LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Läkemedelsverket 2014-09-09

Public Assessment Report
Scientific discussion

Valerina Forte, coated tablet

Valeriana officinalis L., dried root, dry extract (5.25-7.5:1) ethanol 60 %

Asp no: 2008-0615

This module reflects the scientific discussion for the approval of Valerina Forte, coated tablet. The procedure was finalised 8 June 2009. For information on changes after this date please refer to the module 'Update'.

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LAY SUMMARY

The Medical Products Agency (Läkemedelsverket, MPA) has granted Pharbio Medical International AB, Sweden, a marketing authorisation for the herbal medicinal product Valerina Forte, coated tablet. The product is available without prescription and can be bought from pharmacies and other outlets.

Valerina Forte has an extensive medicinal use in the EU for treatment of mild nervous tension and sleep disorders. The active ingredient is dry extract of *Valeriana officinalis* L. (vänderot, valerian).

The Medical Products Agency has concluded that the active substance in Valerina Forte has a well-established medicinal use with a recognised efficacy and acceptable level of safety.

The chemical/pharmaceutical quality of the product is acceptable and no new or unexpected safety concerns have been identified during the assessment. It was therefore decided that Valerina Forte, coated tablet, could be granted a marketing authorisation as a herbal medicinal product.

I. INTRODUCTION

Pharbio Medical International AB, Sweden, has applied for a marketing authorisation for Valerina Forte, coated tablet. The application was submitted under Article 10a Well-established use application of the Directive 2001/83 EC, as amended.
The application is a national application for Sweden.

The active substance is *Valeriana officinalis* L., dried root, dry extract (5.25-7.5:1) extraction solvent: ethanol 60 %. The extract contains 25 % excipients.
For approved indications, see the Summary of Product Characteristics (SmPC).

Valerina Forte, coated tablet, was first authorised as a natural remedy in 1995. As a consequence of the new legislation regarding herbal medicinal products the product was reclassified as a herbal medicinal product in 2009.

II. QUALITY ASPECTS

II.1 Introduction

Valerina Forte is presented in the form of a coated tablet containing 200 mg of dry extract (5.25-7.5:1) of *Valeriana officinalis* L. containing:

- 150 mg soft extract of *Valeriana officinalis* L., radix (7-10:1) extraction solvent: ethanol 60% corresponding to approximately 1-1.5 g dried root of *Valeriana officinalis* L.
- 50 mg of fillers to produce a dry extract

The excipients are: lactose monohydrate, calcium hydrogen phosphate dehydrate, potato starch, powdered cellulose, hypromellose, magnesium stearate, colloidal anhydrous silica, macrogol, titanium dioxide, red iron oxide, and hard paraffin.

All manufacturers involved in the production operate in accordance with EU-GMP, or where relevant, GACP (Good Manufacturing Practise, respectively Good Agricultural and Collection Practice).

II.2 Drug Substance

The herbal substance *Valeriana officinalis* L., radix complies with the monograph “Valerian root, Valerianae radix” in the European Pharmacopoeia.

The plants used are cultivated in central Europe, mainly Poland and Germany. Relevant information on growing conditions and controls of the herbal substance (such as residues of heavy metals and pesticides as well as microbiological quality) has been provided.

The herbal drug is dried, ground and extracted using a maceration process with 60% ethanol. Extraction is followed by separation and finally concentration under low pressure to yield a soft extract with DER: 7-10:1.The soft extract is then mixed with fillers which are added in a quantity to produce a dry extract with a final DER of 5.25-7.5:1.

The manufacturing process has been adequately described and satisfactory specifications have been provided for starting materials and solvents.

The active substance specification includes relevant tests and the limits for impurities have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Valerina Forte, coated tablet, is formulated using excipients described in the current European Pharmacopoeia (Ph. Eur.), except for red iron oxide which is controlled according an in-house specification. All raw materials used in the product are safe with view to possible TSE/BSE risk.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued a Community monograph on *Valeriana officinalis* L. radix in 2006. In this monograph, it was concluded that the active substance in Valerina Forte, coated tablet (dry extract of *Valeriana officinalis* L.) has a well-established medicinal use with a recognised efficacy and acceptable level of safety in the Community in accordance with Directive 2001/83/EC.

The reader is referred to the Community monograph and the pertinent assessment report for details.

III.2 Pharmacology

The sedative effects of preparations of valerian root, which have long been recognised empirically, have been confirmed in preclinical tests and controlled clinical studies. Orally administered dry extracts of valerian root prepared with ethanol/water (ethanol max. 70 % (V/V)) in the recommended dosage have been shown to improve sleep latency and sleep quality. 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.

III.3 Pharmacokinetics

Constituents responsible for the therapeutic effect of the extracts are not entirely known, and thus pharmacokinetic studies are neither possible nor relevant.

III.4 Toxicology

No mutagenic effect was detected in an extract specific Ames test.

Extracts with ethanol and the essential oil of valerian root have shown low toxicity in rodents during acute tests and from repeated dose toxicity studies over periods of 4 – 8 weeks. Tests on reproductive toxicity and carcinogenicity have not been performed.

III.5 Ecotoxicity/environmental risk assessment

Valerina Forte, coated tablet, is a herbal medicinal product. According to the *Guideline on the environmental risk assessment of medicinal products for human use* (EMEA/CHMP/SW4447/00), herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

III.6 Discussion on the non-clinical aspects

Dry extract of *Valeriana officinalis* L. has been in medicinal use in the Community for a long period of time. The dry extract in Valerina Forte, coated tablet, is recognised to have a well established medicinal use with an acceptable level of safety in the European Community. No serious safety concerns have been identified.

IV. CLINICAL ASPECTS

IV.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued a Community monograph on *Valeriana officinalis* L. radix in 2006. In this monograph, it was concluded that the active substance in Valerina Forte, coated tablet (dry extract of *Valeriana officinalis* L.) has a well-established medicinal use with a recognised efficacy and acceptable level of safety in the Community in accordance with Directive 2001/83/EC.

The reader is referred to the Community monograph and the pertinent assessment report for details.

IV.2 Pharmacokinetics

There are no studies concerning pharmacokinetics. The lack of pharmacokinetic data is acceptable since constituents responsible for the therapeutic effect of the extracts are not entirely known, and thus pharmacokinetic studies are neither possible nor relevant.

IV.3 Pharmacodynamics

The mechanism of therapeutic action cannot be considered clarified at present.

The entire dry extract is regarded as being the active constituent of Valerina Forte, coated tablet.

IV.4 Clinical efficacy

In the assessment report pertaining to the Community monograph on *Valeriana officinalis* L. radix an extensive review of clinical trials on all types of extracts prepared with ethanol/water (ethanol 40 -70 % (V/V)) was presented.

The outcome is that valerian root seems to improve sleep structure with a gradual onset of efficacy rather than to exert a general sedating effect. After single intake valerian root changed mainly subjective perception of sleep, while sleep EEG changes were more pronounced after several days of intake. These observations are in concordance with clinical experiences showing a gradual improvement of symptoms over 2 – 4 weeks. Valerian root probably exerts its effects in pathological conditions rather than in healthy volunteers.

IV.5 Clinical safety

There are no new signals of safety concern in the submitted product specific documentation relating to Valerina Forte, coated tablet.

Gastrointestinal disorders (e.g. nausea and abdominal pain) may occur after ingestion of valerian root preparations.

Only limited data on pharmacological interactions with other medicinal products are available. Clinically relevant interactions with other drugs metabolised by the CYP 2D6, CYP 3A4/5, CYP 1A2 or CYP 2E1 pathway have not been observed. Combination with synthetic sedatives requires medical diagnosis and supervision.

As no data on use in children are available, products containing *Valeriana officinalis* L. radix *cannot* be recommended for use in children below the age of 12 years.

Due to lack of safety data, the use of products containing *Valeriana officinalis* L. radix, during pregnancy and lactation is not recommended.

The clinical safety documentation on Valerina Forte, coated tablet, indicates no signals of safety concern. Approval of Valerina Forte, coated tablet, as a herbal medicinal product with well-established use for treatment of mild nervous tension and sleep disorders is therefore recommended with respect to clinical safety.

IV.6 Discussion on the clinical aspects

Valerina Forte, coated tablet, is a herbal medicinal product available without prescription for the treatment of mild nervous tension and sleep disorders.

V. PRODUCT INFORMATION

The product information (Summary of Product Characteristics, Package Leaflet and labelling) has been assessed and accepted by the Medical Products Agency.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The adverse reactions reported during an extensive use of dried root of *Valeriana officinalis* L. are no cause for safety concern. No new safety signals have been identified in the submitted product specific documentation relating to Valerina Forte, coated tablet.

The benefit/risk ratio is considered positive and Valerina Forte, coated tablet, is recommended for approval.

VII. APPROVAL

Valerina Forte, coated tablet, was approved in the national procedure on 2009-06-08.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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