EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 September 2019
EMA/HMPC/441766/2017
Committee on Herbal Medicinal Products (HMPC)

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

Final - 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

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		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
First assessment	Rapporteur	A Vlietinck
	Peer-reviewer	H Pittner
Revision	Rapporteur	G Laekeman
	Peer-reviewer	S Girotto

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1. Introduction

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

- Herbal substance(s)

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

- Herbal preparation(s)

The phytochemical composition of both valerian root and hop strobile 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.

The herbal preparations with marketing authorisations consist of fixed combinations of dry extracts (prepared with ethanol/water, methanol/water or water) or liquid extracts (prepared with ethanol) of valerian root and hop strobili. The monograph relies on products for WEU or TU marketed in Germany, Austria, Hungaria, Poland, Spain, the Czech Republic, Slovenia and Sweden.

This Assessment Report does not assess possible fixed combinations of Valerian root and hop strobile for herbal tea as it is assessed in the Monograph on Species sedativae.

- Composition and analysis of substances

Prieto *et al*. (2016) explored 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 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% *Valeriana officinalis* root and 50% fresh Hummulus lupulus herb tinctures was also purchased (alcohol strength 61% V/V).

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 revealed 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 original 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 September 2017).

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** **Posology** **Duration of use**	**Regulatory Status**
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: maximum 3 times 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 tablet in the evening; restlessness: maximum 3 times 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 [**see footnote 1 on page 33**]: 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

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 times 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 times daily 2 tablets.	TU 2002 AT
Valerian extract (6:1, standard to minimum 5% sesquiterpene acids, ethanol), hops extract (7.5:1, standard to minimum 0.4% flavonoids, ethanol)	Nervous sleep disorders	Coated tablets: 220 mg Valerian extract (6:1, standard to minimum 5% sesquiterpene acids, ethanol), 50 mg hops extract (7.5:1, standard to minimum 0.4% flavonoids, ethanol). In the evening 1-2 capsules.	TU 1996 AT
Valerian extract (6:1, standard to minimum 5% sesquiterpene acids, ethanol) hops extract (7.5:1, standard to minimum 0.4% flavonoids, ethanol)	Restlessness, nervous sleep disorders	Coated tablets: 220 mg Valerian extract (6:1, standard to minimum 5% sesquiterpene acids, ethanol), 50 mg hops extract (7.5:1, standard to minimum 0.4% flavonoids, ethanol). Up to 3 times daily 1 capsule, in case of sleep disorders 1-2 capsules in the evening.	TU 1998 AT

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Valerian root dry extract (4.5:1, methanol 50%, V/V) and hops dry extract (4:1, methanol 50% V/V)	Restlessness, nervous sleep disorders	Coated tablets 1 tablet contains 250 mg valerian root dry extract (4.5:1, methanol 50%, V/V) and 65 mg hops dry extract (4:1, methanol 50% V/V). Adults, adolescents>12 years, sleep disorders;1-2 tablets in the evening, restlessness ;1-2 tablets 3 times daily.	WEU 2000 BE (not any longer on the market)
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 per 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 2013 BE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 per tablet Dry extract from Hop strobile, DER 4-8:1, extraction solvent methanol 40% (V/V)–45.5 mg per tablet For oral use Sleep disturbances: Adults: 2 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: 1 coated tablets (corresponding to 200.2 mg of Valerian extract and 45.5 mg of Hop extract) ½ hour before bedtime. Restlessness, nervosity, anxiety: 1 tablet (corresponding to 200.2 mg of Valerian extract and 45.5 mg of Hop extract) 3 times daily.	WEU 1999 until 2017 CZ

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Dry extract from Valerian root, DER 4-7:1, extraction solvent ethanol 70% (V/V) Dry extract from Hop strobile, DER 11-14:1, extraction solvent ethanol 96% (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 mg per tablet Dry extract from Hop strobile, DER 11-14:1, extraction solvent ethanol 96% (V/V)–100 mg per tablet For oral use Adults: 2–3 coated tablets (corresponding to 120–180 mg of Valerian extract and 200–300 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 100-200 mg of Hop extract) 1 hour before bed time.	Registered since 1993 until 2008 CZ
Dry extract from Valerianae radix (4-6:1), extraction solvent (ES) water and dry extract from Lupuli flos (3-6:1), ES water	Indication 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 3 coated tablets. Indication 2): 3 coated tablets ½ to 1 hour before bedtime. If necessary, additionally 3 coated tablets earlier in the evening.	TU 1976 DE

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): 1-3 times daily 1 coated tablet. Indication 2): 1-2 coated tablets ½ to 1 hour 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	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. 2 coated tablets ½ to 1 hour 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 85% V/V and dry extract from Lupuli flos (9-11:1), ES ethanol 90% V/V	Indication 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): Herbal medicinal product for the relief of difficulty in falling asleep.	1 coated tablet contains 77 mg dry extract from Valerianae radix and 18.8 mg dry extract from Lupuli flos. Indication 1): Up to 3 times daily 2 coated tablets. Indication 2): 2 coated tablets ½ to 1 hour before bedtime. If necessary, additionally 2 coated tablets earlier in the evening.	TU 1976 DE

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): 1-3 times daily 2 coated tablets. Indication 2): 2 coated tablets ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 2 coated tablets Indication 2): 2 coated tablets ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour before bedtime.	WEU 1976 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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	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. 1 coated tablet ½ to 1 hour before bedtime. If necessary, additionally 1 coated tablet earlier in the evening.	TU 1999 DE
Dry extract from Valerianae radix (4-7:1), extraction solvent ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	Indication 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 soft capsule. Indication 2): 1 soft capsule 1 hour before bedtime.	TU 1998 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 soft capsule. Indication 2): 1 soft capsule 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 soft capsule. Indication 2): 1 soft capsule ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): Herbal medicinal product for the relief of difficulty in falling asleep.	1 coated tablet contains 175 mg dry extract from Valerianae radix and 35 mg dry extract from Lupuli flos. Indication 1): Up to 3 times daily 2 coated tablets. Indication 2): 2 coated tablets ½ to 1 hour before bedtime.	WEU 1976 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 2 coated tablets. Indication 2): 2 coated tablets ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1) and 2): Up to 3 times daily 3 coated tablets.	TU 1976 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): 2-3 times daily 2 soft capsules. Indication 2): 2 soft capsules approximately 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): 1-3 times daily 2 soft capsules. Indication 2): 2 soft capsules ½ to 1 hour 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	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. 2 soft capsules ½ to 1 hour before bedtime.	TU 1976 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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	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. 2 soft capsules ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 2 coated tablets. Indication 2): 2 coated tablets ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour before bedtime.	TU 1976 DE

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 film-coated tablet. Indication 2): 1 film-coated tablet ½ to 1 hour 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 flos (4-8:1), ES ethanol 40% V/V	Indication 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): 2-3 times daily 2 soft capsules. Indication 2): 2 soft capsules ½ hour 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	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. 2 soft capsules ½-1 hour before bedtime.	WEU 1976 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 2 coated tablets. Indication 2): 2 coated tablets ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 3 coated tablets. Indication 2): 3 coated tablets ½ to 1 hour before bedtime. If necessary, additionally 2 times 3 coated tablet earlier in the evening.	WEU 1976 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): 1 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): 1-3 times daily 2 soft capsules. Indication 2): 2 soft capsules ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): 2 times daily 1 soft capsule. Indication 2): 1 soft capsule ½ to 1 hour before bedtime.	WEU 1976 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 2 coated tablets. Indication 2): 2 coated tablets ½-1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 2 coated tablets. Indication 2): 2 coated tablets ½-1 hour before bedtime.	WEU 1996 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 2 times daily 1 soft capsule. Indication 2): 1 soft capsule ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour 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 1): Herbal medicinal product for the relief of mild nervous tension. Indication 2): 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 1): Up to 3 times daily 1 coated tablet. Indication 2): 1 coated tablet ½ to 1 hour before bedtime. If necessary, additionally 1 coated tablet earlier in the evening.	WEU 1998 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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	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 and adolescents over 12 years 1 coated tablet contains 32 mg dry extract from Valerianae radix and 9 mg dry extract from Lupuli flos. 2-3 times daily 1 coated tablet.	TU 1976 DE
Liquid extract (1:6.3) from a mixture of Valerianae radix : Lupuli flos (1:1), ES ethanol 40% V/V	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 times daily 20 ml containing 12% V/V extract	TU 1976 DE
Aoft extract (5-6.7:1) from a mixture of Valerianae radix : Lupuli flos (5.7:1), ES methanol 40% V/V	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 [**see footnote 2 on page 34**]: 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 times weekly. Bath duration 10-20 minutes, bath temperature 34-37ºC.	TU 1976 DE

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 film tablets ½ hour before going to bed. Restlessness, nervousness, anxiety: 3 times 1-2 film tablets daily.	WEU 1996 HU
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 ½ hour before going to bed. Restlessness, nervousness, anxiety: 1-3 times 1 film tablets daily.	WEU 1999 HU

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 radix dry extract methanolic 45%, (5-8:1) 42 mg Lupuli strobuli dry extract methanolic 45%, (7-10:1). Adults: 2 'db' film tablets 1 hour before going to bed. This dosage can be enhanced for 3 film tablets. Children: 6 years or above 1 film tablet. Elderly: the same as adults.	WEU 2003 HU
Valerianae radix extract sicc. (4-6:1) extractant: aqua purificata Lupuli flos extract sicc. (3-6:1) extractant: aqua purificata	Reduces nervousness, tensions, facilitates getting to sleep.	Film coated tablets: 80.00 mg Valerianae radix extract sicc. (4-6:1) extractant: aqua purificata. 20.00 mg Lupuli flos extract sicc. (3-6:1) extractant: aqua purificata. Adults and elderly: 2-3 times 1-2 dragées.	TU 1994 HU TU 2010 HR
Valerianae radix officinalis extract aqua sicc. (4-6:1) Lupulis flos extract aqua sicc. (3-6:1)	Reduces nervousness, tensions, facilitates getting to sleep.	Film coated tablets: 160.00 mg Valerianae radicis officinalis extract aqu..sicc. (4-6:1). 40.00 mg Lupulis flos extract aqu. sicc. (3-6:1). Adults and elderly: 1-2 times 1 dragées.	TU 2002 HU

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
Valerianae radix, extractum siccum (4-7:1) 220mg, extraction solvent–ethanol 70% V/V Lupuli strobilus, extractum siccum (4-8:1) 65mg, extraction solvent methanol 40% V/V	Sleep disorders. Psychosomatic stomach spasms.	Valerianae radix, extractum siccum (4-7:1) 220 mg, extraction solvent–ethanol 70% V/V Lupuli strobilus, extractum siccum (4-8:1) 65 mg, extraction solvent methanol 40% V/V. Oral use: 1 tablet 1-3 times daily.	TU 1999 PL
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: 250.0 mg Valerianae radix extractum siccum (4-6:1). Extration solvent: Methanol 45%; Carrier: maltodextrin 25%. 60.0 mg Lupuli flos extractum siccum (5-7:1) Extraction solvent: Methanol 45%; Carrier: maltodextrin 30%; Excipiens q.s. ad 570 mg. 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

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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 SLO

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
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	Traditional herbal medicinal product used for temporary insomnia and minor nervous tension. The 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).	Strobile 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). Oral drops, solution. Posology: Adults, elderly and adoscelents above 12 years of age: Minor nervous tension: 1 ml (approximately 40 drops) in ½ glass of water 3-5 times daily. Temporary insomnia: 2 ml (approximately 80 drops) in ½ glass of water (SWE). Adolescents and adults: "to aid sleep: 30 drops ½ hour before bedtime. For relief of mild symptoms of mental stress: 10 to 20 drops once to twice daily" (SLO).	TU 1978 SE TU 2015 SLO TU 2014 IRL

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
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) "Traditional herbal medicinal product for relief of mild symptoms of mental stress." Coated tablets; Adolescents, adults and elderly: 1 tablet 3 times daily; Duration of use: 2 weeks.	TU 2014 SV
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 per day Sleep disorders: 1-2 capsules ½ to 1 hour before bedtime and if needed 1 more capsule later. 2-4 weeks	WEU 2000 ES

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
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 per 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 2013 ES

Active substance	Indication	Pharmaceutical form Strength Posology Duration of use	Regulatory Status
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. Extraction solvent: Ethanol 60% V/V. Each tablet contains 9 mg of extract (as dry extract) from *Humulus lupulus* L., strobile. Film coated tablet For oral short term use only. Adults and the elderly: One tablet to be taken 3 times per day. As treatment effects may not be apparent immediately, the tablets should be taken for 2 weeks continuously. Not recommended for children or adolescents under 18 years.	TU 2013 IRL

Active substance	**Indication**	**Pharmaceutical form** **Strength** **Posology** **Duration of use**	**Regulatory Status**
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 ½ 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:

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 times daily 1 coated tablet, children from 6-12 years of age (when recommended by a doctor) 1-2 times daily 1 coated tablet.

[2] At that 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 to:

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).

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

There are combinations of valerian and hop with other species e.g. Valerian-Hop-Melissa or Valerian-Hop-Passiflora (DE). These combinations are not within the scope of the actual monograph.

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

Data about historical use can be found in the assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013, respectively).

Table 2: Overview of historical data

Herbal preparation	Documented use / traditional use	Pharmaceutical form	Reference
Fixed combination of valerian and hop.	Sleep disorders due to nervousness and feeling of unrest (Nervös bedingte Einschlafstörungen; Unruhezustände). Pharmacological investigations of the combinations confirmed the tranquillizing and sleep promoting activity.	Valerian root (BAnz. Nr.90 dd. 15.05.1985) Hop strobili (BAnz Nr.228 dd. 05.12.1984) Dried herbal substances for infusions or other pharmaceutical forms. The amount in the combined preparation should include 50% to 75% of the daily dose of monopreparations. All deviations of this posology should be substantiated. No duration of use specified.	Commission E Valerian-Hop 1991 BAnz Nr.40.

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	WEU 2008 AT

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
		1 hour before bedtime. 2 weeks	
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 ½ to 1 hour before bedtime, not exceeding 500 mg of valerian extract.	WEU 1976 DE 1993 DE 1998 DE 2003 HU 2004 PL 2000 ES
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 times daily 1 tablet. Children 6-12 years (if recommended by a doctor): sleep disorders 1 tablet in the evening; restlessness: 1-2 times daily 1 tablet. 2-4 weeks	WEU 1993 AT

Herbal preparation **Pharmaceutical form**	**Indication**	**Strength** **Posology**	**Period of medicinal use**
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 disorders 2 tablets in the evening; restlessness: maximum 3 times daily 2 tablet. No limitation of the duration of use.	WEU 2003 AT
b) Dry extracts of valerian root (DER 4-7:1, ethanol 70% V/V) and hop strobile (DER 4-8:1, methanol 40% V/V).	Herbal medicinal product for the relief of sleep disorders.	Fixed combination of 200 mg/45-mg–350 mg/70 mg of 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.	WEU 1993 AT 2003 AT 2005 AT 1999 CZ 1976 DE 1996 HU 1999 HU 2003 (withdrawn) HU 1999 PL 1999 SLO
Traditional Use – TU: Liquid extracts			
a) Liquid extract (DER 1:6.3) from a	Indication 1): Traditional herbal	Single dose 20 ml containing 12% V/V	TU 1976 DE

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
mixture of valerian root-hop strobile (1:1), extraction solvent ethanol 40% V/V.	medicinal product for relief of mild symptoms of mental stress. Indication 2): Traditional herbal medicinal product used to aid sleep.	extract, 3 times daily	
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 (IRL, SLO). The product is a traditional herbal medicinal product for use in the specified indication exclusively based upon long-standing use.	Oral drops, solution Posology: Adults, elderly and adoscelents above 12 years of age: Minor nervous tension: 1 ml (approximately 40 drops) in ½ glass of water 3-5 times daily. Temporary insomnia: 2 ml (approximately 80 drops) in ½ glass of water.	TU 1978 SV

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal 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 times 3 doses or 3 times 2 doses for Indication 1) and 3 times 1 or 2 times 1 doses 1 hour before bedtime for Indication 2).	TU 1976 DE
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 times 1 doses for Indication 1) and 1 dose 1 hour before bedtime for Indication 2).	TU 1976 DE
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. Indication 2): Traditional herbal medicinal product used to aid sleep.	Fixed combinations of 100 mg/30 mg of dry extracts of valerian root and hop strobile, respectively Daily dosage: 2-3 doses for Indication 1) and 2 doses 1 hour before bedtime for Indication 2).	TU 1976 DE
d) Dry extracts of valerian root (DER 4-7:1), extraction solvent methanol 45% V/V and hop strobile (DER 4-8:1),	Indication 1): Traditional herbal medicinal product for relief of mild symptoms of mental	Fixed combinations of 125 mg/25 mg of dry extracts of valerian root and hop strobile, extracts of valerian root and	TU 1976 DE

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
extraction solvent ethanol 40% V/V	stress. Indication 2): Traditional herbal medicinal product used to aid sleep.	hop strobile, respectively. Daily dosage: 3 times 1 doses for Indication 1) and 1-2 doses 1 hour before bedtime for Indication 2).	
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 times 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 times 3 doses for Indication 1) and 3 doses 1 hour before bedtime for Indication 2). e3) Fixed combinations of 200 mg/46-68 mg of dry extracts from valerian root and hop strobile, respectively. Daily dosage: 1 dose 3 times daily for Indication 1) and 1-2 doses ½ to 1 hour before bedtime for Indication 2).	TU 1976 DE
f) Dry extracts of valerian root (DER 6-7:1), extraction solvent ethanol 70% V/V and hop strobile (DER 11-14:1),	Indication 1): Traditional herbal medicinal product for relief of mild symptoms of mental	Fixed combinations of 225 mg/30 mg dry extracts of valerian root and hop	TU 1976 DE

Herbal preparation Pharmaceutical form	Indication	Strength Posology	Period of medicinal use
extraction solvent ethanol 96% V/V.	stress. Indication 2): Traditional herbal medicinal product used to aid sleep.	strobile, respectively. Daily dosage: 3 times 1 dose for Indication 1) and 1-2 doses 1 hour before bedtime for Indication 2).	
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 times 2 doses for Indication 1) and 2 doses 1 hour before bedtime for Indication 2).	TU 1976 DE

Overall conclusions on clinical use

The valerian-hop preparations in Table 3 are selected for clinical use (WEU and TU) in the monograph, based upon the periods of marketing in EU countries (see Table 3) and clinical studies (see Table 4).

The herbal preparations already accepted in the first version of the assessment report are acknowledged 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/m).

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.

No change in therapeutic indications has been made as compared to the first version of the monograph.

WEU: Herbal medicinal product for the relief of sleep disorders.

TU: Traditional herbal medicinal product for relief of mild symptoms of mental stress Indication 1) and traditional herbal medicinal product used to aid sleep Indication 2).

No changes have been made to posology in the monograph. The posologies remain restricted for adolescents, adults and elderly (see also section 5.5.1.).

Based on the product information in Table 3, the posologies have been calculated based upon single doses. This resulted in the posologies transferred to the monograph as listed below.

Herbal preparations for WEU

a) Fixed combinations of 187-374 mg/28 mg-500 mg/65 mg dry extracts of valerian root and hop strobile, respectively: 1-2 doses ½ to 1 hour before bedtime, not exceeding 500 mg of valerian extract.

b) Fixed combination of 200 mg/45 mg–350 mg/70 mg of dry extracts of valerian root and hop strobile, respectively 1-2 doses ½ to 1 hour before bedtime, not exceeding 500 mg of valerian extract.

Herbal preparations for TU

Liquid extracts:

a) Liquid extract (DER 1:6.3):

Indication 1): 2.4 ml, 3 times daily

Indication 2): 2.4 ml 1 hour before bedtime

b) Liquid extract (1:1):

Indication 1): 1 ml in ½ glass of water 3-5 times daily

Indication 2): 2 ml in ½ glass of water 1 hour before bedtime

Dry extracts:

a) Fixed combinations of 80 mg/20 mg or 160 mg/40 mg dry extracts of valerian root and hop strobile, respectively.

Indication 1): 240 mg/60 mg or 320 mg/480 mg, 3 times daily

Indication 2): 240 mg/60 mg or 320 mg/80 mg, 1 hour before bedtime

b) Fixed combination of 187 mg/45 mg dry extracts of valerian root and hop strobile, respectively.

Indication 1): 187 mg/45 mg, up to 3 times daily

Indication 2: 187 mg/45 mg, 1 hour before bedtime

c) Fixed combinations of 100 mg/30 mg of dry extracts of valerian root and hop strobile, respectively.

Indication 1): 100 mg/30 mg, 2-3 times daily

Indication 2: 200mg/60 mg, 1 hour before bedtime

d) Fixed combinations of 125 mg/25 mg of dry extracts of valerian root and hop strobile, respectively.

Indication 1): 125 mg/25 mg, 3 times daily

Indication 2): 125 mg/25 mg or 250 mg/50 mg, 1 hour before bedtime

e1) Fixed combinations of 100 mg/24 mg–32 mg dry extracts of valerian root and hop strobile, respectively.

Indication 1): 200 mg/48-64 mg, 3 times daily

Indication 2): 200 mg/48-64 mg, 1 hour before bedtime

e2) Fixed combinations of 68 mg/16 mg of dry extracts of valerian root and hop strobile, respectively.

Indication 1): 204 mg/48 mg, 3 times daily

Indication 2): 204 mg/48 mg, 1 hour before bedtime.

e3) Fixed combinations of 200 mg/46-68 mg of dry extracts from valerian root and hop strobile, respectively.

Indication 1): 200 mg/46-68 mg, 3 times daily

Indication 2: 200 mg/46-68 mg or 400 mg/92-136 mg, ½ to 1 hour before bedtime.

f) Fixed combinations of 225 mg/30 mg dry extracts of valerian root and hop strobile, respectively.

Indication 1): 225 mg/30 mg 3 times daily

Indication 2): 225 mg/30 mg or 450 mg/60 mg 1 hour before bedtime

g) Fixed combinations of 77 mg/18.8 mg of dry extracts of valerian root and hop strobile, respectively.

Indication 1): 154 mg/37.6 mg 3 times daily

Indication 2): 154 mg/37.6 mg 1 hour before bedtime

The duration of use from the first version of the monograph is maintained: *If the symptoms persist longer than 4 weeks of continued use of the medicinal product, a doctor or a qualified health care practitioner should be consulted*.

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

Reference is made to studies with the single ingredients of the combination by referring to the respective assessment reports on valerian root and hop strobile (EMA/HMPC/150848/2015 and EMA/HMPC/682384/2013, respectively).

Valerian

Both, aqueous-ethanolic (extraction solvent: ethanol 60% V/V) and total aqueous extract as well as the aqueous fraction derived from the aqueous-ethanolic extract showed low (IC=50-1000 times lower than IC of GABA) affinity for the $GABA_A$ receptor. The chemical nature of the compounds responsible for this activity could not be correlated with sesquiterpenes or valepotriates (Mennini *et al*., 1993).

An aqueous-ethanolic valerian root extract (no further information) caused an inhibitory effect (IC_{50}=2.0 µM) on muscimol-sensitive NTS neurons which was mediated via $GABA_A$-receptors (Yuan *et al*., 2004).

Aqueous and ethanolic (extraction with absolute ethanol, dry extract diluted with water) extracts of valerian root showed an interaction with the $GABA_A$-receptor by displacing [^{3}H] muscimol from synaptic membranes from rat brain cortices (Cavadas *et al*., 1995). For valerenic acid no effect was shown.

Ortiz *et al*. (1999) showed that, besides influence on GABA-release and -uptake, valerian root extracts (extraction solvent: 95% ethanol (1:40 w/v), no further information) interact with benzodiazepine binding sites. At low concentrations, valerian root extracts enhanced [3H]-flunitrazepam binding while it was inhibited at higher extract concentrations. These results may point to at least two different biological activities interacting with [3H]-flunitrazepam binding sites.

Another experiment demonstrated the interaction of a hydroalcoholic extract (no further information) of valerian root with adenosine receptors, but not with benzodiazepine receptors. However, this extract contained 1.38% of valtrate whereas an aqueous extract devoid of valepotriates produced only a weak effect under similar conditions (Balduini & Cattabeni, 1989).

The lignan hydroxypinoresinol, found in valerian root, showed a high affinity with IC_{50} of 2.5 mmol/L for the 5-HT1A receptor, which plays a role in sleep induction and anxiety reactions. Affinity for $GABA_A$-, benzodiazepine- and µ-opiate-receptors was distinctly lower (Hölzl, 1998; Bodesheim & Hölz, 1997). The kind of action at the receptor (agonistic/antagonistic activity) was not investigated.

Effects on spontaneous motility, thiopental sleeping-time and pentetrazol-induced toxicity were tested on mice by administering a commercially available aqueous dry valerian root extract (DER 5-6:1,

extraction solvent: water). In spontaneous motility tests, doses of 20 and 200 mg/kg diminished the motility moderately, while in control animals 5 mg and 25 mg of diazepam resulted in substantial reductions in motility shortly after administration. The extract increased thiopental-induced sleeping time by factors of 1.6 at 2 mg/kg ($p<0.01$) and 7.6 at 200 mg/kg ($p<0.01$) compared to a factor of 4.7 for chlorpromazine at 4 mg/kg (Leuschner *et al*., 1993).

Hops

Orally administered of a dry extract of hops (DER 5-7:1; exrtaction solvent methanol/water 45% w/w) in mice have shown to decrease body temperature in oral doses of 250 mg/kg after 120 minutes. Its effect was compared with intraperitoneal melatonin 50 mg/kg after 60 and 120 minutes. The body temperature lowering effect was neutralized by intraperitoneal luzindole 30 mg/kg, administered 15 minutes before melatonin or hops extract. This body lowering temperature is thought to be the result of melatonin receptor activation, inhibited by luzindole a competitive antagonist of melatonin receptors. The dose-response curve had a U-shape, which was explained by the authors as the widespread occurence of biological optimisation processes (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 with the combination

One pharmacological study has been performed with both a valerian preparation and a fixed valerian-hops preparation. An *in vitro* radioligand binding assay at A_1 and A_{2A} 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 A_1 ARs K(i)=0.15-0.37 mg/ml versus [3H]-N6-cyclopentenyladenosine (CPA). The same extracts exhibited partial agonist activity at the A_1 receptor as indicated by a lower degree of stimulation of [35S]-CTPγS binding in membrane preparations of CHO-hA1 cells as compared to full A_1 AR agonist N6-CPA. In addition valerian extract inhibited c-AMP accumulation in CHO-hA_1 cell membranes. The partial agonistic activity at A_1 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-HT_{4e}, 5-HT_6, 5-HT_7 and melatoninergic ML_1 and ML_2 receptors (Abourashad *et al.*, 2004; Brattström, 2007).

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 hours. Hops 40 g were extracted with 800 ml of 70% ethanol with a Soxhlet apparatus for 3 hours, twice (DER not given).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 hours 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. However it is not very clear which concentrations were tested, as the authors further mentioned: *The Valerian/Hops mixture was composed of Valerian (20 µg/ml) and Hops (10 µg/ml) in sucrose-agar media.*

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 (about 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.

According to the authors this study demonstrated that a valerian/hops mixture extract improves sleep-related behaviors, including sleeping time, by modulating GABAergic/serotonergic signalling in fruit flies (Choi *et al.*, 2017). These results reported by Choi *et al.* (2017) were already announced in an abstract published by Jo *et al.* (2015).

Assessor's comments

The extrapolation of these results to humans is highly questionable. Regulation of or binding to genes and/or receptors of Drosophila melanogaster may or may not translate to human situation. The findings may be over-emphasised. In addition, the extracts do not correspond to to those included in the WEU part of the monograph and phytoequivalence is unlikely. In particular, this study should not be a sufficient base to question the hitherto formulated mechanisms of action.

3.1.2. Secondary pharmacodynamics

Not applicable

3.1.3. Safety pharmacology

No data available.

3.1.4. Pharmacodynamic interactions

Not applicable

3.1.5. Conclusions

The phytochemical composition, pharmacology 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).

The sedative effects of preparations of valerian root and hop strobiles have been long recognised empirically and have been confirmed for valerian root preparations in preclinical tests. Several mechanisms of action possibly contributing to the clinical effect have been investigated for diverse constituents of valerian root (sesquiterpenoids, lignans, flavonoids) and include interactions with the GABA-system, agonism at the A-1 adenosine receptor and binding to the 5-HT_{1A} receptor. Several mechanisms of action also have been investigated for diverse constituents of hop strobiles (bitter acids, flavonoids) and include interactions with the GABA-system, agonism at the melatonin receptors (ML_1 and ML_2) and binding to serotonin receptor subtypes (5-HT_{4e}, 5-HT_6 and 5-HT_7).Since isolated constituents of valerian were used in non physiological high doses to achieve effects, the clinical relevance of these investigations may be questionable.

Doses of hops extract to demonstrate an influence on body temperature in mice in *in vivo* experiments were also supratherapeutic when compared with the human equivalent dose. Moreover, the U-shape of the dose-response curve was explained as a biological optimization process.

Whether hop strobile extract acts either as a mild sedative independently or as a synergist for valerian root extract, is not yet known.

As compared to the former version of the assessment report, no relevant new data on the biological activity of valerian/hops mixture have been published.

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 on combinations. Kelber *et al.* (2014) provided a practical application of a "bracketing and matrixing concept" using Valerianae radix according to the HMPC Guidelines (EMEA/HMPC/107079/2007) and (EMEA/HMPC/67644/2009).

Genotoxicity data of valerian root preparations are available. The following extracts, representing the extremes of the polarity range and including also mid-range extraction solvents, were used, covering the entire spectrum of phytochemical constituents of Valerianae radix, thereby including polar and non-polar constituents:

1) dry extract (3-6:1); extraction solvent: water,

2) dry extract (4-7:1); extraction solvent: ethanol 40% (V/V),

3) dry extract (3-6:1); extraction solvent: ethanol 70% (V/V),

4) extract (1:10); extraction solvent: ethanol 96% (V/V) (oily macerate),

5) extract (167:1); extraction solvent: heptane.

The concentrations were ranging from 100 to 5000 µg/plate. S. typhimurium strains TA98, TA100, TA102, TA1535 and TA1537 were used with and without metabolic activation (S9 mix from induced rat liver microsomes). Results were unequivocally negative for all extracts.

Only preparations 1) (TU) and 3) (WEU) in bold, are included in the monograph.

Other genotoxicity tests have been performed on valerian root preparations. However the preparations, as well as the experimental setup do not comply with standard methodology for genotoxicity testing (see assessment report on valerian root: EMA/HMPC/150848/2015).

In the Ames mutagenicity test, a hydroethanolic extract (no specifications given) of hop strobile showed weakly mutagenic potential in *Salmonella typhimurium* strains TA98 and TA100 with or without activation (Göggelmann & Schimmer, 1986). These data were confirmed for TA98 strains only for a hop extract enriched in 8-PN (unpublished data) (see assessment report on hop strobile: EMA/HMPC/682384/2013).

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 substances 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).

The sedative effects of preparations of valerian root and hop strobiles have been long recognised empirically and have been confirmed for valerian root preparations in preclinical tests. Several mechanisms of action possibly contributing to the clinical effect have been investigated for diverse constituents of valerian root (sesquiterpenoids, lignans, flavonoids) and include interactions with the GABA-system, agonism at the A-1 adenosine receptor and binding to the 5-HT_{1A} receptor. Also several mechanisms of action have been investigated for diverse constituents of hop strobiles (bitter acids, flavonoids) and include interactions with the GABA-system, agonism at the melatonin receptors (ML_1 and ML_2) and binding to serotonin receptor subtypes (5-HT_{4e}, 5-HT_6 and 5-HT_7).

There are no new relevant 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 minutes. 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, vs. placebo, first clinical trial ; 2nd dosage: 1500 mg valerian and 360 mg hops, vs. placebo, second clinical trial). These doses are in the same range as these in the monograph. 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 hours 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. According to the authors this investigation showed evidence that a valerian/hops fluid extract can be used successfully using a single administration. Unfortunately their conclusions have a limited value, as no composition of the preparation is given (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

In the assessment report on valerian root it is concluded that data from clinical studies with dry extract (DER 3-7.4:1), extraction solvent: ethanol 40-70% (V/V) support a WEU (see assessment report on valerian root: EMA/HMPC/150848/2015) (Vorbach *et al.* 1996; Dorn, 2000; Ziegler *et al.*, 2002).

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.

Non-controlled as well as controlled clinical studies, have been performed for combinations of hop strobile with valerian root 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), although an adaption to the noise could be observed. The results from the two treatment arms (second versus 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 [1].

Drug extract ratio and extraction solvents 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 analysed 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 improved 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 randomised order. Nevertheless, the results are congruent with those of better designed and reported trials.

In a placebo-controlled, double-blind, randomised 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 a commercial preparation (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 recommended valerian preparations in patients with mild, non-chronic 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 45.5 mg of dry extract of hop strobile (DER 5.5:1, methanol 40% V/V); extraction solvents identified by the brand name) was compared to that of 3 mg bromazepam in a two-week reference-controlled, double-blind, randomised 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. During treatment with the herbal combination the percentage of patients subjectively feeling

[1] Composition: Radix Valerianae 200.20 mg dry extract (4-7:1) ethanol 70% (V/V), Flos Lupuli 45.50 mg dry extract (4-8:1) ethanol 40% (V/V)

"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).

Assessor's comments

In the study by Schmitz and Jäckel (1998) the statistical test used is acceptable for a lower number of participants. The Mann-Withney-U test is a non-parametric statistical approach wherein the results of every patient are individually compared, leading to a score. In their approach the authors set limits of acceptance of equivalence on beforehand.

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, randomised, 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 included.

The 3 groups included (1) valerian-hops combination (2 tablets each night for 28 days; each tablet contained 187 mg of valerian native extracts and 41.9 of hops native extracts) (n=59 of 68); (2) placebo (2 tablets each night for 28 days; these tablets of inactive ingredients matched the size, shape, and color of the valerian-hops tablets) (n=65 of 72); (3) diphenhydramine (2 tablets each night for 14 days; these were 25-mg tablets followed by 2 placebo tablets for the remaining 14 nights) (n=60 of 70). Following the screening visit, participants kept daily sleep diaries for at least a 14-day baseline period, a 28-day treatment period, and an additional 14-day follow-up after treatment discontinuation. This means that no comparison could be made between valerian-hops and diphenhydramine at the end of week 4. As a consequence the study must be considered as a comparative study between the combination and placebo.

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. Sleep latency was reduced from baseline to week 2 in all 3 groups, with reductions of 7.4 minutes in the valerian-hops group, relative to 4.1 minutes in both the placebo and diphenhydramine groups. Those differences were not statistically significant.

Comparison of baseline to Week 4 differences between valerian (9.5 minutes) and placebo (3.9 minutes) was nearly significant (P=.0795). Sleep efficiency was increased from baseline to Week 2 in all 3 conditions, with significantly larger gains made in the diphenhydramine (4.6%) condition relative to placebo (2.5%) (P=.039). Valerian-hops produced an average increase of 3.1%, which was not significantly different from either of the other 2 groups. Changes from baseline to Week 4 averaged 5% for the valerian-hops relative to 3.3% for the placebo (NS). Valerian-hops produced an average increase in sleep efficiency of 3.1%, which was not significantly different from either of the other 2 groups. Average gains in total sleep time from baseline Week 4 was 27.5 minutes for valerian and 22.1 for placebo subjects (NS).

All 3 conditions reduced their total Insomnia Severity Index scores from baseline to Week 2 (see Table 3). Comparisons of baseline and Week 2 differences using ANCOVAs (treatment, center, and the interaction treatment-by-center) showed that diphenhydramine (P=.003), but not valerian-hops (P=.06), produced greater changes than placebo. There was no significant difference between the 2 treatment groups (P=.24). Differences between Baseline and Week 2 scores averaged 4.9 for valerianhops, 3.3 for placebo, and 5.6 for diphenhydramine. Comparisons between valerian-hops and

placebo for baseline to Week 4 differences were not significant. Chi²-analyses revealed no significant group differences in the clinicians' ratings of therapeutic effect on the Clinical Global Impression scale at Week 1, Week 2, or Week 4 (all P values>0.2).

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 (p=0.028). 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 (Morin *et al.*, 2005).

Assessor's comments

At the end of the study, results are only available for the combination and placebo. Conclusions for diphenhydramine versus the combination cannot be made. The study bu Morin et al. has to be considered as a comparative study with the combination versus placebo.

Another randomised 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 (≥30 minutes) 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 analysis was performed non-parametrically and two sided by means of the Mann-Whitney test in the intention-to treat collective. Taking into account the individual instability of the sleep parameters together with the small number of patients in this pilot study a value of p=0.10 was considered statistically significant.

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).

Assessor's comments

The analysis was performed non-parametrically and two sided by means of the Mann-Whitney test in the intention-to treat collective. The study was handled by one study centre to ensure equal performance of all the patients, since the number of patients in this pilot study was limited to 30, i.e.

10 patients in each study arm. The registrations by means of the transportable recorder were performed under the usual sleep condition, i.e. at home.

Table 4: Clinical studies on humans

Type	Study design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
studies with defined extracts							
Morin *et al.*, 2005 Sleep quality	Randomised, double blind, placebo controlled, multicentre, reference controlled (14 days). 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 night time. 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 Sleep latency and sleep efficiency not significantly improved with valerian-hops vs. placebo. Average gains in total sleep time from baseline Week 4 was 27.5 minutes for valerian and 22.1 for placebo subjects (NS). Quality of life SF36 (physical component) significantly improved for valerian-hops vs. placebo group at the end of 28 days (p=0.028). Both treatments appear safe, without rebound insomnia after	ANCOVA, Cochran-Mantel-Haenszel and Fisher exact test Quality of life improved with herbal treatment (P=0.028). Quality of life also improved with diphenhydramine but no comparison or P-value	To be considered as a comparison between valerian-hop and placebo. Only significant difference for the quality of life which is not necessarily related to sleep quality.

Type	Study design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
					discontinuation.		
Schmitz and Jäckel, 1998 Sleep quality	Randomised, double-blind, reference controlled parallel group design (3 mg bromazepam) Duration: 2 weeks treatment	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 (reference) 30 minutes before bedtime per day	N=46	Patients with non-psychiatric sleep disorders	Psychometric tests Psychopathological scales Sleep questionnaires Better results with the combination as compared to bromazepam.	Equivalence of both therapies according to sleep quality, fitness and quality of life tested by a Mann-Whitney-Statistic of 0.50 with a lower boundary of the 95% confidence interval of 0.46. Superiority of herbal medicine over bromazepam 'Bad' or 'moderate' feeling: herbal-62.6% vs bromazepam-32.7%	Number of participants limited.

Type	Study design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
Kötter *et al.*, 2007 Sleep quality	Randomised, double-blind, placebo-controlled. 4 weeks	3 treatment groups: Valerian dry extract (DER 5.3:1; extraction solvent methanol 45% m/m) 500 mg hop dry extract (DER 6.6:1; methanol 45% m/m Versus Pure valerian extract (=same as in combination) Placebo 1 dose per day	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. Clinical gobal impression scale. Reduction of sleep latency. 44.5 minutes with valerian-hop. 22.1 minutes with mono-preparation (not superior to placebo) 5 minutes placebo	Mann-Whitney test ITT. Reduction of sleep latency: fixed combination superior to placebo (P<0.10)	Objectively recorded sleep measures, but the number of patients is insufficient.
studies with non-defined extracts							
Rodenbeck & Hajek, 1998 Sleep quality	Randomised, double blind, placebo controlled. 4 weeks (57 weeks of	Tablets with 250 mg valerian dry extract (DER 5:1; no info on extraction solvent) and 60 mg hop dry extract	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.	Small sample size does not permit statistical analysis.	No clinical relevance, since number of patients limited and

Type	Study design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
	therapy)	(DER 6:1; no info on extraction solvent). 2 tablets per day 30 minutes before bedtime.					the extraction solvents not known.
studies in healthy subjects							
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 noise during nights 3, 4 and 5. Oral administration of 4 tablets to 6 patients prior to	N=12	Healthy subjects	Polysomnography. Reduction of the noise induced disturbance of sleep stage pattern. Slow-wave sleep and stage REM.	Flat statistical analysis: small scale study.	Low relevance due to the low number of subjects and inclusion of healthy subjects.

Type	Study design	Test Product(s):	Number of subjects	Type of subjects	Outcomes	Statistical analysis	Clinical relevance
		night 2 and to 6 patients prior to night 3. Remaining nights 4 tablets of placebo.					
Leathwood *et al.*, 1982 Sleep quality	Cross over, double blind, placebo controlled, cross-over trial	400 mg valerian dry extract (DER 2.8:1, extraction solvent water), 60 mg valerian dry extract and 30 mg hop dry extract (no information on specification) Placebo. 3 doses of each preparation to be taken on 9 non-consecutive nights.	N=128	Healthy subjects Poor sleepers: N=61 Good sleepers: N=67	Questionnaire to reply by volunteers. Significant differences between valerian extract and placebo, for time to fall asleep and quality of sleep. No differences between combination and placebo.	128 patients out of 166 completed the study. Per protocol analysis. Results expressed as % of patients responding (P<0.01).	Low relevance due to the inclusion of healthy subjects. Question-naire not validated. It is not clear whether the order of therapeutic regimens was randomised.

Assessor's comments:

In the first edition of the assessment report the following fixed combinations of dry extracts were considered for WEU:

- *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% mm/).*

The WEU herbal preparations a) 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) and b) dry extracts of valerian root (DER 4-7:1, ethanol 70% V/V) and hop strobile (DER 4-8:1, methanol 40% V/V) were included in the first version of the monograph, published in 2010. In this revision of the monograph, no new clinical studies to substantiate efficacy of these herbal preparations were found (see section 4.2 Clinical studies). The quality and clinical outcome of these studies to substantiate efficacy are considered weak in relation to the requirements in the current Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products (EMA/HMPC/104613/2005–Rev. 1). However, as there are no new data that change the benefit-risk assessment, the preparations are retained in the revision of the WEU monograph.

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.

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 medicinal 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 complains (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 4 patients, and explicitly stated by two: 1 time oedema, 1 time 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 and 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 (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 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 4.

Taking into account these data, 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

The WEU herbal preparations a) 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) and b) dry extracts of valerian root (DER 4-7:1, ethanol 70% V/V) and hop strobile (DER 4-8:1, methanol 40% V/V) were included in the first version of the monograph, published in 2010. In this revision of the monograph, no new clinical studies to substantiate efficacy of these herbal preparations were found (see section 4.2 Clinical studies). The quality and clinical outcome of these studies to substantiate efficacy are considered weak in relation to the requirements in the current Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products (EMA/HMPC/104613/2005–Rev. 1). However, as there are no new data that change the benefit-risk assessment, the preparations are retained in the revision of the WEU monograph.

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).

No additional data are known for the combination.

Table 5: Clinical safety data from clinical trials

Type	Study design	Test Product(s)	Number of subjects	Type of subjects	Adverse reactions	Comments
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 per day 30 minutes before bedtime	N=15 Verum: n=8 Placebo: n=7	Non-organic insomnia (DSM III-R) (ApA, 1987)	Gastro-intestinal complaints and headache Placebo=2 Verum=4	Small sample size. Only of qualitative importance, see section 5.3 below.
Schmitz and Jäckel, 1998 Sleep quality	Randomised, double-blind, reference controlled parallel group design (3 mg bromazepam). Duration: 2 weeks treatment	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 (reference) 30 minutes before bedtime per day	N=46	Patients with non-psychiatric sleep disorders.	7 adverse events of which 2 possibly in relation with medication. Both were gastrointestinal complaints, which led to dropout.	Small sample size. Only of qualitative importance , see section 5.3 below.

5.2. Patient exposure

The patient exposure to the products with the combination valerian-hops can be derived from Table 4 in sections 4.1 and 4.2.

5.3. Adverse events, serious adverse events and deaths

Gastrointestinal symptoms e.g. nausea, abdominal cramps 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. However, as gastro-intestinal symptoms are mentioned independently in several studies, it will be kept under section 4.8 of the Monograph.

In the study by Rodenbeck & Hajek, 1998 headache was reported in the verum as well as in the placebo group. There was no significant difference between both groups (number of patients limited: n=15). It is proposed not to mention headache as an undesirable effect. Headache is among the set of symptoms in the syndrome of sleep disorders (sleep questionnaire SF-A or SF-B by Görtelmeier R, 2005).

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). However, patients with known hypersensitivity to the active substances should not use valerian root/hop strobile preparations, see section 5.5.2. below. Hypersensitivity to the active substances is a contraindication in the monograph.

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.

No cases of withdrawal or rebound are reported.

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).

No additional data are known for the combination.

5.5. Safety in special populations and situations

No additional data are known for to the combinations.

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

Preparation (b) (WEU) and preparation (f) (TU) can be used in children from 6 years on in the Czech Republic. No other EU countries allow the use in children.

It was decided that the use of these fixed combinations is not recommended in children below the age of 12 years, due to lack of adequate data. Posologies in the monograph are given for adolescents, adults and elderly.

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.

The application of valerian root containing preparations may theoretically contribute to tiredness dizziness and somnolence when taken in combination with other sedating psychiatric drugs (see assessment report on valerian root: EMA/HMPC/150848/2015).

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.

No fertility data are available.

5.5.6. Overdose

Valerian root as a monopreparation at a dose of approximately 20 g caused symptoms such as fatigue, abdominal cramp, chest tightness, light-headedness, hand tremor and mydriasis, which disappeared within 24 hours (see assessment report on valerian root: EMA/HMPC/150848/2015). There are no reports about overdose with the combination.

There are also no cases of drug abuse known.

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 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 clinical studies have been performed and give some support for this use.

The WEU herbal preparations a) 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) and b) dry extracts of valerian root (DER 4-7:1, ethanol 70% V/V) and hop strobile (DER 4-8:1, methanol 40% V/V) were included in the first version of the monograph, published in 2010. In this revision of the monograph, no new clinical studies to substantiate efficacy of these herbal preparations were found (see section 4.2 Clinical studies). The quality and clinical outcome of these studies to substantiate efficacy are considered weak in relation to the requirements in the current Guideline on the assessment of clinical safety and efficacy in the preparation of EU herbal monographs for well-established and traditional herbal medicinal products (EMA/HMPC/104613/2005–Rev. 1). However, as there are no new data that change the benefit-risk assessment, the preparations are retained in the revision of the WEU monograph.

The 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. 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, these preparations can also be accepted as traditional herbal medicinal products for relief of mild symptoms of mental stress and to aid sleep.

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 or quantification 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