# VALDRIAN Capsules

# THR 15817/0004

# UKPAR

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**VALDRIAN Capsules**

**THR 15817/0004**

## LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Bio-Health Limited a Traditional Herbal Registration certificate for the traditional herbal medicinal product VALDRIAN Capsules (Traditional Herbal Registration number: THR 15817/0004). This product is available without prescription and can be bought from pharmacies and other outlets.

The active ingredient of VALDRIAN Capsules comes from the roots of the valerian plant, which is also known as *Valeriana officinalis* L. Valerian root is a traditional herbal medicine used for the temporary relief of mild anxiety and to aid sleep. 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 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.

**VALDRIAN Capsules**

**THR 15817/0004**

## SCIENTIFIC DISCUSSION

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# INTRODUCTION

The MHRA granted a Traditional Herbal Registration Certificate for the traditional herbal remedy VALDRIAN Capsules (THR 15817/0004) to Bio-Health Limited on 11 July 2008. 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.

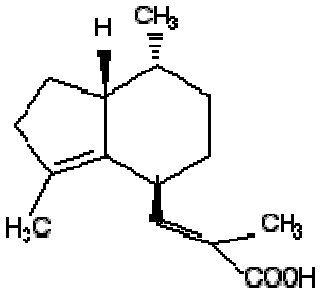
The data supplied by the applicant demonstrate 30 years of traditional use of Valerian (*Valeriana officinalis* L.) root in the European Community. A satisfactory review of the available safety data on valerian root has also been provided, together with an expert report supporting the proposed product.

## PHARMACEUTICAL ASSESSMENT

### HERBAL SUBSTANCE: VALERIAN ROOT

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

**Figure 1** Valerenic acid




**Manufacture**
The plant material is collected from the wild in accordance with Good Agricultural and Collection Practice (GACP) guidelines, without the use of pesticides and herbicides. The material is gathered in early autumn in dry weather during the non growing phase. The material is harvested in Eastern Europe, primarily in Poland.

The roots are harvested and air dried. The roots are stored at room temperature and are protected from direct sunlight.

Chemical treatments are not used on the wild collected plant material. Assurance is provided from the supplier that the valerian root has not been treated with fumigants (including ethylene oxide) or irradiation, or, in cases where fumigation does take place, carbon dioxide only is used.

**Control of Herbal Substance**
An appropriate specification based on the Ph Eur monograph for valerian root is used and is acceptable.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specification. The specification is supported by the batch data provided.

**Container Closure System**

Certification have been provided by the herbal substance manufacturer confirming that the primary and secondary packaging material used meets the requirements given by EU Guidelines 2007/19/EG, 2004/1/EG and 2005/79/EG.

**Stability**
No details are given as the herbal substance is not stored before encapsulation.

## HERBAL PRODUCT

### Description and Composition of the Herbal Product

The product consists simply of hypromellose, clear, size 0 capsules containing 400 mg powdered valerian root. There are no excipients.

The product has been manufactured by the applicant as a herbal remedy exempt from licensing under Section 12(2) since 1996. The product rationale, in keeping with herbal philosophy, is to administer a dose from the whole part of the plant with the minimum of processing.

### Control of Excipients

No excipients are used apart from the hypromellose capsule shells. The capsules are supplied by a reputable supplier.

### Manufacture

The manufacturing process is a standard procedure, which involves simply filling the powdered root into the capsules. A satisfactory flow diagram outlining the various stages of the manufacturing process and the in-process controls is provided.

A number of in-process control tests are performed during the manufacturing process to ensure the quality of the product. All are considered adequate.

### Control of Herbal Product

The finished product specification is detailed and the tests and limits applied were found to be satisfactory for a product of this nature.

Satisfactory details have been provided on all analytical procedures and these analytical procedures are valid.

Certificates of Analysis have been presented for batches of the drug product demonstrating little inter-batch variation.

### Reference Standards or Materials

Certificates of Analysis for the reference substance have been provided by the finished product manufacturer.

### Product literature

The product literature (Summary of Product Characteristics, Patient Information Leaflet and labelling) for this product are pharmaceutically 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.

### Container Closure System

The product is presented in a Duma 110ml HDPE plastic container and tamper evident threaded Duma cap containing 60 capsules.

Suitable specifications have been provided by the packaging suppliers and a declaration of compliance with the Directive for food contact has also been provided.

**Stability**
Stability studies were conducted under ICH conditions on product batches in the container proposed for marketing.

Based on the results, the proposed shelf life of 2 years with the storage precaution “Store below 25°C in the original package” is justified.

## ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY

This application is for a very simple product consisting of hard hypromellose capsules containing solely powdered valerian root. There are no pharmaceutical issues to be addressed with the herbal substance or the finished product.

The grant of a Traditional Herbal Registration is acceptable.

# NONCLINICAL ASSESSMENT

## 1 NONCLINICAL ASPECTS

The Expert Safety Report submitted by the applicant lists relevant references to published work studying the toxicology of valerian.

## 2 NONCLINCIAL OVERVIEW

The applicant has submitted a literature review with this application. An Expert Report on Safety was provided, which included reviews of some non-clinical data. The Expert Safety Report was written by a medically qualified expert.

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 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.

## 3 SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC for this product is satisfactory from a preclinical point of view.

## 4 ENVIRONMENTAL RISK ASSESSMENT

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

## 5 CONCLUSION

The information supplied demonstrates the traditional use of valerian root. An adequate literature review of valerian has been carried out by the applicant and no new non-clinical data was submitted for assessment with this application. Granting of a THR is acceptable.

# CLINICAL ASSESSMENT

## BACKROUND INFORMATION

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 currently used as an ingredient in a number of licensed products.

## LEGAL STATUS

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

## PROPOSED INDICATION

The applicant has proposed the following:

"VALDRIAN is a traditional herbal medicinal product used for the temporary relief of symptoms of mild anxiety and to aid sleep, based on traditional use only."

The indication is acceptable and in line with UK position on Valerian and, hence, recently granted THR 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 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.

***Assessor's comment:***

The use of Valerian root is in line with the adopted HMPC Community Monograph which refers to traditional use for 0.3g – 1.0 g root up to three times a day for mental stress, with an additional dose to aid sleep half an hour before bedtime.

The traditional use and the posology have been demonstrated.

## SAFETY REVIEW

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

***Assessor's comment***

A safety review has been presented. The HMPC assessment report for valerian root covers the bibliographic data available for valerian.

The safety of valerian has in principle been demonstrated. However, in line with the HMPC Community Monograph the applicant has committed to address the issue of valepotriates surviving in the root capsules.

### Product literature

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

**DISCUSSION**

This is an application for registration under the Traditional Herbal Medicinal Products Directive.

The data supplied by the Applicant are sufficient to demonstrate 30 years of traditional use within the European Community as required for registration under the Traditional Herbal Medicines Product Directive. A review of the available safety data relating to *Valeriana officinalis* is available in the HMPC Assessment Report on Valerian root.

**RECOMMENDATIONS**

A Traditional Registration may be granted.

## OVERALL CONCLUSION AND RISK ASSESSMENT

**QUALITY**
Bio-Health Ltd has over 25 years of experience in manufacturing herbal medicinal products. The quality data submitted with this application are satisfactory.

**PRECLINICAL**
No 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 root within the EU for a period exceeding 30 years.

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.

**VALDRIAN Capsules**

**THR 15817/0004**

## STEPS TAKEN FOR ASSESSMENT

| | |
|---|---|
| 1 | The MHRA received the Traditional Herbal Registration application on 14 January 2008 |
| 2 | Following standard checks and communication with the applicant the MHRA considered the application valid on 31 January 2008 |
| 3 | Following assessment of the application the MHRA requested further information relating to the clinical and the quality dossiers on 14 April 2008 |
| 4 | The applicant responded to the MHRA's requests, providing further information on the dossiers on 19 May 2008 |
| 5 | Following assessment of the response the MHRA requested further information relating to the quality dossier on 28 May 2008 |
| 6 | The applicant responded to the MHRA's requests, providing further information on the quality dossier on 3 June 2008 |
| 7 | A THR was granted on 11 July 2008 |

# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

VALDRIAN Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 400mg of Valerian root. *(Valeriana officinalis* L.*)*
For list of excipients see section 6.1.

## 3 PHARMACEUTICAL FORM

Hard capsules.
Clear size 0 hard capsules.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

VALDRIAN is a traditional herbal medicinal product used for the temporary relief of symptoms of mild anxiety and to aid sleep, based on traditional use only.

### 4.2 Posology and method of administration

For oral short term use only.
Adults and the elderly.
For the temporary relief of symptoms of mild anxiety take one capsule 3 times daily swallowed with water.
To aid sleep, take one capsule 30 minutes before bedtime with an earlier dose during the evening if necessary.
As treatment effects may not be apparent immediately, VALDRIAN should be taken 2-4 weeks continuously.
Maximum daily dose:- 4 single doses.
Duration of use:-
If symptoms persist, worsen or do not improve after 4 weeks during the use of VALDRIAN a doctor or a qualified
healthcare care practitioner should be consulted.
Not recommended for children or adolescents under 18 years.

### 4.3 Contraindications

Patients with known hypersensitivity to Valerian root should not use VALDRIAN.

### 4.4 Special warnings and precautions for use

The use of this product is not recommended in children and adolescents below the age of 18 years.

### 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

has not been observed. Additive effects with hypnotics and other sedatives cannot be excluded and therefore
comedication 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**

The safety of VALDRIAN 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**

VALDRIAN may impair ability to drive and use machines.
Patients who are affected should not drive or operate machinery.

**4.8 Undesirable effects**

Gastrointestinal symptoms (eg nausea, abdominal cramps) may occur after ingesting VALDRIAN (valerian root).
The frequency is not known. If other adverse reactions not mentioned above occur, a doctor or qualified health
care practitioner should be consulted.

**4.9 Overdose**

Valerian root at a dose of approximately 20g (equivalent to 50 VALDRIAN capsules) 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 30g of the drug) withdrawal symptoms (delirium) have been reported.

## 5 PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Hypnotics and sedatives, ATC Code: NO5C MO9
Not Applicable.

**5.2 Pharmacokinetic properties**

No data available.

**5.3 Preclinical safety data**

Extracts with ethanol and the essential oil of Valerian root have shown low toxicity in rodents during acute tests and
from repeated dose toxicity over periods of 4-8 weeks.
Test on reproductive toxicity, genotoxicity and carcinogenicity have not been performed.

## 6 PHARMACEUTICAL PARTICULARS

**6.1 List of excipients**
Hypromellose (capsule shell)

**6.2 Incompatibilities**
Not Applicable.

**6.3 Shelf life**
2 years.

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

**6.5 Nature and contents of container**
Duma 110ml HDPE plastic container and tamper evident threaded Duma cap.
VALDRIAN pack contains 60 Capsules.

**6.6 Special precautions for disposal**
There are no special precautions for disposal of VALDRIAN capsules. When the container is empty the label should be removed and the container placed in a recycling bin.

## 7 MARKETING AUTHORISATION HOLDER

Bio-Health Limited
Culpeper Close
Medway City Estate
Rochester
Kent
ME2 4HU

## 8 MARKETING AUTHORISATION NUMBER(S)

THR 15817/0004

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

11/07/2008

## 10 DATE OF REVISION OF THE TEXT

11/07/2008

**PATIENT INFORMATION LEAFLET**

User Information Leaflet

BIO-HEALTH®

# Valdrian®

**VALERIAN ROOT 400mg**
**60 CAPSULES**

**Please read this leaflet carefully before using Valdrian.**
**It contains important information about this medicine.**

**Keep this leaflet.** You may want to read it again. if you need more information or advice, please ask your doctor, pharmacist or qualified health care practitioner.

**What is in this leaflet**

## 1 What Valdrian is

Valdrian is a traditional herbal medicinal product.

## 2 What Valdrian is used for

Valdrian is a traditional herbal medicinal product used for the temporary relief of mild anxiety and to aid sleep, based on traditional use only.

## 3 Before you take Valdrian

Do not take if you:

- are allergic to the ingredient (see section 7).
- are pregnant or breastfeeding.
- are under 18 years of age.

Tell your doctor if you have an intolerance to any of the ingredients.

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

## 4 How to take Valdrian

Valdrian should be taken at the recommended dose until symptoms of anxiety and sleeplessness are relieved.

**Dosage**

Swallow the capsules whole with water. Do not chew the capsules.

**Adults and elderly:**

Take 1 capsule 3 times daily swallowed with water,
or to aid sleep take 1 capsule 30 minutes before bedtime, with an additional dose earlier in the evening if necessary.

**This product is not suitable for children or adolescents under 18 years old.**

**Do not exceed the recommended dose** unless told otherwise by your doctor, pharmacist or qualified health care practitioner.

**If you take too much Valdrian (overdose)**
If you take more than the recommended dose, see a doctor, pharmacist or qualified health care practitioner and take this leaflet with you.

**If you are unsure about anything relating to Valdrian**
If you have any questions, or are unsure about anything, please ask your doctor, pharmacist or qualified health care practitioner.

## 5 Side effects

There are no known side effects from taking Valdrian as instructed in this leaflet. However, if you notice any side effects after taking Valdrian, please inform your **doctor** or **pharmacist**.

Nausea or abdominal cramp has been known to occur from taking Valerian root preparations such as Valdrian.

This product may cause drowsiness. If you are affected do not drive or operate machines.

## 6 Further information on using and storing Valdrian

If your mild symptoms of mild anxiety and sleeplessness persists for more than four weeks after using this product, tell your doctor.

**Do not use the capsules after the expiry date.**
The expiry date is printed on the pot label. Return any unused capsules to your pharmacist who will dispose of them for you.

**Store below 25°C in the original package.**

**Keep all medicines out of sight and reach of children.**

Manufacturer and Traditional Herbal Registration Holder:

**Bio-Health Ltd.**
Culpeper Close,
Medway City Estate,
Rochester,
Kent ME2 4HU.

**Traditional Herbal Registration number:**
THR 15817/0004

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## 7 Product Description

**Each hard capsule of Valdrian contains the following active herbal ingredient:**

Valerian root 400mg (*Valeriana officinalis* L.).
There are no other ingredients in Valdrian.

The capsule shell is made from hypromellose.

**Each pot of Valdrian contains 60 capsules.**

This leaflet was produced in May 2008.

# LABELLING

Expiry Date:

Lot No:

**Valdrian**
60 capsules
ID No. VAL.001

BIO-HEALTH

# Valdrian®

**VALERIAN ROOT 400mg**
**60 CAPSULES**

Traditional herbal medicinal product for the temporary relief of symptoms of mild anxiety and to aid sleep, based on traditional use only.

**Do not purchase if seal is broken.**
**Keep out of reach of children.**
**Store below 25°C in the original package.**

Do not take during pregnancy or lactation. Not recommended for children or adolescents under 18 years of age.

**DOSAGE INSTRUCTIONS**
Adults and elderly:

For the temporary relief of symptoms of mild anxiety, take 1 capsule 3 times daily, swallowed with water.

To aid sleep, take 1 capsule 30 minutes before bedtime, swallowed with water, with an additional dose earlier in the evening if necessary.

Maximum daily dose 4 capsules.

**Do not exceed the stated dose.**

**EACH HARD CAPSULE CONTAINS**
Valerian root 400mg.
(*Valeriana officinalis* L.)

Valdrian is a traditional herbal medicinal product for the temporary relief of symptoms of mild anxiety and to aid sleep, based on traditional use only.

Patients with known hypersensitivity to Valerian root should not use Valdrian.

If symptoms persist, or adverse reactions not mentioned in the leaflet occur, consult a doctor or qualified healthcare practitioner.

**Read the leaflet enclosed before use.**

Traditional herbal registration holder/manufacturer:
**Bio-Health Ltd.**,
Rochester England ME2 4HU
THR 15817/0004