CBG MEB

Public Assessment Report
Herbal medicinal product

Scientific discussion

Vemedia Valeriaan 450 mg, coated tablets

Dry extract (DER 3-6:1) of *Valeriana officinalis* L. radix

Extraction solvent: ethanol 70% (v/v)

NL/H/3667/001/DC

Date: 19 October 2018

This module reflects the scientific discussion for the approval of Vemedia Valeriaan 450 mg, coated tablets. The procedure was finalised on 26 October 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CMS	Concerned Member State
DER	Drug-extract ratio
EEA	European Economic Area
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vemedia Valeriaan 450 mg, coated tablets from VEMEDIA Manufacturing B.V.

This herbal medicinal product is indicated for the relief of mild nervous tension and sleep disorders in adults and children older than 12 years.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a bibliographical application for Vemedia Valeriaan 450 mg, coated tablets based on the well-established use procedure according to Article 10a of Directive 2001/83/EC. Well-established use refers to the use for a specific therapeutic use for at least 10 years within the community. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the Marketing Authorisation Holder (MAH) should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

Valerian root belongs to the pharmacotherapeutic group of hypnotics and sedatives (ATC-Code N05C M09). The sedative effects of preparations of valerian root have long been recognised empirically. These effects cannot be attributed with certainty to any known constituents. Several mechanisms of action possibly contributing to the clinical effect have been identified for diverse constituents of valerian root (sesquiterpenoids, lignans, flavonoids) and include interactions with the GABA-system, agonism at the A1 adenosine receptor and binding to the 5-HT1A receptor.

The herbal substance is not considered a new active substance. For valerianae radix, a Community herbal monograph (HMPC, 2016) is available. The extract preparation and pharmaceutical form of the product, the therapeutic indication, the posology and the SmPC are in accordance with the Community Herbal Monograph on *Valeriana officinalis* L. radix, for well-established use (EMA/HMPC/150848/ 2015, Corr.). In addition, reference is made to a WHO-monograph (WHO, 1999) and an ESCOP-monograph (ESCOP, 1997).

The concerned member states (CMS) involved in this procedure were Greece, France and Italy.

II. QUALITY ASPECTS

II.1 Introduction

Vemedia Valeriaan is a round, white, glossy, biconvex coated tablet. Each tablet contains 450 mg of extract (as dry extract) from *Valeriana officinalis* L. radix (valerian root) (3-6:1), extraction solvent ethanol 70% (v/v).

The coated tablets are packed in PVC/PVDC-Alu blisters.

The excipients are:
tablet core – liquid glucose (spray dried), colloidal anhydrous silica, powdered cellulose, croscarmellose sodium, stearic acid, and talc
tablet coat – sucrose, talc, calcium carbonate (E170), acacia, tragacanth, titanium dioxide (E171), liquid glucose (spray dried) and capol 600 T.S. (containing white beeswax; carnauba wax and shellac).

II.2 Herbal Substance

The herbal substance is the dried, whole or fragmented underground parts, including the rhizomes surrounded by roots and stolons of *Valeriana officinalis* L. radix as defined in the European

Pharmacopoeia (Ph. Eur.) monograph on Valerianae radix. It is cultivated in Poland, Germany, The Netherlands, Morocco, Bulgaria, Hungary and Romania.

Manufacturing process
Cultivation of the raw material is done in line with the principles of Good agricultural and collection practice (GACP), A GACP confirmation is presented. It is confirmed that the principles of GACP are part of the contracts with suppliers. Satisfactory details were provided for all pre- and postharvest treatments. During cultivation pest management is applied using minimal necessary dose that meets national and European legal requirements of herbicides, fungicides and insecticides herbicides. No fumigation is applied, however, during storage the material may be treated with CO_2 under pressure.

Quality control of herbal substance
The herbal substance is specified according to the Ph. Eur. monograph on Valerian root with additional specifications for heavy metals, pesticide residues, microbiological quality and aflatoxins which are specified according to the relevant Ph. Eur. monographs. The reduced testing program for impurities is considered acceptable for heavy metals and aflatoxines. Pesticides are tested routinely. Certificates of analysis of two batches raw material have been provided fulfilling the specifications. A specification for radioactivity is not necessary.

Stability of herbal substance
No stability data are presented for the herbal substance. This is acceptable because the material is processed immediately after testing in accordance with the specifications.

II.3 Herbal Preparation

The herbal preparation is a dry valerian hydroalcoholic extract of valerian root. The extract is manufactured using ethanol 70% v/v as extraction solvent. Subsequently the extract is dried, resulting in a brown, hygroscopic powder that complies with the Ph. Eur. monograph 'Valerian dry hydroalcoholic extract'. The extract preparation consists of 80% native extract. The native drug-extract ratio (DER) is 3-6:1.

Manufacturing process
A flow chart of the manufacturing process has been provided. The method of manufacture is an 'exhausted extraction'. The information provided on the manufacturing process is considered satisfactory.

Quality control of herbal preparation
Specifications and a description of the herbal preparation have been provided and comply with its respective monographs of the Ph. Eur with an additional specification for pyrrolizidine alkaloids and particle size. The specification includes tests for description, characters, particle size, loss on drying, residual ethanol, identity, assay, pyrrolizidine alkaloids and microbial quality. Most analytical methods are performed according to Ph. Eur. and therefore are considered validated. The method for analyzing pyrrolizidine alkaloids has been sufficiently validated. Analytical data demonstrating compliance with this specifications have been provided for two batches of the herbal preparation.

Stability of the herbal preparation
Stability data on the herbal preparation have been provided for two production batches stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). No significant changes were observed in the parameters during storage. Based on the data submitted, a retest period for the herbal preparation could be granted of 18 months.

II.4 Herbal Medicinal Product

Pharmaceutical development
The pharmaceutical development presented is considered acceptable. The choice for the pharmaceutical form has been justified. The formulation is based on pharmaceutical literature and on a very long experience of the manufacturer with tabletting herbal medicinal products. In addition, the compatibility of the active ingredient with the chosen excipients is supported by results obtained within the stability studies

Manufacturing process
A flow diagram is presented giving the steps of the process and showing where materials enter the process. In short, the process consists of tabletting, coating and blistering and packaging. The specifications at release and analytical methods are acceptable. Process validation have been provided for three full-scale production batches.

Control of excipients
All excipients used are described in the European Pharmacopoeia and are tested according to the specifications of the corresponding monograph. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specifications include tests for organoleptic, tablet mass, tablet height, tablet diameter, disintegration time, identity, assay, contents of valerenic acids and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. All methods have been described sufficiently and are properly validated. Satisfactory validation data for the analytical methods have been provided. Certificates of analysis including photocopies of chromatograms were submitted for four production batches. The data presented are considered adequate to support the specifications.

Stability of drug product
Stability data on the product have been provided for 2 pilot batches and 3 production batches stored at 25°C/60% RH, 30°C/65% RH and at 40°C/75% RH up to 48 months. On basis of the data provided, a shelf-life could be granted of 48 months when stored below 25ºC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only excipient of animal origin used is the film forming agent shellac. Shellac is obtained from the resinous secretion of the female insect *Kerria lacca* (Kerr) by purification. There is no risk of transmission of TSE by shellac, because this type of diseases affects only vertebrates.

II.5 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Vemedia Valeriaan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the herbal substance, herbal preparation and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Among the components of valerian root no single or main active ingredient has been identified. Various trials with isolated constituents could not fully explain the observed pharmacological activities of valerian root. A possible synergistic action of several components is assumed. The whole extract of valerian root must therefore be considered as the active ingredient. The results of trials that can be found in scientific literature, point to both a sedative and an anxiolytic effect, possibly mediated by different constituents, which both might contribute to sleep promotion and improvement in nervous state.

III.2 Pharmacokinetics

Since the valerian root dry hydroalcoholic extract contains a mixture of numerous ingredients, it is not feasible to conduct pharmacokinetic studies at this stage. Studies on the pharmacokinetics and metabolism of valerenic acid, a main active constituent of valerian, have been identified in the literature and presented adequately.

III.3 Toxicology

Single-/repeat-dose toxicity
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, no new studies were conducted.

Genotoxicity
The genotoxic potential of the valerian root extract used in Vemedia Valeriaan 450 mg, Coated Tablets has not been investigated. Data on the mutagenic activity of whole valerian extracts or isolated components is limited. The nonclinical overview refers to the studies discussed in the HMPC Assessment Report on *Valeriana officinalis* L., radix (EMA/HMPC/167391/2006). The results of these studies provide no basis for an assessment of the genotoxic risk of the current preparation. The draft HMPC assessment of 2015 on *Valeriana officinalis* L., radix and *Valeriana officinalis* L., aetheroleum (EMA/HMPC/150846/2015) refers to an Ames-test described in public literature (Kelber et al, 2014). The results of that test did not give any reason for concern on the mutagenicity for the dry extract (DER 3-6:1, extraction solvent: ethanol 70%). The test was conducted in five strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA102), with various nonpolar and polar valerian extracts, including the 70 % ethanolic valerian root dry extract (DER 3-6:1) used in the concerned product, Vemedia Valeriaan 450 mg, Coated Tablets. The authors indicated that the Ames test was performed by the Laboratory of Pharmacology and Toxicology in Hamburg, Germany and in compliance with OECD guideline 471, ICH guideline S2(R1) and GLP regulations.

Carcinogenicity
There are neither literature data nor studies available reporting or evaluating a potential carcinogenic risk of valerian root. According to the Guideline on Non-clinical Documentation for Herbal Medicinal Products in Applications for Marketing Authorisation (Bibliographical and Mixed Applications) and in Applications for simplified Registration (EMEA/HMPC/32116/2005) carcinogenicity studies are not needed in cases where there is no suspicion for a carcinogenic potential.

Reproductive and developmental toxicity
There is very limited information on reproductive and developmental toxicity of valerian in animals. Surveys in 2008-2013 indicated that valerian was one of the most commonly used herbal products during pregnancy, but there are no controlled human data. No reports describing the use of valerian during lactation have been located. As there is limited information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Vemedia Valeriaan is a herbal medicinal product, containing valerian dry hydroalcoholic extract as an active substance, the statement of the Committee on Herbal Medicinal Products (HMPC) on Environmental Risk Assessment of herbal medicinal products (EMA/HMPC/121934/2010) provides a general justification for the exemption of an ERA for herbal medicinal products. According to this HMPC statement the use of herbal substances in small amounts in medicinal products is not considered to be a risk for the environment. As this herbal medicinal product containing valerian extract is considered a natural product, it is not anticipated that its use will result in any potential risk to the environment.

III.5 Discussion on the non-clinical aspects

Pharmacological, pharmacokinetic and toxicological characteristics of Valeriana officinalis as presented in the non-clinical overview are based on literature review and the non-clinical overview is considered appropriate. The non-clinical overview has addressed the pharmacological and toxicological literature as well as some product-specific consideration. There are no issues relating to the pharmacology or toxicology and formulation of Vemedia Valeriaan. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

For this well-established use application, bibliographic data have been provided based on scientific literature. The application is based on:

- the evaluation of efficacy and safety of the product in the recently updated Community Herbal Monograph on *Valeriana officinalis* L. radix (EMEA/HMPC/150848/2015), and the corresponding assessment report dated February 2016 (EMEA/HMPC/150846/2015; assessment report available on http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2016/04/WC500205373.pdf)
- the literature published on the medicinally active substance since the time of publication of this Community Herbal monograph.

IV.2 Pharmacodynamics

Electroencephalography studies (EEG) in patients and in healthy volunteers showed either no effect on EEG or, if an effect was found, it was with higher doses than advised in the product information or with aqueous-alcoholic valerian (i.e. the effect of alcohol cannot be disentangled form the effect of valerian).

IV.3 Clinical efficacy

The description of the studies that were submitted in support of the efficacy of valerian is not entirely clear, especially with respect to the endpoint used, the size of the effect and its clinical relevance. Nevertheless, the studies suggest that valerian has some effect on subjective sleep parameters (i.e. sleep latency and sleep quality) and that it is non-inferior to oxazepam with respect to the subjective effect on sleep quality. There are fewer studies that examined the effect of valerian on nervous tension and here too the description of the endpoint is not entirely coherent. Nevertheless, the results suggest an effect on endpoints possibly reflecting “nervous tension” .
Furthermore, these conclusions regarding efficacy are consistent with the conclusion reached in the Community Herbal Monograph and the corresponding assessment report. The above mentioned report refers to valerian root extracts prepared with ethanol/water (ethanol 40 - 70 % (V/V) . The report concludes: “For the clinical use of valerian root, a substantial body of general evidence is available from handbooks, expert reports etc. Valerian root has been used for centuries in many countries. Additional evidence results from several randomised, controlled, double-blind clinical trials, partly with EEG recordings. Taking into account these clinical trials, the indication “relief of sleep disorders” is based on level Ib evidence and the indication “relief of mild nervous tension” on level III1 evidence.”
Hence, consistent with the HMPC AR, it is concluded that the efficacy of valerian on the relief of mild nervous tension and sleep disorders is demonstrated.

IV.4 Clinical safety

The published studies and case reports since the assessment of the evidence for valerian root in 2007 do not suggest any new safety issues which would justify change in the conclusion regarding safety.
The assessment from 2007 concluded that valerian root does not reduce vigilance on the next morning when taken in the evening. Only high doses of the extract may cause a slight sedation during the first few hours after ingestion. A warning in the SmPC of the product regarding the effects on the ability to drive and use machinery is recommended in the Community herbal monograph as a general precaution for medical products negatively influencing vigilance. In addition, data collected for several valerian root combinations (i.e. with lemon balm extract, Hops and St. John’s wort) showed that this root does not act synergistically with alcohol.
No new relevant data concerning the clinical pharmacodynamic effect of valerian extract have been published. Overall, the conclusion with respect to the benign safety profile of valerian that was drawn in the assessment of 2007 can remain unchanged.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the herbal monograph and additional safety data retrieved since its adoption. Considering the very extensive use of valerian products the two case reports indicating a probable causal association between valerian use and hepatotoxicity seem isolated occurrences. However, large underreporting of spontaneously reported cases should be taken into account, in particular concerning OTC and herbal products. Therefore, hepatotoxicity has been included as important potential risk in the RMP.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Impairment of ability to drive and use machines - Additive sedation when combined with synthetic sedatives
Important potential risks	- Hepatotoxicity
Missing information	- Safety in children <12 years of age - Adverse effects on fertility and regarding use during pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

The efficacy of valerian in the indication relief of sleep disorders or of mild nervous tension is considered limited and restricted to subjective experiences. However, it is considered that given its benign safety profile and given the fact that the same substance (valerian root) was considered acceptable in the HMPC WEU monograph, there is sufficient ground to accept Vemedia Valeriaan as a herbal medication for the requested indication. From the clinical aspect the medicinal product is approvable.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test was performed in two rounds, with 10 participants in each round. The technical readability, comprehensibility of the text, traceability of information and the applicability were investigated. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vemedia Valeriaan 450 mg, coated tablet has a proven chemical-pharmaceutical quality and its use is considered widely established. The benefit/risk balance is considered positive for this herbal medicinal product.

The Board followed the advice of the assessors. The application meets the requirements for a bibliographic application: well-established medicinal use within the Community for at least 10 years has been demonstrated, with recognised efficacy and an acceptable level of safety.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Vemedia Valeriaan, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 October 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3667/ IB/001/G	Change of name and address of the MAH from Labima to Vemedia	Yes	27-02-2018	Approved	-