Public Assessment Report
Scientific discussion

Valerina Natt, coated tablet

(Valeriana officinalis L. (valerian) dried root; dry extract (5.25-7.5:1); ethanol 60 %. The extract contains 25 % excipients.

Humulus lupulus L. (hops) dried strobile; dry extract (3.4-6.4:1); ethanol 70 %. The extract contains 25 % excipients.

Melissa officinalis L. (melissa) dried leaf; dry extract (5-8:1); ethanol 60 %. The extract contains 30 % excipients)

Asp. No: 2008-0621

This module reflects the scientific discussion for the approval of Valerina Natt, coated tablet. The procedure was finalised at 30 April 2012. For information on changes after this date please refer to the module ‘Update’.
LAY SUMMARY

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

Valerina Natt is traditionally used to aid sleep. The active ingredients are extracts from Valerian root (*Valeriana officinalis*, vänderot), Hop strobile (*Humulus lupulus*, humle) and Lemon Balm leaves (*Melissa officinalis*, citronmeliss). This registration is based exclusively upon evidence of traditional use of Valerian, Hops and Lemon Balm as a herbal medicinal product and not upon data generated from clinical trials. For traditional herbal medicinal products there is no requirement to scientifically prove the effect; adequate evidence of traditional use is sufficient.

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 Natt, coated tablet could be registered as a traditional herbal medicinal product.
I. INTRODUCTION

Pharbio Medical International AB has applied for a traditional-use registration for Valerina Natt, coated tablet. The application was submitted under Article 16a traditional use registration for herbal medicinal product of the Directive 2001/83 EC, as amended. The application is a national application for Sweden.

The active substances are:
- *Valeriana officinalis* (valerian) dried root; dry extract (5.25-7.5:1); ethanol 60 %. Contains 25 % excipients
- *Humulus lupulus* (hops) dried strobile; dry extract (3.4-6.4:1); ethanol 70 %. The extract contains 25 % excipients
- *Melissa officinalis* (melissa) dried leaf; dry extract (5-8:1); ethanol 60 %. The extract contains 30 % excipients

For approved indications, see the Summary of Product Characteristics.

Valerina Natt, coated tablet, was first authorised as a natural remedy in 1996. As a consequence of the new legislation regarding (traditional) herbal medicinal products the product was reclassified as a traditional herbal medicinal product in 2012.

II. QUALITY ASPECTS

II.1 Introduction

Valerina Natt is presented in the form of a coated tablet containing:
- 80 mg dry extract of *Valeriana officinalis* L., radix (5.25-7.5:1) with extraction solvent ethanol 60 %, corresponding to approximately 420-600mg dried root of *Valeriana officinalis* L. The extract contains 25 % excipients.
- 86.7 mg dry extract of *Humulus lupulus* L., flos (3.4-6.4:1), extraction solvent ethanol 70 %, corresponding to approximately 292-552 mg dried strobile of *Humulus lupulus* L. The extract contains 25 % excipients.
- 25 mg dry extract of *Melissa officinalis* L., folium (5-8:1), extraction solvent ethanol 60 %, corresponding to approximately 124-200 mg dried leaf of *Melissa officinalis* L. The extract contains 30 % excipients.

The excipients are: lactose monohydrate, potato starch, powdered cellulose, hypromellose, magnesium stearate, colloidal anhydrous silica, macrogol 6000, titanium dioxide and hard paraffin.

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

II.2 Drug Substance

The herbal substances *Valeriana officinalis* L., *Humulus lupulus* L., and *Melissa officinalis* L. comply with their respective monographs Valerian root, Hop strobili and Melissa leaf, in the European Pharmacopoeia (Ph. Eur.), and with the general monograph for herbal drugs.
The Valerian used in the manufacture is cultivated in The Netherlands, Belgium, Germany and Eastern Europe; the Hops are cultivated in US, Germany, Great Britain, Czech Republic and China; and the Lemon Balm is cultivated in Europe and USA. Relevant information on growing conditions and controls of the herbal substances (such as residues of heavy metals and pesticides as well as microbiological quality) has been provided.

The herbal substance *Valeriana officinalis* L. is dried, grinded and extracted using a maceration process with 60 % ethanol. Extraction is followed by separation and concentration under low pressure to yield a soft extract, which is then mixed with fillers and dried to produce the final dry extract.

The herbal substance *Humulus lupulus* L. is dried, grinded and extracted using a maceration process with 70 % ethanol. Extraction is followed by separation and concentration under low pressure to yield a soft extract, which is then mixed with fillers and dried to produce the final dry extract.

The herbal substance *Melissa officinalis* L. is dried, grinded and extracted using a maceration process with 60 % ethanol. Extraction is followed by separation and concentration under low pressure to yield a soft extract, which is then mixed with fillers and dried to produce the final dry extract.

In summary, the manufacturing processes have been adequately described and satisfactory specifications have been provided for starting materials (herbal substance) and excipients/solvents. The tests and limits in the specifications are considered appropriate to control the quality in relation to the intended purpose.

All active substance (herbal preparation) specifications include 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 a retest period for the dry extracts of Valerian root and Lemon Balm leaves. However, no retest period was concluded for the dry extract of Hop strobile. Instead, complete testing according to the specification for the dry extract of *Humulus lupulus* L. is performed immediately prior to manufacture of the finished product.

II.3 Medicinal Product

Valerina Natt, coated tablet, is formulated using excipients described in the current Ph. Eur. All raw materials used in the product are safe with view to a 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 AND CLINICAL ASPECTS

III.1 Introduction

The Committee on Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) has issued Community monographs on Valeriana officinalis L., radix (2006), Humulus lupulus L., flos (2008) and Melissa officinalis L., folium (2007, rev. 2013) respectively. However, there is no Community monograph for the fixed combination. The reader is referred to the Community monographs and the pertinent assessment reports for details.

III.2 Non-clinical aspects

The applicant has collected available information from the literature in the areas of non-clinical pharmacology and toxicology. This information has been assessed by the MPA and no signals of non-clinical safety concern have been identified. The exact mechanism of action of Valeriana officinalis L., radix, Humulus lupulus L., flos, and Melissa officinalis L., folium in relation to their traditional medicinal use cannot be considered clarified.

A product specific study on mutagenic activity has been performed. The extracts have been shown not to be mutagenic in Ames test.

Based on the non-clinical information, both from the literature and the product specific study, no objections are raised to the approval of Valeriana officinalis L., radix, Humulus lupulus L., flos, and Melissa officinalis L., folium as active ingredients in a traditional herbal medicinal product.

III.3 Ecotoxicity/environmental risk assessment

Valerina Natt is a traditional herbal medicinal product. According to “Guideline on the environmental risk assessment of medicinal products for human use” (EMEA/CHMP/SWP/4447/00), (traditional) herbal medicinal products are exempted from the obligation to present an environmental risk assessment due to the nature of their constituents.

III.4 Clinical aspects

Results of clinical trials concerning clinical efficacy and safety are not required for the registration of a traditional herbal medicinal product.

III.5 Traditional use

The medicinal use of the combination of Valeriana officinalis L., Humulus lupulus L. and Melissa officinalis L. has a long traditional use exceeding 30 years in the Community. The traditional use of the combination is based on the product itself, Valerina Natt was first registered as a naturopathic remedy (naturmedel) in Sweden in 1978. The composition, uses and dosage of the product have remained essentially the same since this time period. Both the original product and the individual HMPC monographs for each active substance, state the use of oral dosage forms to aid sleep. The recommended dosage of Valerina Natt is in the same range as the individual dosages of each active substance listed in their respective HMPC monographs and in the literature.
In summary, the applicant has provided a bibliographic review which shows sufficient
evidence for the medicinal use of the combination of *Valeriana officinalis* L., *Humulus lupulus*
L. and *Melissa officinalis* L., throughout a period of at least 30 years, including at least 15
years within the Community.

### III.6 Clinical safety

Conventional clinical safety data are virtually absent. However, longstanding medicinal use
and experience of *Valeriana officinalis* L., *radix*, *Humulus lupulus* L., *flos* and *Melissa
officinalis* L., *folium* have been documented. During this time, no clinical signals that
*Valeriana officinalis* L., *radix*, *Humulus lupulus* L., *flos* or *Melissa officinalis* L., *folium* are
harmful under normal conditions of use have been identified.

As no data on use in children are available, products containing *Valeriana officinalis* L., *radix*,
*Humulus lupulus* L., *flos*, and *Melissa officinalis* L., *folium* 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*,
*Humulus lupulus* L., *flos* and *Melissa officinalis* L., *folium* during pregnancy and lactation is
not recommended.

Based on the clinical safety information available, no objections are raised to the approval of
Valerina Natt as a traditional herbal medicinal product.

### IV. PRODUCT INFORMATION

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

### V. OVERALL CONCLUSION, RISK ASSESSMENT AND
RECOMMENDATION

For Valerina Natt, coated tablet, the handling, manufacture and quality control of raw
materials, active substances and finished product are in line with GMP and pharmacopoeial
requirements. The applicant has shown that the chemical/pharmaceutical quality is acceptable
and can confirm that the process is under control and ensures both batch reproducibility and
compliance with the product specification.

The traditional use of the individual extracts in Valerina Natt are covered by the Community
monographs on *Valeriana officinalis* L., *radix*, *Humulus lupulus* L., *flos* and *Melissa officinalis*
L., *folium*, respectively. In addition, it has been adequately documented that the combination
of the extracts in Valerina Natt has had a medicinal use for at least 30 years, including at least
15 years within the Community.

No signals of preclinical or clinical safety concern have been identified under normal
conditions of use.
Valerina Natt, coated tablet, can be recommended for registration as a traditional herbal medicinal product.

VI. APPROVAL

Valerina Natt, coated tablet, was approved in the national procedure on 2012-04-30.
## Public Assessment Report – Update

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