De Tuinen Valeriaan, capsules for oral use
De Tuinen BV, the Netherlands

RVG 104935

NL-PAR
TRADITIONAL HERBAL MEDICINAL PRODUCT

Route of administration: oral
Prescription status: non-prescription, uitsluitend apotheek of drogist (UAD)
Therapeutic indication: Traditioneel kruidengeneesmiddel ter verlichting van symptomen van nerveuze spanning en stress en ter bevordering van de slaap. De toepassing berust uitsluitend op langdurige gebruikservaring en niet op klinisch bewijs.
Date of authorisation in NL: 1 June 2010
Application type/legal basis: Directive 2001/83 article 16a
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I LAY SUMMARY

The Medicines Evaluation Board (MEB) has granted De Tuinen BV from the Netherlands registration for De Tuinen Valeriaan capsules, capsules for oral use as a Traditional Herbal Medicinal Product (Registration number: RVG 104935). This product is available without prescription and only sold at pharmacies and drugstores as UAD product (uitsluitend apotheek en drogist).

The active ingredient of De Tuinen Valeriaan is obtained from Valeriana officinalis roots. It is used as "Traditioneel kruidengeneesmiddel ter verlichting van symptomen van nerveuze spanning en stress en ter bevordering van de slaap. De toepassing berust uitsluitend op langdurige gebruikservaring en niet op klinisch bewijs."

"Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep, exclusively based upon long-standing use."

This registration is based exclusively upon the longstanding use of Valeriana officinalis root as a traditional herbal medicinal product and not upon data generated from clinical trials. For a Traditional Herbal Registration there is no requirement to scientifically prove that the product works.

The three most important areas of assessment (traditional use, quality and safety) are satisfactory and it was therefore decided that a registration as Traditional Herbal Medicinal product could be granted.

Legal background:

What are Traditional herbal medicinal products?
Some plants contain substances that may be used to treat diseases. Medicinal products that are prepared from plants are known as "herbal medicinal products". Even though they are "natural", a number of these products may be potentially dangerous for patients. This is why herbal medicinal products are covered by pharmaceutical legislation, with aims to protect public health by ensuring the safety, efficacy and quality of medicinal products.

Within the group of herbal medicinal products, some have a long tradition of use. European Union (EU) legislation classifies as traditional herbal medicinal products those herbal medicinal products that have been used for at least 30 years, including at least 15 years within the EU, are intended to be used without the supervision of a medical practitioner (in NL normally classified as UAD) and are not administered by injection.

Why did the EU decide to adopt specific legislation on traditional herbal medicinal products?
All medicinal products, including herbal medicinal products, need a marketing authorisation to be placed on the EU market. Traditional herbal medicinal products have particular characteristics, notably their long tradition of use. To take account of this, the EU introduced a lighter, simpler and less costly registration procedure for them, while providing the necessary guarantees of quality, safety and efficacy.

The Herbal Directive (Directive 2004/24/EC) was adopted to facilitate the placing on the EU market of traditional herbal medicinal products. This simplified procedure allows the registration of traditional herbal medicinal products without requiring safety tests and clinical trials, which the applicant is obliged to provide under the full marketing authorisation procedure.

The long tradition of the herbal medicinal product makes it possible to reduce the need for these tests and trials that can be replaced by documentation which indicates that the product is not harmful in specified conditions of use and that its efficacy is plausible on the basis of long-standing use and experience. However, occasionally even a long tradition of use does not exclude concerns about the product’s safety. In such cases competent authorities of the Member States are entitled to ask for additional data, if they deem it necessary to assess the safety of the traditional herbal medicinal product.
Does the Herbal Directive impose new requirements for the placing on the market of traditional herbal medicinal products?

Before 2004, herbal medicinal products were covered by the same requirements as other medicinal products. The Herbal Directive amends those requirements and provides for a simplified registration procedure introduced to facilitate the placing on the market of traditional herbal medicinal products. This simplified procedure allows registration of traditional herbal medicinal products based on sufficient evidence of medicinal use throughout a period of at least 30 years, including at least 15 years in the European Union. The long tradition of the herbal medicinal product makes it possible to reduce the need for clinical trials, in so far the pharmacological effects or efficacy are plausible on the basis of long-standing use and experience. Non-clinical tests are considered unnecessary, where the herbal medicinal product on the basis of its traditional use proves not to be harmful in specified conditions of use. The quality of the herbal medicinal product is independent of its traditional use so no derogation is made with regard to the regular quality requirements. Traditional herbal medicinal products should comply with quality standards in the European Pharmacopoeia.

II SCIENTIFIC DATA

II.1 Introduction

This application was submitted according to Article 16a of Directive 2001/83 EC, as amended.

The CBG-MEB granted a registration as traditional herbal medicinal product for De Tuinen Valeriaan from De Tuinen BV, the Netherlands. This product is classified as UAD (Uitsluitend Apotheek en Drogist), which means that sale is restricted to only pharmacies or drugstores.

This product consists of capsules containing 337 mg of dried ethanolic extract of the root of Valeriana officinalis L.. This product is indicated “Traditioneel kruidengeneesmiddel ter verlichting van symptomen van nerveuze spanning en stress en ter bevordering van de slaap. De toepassing berust uitsluitend op langdurige gebruikservaring en niet op klinisch bewijs”.

The data supplied by the MAH substantiates 30 years of medicinal use of Valeriana officinalis, including at least 15 years in the European Community. A satisfactory review of the available safety data on Valeriana officinalis has also been provided, together with an Expert Report supporting on Safety of the product.

For the assessment the Community Herbal Monograph of Valeriana officinalis L., radix, Doc. Ref. EMA/HMPC/340719/2005, was taken into account as a basis for registration.

At the time of assessment preparations of Valeriana officinalis with comparable amount of active substance, posology and indication, were registered on the Dutch market since 2004.

Community Monographs/ -List Entries:

What is the role of the Community Herbal Monographs and Community List Entries, as established by the Herbal Medicinal Products Committee (HMPC), at the European Medicines Agency in London?

The European Medicines Agency does not have a role in the registration of traditional herbal medicinal products in a Member State. The simplified procedure is a national one. This means that applications for registration as traditional herbal medicinal product needs to be submitted in each Member State where the product is to be marketed. These applications are evaluated by the competent authority in each Member State. (in the Netherlands: Medicines Evaluation Board).

The Herbal Medicinal Products Committee in London has the task to prepare a Community List of traditional herbal substances and -preparations, as well as establish Community Herbal Monographs for traditional herbal medicinal products. Where a Community Herbal Monograph or Community List entry is established, this shall be recognized by competent authorities as a basis for registration.

When new Community herbal monographs will be established, the registration holder shall consider whether it is necessary to modify the registration dossier accordingly.
II.2 Quality

II.2.1 HERBAL SUBSTANCE

General information
Latin name: Valeriana officinalis L.s.l.
Family: Valerianaceae
Parts of plant used: Roots (dried)

Manufacture
For the herbal substance the Active Substance Master File (ASMF) procedure is used. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Production of the herbal substance is in line with the Guideline on GACP-EMEA/HMPC/246816/2005 and adequately documented.

Control of herbal substance
The crude plant material complies with the requirements of the Ph. Eur.. The specification includes tests for identity, purity and content of marker compound. Specifications are in accordance with Ph. Eur. requirements where appropriate or otherwise justified.
Analytical testing meets the requirements of the Ph. Eur. where appropriate or has been otherwise justified and validated.

Reference Standards or Materials
Satisfactory characterization of the reference standards has been provided.

Stability
The manufacturer of the active substance has made a commitment that the herbal substance is tested directly before further processing, so no stability data are assessed.

II.2.2 HERBAL PREPARATION

General information
Herbal preparation: Valeriana officinalis dry extract
Scientific name of the plant: Valeriana officinalis L.s.l.
Parts of the plant used: root, rhizome and stolon
Extraction solvent: ethanol 70% (v/v)
Drug Extract Ratio (DER): 5-6:1

Manufacture
The herbal preparation is produced under GMP (Good Manufacturing Practice) conditions. A detailed description of the manufacturing process (extraction, drying, blending), including batch size, manufacturing formula, process conditions, in-process controls and flow diagram, has been provided in a separate ASMF dossier and is satisfactory.

The in-process controls and specifications are sufficiently detailed, and justified.

Control of the herbal preparation
The specifications for the herbal preparation have been laid down in an in-house monograph. Release specifications for the extract comprise appearance, identification by TLC fingerprint, content of marker

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substance, loss on drying, residual solvent, pesticides, heavy metals, aflatoxins and microbial purity. Specifications are in accordance with Ph. Eur. requirements where appropriate or otherwise justified. Analytical testing meets the requirements of the Ph. Eur. where appropriate or has been justified and Certificates of analysis of three batches of extract were presented. All data comply with the established validated otherwise specifications.

Reference Standards or Materials
Satisfactory characterization of the primary and working reference standards has been provided.

Container closure system
The suitability of the container closure system was sufficiently demonstrated.

Stability
Stability tests with the herbal preparation were performed under ICH-conditions. Based on the presented results a storage period of 9 months was considered justified.

II.2.3 FINISHED PRODUCT

Description and Composition herbal medicinal product
The product is a hard capsule containing a dried extract (5-6:1; ethanol 70% (w/w)) of the subterrenean parts (roots, rhizomes & stolons) of Valeriana officinalis L. as active component. The used excipients magnesium stearate and hydroxypropylmethyl cellulose are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph. Eur. monographs.

Manufacturing process
The product is manufactured in Canada, batch release for the EU is done in Europe (UK). Before manufacturing the extract is controlled and analysed to ensure compliance with the specification. A flow diagram of the production process was included in the dossier. The manufacturing process and in-process controls have been described adequately.

In-process controls are appropriate considering the nature of the product and the method of manufacture.

Control of the finished product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average and fill weight of capsule, uniformity of mass, disintegration, identification (TLC, HPLC), assay (total valerenic acids) and microbiology. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data of two batches from the proposed production site have been provided, demonstrating compliance with the specification.

Container closure system
The container consists of dark amber polyethylene terephthalate (PETE) bottle with a black low density polyethylene (LDPE) hinge guard cap. Both plastic materials meet EU-requirements for foodstuffs. Fill sizes are 30 and 60 capsules.

Reference Standards or Materials
Satisfactory characterization of the primary and working reference standards has been provided in the ASMF dossier.

Stability
Overall - Studied parameters in the different stability studies were described sufficiently. Limit values are identical to those of the release specifications (except the tolerance interval for the marker which was 90 – 110% related to t₀, (EMA Guideline on quality of (Traditional) Herbal Medicinal Products). Analytical procedures are identical to those used for the testing of release specifications.
Real time, intermediate and accelerated studies - Stability of the finished product was investigated at real time, intermediate and accelerated conditions. The studies were performed in accordance with the relevant ICH guidelines. Based on the results available so far a shelf-life of 20 months was granted, with the storage condition "Store below 25ºC".

II.3 Safety & Safe use

II.3.1 Non-clinical safety data

According to Article 16c (1)d of Directive 2001/83 safety should be justified by “a bibliographic review of safety data together with an expert report”.

A bibliographic review of non-clinical data (both published and unpublished), including toxicological information, is presented. Also an expert report written by a non-clinical expert has been submitted.

Toxicity studies:
The submitted scientific references on single-dose and repeated dose toxicity show that an ethanolic extract of *Valeriana officinalis* is non-toxic in animal studies in doses beyond the advised daily dose for humans. LD50 was found to be 3.3 g/kg bodyweight following intraperitoneal administration (IP); IP-injection of up to 600 mg/kg bodyweight of extract to rats for 30 days did not produce signs of haematological or organ toxicity.

Inconclusive study results have been documented for genotoxic/mutagenic potentials of valerian at high doses, but clinical significance is considered limited. Results of ongoing study conform ICH guidelines for genotoxicity are awaited.

Animal study results suggested that *Valeriana officinalis* extract has no effect on fertility and embryo-foetal development. However, as no specific reproduction toxicological studies are available in humans, a statement has been included in SPC and package leaflet that *Valeriana officinalis* extract should not be taken during pregnancy and lactation.

Evidence from controlled clinical trials show that valerian is well tolerated in humans. Long-term experience with the product demonstrates no safety concerns.

Though a potential link between valerian and hepatotoxicity was mentioned in 4 case reports, the causality was not proven, as scientific or clinical evidence could not be indicated, and neither was it detected in a hepatotoxicity animal study.

*Interactions*:

Although scientific data has not shown evidence of clinically significant effect of valerian on drug metabolizing enzymes, it may induce pharmacodynamic herb-drug interactions by potentiating the central nervous system depressant effects of alcohol, barbiturates, and possibly other CNS depressants when administered concomitantly.

The herb should be avoided following alcohol consumption.

*Pharmacokinetic studies:*

Pharmacokinetic studies are not required according to the legislation for traditional herbal medicinal products.

II.3.2 Clinical Safety data

Whereas clinical data are not obligatory for demonstration of efficacy, they are of use to justify the safety of the product, because side-effects might be reported. A total of 9 published clinical studies including 407 individuals were provided by the MAH and have been evaluated for safety aspects. Rare and only mild side effects could be related to the use of *Valeriana officinalis* extract: dizziness, headache, hang-over effect, tiredness, diarrhoea, nausea, and vomiting.
As a precaution the contraindication for hypersensitivity has been taken up.

Due to the lack of experience *Valeriana officinalis* should not be used during pregnancy and lactation. *Valeriana officinalis* may influence on the ability to drive and use machines as intake of valerian may cause drowsiness.

The extensive long-term experience with valerian root products did not give reasons for any serious safety concerns, which is also in compliance with the HMPC monograph.

**Conclusion**
The presented data, together with the extensive experience with valerian root preparations, demonstrate that De Tuinen Valeriaan capsules can be used safely.

**Background of Safety Assessment:**
An application for registration as traditional herbal medicinal product must be accompanied by, among others, a bibliographic review of safety data together with an expert report. Where required by the competent authority upon additional request further data necessary for assessing the safety of the herbal medicinal product should be added. Non-clinical tests are considered unnecessary, where the herbal medicinal product on the basis of the information on its traditional use proves not to be harmful in specified conditions of use. Additional data on the traditional use of the herbal medicinal product, e.g. marketing experience in another Member State shall be taken into account, because even a long tradition does not exclude the possibility that there may rise concerns with regard to the product’s safety. Therefore, competent authorities are entitled to ask for all other data necessary to assess the safety.
II.4 Justification of Traditional use

According to Directive 2001/83 EC Art 16 (4)c traditional use shall be justified by bibliographical 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 preceding the date of the application, including at least 15 years within the Community.

Evidence of Traditional Use
For the justification of traditional use reference is made to the British Pharmacopoeia, herbal Materia Medica, Commission E monograph, scientific literature and handbooks.

The data supplied by the MAH clearly demonstrate the medicinal use of Valeriana officinalis root for 30 years, of which 15 years in the European Community. Reference was also made to the HMPC monograph on Valeriana officinalis L, radix.

The medicinal use of 30 years and 15 years in the European Community has been proven satisfactorily.

Proposed indication
The following indication has been accepted:

"Traditioneel kruidengeneesmiddel ter verlichting van symptomen van nerveuze spanning en stress en ter bevordering van de slaap. De toepassing berust uitsluitend op langdurige gebruikservaring en niet op klinisch bewijs".

Efficacy
No clinical efficacy data have been assessed for registration as Traditional Herbal Medicinal Product.

Conclusion
The data supplied by the MAH substantiates 30 years of medicinal use of Valeriana officinalis L. root, including at least 15 years in the European Community and support the traditional indication.

Background of Assessment on the basis of long-standing use and experience:

The long tradition of the herbal medicinal product makes it possible to reduce the need for clinical trials, in so far as the pharmacological effects or efficacy of the herbal medicinal product are plausible on the basis of long-standing use and experience.

Bibliographic or expert evidence is required to the effect that the herbal medicinal product, or a corresponding product has been in medicinal use throughout a period of at least 30 years preceding the date of application, including at least 15 years within the European Union. Furthermore, the pharmacological effects or efficacy are plausible on the basis of long-standing use and experience.

In cases of doubt and at the request of the Member State where the application has been submitted, the Herbal Medicinal Products Committee shall draw up an opinion on the adequacy of the evidence of the long-standing use of the herbal medicinal product.
III OVERALL CONCLUSION AND RISK ASSESSMENT

This is an application for registration as a Traditional Herbal Medicinal Product, under article 16a of Directive 2001/83/EC.

Quality
De Tuinen Valeriaan capsules for oral use have a proven chemical-pharmaceutical quality.

Safety
A satisfactory review of the available safety data has been provided. The presented data demonstrate that De Tuinen Valeriaan can be used safely.

Efficacy
No clinical efficacy data are required for registration as Traditional Herbal Medicinal Product.

Traditional use
The MAH provided a bibliographic review with adequate evidence that the extract of Valeriana officinalis L. root has been in medicinal use for 30 years, including 15 years in the European Community. The first valerian containing product on the Dutch market dates from 1969. The long-standing use and experience is also substantiated by the HMPC-monograph on Valeriana officinalis, radix.

Classification
The herbal medicinal product is classified as a non prescription product and for UAD (Uitsluitend Apotheek en Drogist).

SPC, PIL and labelling
The SPC, PIL’s and labelling have been established in which attention has been paid to the Community Herbal Monograph on Valeriana officinalis, radix.

Marketing authorisation
The MEB, on the basis of the data submitted, considered that De Tuinen Valeriaan, capsules for oral use demonstrated adequate evidence of traditional use, quality and safety, can be registered. De Tuinen Valeriaan, capsules for oral use has been registered in the Netherlands on 1 June 2010 with the following indication: “Traditioneel kruidengeneesmiddel ter verlichting van symptomen van nerveuze spanning en stress en ter bevordering van de slaap. De toepassing berust uitsluitend op langdurige gebruikservaring en niet op klinisch bewijs”.

The date for the first renewal will be: 1 June 2015.
List of abbreviations

GMP  Good Manufacturing Practice: part of a quality system covering the manufacture and testing of active pharmaceutical ingredients and products
HMPC  European Medicines Agency’s Committee on Herbal Medicinal Products
HPLC  High Performance Liquid Chromatography
ICH  International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
MAH  Marketing Authorisation Holder
Ph. Eur.  European Pharmacopoeia

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

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