Return any out-of-date tablets to your pharmacist who will dispose of them for you. The expiry date is printed on the box and the blister pack.

Store the tablets in a cool dry place below 25°C.

Keep the tablets out of the reach and sight of children.

Keep your tablets in the blister pack until it is time to take them.

3

6: Product description

Each coated tablet of this product contains 150mg of extract (as dry extract) from Valerian root (*Valeriana officinalis* L.) (equivalent to 450-900mg of Valerian root. Extraction solvent: ethanol 70%v|v.

This product also contains the following ingredients:

Liquid glucose, silica colloidal anhydrous, cellulose powdered, croscarmellose sodium, stearic acid, talc, sucrose, calcium carbonate (E170), acacia, tragacanth, white beeswax, carnauba wax, shellac.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this product. Each tablet contains 35mg of glucose and 136mg of sucrose.

Each pack contains 30 or 60 coated tablets.

Registration holder for this product

M H Pharma (UK) Ltd, t/a MedicHerb,
PO Box 2835,
Brewery Courtyard, Draymans Lane,
Marlow, Bucks, SL7 2XG

Manufacturer of this product

Wiewelhove GmbH, Gildestrasse 39, 49477 Ibbenbüren, Germany

Traditional herbal registration number: THR 23056/0006

If you would like further information about this product, please contact:

M H Pharma (UK) Ltd,
PO Box 2835,
Marlow, Bucks SL7 2XG

Telephone: 01628 488487
Email: info@medicherb.co.uk

This leaflet was prepared in October 2007

For a large print, Braille or audio version of this leaflet, call 01628 488487

4

LABELLING

Blister:



Carton:



Batch No:
Expiry date:

Carton with Braille:



Batch No:
Expiry date: