EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 November 7 December 2017
EMA/HMPC/441766/2017EMA/HMPC/441766/2017
Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Valeriana officinalis* L., radix and *Humulus lupulus* L., flos

Draft - Revision 1

Based on Article 10a of Directive 2001/83/EC (well-established use)

Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Fixed combinations of *Valeriana officinalis* L., radix (valerian root) and *Humulus lupulus* L., flos (hop strobile)
Herbal preparation(s)	Dry extracts of valerian root (DER 4-8:1, methanol 45-51% m/m) and hop strobile (DER 3-10:1, methanol 40-51% m/m) Dry extracts of valerian root (DER 4-7:1, ethanol 70% V/V) and hop strobile (DER 4-8:1, methanol 40% V/V) Liquid extract (DER 1:6.3) from a mixture of valerian root-hop strobile (1:1), extraction solvent ethanol 40% V/V Mixture (1:1) of valerian root tincture (DER 1:10-11), extract solvent ethanol 58% V/V and hop strobile tincture (DER 1:12-13) extract solvent ethanol 65% V/V Dry extracts of valerian root (DER 4-6:1), extraction solvent water and hop strobile (DER 3-6:1), extraction solvent water Dry extracts of valerian root (DER 5-7:1), extraction solvent methanol 45% m/m and hop strobile (DER 5-7:1), extraction solvent water Dry extracts of valerian root (DER 4-5:1), extraction solvent ethanol 60% V/V and hop

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

	strobile (DER 5-9:1), extraction solvent water Dry extracts of valerian root (DER 4-7:1), extraction solvent methanol 45% V/V and hop strobile (DER 4-8:1), extraction solvent ethanol 40% V/V Dry extracts of valerian root (DER 3-7:1), extraction solvent ethanol 70% V/V and hop strobile (DER 4-8:1), extraction solvent ethanol 40% V/V Dry extracts of valerian root (DER 6-7:1), extraction solvent ethanol 70% V/V and hop strobile (DER 11-14:1), extraction solvent ethanol 96% V/V Dry extracts of valerian root (DER 5-8:1), extraction solvent ethanol 85% V/V and hop strobile (DER 9-11:1), extraction solvent ethanol 90% V/V
Pharmaceutical form(s)	Herbal preparation in solid or liquid dosage forms for oral use.
Rapporteur(s)	G. Laekeman (revision), A. Vlietinck (first version)
Assessor(s)	
Peer-reviewer	S. Girotto (revision), H. Pittner (first version)

Note: This draft assessment report is published to support the public consultation of the draft revised European Union herbal monograph on *Valeriana officinalis* L., radix (valerian root) and *Humulus lupulus* L., flos (hop strobile). It is a working document, not yet edited, and shall be further developed after the release for consultation of the revised monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation', will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft revised monograph.

Table of contents

1. Introduction

1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

Not applicable

- Herbal preparation(s)

The phytochemical composition of both valerian root and hop strobile and their preparations have amply been discussed in the assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

Not applicable

- Composition and analysis of substances

Prieto et al. (2016) explore the application of direct one-dimensional (1D) NMR analysis to assess the quality and stability of commercial valerian-hops tinctures.

Different batches of commercial tinctures were purchased in a health shop in London. All were labelled as organically grown and consisted in tinctures of *Valeriana officinalis* L. root, one within its expiry date (alcohol strength 56% v/v) and a second that had been expired for over nine months (alcohol strength 67% v/v). A preparation containing 50% V. officinalis root and 50% fresh Hummulus lupulus herb tinctures was also purchased (alcohol strength 61%v/v).

All the tinctures (0.65 mL) were directly analysed by NMR after adding 0.05mL of D_2O (0.05% TSP) as a solvent for internal lock. In addition, a volume of 0.65 mL of each tincture was measured and transferred to a microcentrifuge tube, carefully dried under oxygen-free nitrogen (BOC, UK) and the residue completely redissolved in different deuterated solvents. Standard solutions of valerenic acid and hydroxyvalerenic acid in ethanol-d6/D_2O (60%) were similarly analysed by NMR: a volume of 0.65mL was transferred to an NMR tube and 0.05mL of D_2O (0.05% TSP) was added.

The analytical technique used revealed to be a simple approach which could be easily processed and interpreted in the same manner of a 1D HPLC chromatogram or a TLC plate. The application of NMR to valerian and hops products successfully reveals the presence of the characteristic peaks of valerenic acid and prenylated moieties from aplha-acids in fresh tinctures as well as hydroxyvalerenic acid only in expired/degraded ones. Therefore direct NMR may be used as a rapid technique to provide additional information in the quality control of herbal constituents of complex herbal pharmaceutical products (Prieto et al. 2016).

1.2. Search and assessment methodology

Primary source is the assessment report as published in May 2010.

Databases Pubmed / Embase: search on *valerian* OR *Valeriana* AND *hops* OR *Humulus; valerian/hops* OR *valeriana/humulus* since 2009, extending the search until June 2017, yielding 21 references. Selected on abstract and content: 6 references. None of them related to original clinical studies. Finally, 4 references were taken to the revised assessment report, one of them dating from 2008.

Data received from the call of scientific data: containing product information.

Market overview from the EU-members (until December 2016).

2. Data on medicinal use

2.1. Information about products on the market

2.1.1. Information about products on the market in the EU/EEA Member States

Information on combination medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	**Indication**	**Pharmaceutical form** **Strength (where relevant)** **Posology** **Duration of use**	**Regulatory Status (date, Member State)**
Valerian extract (4-7:1, ethanol 70% v/v), hops extract (4-8:1, ethanol 40% v/v)	Restlessness, mild forms of sleep disorders	Coated tablets: 1 coated tablet: 100 mg Valerian extract (4-7:1, ethanol 70% v/v), 24 mg hops extract (4-8:1, ethanol 40% v/v) Adults, adolescents and children > 10 years: sleep disorders 2 tablets in the evening; restlessness: max. 3 x daily 2 tablets	WEU 2003 AT
Valerian extract (4-7:1, ethanol 70% v/v), hops extract (4-8:1, ethanol 40% v/v)	Restlessness, mild forms of sleep disorders	Coated tablets: 1 coated tablet: 200 mg Valerian extract (4-7:1, ethanol 70% v/v), 68 mg hops extract (4-8:1, ethanol 40% v/v) Adults, adolescents and children > 10 years: sleep disorders 1 tablets in the evening; restlessness: max. 3 x daily 1 tablet	WEU 2005 AT

Valerian extract (4-7:1, ethanol 70% v/v), hops extract (4-8:1, methanol 40% v/v)	Restlessness, nervous sleep disorders	Film coated tablets [1]: 1 coated tablet contains: 200.2 mg Valerian extract (4-7:1, ethanol 70% v/v), 45.5 mg hops extract (4-8:1, methanol 40% v/v) Restlessness: 1-3 times daily 1 tablet; nervous sleep disorders: 2 tablets in the evening (children 6-12 years: 1 tablet)	WEU 1993 AT
Valerian extract (3:1, water), hops extract (3:1, water)	Restlessness, mild forms of sleep disorders, nervousness	Coated tablets: 55 mg Valerian extract (3:1, water), 10 mg hops extract (3:1, water) Sleep disorders 3-5 tablets in the evening; restlessness: 3 x daily 2 tablets	TU 1991 AT
Valerian extract (3-6:1, ethanol), hops extract (4-8:1, water)	To aid sleep, nervousness, restlessness	Coated tablets: 68 mg Valerian extract (3-6:1, ethanol), 16 mg hops extract (4-8:1, water) Sleep disorders 3 tablets in the evening; restlessness: 3 x daily 2 tablets	TU 2002 AT
Valerian extract (6:1, stand. to min. 5% sesquiterpene acids, ethanol), hops extract (7.5:1, stand. to min. 0.4% flavonoids, ethanol)	Nervous sleep disorders	Coated tablets: 220 mg Valerian extract (6:1, stand. to min. 5% sesquiterpene acids, ethanol), 50 mg hops extract (7.5:1, stand. to min. 0.4% flavonoids, ethanol) In the evening 1-2 capsules	TU 1996 AT
Valerian extract (6:1, stand. to min. 5% sesquiterpene acids, ethanol) hops extract (7.5:1, stand. to min. 0.4% flavonoids, ethanol)	restlessness, nervous sleep disorders	Coated tablets: 220 mg Valerian extract (6:1, stand. to min. 5% sesquiterpene acids, ethanol), 50 mg hops extract (7.5:1, stand. to min. 0.4% flavonoids, ethanol) up to 3 x daily 1 capsule, in case of sleep disorders 1-2 capsules in the evening	TU 1998 AT
Valerian root dry extract(4.5:1, methanol 50%, v/v) and hops dry extract (4:1, methanol 50%	Restlessness, nervous sleep disorders	Coated tablets 1 tablet contains 250mg valerian root dry extract(4.5:1, methanol 50%, v/v) and 65 mg hops dry extract	WEU 2000 BE (not any longer on the market)

v/v)		(4:1, methanol 50% v/v) Adults, adolescents>12 years, sleep disorders;1-2 tablets in the evening, restlessness ;1-2 tablets 3x daily	
Dry extract from valerian root DER 4-6.7:1, extraction solvent ethanol 70% (V/V) – Dry extract from hop strobile DER 4-8:1, extraction solvent ethanol 40% (V/V)	Traditional herbal medicine to alleviate light symptoms of mental stress	Dry extract from valerian root DER 4-6.7:1, extraction solvent ethanol 70% (V/V) 200 mg/tablet– Equivalent to 800 – 1340 mg dried valerian root. Dry extract from hop strobile DER 4-8:1, extraction solvent ethanol 40% (V/V) 68 mg equivalent to 272 – 544 mg dried hop strobile.	TU BE 2013
Dry extract from Valerian root, DER 4-7:1, extraction solvent ethanol 70% (V/V) - Dry extract from Hop strobile, DER 4-8:1, extraction solvent methanol 40% (V/V) –	therapy of sleep disorders due to nervosity; restlessness, nervosity, anxiety	Dry extract from Valerian root, DER 4-7:1, extraction solvent ethanol 70% (V/V) - 200.2 mg/tbl Dry extract from Hop strobile, DER 4-8:1, extraction solvent methanol 40% (V/V) – 45.5 mg/tbl for oral use sleep disturbances: adults - two coated tablets (corresponding to 400.4 mg of Valerian extract and 91 mg of Hop extract) ½ hour before bedtime children over 6 years and adolescents - one coated tablets (corresponding to 200.2 mg of Valerian extract and 45.5 mg of Hop extract) ½ hour before bedtime restlessness, nervosity, anxiety: one tablet (corresponding to 200.2 mg of Valerian extract and 45.5 mg of Hop extract) 3 times daily	WEU 1999 CZ
Dry extract from Valerian root, DER 4-7:1, extraction solvent ethanol 70% (V/V) -	sleep disorders due to restlessness, anxiety, excitement and tension	Dry extractfrom Valerian root, DER 4-7:1, extraction solvent ethanol 70% (V/V) – 60	TU 1993 CZ

Dry extract from Hop strobile, DER 11-14:1, extraction solvent ethanol 96% (V/V)		mg/tbl Dry extract from Hop strobile, DER 11-14:1, extraction solvent ethanol 96% (V/V) – 60 mg/tbl for oral use adults 2 – 3 coated tablets (corresponding to 120 – 180 mg of Valerian extract and 120 – 180 mg of Hop extract) 1 hour before bedtime children over 6 years 1 – 2 coated tablets (corresponding to 60 - 120 mg of Valerian extract and 60 - 120 mg of Hop extract) 1 hour before bed time	
Dry extract from Valerianae radix (4-6:1), ES water and dry extract from Lupuli flos (3-6:1), ES water	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 80 mg dry extract from Valerianae radix and 20 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 3 coated tablets Indication B) 3 coated tablets 1/2 - 1 h before bedtime. If necessary, additionally 3 coated tablets earlier in the evening.	TU 1976 DE
Dry extract from Valerianae radix (6-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (11-14:1), ES ethanol 96% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 225 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication A) 1-3 x daily 1 coated tablet Indication B) 1-2 coated tablets 1/2 - 1 h before bedtime	TU 1976 DE
Dry extract from Valerianae radix (4-6.7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4.3-7.7:1), ES ethanol 40% V/V	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 100 mg dry extract from Valerianae radix and 24 mg dry extract from Lupuli flos Indication B) 2 coated tablets 1/2 - 1 h before bedtime If necessary, additionally 2 coated tablets earlier in the evening	TU 1976 DE
Dry extract from Valerianae radix (5.5-7.4:1), ES ethanol	Indication A) "Unruhezustände" Herbal medicinal	1 coated tablet contains 77 mg dry extract from Valerianae radix and	TU 1976 DE

85% V/V and dry extract from Lupuli flos (9-11:1), ES ethanol 90% V/V	product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	18.8 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime. If necessary, additionally 2 coated tablets earlier in the evening	
Dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli flos (7.7-9.5:1), ES methanol 45% m/m	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 200 mg dry extract from Valerianae radix and 14 mg dry extract from Lupuli flos Indication A) 1-3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime	WEU 1976 DE
Dry extract from Valerianae radix (4-6:1), ES water and dry extract from Lupuli flos (3-6:1), ES water	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 160 mg dry extract from Valerianae radix and 40 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime. If necessary, additionally 2 coated tablets earlier in the evening.	TU 1976 DE
Dry extract from Valerianae radix (4-5:1), ES methanol 50% V/V and dry extract from Lupuli flos (3.4-4.2:1), ES methanol 50% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 250 mg dry extract from Valerianae radix and 65 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime.	WEU 1976 DE
Dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 200 mg dry extract from Valerianae radix and 68 mg dry extract from Lupuli flos Indication B) 1 coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 coated tablet earlier in the	TU 1999 DE

		evening.	
dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 200 mg dry extract from Valerianae radix and 68 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 coated tablet earlier in the evening	TU 1998 DE
Dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 170 mg dry extract from Valerianae radix and 25 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 soft capsule Indication B) 1 soft capsule 1 h before bedtime.	TU 1998 DE
dry extract from Valerianae radix (6-7.4:1), ES ethanol 70% V/V and dry extract from Lupuli flos (11-14:1), ES ethanol 96% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 170 mg dry extract from Valerianae radix and 25 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 soft capsule Indication B) 1 soft capsule 1 h before bedtime.	TU 1999 DE
dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli flos (7.7-9.5:1), ES methanol 45% m/m	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 200 mg dry extract from Valerianae radix and 35 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 soft capsule Indication B) 1 soft capsule 1/2 - 1 h before bedtime	WEU 1976 DE
dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES methanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of	1 coated tablet contains 175 mg dry extract from Valerianae radix and 35 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime.	WEU 1976 DE

	difficulty in falling asleep		
dry extract from Valerianae radix (5.3-6.6:1), ES methanol 45% m/m and dry extract from Lupuli flos (5.5-6.5:1), ES water	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 187.5 mg dry extract from Valerianae radix and 45 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime	TU 1976 DE
dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 125 mg dry extract from Valerianae radix and 25 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime	TU 1976 DE
dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 68 mg dry extract from Valerianae radix and 16 mg dry extract from Lupuli flos Indication A and B) Up to 3 x daily 3 coated tablets	TU 1976 DE
dry extract from Valerianae radix (4-5:1), ES ethanol 60% V/V and dry extract from Lupuli flos (5.88-6.6:1), ES water	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 100 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication A) 2- 3 x daily 2 soft capsules Indication B) 2 soft capsules approx. 1 h before bedtime	TU 1976 DE
dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli flos (4-8:1), ES methanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling	1 soft capsule contains 100 mg dry extract from Valerianae radix and 25.02 mg dry extract from Lupuli flos Indication A) 1- 3 x daily 2 soft capsules Indication B) 2 soft capsules ½ - 1 h before bedtime	WEU 1976 DE

	asleep		
dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 100 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication B) 2 soft capsules 1/2 - 1 h before bedtime	TU 1976 DE
dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 100 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication B) 2 soft capsules 1/2 - 1 h before bedtime	WEU 1976 DE
dry extract from Valerianae radix (3-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	contains 100 mg dry extract from Valerianae radix and 24 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime	WEU 1976 DE TU 2013 BE TU 2013 HR TU 2013 ES
dry extract from Valerianae radix (5.3-6.6:1), ES methanol 45% m/m and dry extract from Lupuli flos (5.5-6.5:1), ES water	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 187 mg dry extract from Valerianae radix and 45 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime	TU 1976 DE
dry extract from Valerianae radix (5-8:1), ES methanol 45% m/m and dry extract from Lupuli flos (7-10:1), ES methanol 45% m/m	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 film-coated tablet contains 187 mg dry extract from Valerianae radix and 41.88 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 film-coated tablet Indication B) 1 film-coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 film-coated tablet earlier in the evening	WEU 1976 DE
dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension.	1 soft capsule contains 100 mg dry extract from Valerianae radix and 25.02 mg dry extract from Lupuli flos	WEU 1976 DE

flos (4-8:1), ES ethanol 40% V/V	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	Indication A) 2-3 x daily 2 soft capsules Indication B) 2 soft capsules 1/2 h before bedtime	
dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 100 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication B) 2 soft capsules 1/2 - 1 h before bedtime	WEU 1976 DE
dry extract from Valerianae radix (5.3-6.6:1), ES methanol 45% m/m and dry extract from Lupuli flos (5.5-6.5:1), ES water	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 187 mg dry extract from Valerianae radix and 45 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 coated tablet earlier in the evening	TU 1976 DE
dry extract from Valerianae radix (4-6.7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4.3-7.7:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 100 mg dry extract from Valerianae radix and 32 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime	WEU 1976 DE
dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 68 mg dry extract from Valerianae radix and 16 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 3 coated tablets Indication B) 3 coated tablets 1/2 - 1 h before bedtime If necessary, additionally 2 x 3 coated tablet earlier in the evening	WEU 1976 DE
dry extract from Valerianae radix (5.3-	Indication A) "Unruhezustände"	1 coated tablet contains 187.5 mg dry extract	TU 1976 DE

6.6:1), ES methanol 45% m/m and dry extract from Lupuli flos (5.5-6.5:1), ES water	Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	from Valerianae radix and 45 mg dry extract from Lupuli flos Indication A) 1 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime	
dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli flos (4-8:1), ES methanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 100 mg dry extract from Valerianae radix and 25.02 mg dry extract from Lupuli flos Indication A) 1- 3 x daily 2 soft capsules Indication B) 2 soft capsules ½ - 1 h before bedtime	WEU 1976 DE
dry extract from Valerianae radix (4-6.7:1), ES methanol 45% V/V and dry extract from Lupuli flos (7.7-9.5:1), ES methanol 45% m/m	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 200 mg dry extract from Valerianae radix and 35 mg dry extract from Lupuli flos Indication A) 2 x daily 1 soft capsule Indication B) 1 soft capsule 1/2 - 1 h before bedtime	WEU 1976 DE
dry extract from Valerianae radix (4-6.7:1), ES methanol 45% V/V and dry extract from Lupuli flos (4.3-7.7:1), ES methanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 200 mg dry extract from Valerianae radix and 48 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime	WEU 1976 DE
dry extract from Valerianae radix (4-6:1), ES water and dry extract from Lupuli flos (3-6:1), ES water	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 160 mg dry extract from Valerianae radix and 40 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime. If necessary, additionally 2 coated tablets earlier in the evening.	TU 1976 DE

dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 100 mg dry extract from Valerianae radix and 24 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime	WEU 1996 DE
dry extract from Valerianae radix (4-5:1), ES methanol 51.25% V/V and dry extract from Lupuli flos (3.4-4.2:1), ES methanol 51.25% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 soft capsule contains 250 mg dry extract from Valerianae radix and 65 mg dry extract from Lupuli flos Indication A) Up to 2 x daily 1 soft capsule Indication B) 1 soft capsule 1/2 - 1 h before bedtime	WEU 1993 DE
dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep	1 coated tablet contains 200 mg dry extract from Valerianae radix and 68 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 coated tablet earlier in the evening	WEU 1998 DE
dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asle	1 coated tablet contains 200 mg dry extract from Valerianae radix and 68 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 coated tablet earlier in the evening	WEU 1998 DE
dry extract from Valerianae radix (4-6.7:1), ES ethanol 40% V/V and dry extract from Lupuli flos (4.3-7.7:1), ES ethanol 40% V/V	"Traditionell angewendet zur Besserung des Befindens bei nervlicher Belastung. Diese Angabe beruht ausschließlich auf	for oral use in adults and adolescents over 12 years 1 coated tablet contains 32 mg dry extract from Valerianae radix and 9 mg dry extract from	TU 1976 DE

	Überlieferung und langjähriger Erfahrung." Traditional herbal medicinal product for support of mental relaxation. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use	Lupuli flos 2-3 x daily 1 coated tablet	
liquid extract (1:6.3) from a mixture of Valerianae radix : Lupuli flos (1:1), ES ethanol 40% V/V	"Traditionell angewendet zur Besserung des Befindens bei nervlicher Belastung. Diese Angabe beruht ausschließlich auf Überlieferung und langjähriger Erfahrung." Traditional herbal medicinal product for support of mental relaxation. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use	for oral use in adults 3 x daily 20 ml containing 12% V/V extract	TU 1976 DE
soft extract (5-6.7:1) from a mixture of Valerianae radix : Lupuli flos (5.7:1), ES methanol 40% V/V	"Traditionell angewendet zur Besserung des Befindens bei nervlicher Belastung. Diese Angabe beruht ausschließlich auf Überlieferung und langjähriger Erfahrung." Traditional herbal medicinal product for support of mental relaxation. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use	Liquid bath additive [2]: for external use as bath additive in adults and adolescents over 12 years 100 g (= 92.2 ml) bath additive contain 11.7 g soft extract 30 ml liquid bath additive / 120 l water maximal 2 x weekly bath duration 10-20 min bath temperature 34-37ºC	TU 1976 DE
Valerianae radix, dry extract ethanolic 70% (V/V), (4-7:1) 100 mg Lupuli flos, dry extract methanolic 40% (V/V), (4-8:1)	Sleeping disorders based on nervous condition. Restlessness, nervousness, anxiety	Film coated tablets: 25 mg Valerianae radix, dry extract ethanolic 70% (V/V), (4-7:1) 100 mg Lupuli flos, dry extract methanolic 40% (V/V), (4-8:1) Adults: Sleeping disorders: 4-5	WEU 1996 HU

		film tablets half an hour before going to bed. Restlessness, nervousness, anxiety: 3 x 1-2 film tablets daily	
Valerianae radix, dry extract ethanolic 70% (V/V), (4-7:1) Lupuli flos, dry extract methanolic 40% (V/V), (4-8:1)	Sleeping disorders based on nervous condition. Restlessness, nervousness, anxiety	Film coated tablets: 200.2 mg Valeriaenae radix, dry extract ethanolic 70% (V/V), (4-7:1) 45.5 mg Lupuli flos, dry extract methanolic 40% (V/V), (4-8:1) Adults: Sleeping disorders: 2 db film tablets half an hour before going to bed. Restlessness, nervousness, anxiety: 1-3 x 1 film tablets daily.	WEU 1999 HU
Valerianae rad. dry extr.methanolic 45% , (5-8:1) Lupuli strobuli dry extr.methanolic 45% ,(7-10:1)	Sleeping disorders based on nervous condition	Film coated tablets: 187.5 mg Valerianae rad. dry extr.methanolic 45% , (5-8:1) 42 mg Lupuli strobuli dry extr.methanolic 45% ,(7-10:1) Adults: 2 db film tablets an hour before going to bed. This dosage can be enhanced for 3 filmtablets Children: 6 years or above 1 filmtablet Elderly : the same as adults	WEU 2003 HU
Valerianae radix extr. sicc. (4-6:1) extractant: aqua purificata Lupuli flos extr. sicc. (3-6:1) extractant: aqua purificata	Reduces nervousness, tensions, facilitates getting to sleep	Film coated tablets: 80.00 mg Valerianae radix extr. sicc. (4-6:1) extractant: aqua purificata 20.00 mg Lupuli flos extr. sicc. (3-6:1) extractant: aqua purificata Adults and elderly: 2-3 x 1-2 dragées	TU 1994 HU TU 2012 HU TU 2010 HR
Valerianae radicis officinalis extr. aqu..sicc. (4-6:1) Lupulis flos extr. aqu. sicc. (3-6:1)	Reduces nervousness, tensions, facilitates getting to sleep	Film coated tablets: 160.00 mg Valerianae radicis officinalis extr. aqu..sicc. (4-6:1) 40.00 mg Lupulis flos extr. aqu. sicc. (3-6:1) Adults and elderly: 1-2 x 1 dragées	TU 2002 HU
Valerianae radix, extractum siccum (4-	sleep disorders psychosomatic	Valerianae radix, extractum siccum (4-	TU 1999 PL

7:1) 220mg, extraction solvent – ethanol 70% v/v Lupuli strobilus, extractum siccum (4-8:1) 65mg, extraction solvent methanol 40% v/v	stomach spasms	7:1) 220mg, extraction solvent – ethanol 70% v/v Lupuli strobilus, extractum siccum (4-8:1) 65mg, extraction solvent methanol 40% v/v oral use – 1 tablet 1-3 times daily	
Valerianae radix extractum siccum (4-6:1) Extration solvent:Methanol 45%; Lupuli flos extractum siccum (5-7:1) Extraction solvent:Methanol 45%:	Adjuvant in case of difficulties in falling asleep and sleeping through the night as well as uneasy sleep.	Film coated tablets; MA: 2004 Composition: 250.0mg Valerianae radix extractum siccum (4-6:1) Extration solvent:Methanol 45%;Carrier: maltodextrin 25% 60.0mg Lupuli flos extractum siccum (5-7:1) Extraction solvent:Methanol 45%: Carrier: maltodextrin 30% Excipiens q.s. ad 570mg Adults: 2 tablets one hour before going to bed. If required, the dose can be increased to 3 tablets. Children over 12 years of age: 1 tablet one hour before going to bed Elderly: as for adults:	WEU 2004 RO
Valeriana officinalis L., radix, extractum siccum (5:1); extraction solvent: 70% (V/V) ethanol and Humulus lupulus L., flos, extractum siccum (5,5:1); extraction solvent: 40% (V/V) methanol	a) Mild insomnia as a consequence of tenseness, restlessness b) Mild nervous tension	Film coated tablets: 1 tablet contains 200.2 mg of Valeriana officinalis L., radix, extractum siccum (5:1); extraction solvent: 70% (V/V) ethanol and 45.5 mg of Humulus lupulus L., flos, extractum siccum (5,5:1); extraction solvent: 40% (V/V) methanol a) Adults and children above 12 years: 2 film-coated tablets half to one hour before bedtime b) Adults and children above 12 years: 1 film-coated tablets up to three times a day	WEU 1999 SI
Mixture (1:1) of valerian root tincture (DER 1:10-11), extract solvent ethanol 58% v/v and hop	Traditional herbal medicinal product used for temporary insomnia and minor nervous tension. The	strobile 1 ml contains: 460 mg Valeriana officinalis L., fresh root, tincture (DER 1:10).	TU 1978 SE TU 2015 SI TU 2014 IE

strobile tincture (DER 1:12-13) extract solvent ethanol 65% v/v	product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use (SWE). Indication 1 Traditional herbal medicinal product for relief of mild symptoms of (mild) mental stress (SLO, IRL). Indication 2 Traditional herbal medicinal product used to aid sleep (SLO).	Extraction solvent: ethanol 58 % (v/v). 460 mg Humulus lupulus L., fresh strobile, tincture (DER 1:12). Extraction solvent: ethanol 65 % (v/v) Oral drops, solution Posology: Adults, elderly and adoscelents above 12 years of age: Minor nervous tension: 1 ml (approx. 40 drops) in ½ glass of water 3-5 times daily Temporary insomnia: 2 ml (approx. 80 drops) in ½ glass of water (SWE) Adolescents and adults: "to aid sleep: 30 drops half an hour before bedtime; for relief of mild symptoms of mental stress: 10 to 20 drops once to twice daily" (SLO)	
Valeriana officinalis L. s.l., dried root, dry extract (DER 4-6.7:1). Extraction solvent: ethanol 70 % (v/v). Humulus lupulus L., dried strobile, dry extract (DER 4-8:1). Extraction solvent: ethanol 40 % (v/v)		1 tablet contains: 200 mg Valeriana officinalis L. s.l., dried root, dry extract (DER 4-6.7:1). Extraction solvent: ethanol 70 % (v/v). 68 mg Humulus lupulus L., dried strobile, dry extract (DER 4-8:1). Extraction solvent: ethanol 40 % (v/v)	SE 2014
Valeriana officinalis L., radix dry extract (DER 4:1), extraction solvent: methanol 45% (V/V) Humulus lupulus L., flos (hop strobile) dry extract (DER 5:1) extraction solvent methanol 40% V/V	Herbal medicinal product for the relief of mild nervous tension and sleep disorders	Valeriana officinalis L., radix 125 mg of Dry extract (DER 4:1), extraction solvent: methanol 45% (V/V) Humulus lupulus L., flos (hop strobile) 27.8 mg of Dry extract (DER 5:1) extraction solvent methanol 40% V/V Soft capsules Relief of nervous tension: 1-2 capsules, 1-3 times/ day	WEU ES 2000

		Sleep disorders: 1-2 capsules half to one hour before bedtime and if needed 1 more capsule later 2-4 weeks	
Valeriana officinalis L., radix dry extract (DER 4-6.7:1), extraction solvent: ethanol 70% V/V Humulus lupulus L., flos (hop strobile) dry extract (DER 4-8:1) extraction solvent ethanol 40% V/V	Traditional herbal medicinal product for relief of mild symptoms of mental stress	Valeriana officinalis L., radix 200 mg of Dry extract (DER 4-6.7:1), extraction solvent: ethanol 70% V/V Humulus lupulus L., flos (hop strobile) 68 mg of Dry extract (DER 4-8:1) extraction solvent ethanol 40% V/V 1 tablet 3 times/day If the symptoms persist longer than 2 weeks of continued use of the medicinal product, a doctor or a qualified health care practitioner should be consulted.	TU ES 2013
Dry extract of valerian root (DER 4-5:1), extraction solvent ethanol 60% v/v and hop strobile (DER 9-11:1), extraction solvent ethanol 45% v/v.	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress.	Each tablet contains 52 mg of extract (as dry extract) from Valeriana officinalis L., radix (equivalent to 208 mg – 260 mg of Valerian root). Extraction solvent: Ethanol 60% V/V. Each tablet contains 9 mg of extract (as dry extract) from Humulus lupulus L., strobile (equivalent to 81 mg – 99 mg of Hop strobile). Film coated tablet For oral short term use only Adults and the elderly: One tablet to be taken 3 times a day. As treatment effects may not be apparent immediately, the tablets should be taken for 2 weeks continuously. Duration of use: If symptoms persist, worsen or do not improve after 2 weeks use of a qualified	TU 2013 IE

		healthcare professional e.g. a doctor or pharmacist should be consulted. Not recommended for children or adolescents under 18 years	
Dry extract of valerian root (DER 4-5:1) extraction solvent ethanol 60% v/v and hop strobile (DER 4-8:1) extraction solvent ethanol 40% v/v	A traditional herbal medicinal product used to aid sleep based on traditional use only.	Each film coated tablet contains: 62.5 mg of extract (as dry extract) from Valerian root (Valeriana officinalis L.) (4:1) Extraction solvent: Ethanol 60% (v/v) and 33.4 mg of extract (as dry extract) from Hops strobile (Humulus lupulus L.) (4-8:1) Extraction solvent : Methanol 40% (v/v) Film coated tablet Adults & the elderly: one to three tablets half an hour before bed. As treatment effects may not be apparent immediately, the tablets should be taken 2-4 weeks continuously. If symptoms worsen or do not improve after 4 weeks, a doctor or qualified healthcare practitioner should be consulted.	TU – 2013 UK

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.

[1] Additional information for Coated tablets No 4:

1 coated tablet contains 45.5 mg dry extract of hop strobile, DER 4-8:1, extraction solvent methanol 40% (v/v) 200.2 mg dry extract of valerian root, DER 4-7:1, extraction solvent ethanol 70% (v/v)

Posology: As an aid to sleep: adults and adolescents 2 coated tablets in the evening, children from 6-12 years of age (when recommended by a doctor) 1 coated tablet. Restlessness, nervousness: adults and adolescents 1-3 x daily 1 coated tablet, children from 6-12 years of age (when recommended by a doctor) 1-2 x daily 1 coated tablet.

[2] For the publication of Müller-Limmroth & Ehrenstein (1977) the medicinal product "Seda-Kneipp" was used, as referred to in the article. At this time the product was composed of:

60 mg dry extract of Valeriana (4.5:1); methanol 40% (V/V)

100 mg dry extract from Hop (5:1); methanol 30% (V/V).

Later (1994) the composition was changed.

It was now:

77 mg dry extract from Valerian (5.5-7.4:1); ethanol 85% (V/V),

18.8 mg dry extract from Hop (9-11:1); ethanol 90% (V/V).

Assessor's comments

The herbal preparations with marketing authorisations consist of fixed combinations of dry or liquid extracts or tinctures of valerian root and hop strobile, prepared with water, methanol/water ethanol/ethanol or ethanol/water. Their pharmaceutical forms are coated tablets, soft capsules or film-coated tablets. These products are marketed in Austria, Belgium, Croatia, Czech Republic, Germany, Hungary, Ireland, Romania, Slovenia, Spain and the United Kingdom. A soft extract of a mixture of both herbal substances is traditionally used as bath additive in Germany.

Only the herbal preparations which have been used in the controlled clinical studies of good methodological quality can be considered as preparations for well-established use. It concerns the following fixed combinations of dry extracts:

250 mg or 500 mg valerian dry extract (5.3:1, methanol 45% m/m) and 60 mg or 120 mg hop dry extract (6.6:1, methanol 45% m/m)

200.2 mg valerian dry extract (5:1, ethanol 70% v/v) and 45.5 mg hop dry extract (5.5:1, methanol 50% v/v)

187 mg valerian dry extract (5-8:1, methanol 45% m/m) and 41.9 mg hop dry extract (7-10:1, methanol 45% m/).

By extension, combinations which contain almost the same amounts of valerian and hop extracts and are prepared according to almost the same parameters of DER and strength of solvent are also acceptable for well-established use.

The other fixed combinations including those which have obtained a national marketing authorisation should be considered for traditional use when they have been on the market for more than 30 years. Since no liquid preparations have been clinically tested, they should also be considered for traditional use. Since the clinical studies mainly involve non-organic insomnia, 'restlessness' should not be taken as an indication for herbal preparations intended for well-established use.

Information on relevant combination medicinal products marketed in the EU/EEA

No relevant data on authorised combinations of valerian and hops preparations with other herbal medicinal preparations.

Information on other products marketed in the EU/EEA (where relevant)

No data available.

2.1.2. Information on products on the market outside the EU/EEA

Not applicable.

2.2. Information on documented medicinal use and historical data from literature

Fixed combinations of dry extracts of valerian root and hop strobile have obtained a marketing authorization in several countries for the same indication as valerian preparations alone, viz. relief of

mild nervous tension and sleep disorders, for more than 10 years. Several other fixed combinations of dry extracts, liquid extracts or soft extracts are traditionally used for more than 30 years for the same indication as valerian preparations alone, viz. to support mental relaxation.

Table 2: Overview of historical data

Herbal preparation	**Documented Use / Traditional Use**	**Pharmaceutical form Strength (where relevant) Posology Duration of use**	**Reference**
For this information, the reader is referred to table 1.			

2.3. Overall conclusions on medicinal use

Table 3: Overview of evidence on period of medicinal use (30 years for traditional us, 10 years for well-established use)

Herbal preparation Pharmaceutical form	**Indication**	**Strength Posology**	**Period of medicinal use**
Well Established Use - WEU			
a) dry Valerian extract (5-8:1, methanol 45% m/m), hops extract (7-10:1, methanol 45% m/m)	Sleep disorders	1 film-coated tablet contains: 374 mg dry Valerian extract (5-8:1, methanol 45% m/m), 84 mg hops extract (7-10:1, methanol 45% m/m) Film-coated tablet Adults, adolescents: 1 film-coated tablet 1 hour before bedtime 2 weeks	WEU AT 2008
a) Dry extracts of valerian root (DER 4-8:1, methanol 45-51% m/m) and hops (DER 3-10:1, methanol 40-51% m/m)	Herbal medicinal product for the relief of sleep disorders.	Fixed combinations of 187 mg/28 mg - 500 mg/65 mg dry extracts of valerian root and hop strobile, respectively 1-2 doses half to one hour before bedtime, not exceeding 500 mg	WEU DE 1976 DE 1993 DE 1998 HU 2003 PL 2004 ES 2000

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
		of valerian extract.	
b) Valerian extract (4-7:1, ethanol 70% v/v), hops extract (4-8:1, methanol 40% v/v)	restlessness, mild forms of sleep disorders	1 film-coated coated tablet contains: 200.2 mg Valerian extract (4-7:1, ethanol 70% v/v), 45.5 mg hops extract (4-8:1, methanol 40% v/v) Film-coated tablet Adults, adolescents: sleep disorders 2 tablets in the evening; restlessness: 1-3 x daily 1 tablet Children 6-12 years (if recommended by a doctor): sleep disorders 1 tablet in the evening; restlessness: 1-2 x daily 1 tablet 2-4 weeks	WEU AT 1993
b) Dry extracts od valerian (4-7:1, ethanol 70% v/v), hop strobile extract (4-8:1, methanol 40% v/v)	restlessness, mild forms of sleep disorders	1 coated tablet: 100 mg Valerian extract (4-7:1, ethanol 70% v/v), 24 mg hops extract (4-8:1, ethanol 40% v/v) Adults, adolescents: sleep disorders2 tablets in the evening; restlessness: max. 3 x daily 2 tablet No limitation of the duration of use	WEU AT 2003
b) Dry extracts of valerian root (DER 4-7:1, ethanol 70% v/v) and hop strobile (DER 4-8:1, methanol 40%	Herbal medicinal product for the relief of sleep disorders.	Fixed combination of 200 mg/45-mg – 350 mg/70 mg of	WEU AT 1993 AT 2003 AT 2005

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
v/v)		dry extracts of valerian root and hop strobile, respectively 1-2 doses half to one hour before bedtime, not exceeding 500 mg of valerian extract.	CZ 1999 DE 1976 HU 1996 HU 1999 HU 2003 (withdrawn) PL 1999 SI 1999
Traditional Use – TU: Liquid extracts			
a) Liquid extract (DER 1:6.3) from a mixture of valerian root-hop strobile (1:1), extraction solvent ethanol 40% v/v	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress. Indication 2 Traditional herbal medicinal product used to aid sleep.	Single dose 20 ml	TU DE 1976
b) Liquid extract from a mixture (1:1) of valerian root tincture (DER 1:10-11), extract solvent ethanol 58% v/v and hop strobile tincture (DER 1:12-13) extract solvent ethanol 65% v/v 1 ml contains: 460 mg Valeriana officinalis L., fresh root, tincture (DER 1:10). Extraction solvent: ethanol 58 % (v/v). 460 mg Humulus lupulus L., fresh strobile, tincture (DER 1:12). Extraction solvent: ethanol 65 % (v/v)	Indication 1 Traditional herbal medicinal product for minor nervous tension (SWE). Traditional herbal medicinal product for relief of (mild) symptoms of mental stress (IRL,SLO). Indication 2 Traditional herbal medicinal product used for temporary insomnia (SWE) Traditional herbal medicinal product used to aid sleep	Oral drops, solution Posology: Adults, elderly and adoscelents above 12 years of age: Minor nervous tension: 1 ml (approx. 40 drops) in ½ glass of water 3-5 times daily Temporary insomnia: 2 ml (approx. 80 drops) in ½ glass of water	TU IE 2014 SI 2015 SE 1978

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	(IRL, SLO) The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.		
Traditional Use – TU: dry extracts			
a) Dry extracts of valerian root (DER 4-6:1), extraction solvent water and hop strobile (DER 3-6:1), extraction solvent water	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress. Indication 2 Traditional herbal medicinal product used to aid sleep.	a) Fixed combinations of 80mg/20mg or 160 mg/40 mg dry extracts of valerian root and hop strobile, respectively Daily dosage: 3 x 3 doses or 3 x 2 doses for indication 1 and 3 x 1 or 2 x 1 doses 1 hour before bedtime for indication 2	TU HR 2010 DE 1976 HU 1994 HU 2002 HU 2012
b) Dry extracts of valerian root (DER 5-7:1), extraction solvent methanol 45% m/m and hop strobile (DER 5-7:1), extraction solvent water	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress. Indication 2 Traditional herbal medicinal product used to aid sleep.	Fixed combination of 187 mg/45 mg dry extracts of valerian root and hop strobile, respectively Daily dosage: up to 3 x 1 doses for indication 1 and 1 dose 1 hour before bedtime for indication 2	TU DE 1976
c) Dry extracts of valerian root (DER 4-5:1), extraction solvent ethanol 60% v/v and hop strobile (DER 5-9:1), extraction solvent water	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress.	Fixed combinations of 100 mg/30 mg of dry extracts of valerian root and hop strobile, respectively Daily dosage: 2-3	TU DE 1976

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
	Indication 2 Traditional herbal medicinal product used to aid sleep.	doses for indication 1 and 2 doses 1 hour before bedtime for indication 2	
d) Dry extracts of valerian root (DER 4-7:1), extraction solvent methanol 45% v/v and hop strobile (DER 4-8:1), extraction solvent ethanol 40% v/v	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress. Indication 2 Traditional herbal medicinal product used to aid sleep.	Fixed combinations of 125 mg/25 mg of dry extracts of valerian root and hop strobile, extracts of valerian root and hop strobile, respectively. Daily dosage: 3x1 doses for indication 1 and 1-2 doses 1 hour before bedtime for indication 2.	TU DE 1976
e) Dry extracts of valerian root (DER 3-7:1), extraction solvent ethanol 70% v/v and hop strobile (DER 4-8:1), extraction solvent ethanol 40% v/v	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress. Indication 2 Traditional herbal medicinal product used to aid sleep.	e1) Fixed combinations of 100 mg/24 mg – 32 mg dry extracts of valerian root and hop strobile, respectively. Daily dosage: 3 x 2 doses for indication 1 and 2 doses 1 hour before bedtime for indication 2. e2) Fixed combinations of 68 mg/16 mg of dry extracts of valerian root and hop strobile, respectively. Daily dosage: 3 x 3 doses for indication 1 and 3 doses 1 hour before bedtime for indication 2.	TU AT 2012 BE 2013 HR 2013 DE 1976 DE 1996 DE 1998 DE 1999 ES 2000 SE 2014

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
		e3) Fixed combinations of 200 mg/ 46-68 mg of dry extracts from valerian root and hop strobile, respectively. Daily dosage: 1 tablet 3x daily or 1-2 tablets half to 1 hour before bedtime.	
f) Dry extracts of valerian root (DER 6-7:1), extraction solvent ethanol 70% v/v and hop strobile (DER 11-14:1), extraction solvent ethanol 96% v/v	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress. Indication 2 Traditional herbal medicinal product used to aid sleep.	Fixed combinations of 225 mg/30 mg dry extracts of valerian root and hop strobile, respectively. Daily dosage: 3x1 doses for indication 1 and 1-2 doses 1 hour before bedtime for indication 2	TU DE 1976 DE 1999
g) Dry extracts of valerian root (DER 5-8:1), extraction solvent ethanol 85% v/v and hop strobile (DER 9-11:1), extraction solvent ethanol 90% v/v	Indication 1 Traditional herbal medicinal product for relief of mild symptoms of mental stress. Indication 2 Traditional herbal medicinal product used to aid sleep.	Fixed combinations of 77 mg/18.8 mg of dry extracts of valerian root and hop strobile, respectively. Daily dosage: 3 x 2 doses for indication 1 and 2 doses 1 hour before bedtime for indication 2	TU DE 1976

3. Non-Clinical Data

3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

3.1.1. Primary pharmacodynamics

General introduction

In the former version of the assessment report, reference was made to studies with the single ingredients of the combination.

Orally administered dry extracts of valerian root in the recommended dosage have shown to improve sleep latency and sleep quality. Although these effects cannot be attributed with certainty to any known constituents, several mechanisms of action have been identified for several constituents of valerian root i.e. sesquiterpenes, lignans and flavonoids, including interactions with the GABA-system, agonism at the A1-adenosine receptor and binding to the 5-HT1A receptor (Balduini and Cattabeni, 1989; Mennini et al., 1993; Yuan et al., 2004; Cavadas et al., 1995 and Ortiz et al., 1999).

Orally administered dry extracts of hops in mice have shown to decrease body temperature, through activation of melatonin receptors (Grundmann et al., 2006; Butterweck et al., 2007).

The pharmacology of both single ingredients and their preparations has been updated and discussed in the assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

In vitro experiments

One pharmacological study has been performed with both a valerian preparation and a fixed valerian-hops preparation. An in vitro radioligand binding assay at A1 and A2A adenosine receptors (ARs) was conducted with a fixed extract combination of valerian and hop (Ze 91019) in order to investigate a possible mechanism for the pharmacological activity of the extracts. Component extracts of valerian and hop were also individually investigated. The fixed combination as well as the valerian extracts therein exhibited selective affinity to A1 ARs (K(i) = 0.15-0.37 mg/ml versus [3H]-N6-cyclopentenyladenosine (CPA). The same extracts exhibited partial agonist activity at the A1 receptor as indicated by a lower degree of stimulation of [35S]-CTPγS binding in membrane preparations of CHO-hA1 cells as compared to full A1 AR agonist N6-CPA. In addition valerian extract inhibited c-AMP accumulation in CHO-hA1 cell membranes. The partial agonistic activity at A1 ARs may thus play a role in the sleep inducing effect of Ze 91019 and the valerian extract therein (Müller et al., 2002).

Further studies with a combination of valerian and hops dry extracts have shown interactions with the serotoninergic 5-HT4e, 5-HT6, 5-HT7 and melatoninergic ML1 and ML2 receptors (Abourashad et al.,2004; Brattström, 2007).

According to these authors, the efficacy of a valerian root and hops combination in sleep disorders could scientifically be explained by the adenosine-like action of valerian root and the melatonin-like effect of hops, which respectively would increase the sleep propensity and the entrainment of the circadian rhythm.

In vivo experiments

Studying the sedative effects of valerian/hops in fruit flies is one of the latest developments in preclinical research. Choi et al. (2017) describe the combinational synergetic effect of valerian and hops via analysis of several sleep episodes in a *Drosophila* model.
Valerian roots 40 g were extracted with 1600 mL of 70% ethanol in room temperature by stirring 48 h. Hops 40 g were extracted with 800 mL of 70% ethanol with a Soxhlet apparatus for 3 h, twice. Then, all extracts were filtered by filter paper and evaporated at 40°C using a rotary vacuum evaporator. Valerian and Hops extraction sample were freeze-dried and stored at 4°C.
Wild-type D. melanogaster Canton-S strain were maintained in standard fly bottles containing sucrose medium (sucrose, cornmeal, dried yeast, agar, propionic acid, and p-hydroxybenzoic acid methyl ester solution) and raised under a 12 : 12 h light : dark cycle at 25±1°C in 60% relative humidity (RH). Valerian and/or hops samples were added to sucrose medium with the indicated concentrations. Prior to sample treatment, 2–5-d-old male flies were collected under anesthesia using CO_2.
Valerian and Hops were dissolved in distilled water and mixed in sucrose-agar media (5% sucrose and 1% agar) for the locomotor activity assays. Single treatments of Valerian included 2, 5, 10, and 20 mg/mL concentrations. Single treatments of hops (Cascade type) included 2, 5, and 10 mg/mL concentrations. After evaluating the dose-effect relationship, the highest concentrations of valerian and hops were used: 20 mg/mL and 10 mg/mL respectively
The Drosophila Activity Monitoring system (DAM; TriKinetics, Waltham, MA, U.S.A.), as well as group activity of flies for single treatment and Valerian/Hops mixture groups was assessed. For the latter the Locomotor Activity Monitoring system (LAM, TriKinetics) was used to provide measures of locomotor activity combined with social behaviors. All the experiments were triplicated (DAM: 10 flies per replicate, LAM: 30 flies per replicate).
Total RNA was extracted from the heads of 17–20-d-old flies and expression quantified using PCR (Polymerase Chain Reaction). The GABA A receptor binding assay was performed using homogenised preparations of the cerebral cortex of male Sprague–Dawley rats.

The sleep patterns of fruit flies on during exposure to valerian/hops were examined in both baseline and caffeine-treated conditions. Total activities of flies significantly decreased in 20 mg/mL Valerian (74%), 10 mg/mL hops of the Cascade type (25%), during night time or daytime compared with the control. Valerian/hops mixture showed longer sleeping time (ca. 20%) than control group. This mixture-mediated effect was partly observed in caffeine-treated flies. Valerian/hops mixture upregulated mRNA expressions of gamma-aminobutyric acid (GABA) and serotonin receptors, and GABA receptors were more strongly regulated than serotonin receptors. In competitive GABA receptor binding assay, valerian/Cascade mixture extract showed a higher binding ability on GABA receptors than valerenic acid or/and xanthohumol which are estimated to be active compounds in the extract.

This study demonstrates that a valerian/hops mixture extract improves sleep-related behaviors, including sleeping time, by modulating GABAergic/serotonergic signalling (Choi et al. 2017).

These results reported by Choi et al. (2017) were already announced in an abstract published by Jo et al. (2015).

Table 4: Overview of the study by Choi et al. (2017)

Herbal preparation tested	**Strength** **Dosage** **Route of administration**	**Experimental model** **In vivo/** **In vitro**	**Reference** **Year of publication**	**Main non-clinical conclusions**
other preparations	Ethanolic extracts Valerian 20 mg/ml Hops 10 mg/ml	*In vitro* *Drosophyla* sleep and activity pattern mRNA expression of GABA receptors GABA receptor binding	Choi et al. 2017	Valerian/hops improves sleep related behaviour by modulating GABA-ergic signaling

3.1.2. Secondary pharmacodynamics

Not applicable

3.1.3. Safety pharmacology

Few experimental data are available on the toxicology of valerian root preparations which as a whole point to a low toxicity. The safety assessment has been mainly based on the long experience from the extensive therapeutic use in man, which indicates valerian root preparations to be safe. Adequate data, however, on genotoxicity are lacking (von Skramlik, 1959; Rücker et al., 1978; Hendriks et al., 1985; Bos et al., 1998; Romero-Jimenez et al., 2005).

Given the history of tong term use in humans with no adverse effects, also hops is believed to be non-toxic and safe. The experimental toxicological data on hop preparations are rather limited and incomplete, but as a whole uses in man are pointing to a low toxicity (Milligan et al., 2002; Stevens et al., 2004; Gerhauser et al., 2005). Adequate data on genotoxicity of hop preparations are also lacking (Göggelman et al., 1986).

The safety of both single ingredients and their preparations has been updated and discussed in the assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

3.1.4. Pharmacodynamic interactions

Not applicable

3.1.5. Conclusions

The phytochemical composition, pharmacology, the pharmacokinetics and the toxicology of both valerian root and hop strobile and their preparations have amply been discussed in the assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

As compared to the former version of the assessment report, some new data on the biological activity of valerian/hops mixture have been published, pointing to the influence of sleeping behavior in *Drosophyla* species by modulating GABAergic/serotonergic signalling. The extracts used were prepared with ethanol. These results mainly have a qualitative character, as it is difficult to extrapolate the concentrations used to clinical practice. Nevertheless these experiments contribute to the

pharmacological base for using valerian/hops mixtures as a phytotherapeutic approach, complementary to monopreparations of valerian root and hop strobile.

3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof

The pharmacokinetics of both single ingredients and their preparations has been discussed in the assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof

3.3.1. Single dose toxicity

No data available.

3.3.2. Repeat dose toxicity

No data available.

3.3.3. Genotoxicity

No data available.

3.3.4. Carcinogenicity

No data available.

3.3.5. Reproductive and developmental toxicity

No data available.

3.3.6. Local tolerance

Not applicable

3.3.7. Other special studies

Not applicable

3.3.8. Conclusions

The toxicology of both single ingredients and their preparations has been discussed in the assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

3.4. Overall conclusions on non-clinical data

The phytochemical composition, pharmacology, the pharmacokinetics and the toxicology of both valerian root and hop strobile and their preparations are discussed in the revised assessment reports

on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

Some new data on the biological activity of valerian/hops mixture have been published, pointing to the influence of sleeping behavior in *Drosophyla* species by modulating GABAergic/serotonergic signalling. These experiments contribute to the pharmacological base for using valerian/hops mixtures as a phytotherapeutic approach, complementary to monopreparations of valerian root and hop strobile.

The toxicology of both single ingredients and their preparations has been discussed in the assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

There are no new data necessitating any changes in the monograph. There are also no data permitting the consideration of a list entry for fixed mixtures of valerian root/hop strobile.

4. Clinical Data

4.1. Clinical pharmacology

4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

Two pharmacological studies have been carried out with a fixed combination of valerian and hop extracts (Ze 91019) to investigate the pharmacodynamic effects in healthy volunteers.
In a first study the fixed combination of valerian and hops was investigated aiming at a demonstration of competition between caffeine and this combination.

Electroencephalographic (EEG) recordings were used to describe the action of caffeine on the central nervous system after oral administration (200 mg) in healthy volunteers. In addition to caffeine, the volunteers (16 in each group) received either placebo or verum (2 and 6 tablets containing the valerian/hop extract).
The EEG responses were recorded every 30 min. The verum medication was capable of reducing (2 tablets) or inhibiting (6 tablets) the arousal induced by caffeine. This pharmacological action was observed 60 minutes after oral administration indicating not only competition between the antagonist caffeine and the partial agonist i.e. the valerian/hop extract but also bioavailability of the compound(s) responsible for the agonistic action. The authors concluded that the valerian/hop extract acts via a central adenosine mechanism, which is possibly the reason for its sleep-inducing and- maintaining activity (Schellenberg et al., 2004).

In a second investigation the pharmacodynamic effects of different dosages of a fixed combination of valerian and hop extracts (Ze 91019) on the quantitative topographical EEG (qEEG) in healthy volunteers were compared to placebo. Two different dosages were applied in two single-blind, cross-over designed observation trials in 12 healthy volunteers (1st dosage : 500 mg valerian and 120 mg hops, versus placebo, first clinical trial ; 2nd dosage : 1500 mg valerian and 360 mg hops, versus placebo, second clinical trial). The qEEG was recorded bipolarly from 17 surface electrodes according to the 10:20 system and analysed using the Fast Fourier Transformation prior to, 1, 2 and 4 hours after drug intake in the recording conditions eyes open, eyes closed and under mental demand. The EEG-spectra were cut into six frequency bands. Both resting conditions (eyes open and eyes closed) were analysed together. After application of the low dosage qEEG power changes remained more or less within placebo range following the normal circadian rhythmics, except for a tendentious reduction of alpha- and beta1-power 4 h after drug intake. The high dosage led to power increases in delta,

decreases in alpha and a weak decrease in beta-power. Under mental performance only weak differences to placebo were seen which are not discussed here. In the CPT (completion of complicated additions and substractions) the concentration and performance capability were hardly influenced. However, a minimal increase of mean answer time and mean OK time (time for correct answers) was observed 4 hours after intake of 2 dragees and 1 hour after 6 dragees of valerian and hops mixture with more pronounced changes after the low dosage than the high one.

The authors concluded that the qEEG was able to show slight, but clear visible effects on the CNS especially after intake of the high dosage of Ze 91019 indicating reproducible pharmacodynamic responses of the target organ (Vonderheid-Guth et al., 2000).

Dimpfel and Suter (2008) investigated the effect of a single administration of a valerian/hop combination as a sleep aid. Two parallel groups of n = 20 (verum) and n = 22 (placebo) were tested. Each subject spent two consecutive nights in the lab (reference night and medication night). Medication consisted in giving verum or placebo to poor sleepers identified by a validated sleep questionnaire (Schlaffragebogen SF-B). Two ml of the liquid extract (composition not mentioned) or similar smelling placebo were diluted in 50 ml water (flavoured with honey) and administered 15 minutes before EEG recording during the medication night. The data analysis was based on the electrohypnogram - a method derived from a validated computer assisted automatic analysis for depth of sleep. Differences between the reference nights and medication nights were evaluated and tested for significance. Time spent in sleep (values of the sleep frequency index "SFx" of the electrohypnogram) was significantly higher for the verum group in comparison to the placebo group ($p<0.01$). The difference with respect to time spent in deeper sleep between reference and medication night, was also statistically significant at $p<0.01$. This parameter correlated with the difference in quality of sleep between the two consecutive nights as derived from the sleep inventory SF-A sub-score (subjects evaluation) ($p<0.0001$). The EEG derived parameter "sleep quantity" as calculated from the electrohypnogram proved superiority of the valerian/hops combination over placebo. This investigation showed evidence that a valerian/hops fluid extract can be used successfully using a single administration (Dimpfel and Suter, 2008).

4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents

No data available.

4.2. Clinical efficacy

Besides one dose-finding trial in short-term clinical use of valerian root, which showed a dose-dependent effect for the tested doses of 1300 mg and 2600 mg of valerian root (Leathwood, 1985), four randomized double-blind placebo-controlled and/or reference controlled clinical studies have been carried out with single valerian root preparations in patients suffering from non-organic insomnia (Vorbach et al., 1996, Dorn, 2000, Ziegler et al., 2002, Coxeter et al., 2003). Two further placebo-controlled double-blind clinical studies with valerian root preparations were carried out to assess besides insomnia also nervous tension (Kamm-Kohl et al., 1984, Jacobs et al., 2005). All these studies led to the conclusion that valerian extracts prepared with ethanol/water belong to the herbal preparations with well-established medicinal use for the relief of mild nervous tension and sleep disorders.

Up to now no meaningful clinical studies have been reported to support hops as single preparation for the treatment of sleep disorders or nervous tension.

Nevertheless, several non-controlled as well as controlled clinical studies, have demonstrated that combinations of hop strobile with valerian root are effective for non-organic insomnia.

4.2.1. Dose response studies

Available dose-response data for valerian root and derived preparations have been discussed in the assessment report on valerian root (EMA/HMPC/150848/2015).

No clinical studies have been conducted to date with hop strobile preparations as single component products (EMA/HMPC/682384/2013).

No particular dose response studies are available for combination products. Studies using at least 2 different dosages are included in sections 4.1.1 and 4.2.2.

4.2.2. Clinical studies (case studies and clinical trials)

Controlled clinical studies

A placebo-controlled double-blind study was performed in 12 patients (6 men, 6 women) aged 22-27 years, with traffic noise-induced disturbance of sleep. Patients ingested coated tablets with either 60 mg of valerian root extract (Valeriana officinalis, DER 4.5:1 methanol 40% v/v) and 100 mg extract of hop strobile extract (Humulus lupulus, DER 5:1 methanol 30% v/v), or placebo. Study duration was 6 nights. During the third, fourth and fifth night traffic noise was simulated during the whole night by playing tape recordings. Six patients received four tablets of verum (corresponding to 240 mg of valerian extract or 1572 mg of valerian root, and 400 mg of hop extract or 4000 mg of hop strobile) prior to the second, 6 patients prior to the third noisy night. The remaining nights, 4 tablets of placebo were administered. The traffic noise had an influence on sleep architecture (measured by polysomnography), however, an adaption to the noise could be observed. The results from the two treatment arms (second respectively third noisy night) were not comparable.

However, the results clearly showed a beneficial influence of the valerian-hop combination on sleep architecture by countering the stressful effects of noise. Adverse events were not reported. It is recommended that the initial treatment of severe insomnia by "strong" sleeping pills should be followed by a period during which "weak" sleeping pills are given before the drug administration finally is discontinued (Müller-Limmroth and Ehrenstein, 1977).

In one study, Leathwood et al., 1982, compared the valerian-monopreparation with a combination valerian-hops and placebo in volunteers.

A cross-over trial comparing an aqueous valerian dry extract (400 mg corresponding to 1180 mg of the drug), placebo and a combination of valerian dry extract (120 mg/tablet) plus hop strobile dry extract (60 mg) was performed in 166 volunteers.

Drug/extract ratios for the latter preparation are not given. The volunteers took one dose of totally nine (three/preparation) on non-consecutive nights and documented their sleep quality in a questionnaire (not validated). Results were analyzed only for those volunteers who completed the trial (n = 128). Of them 52% (n=67) were good sleepers and 48% (n=61) were considered as poor or irregular sleepers. On the morning after taking the preparation, time to fall asleep, quality of sleep, natural waking up, dreaming and tiredness in the morning were recorded by means of a questionnaire. Time to fall asleep was reduced in 37% of persons taking the valerian root mono-preparation, in 23% under placebo and in 31% under the combination preparation. The difference between the valerian root mono-preparation and placebo was statistically significant ($p<0.01$). While quality of sleep

remained virtually unchanged in habitually good sleepers with all preparations, in habitually poor or irregular sleepers the sleep quality was enhanced and sleep latency was reduced significantly more often with the valerian preparation compared to placebo. The combination showed no significant superiority. The quality of sleep was improved in 43% of persons with the valerian root mono-preparation and 25% with placebo ($p<0.05$). No differences in waking up during the night, dreaming and tiredness in the morning were found between valerian root and placebo. With regard to the combination preparation, a stronger effect was found for tiredness in the morning, which was statistically significant compared to both placebo and valerian root mono-preparation. No significant differences were found for the other parameters.

The interpretation of these data is restricted by lacking of a confirmatory analysis. No detailed demographic data are given, no validated questionnaires were used in this trial. It is not clear from the publication whether the medications were taken in a randomized order. Nevertheless, the results are congruent with those of better designed and reported trials.

In a placebo-controlled, double-blind, randomized parallel group study, the effects of Ze 91019 on sleep architecture were tested in 15 patients with non-organic insomnia. Patients received 2 tablets of IVEL® (250 mg of valerian extract (5:1; solvent not known) and 60 mg of hop extract (6:1; solvent not known) per tablet; n = 8) or placebo (n = 7). Study duration was 4 weeks. Polysomnographic recordings were obtained in the sleep laboratory at baseline, after 4 weeks of intake of the study medication, and after a 2-week wash-out period. The application of the combination significantly decreased slow-wave-sleep percentages and increased sleep stage II as compared to placebo. This finding points to GABAergic effects of the herbal combination. Mild side effects occurred with two patients in the placebo group and four patients in the verum group consisting of gastro-intestinal complaints and headache. Based on their results, the authors recommend valerian preparations in patients with mild, non-chronified sleep disorders (Rodenbeck and Hajek, 1998).

The efficacy of a valerian-hop combination (coated tablets containing 200.2 mg of dry extract of valerian root (DER 5:1, ethanol 70% v/v) and 45.5mg of dry extract of hop strobile (DER 5.5:1, methanol 40% v/v); extraction solvents not indicated) was compared to that of 3mg bromazepam in a two-week reference-controlled, double-blind, randomized clinical parallel group trial with double-dummy technique. 46 patients (37 women, 9 men; mean age 50.3 years) suffering from non-psychiatric sleep disorders were tested for sleep quality, fitness and quality of life by psychometric tests, psychopathologic scales and sleep-questionnaires. All parameters improved in both treatment groups to a similar extent. During treatment with the herbal combination the percentage of patients subjectively feeling "bad" or "moderate" decreased by 62.6% (from 82.6% to 20%), as compared to a reduction of 32.7% (from 56.5% to 23.8%) in patients treated with bromazepam. Seven adverse events were noted, two of which (one case of gastrointestinal complaints in both treatment arms) were considered to have been caused by the medication. (Schmitz and Jäckel, 1998).

In 2005, Morin et al. evaluated the efficacy and safety of a valerian-hops combination and diphenhydramine for the treatment of mild insomnia. The multicentre, randomized, placebo-controlled, parallel-group study was conducted in 9 sleep disorders centres throughout the US. A total of 184 adults (110 women, 74 men, mean age of 44.3 year) with mild insomnia were treated with two nightly tablets of standardized extracts of valerian (187 mg native extract : 5-8:1, methanol 45% m/m) and hops (41.9 mg native extract : 7-10:1, methanol 45% m/m) combination for 28 days (n = 59) and a placebo for 28 days (n = 65) or 2 tablets of diphenhydramine (25 mg) for 14 days followed by placebo for 14 days (n = 60). Sleep parameters measured by daily diaries and polysomnography, clinical outcome ratings from patients and physicians, and quality of life measures were the outcome measures. Modest improvements of subjective sleep parameters were obtained with both the valerian-

hops combination and diphenhydramine, but few comparisons with placebo reached statistical significance. Valerian-hops produced slightly greater, though non-significant, reductions of sleep latency relative to placebo and diphenhydramine at the end of 14 days of treatment and greater reductions than placebo at the end of 28 days of treatments. Diphenhydramine produced significantly greater increases in sleep efficiency and a trend for increased total sleep time relative to placebo during the first 14 days of treatments. There were no significant group differences on any other sleep continuity variables measured by polysomnography.

In addition, there was no alteration of sleep stages 3 and 4 and rapid eye movement sleep with any of the treatments. Patients in the valerian-hops and diphenhydramine groups rated their insomnia severity lower relative to placebo at the end of 14 days of treatment. Quality life (physical component) was significantly more improved in the valerian-hops group relative to the placebo group at the end of 28 days. There were no significant residual effects and no serious adverse events with either valerian-hops or diphenhydramine and no rebound insomnia following their discontinuation.

The authors concluded that their findings show a modest hypnotic effect for a valerian-hops combination and diphenhydramine relative to placebo. Sleep improvements with a valerian-hops combination are associated with improved quality of life. Both treatments appeared safe and did not produce rebound insomnia upon discontinuation during this study.

Overall, these findings indicate that a valerian-hops combination and diphenhydramine might be useful adjuncts in the treatment of mild insomnia (Morin et al., 2005).

Recently, another randomized blind three-armed clinical study was carried out investigating the fixed extract combination Ze 91019 (valerian and hops) in comparison with a comparable single valerian extract (Ze 911) and a placebo in 30 patients (i.e. 10 patients in each study) suffering from non-organic insomnia (ICD10, F51.0-51.2).

Objective sleep parameters were registered by means of transportable home recorder system (QUISI). The primary outcome was the reduction in sleep latency (SL2) which had to be prolonged at baseline ($\geq$ 30 min) as an inclusion criteria. The treatment period lasted for 4 weeks (one medication daily) with either placebo, single valerian extract (Ze 911) or the fixed valerian hops extracts combination (Ze 91019). The amount of the single valerian extract was identical to that amount contained in the fixed extract combination i.e. 500 mg valerian dry extract. In the extract combination 120 mg hops dry extract was added (Ze 91019). Both the extracts were prepared with 45% methanol m/m with a DER of 5.3:1 (valerian) and 6.6:1 (hops), respectively.

The fixed extract combination was significantly superior to the placebo in reducing the sleep latency, whilst the single valerian extract even if it showed some improvement regarding sleep latency, failed to reach significant superiority compared with the placebo. No adverse events were reported for any of the patients in the different groups which underlined the safety (Koetter et al., 2007).

Table 5: Clinical studies on humans

Type	Study	Test Product(s):	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Muller-Limroth and Ehrenstein 1977 Sleep quality	Double-blind Placebo controlled. 6 days	Coated tablets of 60 mg valerian dry extract (DER 4.5:1 - extraction solvent methanol 40% V/V) and 100 mg hop dry extract (DER 5:1 – extraction solvent methanol 30% V/V). Duration 6 nights. Traffic noice during nights 3, 4 and 5. Oral administration of 4 tablets to 6 patients prior to night 2 and to 6 patients prior to night 3. Remainig nights 4 tablets of placebo.	N = 12	Healthy subjects	Polysomnography. Reduction of the noise induced disturbance of sleep stage pattern. Slow-wave sleep and stage REM	Flat statistical analysis: cf. small scale study.	Low relevance due to the low number of subjects.
Leathwood et al. 1982 Sleep quality	Cross over, double blind, placebo controlled, cross-over trial	400 mg of valerian 400 mg valerian dry extract (DER 2.8:1, extraction solvent water), 60 mg valerian dry extract and 30 mg	N = 128	Healthy subjects Poor sleepers: N = 61 Good sleepers: N = 61	Questionnaire to reply by volunteers. Significant differences between valerian extract and placebo, for time to fall asleep and quality of	Per protocol analysis. Results expressed as % of patients responding.	Questionnaire not validated. Not clear whether the order of therapeutic

Type	Study	Test Product(s):	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		hop dry extract (no info on specification) Placebo.			sleep. No differences between combination and placebo.		regimens where randomised.
Rodenbeck & Hajek 1998 Sleep quality	Randomised, double blind, placebo controlled. 4 weeks (57 weeks of therapy)	Tablets with 250 mg valerian dry extract (DER 5:1; no info on extraction solvent) and 60 mg hop dry extract (DER 6:1; no info on extraction solvent). 2 tablets/ day 30 minutes before bedtime	N = 15 Verum: n = 8 Placebo: n= 7	Non-organic insomnia (DSM III-R) (ApA, 1987)	Polysomnography Subjective feelings. Decrease of slow wave sleep and increase of stage II sleep in the verum group. Gastro-intestinal complaints and headache Placebo = 2 Verum = 4	Small sample size does not permit statistical analysis.	Number of patients limited. Extraction solvents not known.
Schmitz and Jäckel 1998 Sleep quality	Randomized, double-blind, reference controlled (3 mg bromazepam Duration: 2 weeks treatment; 1 week	Valerian dry extract (DER 5:1; extraction solvent ethanol 70% V/V) 200.2 mg; Hop dry extract (DER 5.5:1; extraction solvent methanol 40% V/V) 2 film coated tablets (verum) and 1 capsule 30 min before bedtime/day	N = 46	Patients with sleep disorders	Psychometric tests Psychopathological scales Sleep questionnaires Better results with the combination as compared to bromazepam. 7 adverse events of which 2 possibly in	Quantitative evaluation, no statistical analysis.	Extraction solvent not given in publication but analogy with existing preparation. No placebo included, but fair methodological quality.

Type	Study	Test Product(s):	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
	wash out				relation with medication		
Morin et al. 2005 Sleep quality	Randomised, double blind, placebo controlled, multicentre, reference controlled. Duration 28 days	Valerian dry extract (5-8:1; extraction solvent methanol 45% M/M) 187 mg; and hop dry extract (7-10:1; extraction solvent methanol 45% M/M) 41.9 mg. At nighttime 2 tablets of the combination: N = 59; 2 tablets of placebo: N = 65; 2 tablets of diphenhydramine during 14 days, followed by placebo during 14 days (N = 60)	N = 184 Subdivided in 3 groups	Patients with mild insomnia	Daily diaries Polysomnography Clinical outcome ratings by patients and physicians Quality of life Modest hypnotic effects for valerian-hops combination and diphenhydramine, as compared to placebo. Sleep improvement with valerian-hops, associated with improved quality of life. Both treatments appear safe, without rebound insomnia after discontinuation	No statistical significance detected: only qualitative differences.	Study of fair quality. Valerian-hops and diphenhy-dramine are useful as adjuvant therapy
Kötter et al. 2007 Sleep quality	Randomised, double-blind, placebo-controlled;	One dose/day Valerian dry extract (DER 5.3:1; extraction solvent methanol 45% M/M)	N = 30 divided over 3 groups (N = 10 each)	Non-organic sleep disorders (ICD 10)	Objective sleep parameters measured by means of a transportable home recorder system.	Statistical analysis made, but low evidence due to small	Small study groups do not permit to make conclusions.

Type	Study	Test Product(s):	Number of Subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
	4 weeks	500 mg + hop dry extract (DER 6.6:1; methanol 45% M/M Versus Pure valerian extract (= same as in combination); Placebo			Clinical gobal impression scale Reduction of sleep latency (≥ 30 min) with the combination. The monopreparation was not superior to placebo. No undesirable effects were reported.	samples.	

Other clinical studies

An open, multicentre post-marketing surveillance study assessed the efficacy and safety of Ze 91019 in 3,447 patients with sleep disorders. With the intake of the drug product the number of patients indicating an uninterrupted sleep increased from 7.6 to 32.9%. Patients said to be more relaxed and have a better performance. Efficacy was judged by the physicians as good-very good in 74.9% of cases, and as acceptable in 16.3%. Only 19 patients reported adverse events, of which 6 were assessed as possibly related to the study medication, all of them gastrointestinal complaints (Brattström 1996; Lataster and Brattström 1996).

Benzodiazepine-induced changes in sleep architecture were reported as demonstrated by polysomnography. The report is anecdotal, with no details given. When withdrawn from benzodiazepines and switched to a valerian-hop combination (Ze 91019), the patient's hypnograms distinctly changed towards normal patterns. Tolerability was very good, with the exception of occasional gastrointestinal discomfort (no numbers given) (Flesch 1997).

Another open polysomnographic examination was conducted in 30 patients with non-organic sleep disorders. Patients were tested before and after a 14-day intake of two tablets of Ze 91019 two hours before bedtime. Test parameters were EEG measurements, respiration/snoring, sleep quality (verbal rating scale), and a psychometric test for the detection of trouble with focussing and memory. In all patients a shift towards a normalisation of sleep architecture (REM / non-REM phases) was found. Sleep stage 1 was reduced, and slow wave sleep increased. Sleep latency 2 (mean time to reach sleep stage 2) declined significantly within the 2 weeks of treatment, and the total wake time also declined significantly. Correspondingly, sleep efficiency (ratio of true sleep time to time spent in bed) improved significantly. The effects on sleep parameters were paralleled with a subjectively ameliorated feeling of well-being. No adverse effects occurred in this open pilot study (Brattström 1996; Füssel et al. 2000).

Results of a non-controlled multicentre study with 144 patients (88 women, 56 men; age range 11-91 years) suffering from sleep disorders were reported. Patients received Ze 91019 (1 to 2 coated tablets one hour before bedtime) for 4 weeks. Patients assessed sleep parameters (sleep latency, sleep duration, frequency of awakening) and well-being before and after treatment on a VAS (visual analogical scale). In 25.9% of patients the sleep disorder had completely resolved after therapy. Severity of the sleep disorders had distinctly shifted towards milder forms. A responder rate of 67% was calculated. Patients with complaints of interrupted sleep reacted best to the treatment (71%), followed by trouble falling asleep (67%) and sleep disorders of psychological origin (67%). The improvement of sleep parameters was paralleled by improvements of well-being (e.g. feeling refreshed) in the same scale. Sleep duration was increased by approximately 1 hour in average. 66.9% of patients indicated an onset of effects within the first 10 days of treatment. Tolerability was judged good-very good by 92% of patients. Adverse events were reported by four patients, and explicitly stated by two: 1x oedema, 1x diarrhoea (Notter et al., 2003).

In a non-controlled, multicentre study, 480 patients (305 women, 175 men; mean age 49.5 years) suffering from nervous sleep disorders and restlessness were treated for an average of 22 days with a combination preparation containing 225 mg valerian root extract (DER 6-7:1; 70% ethanol) and 30 mg dry extract of hop strobile extract (DER 11-14:1; 96% ethanol) per coated tablet, corresponding to approximately 1500 mg of valerian root respectively 400 mg of hop strobile per tablet. The mean dose of the combination was 2.6 coated tablets during the day and 1.6 tablets before bedtime in the evening. The mean total daily dose was 3.3 tablets. Main efficacy parameters evaluated were improvement of nervous anxiety and associated psycho-vegetative symptoms (sweating, palpitations, nervous tension) as well as the improvement of sleep disorders. Symptoms were evaluated with a 5-point rating scale (0 = not present to 4 = severe). Therapy with the valerian-hop combination resulted

in pronounced improvement of both, anxiety and sleep disorders. The rating of anxiety related symptoms was reduced by 50-57%, symptoms related to sleep parameters were reduced by 58-61%. Global efficacy was assessed as "excellent" or "good" by 24.6% and 57.2% of patients, respectively. No adverse events were reported throughout the study (Wegener, 2003).

4.3. Clinical studies in special populations (e.g. elderly and children)

Available clinical data with valerian root and derived preparations for special populations have been discussed in the assessment report on valerian root (EMEA/HMPC/167391/2006).

No clinical studies have been conducted to date with hop strobile preparations as single component products (EMEA/HMPC/513618/2006).

No specific studies in special populations are available for combination products. An overview of available studies covering in part adolescents and elderly is given in sections 4.2.2 and 4.2.4 including Table 1.

Taking into account these data, good tolerability of mono and combination products, and existing marketing authorisations for adolescents in several Member States (see market overview in section 1.2) together with the fact that in both monographs on valerian and hops adolescents over 12 years are allowed to use these products, the HMPC decided that combination products are acceptable for adolescents (12-18 years), adults and elderly.

4.4. Overall conclusions on clinical pharmacology and efficacy

Assessor's comments

In conclusion, preclinical and clinical evidence are sufficient to support a well-established use of several fixed combinations of valerian root dry extract and hops dry extract to treat patients suffering from non-organic sleep disorders.

These fixed preparations should be limited to the ones used in the successful controlled clinical studies viz. fixed combinations of 250 mg or 500 mg valerian dry extract (5.3:1, methanol 45% m/m) and 60 mg or 120 mg hop dry extract (6.6:1 methanol 45% m/m) (Ze 91019), 200.2 mg valerian dry extract (5:1, ethanol 70% v/v) and 45.5 mg hop dry extract (5.5:1, methanol 40% v/v) and 187 mg valerian dry extract (5-8:1, methanol 45% m/m) and 41.9 mg hop dry extract (7-10:1, methanol 45% m/m). Nearly equivalent combinations consisting of fixed combinations of 250mg valerian dry extract (4-5:1, methanol 50% v/v) and 65mg hop dry extract (3.4-4.2:1, methanol 50% v/v) x and 250mg valerian dry extract (4-5:1, methanol 51.25% v/v and 65ml hop dry extract (3.4-4.2:1, methanol 51.25% v/v) can be accepted for well-established use.

5. Clinical Safety/Pharmacovigilance

5.1. Overview of toxicological/safety data from clinical trials in humans

The toxicity of both valerian root and hop strobile and their preparations have been discussed in the corresponding assessment reports (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

5.2. Patient exposure

The patient exposure to both the single ingredients valerian root and hop strobile and their preparations can be derived from the corresponding assessment reports (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

5.3. Adverse events, serious adverse events and deaths

Gastrointestinal symptoms e.g. nausea, abdominal cramps and headache have been reported during the clinical studies in a small number of patients. The number of patients or subjects in clinical studies is relatively low to make detailed analysis of undesirable effects and adverse events.

Allergic reactions, which are sometimes seen when handling hop cones or hop oil are not likely to occur when using hop extract, since allergens are supposed to be removed (Estrada et al., 2002).

Although, it is not known whether the dry extracts of hops contain oestrogens such as 8-prenylnaringenin, it might be supposed that if such substances are present, the amounts must be very small, since no special methods have been used to enrich the extracts in prenylated flavonones.

5.4. Laboratory findings

Data for both the single ingredients valerian root and hop strobile and their preparations can be derived from the corresponding assessment reports (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

5.5. Safety in special populations and situations

Data for both the single ingredients valerian root and hop strobile and their preparations can be derived from the corresponding assessment reports (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013 respectively).

5.5.1. Use in children and adolescents

The use of these fixed combinations is not recommended in children below the age of 12 years, due to lack of adequate data.

5.5.2. Contraindications

Patients with known hypersensitivity to the active substances should not use valerian root/hop strobile preparations.

5.5.3. Special Warnings and precautions for use

For extracts containing ethanol, the appropriate labelling for ethanol, taken from the "Guideline on excipients in the label and package leaflet of medicinal products for human use" must be included.

5.5.4. Drug interactions and other forms of interaction

Only limited data on pharmacological interactions of valerian and hop extracts with other medicinal products are available. Clinical relevant interactions with drugs, dietary supplements and other herbs, however, are missing.

Combination with synthetic sedatives requires medical diagnosis and supervision.

5.5.5. Fertility, pregnancy and lactation

Safety during pregnancy and lactation has not been established.

As a precautionary measure, because of lack of data, use during pregnancy and lactation is not recommended.

5.5.6. Overdose

No cases of overdose have been reported.

5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability

May impair ability to drive and use machines. Affected patients should not drive or operate machinery.

5.5.8. Safety in other special situations

No data available.

5.6. Overall conclusions on clinical safety

No additional risk signals can be detected from combination products of valerian root and hop strobile and their preparations as compared to both the single ingredients. The preclinical and clinical studies have also shown that combination products of hops and valerian root dry extracts are well-tolerated except for some gastrointestinal discomforts in a small number of patients.

6. Overall conclusions (benefit-risk assessment)

The sedative effect of valerian and hop preparations has long been recognised empirically. Since more than 10 years fixed combinations of dry extracts of valerian root and hop strobile have been used for the treatment of insomnia and not only pharmacological investigations, but also clinical studies have justified this use. The efficacy of such a combination in sleep disorders can scientifically be explained by the adenosine-like action of valerian root and the melatonin-like effect of hops, which respectively would increase the sleep propensity and the entrainment of the circadian rhythm. *In vitro* studies have suggested the involvement of GABA-receptors in the biological activity of valerian/hops mixtures. The preclinical and clinical studies have also shown that combination products of hops and valerian root dry extracts are well-tolerated and except for some gastrointestinal discomforts in a small number of patients are devoid of side effects. Consequently, well-defined fixed combinations of dry extracts of valerian root and hop strobile can be accepted as well-established herbal medicinal products for the treatment of sleep disorders.

Since several other fixed combinations of valerian root and hop strobile have obtained a marketing authorisation for more than 30 years for the same indications as single preparations of hops or valerian, these preparations can also be accepted as traditional herbal medicinal products for relief of mild symptoms of mental stress and to aid sleep.

Also a fixed combination of liquid extracts and one consisting of tinctures of valerian root and hop strobile can be accepted as traditional herbal medicinal products, taking into account the marketing authorisation of more than 30 years.

There are no data available to consider a list entry for valerian/hops mixtures.

Although phytochemical substances like valerenic acid and xanthohumol are used for qualitative and quantitative analytical purposes, there are no particular secondary metabolites that can be considered

for standardisation of valerian/hops mixtures. As a consequence no constituent with known therapeutic activity or active marker can be recognised by the HMPC.

Annex

List of references