EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

Assessment report on *Valeriana officinalis* L., radix and *Valeriana officinalis* L., aetheroleum

Draft

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

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

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Valeriana officinalis* L., radix
Herbal preparation(s)	**Well-established use** Dry extract (DER 3-7:1), extraction solvent ethanol 40-70% (V/V) **Traditional use** a) Comminuted herbal substance b) Powdered herbal substance c) Expressed juice from fresh root (1:0.60-0.85) d) Dry extract (DER 4-6.1), extraction solvent: water e) Liquid extract (DER 1:4-6), extraction solvent: water f) Dry extract (DER 4-7:1), extraction solvent methanol 45% (V/V) g) Dry extract (DER 5.3-6.6:1), extraction solvent: methanol 45% (m/m) h) Liquid extract (DER 1:7-9), extraction solvent: sweet vine i) Dry extract (DER 4-5:1), extraction solvent: ethanol 35% (m/m) j) Liquid extract (DER 1:1), extraction solvent: ethanol 60% (V/V) k) Tincture (ratio of herbal substance to extraction solvent 1:8), extraction solvent ethanol 60% (V/V) l) Tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent ethanol 56%

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Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Valeriana officinalis* L., radix
	m) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 70% (V/V) n) Tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent ethanol 60-80% (V/V) o) Dry extract (DER 5.5-7.4:1), extraction solvent: ethanol 70-90% (V/V)
Pharmaceutical form(s)	Comminuted herbal substance as herbal tea for oral use. Herbal preparation in solid or liquid dosage forms for oral use. Comminuted herbal substance for use as bath additive.

Herbal substance(s) (binomial scientific name of the plant, including plant part)	*Valeriana officinalis* L., aetheroleum
Herbal preparation(s)	Essential oil
Pharmaceutical form(s)	Herbal preparations in liquid dosage forms for oral use. Herbal preparations in liquid dosage forms for use as bath additive.

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

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1. Introduction

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

- Herbal substance(s)

Valerianae radix has been included into collections of monographs:

- European Pharmacopoeia
- British Pharmacopeia (BP, 2015)
- United States Pharmacopoeia-NF (USP, 2014)

Definitions in the European Pharmacopoeia:

- Valerianae radix, monograph 07/2015:0453

Dried, whole or fragmented underground parts of *Valeriana officinalis* L. s.l., including the rhizome surrounded by the roots and stolons.

content:	essential oil:	minimum 4 ml/kg (dried drug)
	sesquiterpenic acids:	minimum 0.17 per cent m/m, expressed as valerenic acid ($C_{15}H_{22}O_{2;}$ M_r234.3) (dried drug)

- Valerianae radix minutata, monograph 07/2015:2526

Dried, cut underground parts of *Valeriana officinalis* L. s.l., including the rhizome, roots and stolons. It is produced from Valerian root (0453) for the purpose of being used in herbal teas.

content:	essential oil:	minimum 3 ml/kg (dried drug)
	sesquiterpenic acids:	minimum 0.10 per cent m/m, expressed as valerenic acid ($C_{15}H_{22}O_{2;}$ M_r234.3) (dried drug)

According to Wichtl (2009) the most important constituents of the plant are:

- essential oil: 0.3-2.1% (according to Ph. Eur. not less than 0.4% and 0.3% for the whole drug or cut drug, respectively) with variable composition, depending on the origin, consisting of mono- and sesquiterpens; predominant components are bornyl acetate, myrtenyl-isovalerianate and –acetate; camphene, myrtenol, borneol are also found; important sesquiterpens are valerianol, valeranon, α-kessylacetate, β-eudesmol, valerenal, tamariscene and the pacifigorgianes

  heavily volatile sesquiterpenic acids: (according to Ph. Eur. not less than 0.17%, expressed as valerenic acid) such as valerenic, acetoxyvalerenic acids and 3,4-epoxyvalerenic acid, which have been considered species-specific marker compounds but based on recent studies have also been identified in non-aggregate species of *V. officinalis*

- valepotriate: 0.1-2% main components valtrate and isovaltrate, in addition to dihydrovaltrate, IVHD-valtrate and the glycoside of valerosidatum; valepotriate are very unstable, their degradation products are e.g. baldrinal, homobaldrinal, valeric and isovaleric acid

- small amonts of lignans (0.2%), e.g. 8-hydroxypinoresimol, its diglucoside, berchemol glucoside massoresionglucosid and 4'glucosyl-9-0-(6''desoxysaccarosyl)-olivil

- traces of alkaloids do occur (probably artefacts as a result from drying) such as actinidine, valerianine and the "main" valeriana-alkaloid, a pyridine derivative belonging to the monoterpene alkaloids

- free amino acids like arginine, alanine, glutamine, GABA

- flavonoids such as 8-methylapigenin, 2S-hesperidin, linarin
- starch, various carbohydrates (glucose, fructose, saccharose, raffinose), phenol carbon acids and free fatty acids.

- Herbal preparation(s)

Definitions in the European Pharmacopoeia:

- Valerianae tinctura, monograph 07/2010:1899
  Tincture produced from Valerian root (0453)
  Production: The tincture is produced from 1 part of the drug and 5 parts of ethanol (60 to 80 per cent V/V) by an appropriate procedure.
  content: minimum 0.015 per cent m/m of sesquiterpenic acids, expressed as valerenic acid ($C_{15}H_{22}O_2$; M_r234.3)
- Valerianae extractum aquosum siccum, monograph 07/2010:2400
  Extract produced from Valerian root (0453)
  Production: The extract is produced from the herbal drug by a suitable procedure using water at not less than 60°C.
  content: minimum 0.02 per cent m/m of sesquiterpenic acids, expressed as valerenic acid ($C_{15}H_{22}O_2$; M_r234.3) dried extract).
- Valerianae extractum hydroalcoholicum siccum, monograph 07/2014:1898
  Extract produced from Valerian root (0453)
  Production: The extract is produced from the herbal drug by a suitable procedure using ethanol (30-90 per cent V/V) or methanol (40-55 per cent V/V).
  content: minimum 0.25 per cent m/m of sesquiterpenic acids, expressed as valerenic acid ($C_{15}H_{22}O_2$; M_r234.3) anhydrous extract).

Definition in the DAB 6

- Oleum Valerianae
  essential oil obtained from the roots of *Valeriana officinalis* L. (dried, cut) by steam distillation
  clear, yellowish to brown liquid with characteristic odour and bitter taste with optical activity
  major constituents: bornyl acetate and camphene (analysed by gas chromatography)

  The composition of the oil is variable depending on the origin and is consisting of mono- and sesquiterpens. Predominant components are bornyl acetate, myrtenyl-isovalerianate and -acetate, camphene, myrtenol and borneol. Important sesquiterpens are valerianol, valeranon, α-kessylacetate, β-eudesmol, valerenal, tamariscene and the pacifigorgianes (Wichtl, 2009).

This report focusses on findings with aqueous and aqueous-ethanolic extracts since clinical experience has been collected mainly with these types of extracts, and they were used in most non-clinical and clinical trials.

Other long-used preparations like the dried herbal substance[1], herbal tea, aqueous-methanolic extracts, expressed juice from fresh root and valerian root oil are discussed under the chapter 'Traditional use'.

Use of extraction solvents such as dichloromethane and other highly lipophilic solvents may result in substantial differences in the extract composition. No information on comparability of highly lipophilic extracts to conventional valerian roots extracts with respect to constituents and/or biological response

[1] The herbal substance shall comply with the European Pharmacopoeia monograph: Valerianae radix (ref. 07/2005:0453).

and clinical effects is available. For this reason, there is no rational basis for discussion of these kinds of extracts in this report.

- 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.

This assessment report includes all data regarding monopreparations containing herbal substance and herbal preparations from *Valeriana officinalis*, radix, literature regarding combination products is not part of the assessment.

1.2. Search and assessment methodology

Literature search was done via PubMed and SciFinder in medical and scientific databases as MEDLINE, National Center for Biotechnology Information (NCBI) TOXLINE (date of search: August 2014). For the unqualified terms (valeria*; baldrian; clinical trials; valeriana officinalis and in vitro; valeriana officinalis and in vivo; valeriana officinalis and preclin*; and the different indications) as text words in the title, abstract, and full journal article. The search strategy included the terms for valeriana, and terms for the specific diseases or conditions derived from its traditional use and current indications, supplemented with those expected from non-clinical studies with valerian root. In addition to the PubMed and SciFinder literature search, bibliographies of review articles and eligible articles were examined in an effort to identify all available literature that may not have been identified by the database research. The search was limited to English, French, Spanish and German language papers. Randomised studies that used combination products with valerian root as one of its ingredients are not included.

Search engines used: SciFinder; PubMed; DIMDI

Scientific databases: see above

Medical databases: MEDLINE, NCBI,

Toxicological databases: TOXLINE

Pharmacovigilance resources: Vigilance Central

Data from EU and non-EU regulatory authorities: Market overview

Other resources:

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 medicinal products marketed in the EU/EEA

Table 1: Overview of data obtained from marketed medicinal products

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
1) comminuted herbal substance	Traditional herbal product for the relief of nervousness and sleep disorders.	capsule 270 mg adults, adolescents: 3 x 2capsules daily	TRAD, 1998, AT
	For relief of irritability, restlessness and anxiety and mild forms of sleeplessness due to nervous tension.	herbal tea oral use single dose: 1 tea spoon/250 ml of boiling water, 2 x daily in sleeplessness: a single dose before bedtime	WEU, 1996, CZ
	For relief of temporary restlessness and excitability and mild sleep disorders due to psychical lability.	film coated tablet 500 mg single dose: 4 tablets for nervous tension: adults and adolescents: 1-3 x 4 tablets daily to aid sleep: adults and adolescents: 4-6 tablets before bedtime	WEU, 2005, CZ
	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	herbal tea oral use adolescents and adults: single dose: 2 g/150 ml of boiling water, up to 3 x daily in sleeplessness: a single dose 0.5-1 h before bedtime and an earlier dose if necessary	WEU, 1978-2000, DE
	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	coated tablet 500 mg 3 x 4 tablets daily 2 weeks	WEU, 1978, DE
	Traditional herbal medicinal product for support of mental relaxation.	coated tablet 190 mg 3-4 coated tablets daily	TRAD, 1978, DE
	Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.	hard capsule 350 mg adults: 2 x 2 hard capsules daily max. 5 hard capsules daily adolescents: 1 x 2 hard capsule daily	TRAD, 1981, FR

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
	Relief of symptoms of mild mental stress and to aid sleep.	capsule 400 mg mild stress: 3 x 1 capsule daily to aid sleep: 1 capsule before bedtime and an earlier dose if necessary	TRAD, 2011, IE
	A herbal medicine used for the temporary symptomatic relief of mild forms of stress and strains and to promote natural sleep.	capsule 270 mg sleep: 2-3 capsules before bedtime restlessness: 3 x 2 capsules daily	WEU, 1997, UK
2) expressed juice from fresh root (1:0.6-0.85)	a) Herbal medicinal product for the relief of mild nervous tension. b) Herbal medicinal product for the relief of difficulty in falling asleep.	oral liquid (containing 100% expressed juice) adolescents and adults: a) 1-3 x 10 ml daily b) 1-2 x 10 ml before bedtime	WEU, 1978-2010, DE
3) expressed juice from fresh root (1:1.0-1.5)	a) Herbal medicinal product for the relief of mild nervous tension. b) Herbal medicinal product for the relief of difficulty in falling asleep.	oral liquid (containing 100% expressed juice) a) 3 x 10 ml daily b) 1-2 x 10 ml before bedtime	WEU, 1978-2008, DE
4) dry extract (DER 5-6:1), extraction solvent: water	Mildly sedative. For sleep enhancement in temporary disturbance of sleep.	tablet 45 mg 1-3 x 2-5 tablets daily	WEU, 1997, FI
5) dry extract (DER 4-6:1), extraction solvent: water	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	coated tablets 140 mg 3 x 3 tablets daily 2 weeks	WEU, 1978, DE
	Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep.	hard capsules 200 mg adolescents and adults: mental stress: 1-3 hard capsules daily to aid sleep: 1-2 hard capsules in the evening max. 4 hard capsules	TU, 1994, FR

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		daily duration of use: 4 weeks	
6) dry extract (DER 5-9:1), extraction solvent: water	a) Herbal medicinal product for the relief of mild nervous tension b) Herbal medicinal product for the relief of difficulty in falling asleep.	effervescent tablet 308 mg a) 1-3 x 1 tablet b) 1-2 x 1 tablet before bedtime	WEU, 2001, DE
7) liquid extract (DER 1:4-6), extraction solvent: water	Traditional herbal product for the relief of nervousness and sleep disorders.	adolescents and adults 20 ml 3 x daily	TRAD, 1978, DE
8) dry extract (DER 5.3-6.6:1) extraction solvent: methanol 45% (V/V)	Traditional herbal medicinal product for support of mental relaxation and for the relief of difficulty in falling asleep.	coated tablet 48 mg 1-4 x 3-6 tablets daily	TRAD, 1978-2008, DE
9) dry extract (DER 5.3-6.6:1), extraction solvent methanol 45% (m/m)	Traditional herbal product for the relief of nervousness and sleep disorders	coated tablet 150 mg adolescents and adults: 3 x 1 tablet daily	TRAD, 2009, AT
	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	coated tablet 150 mg 3 x 3 tablets daily	WEU, 1978-2014, DE
	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	coated tablet 190 mg adults: 3 x 2-3 tablets daily children: 3 x 1 tablet daily 2 weeks	WEU, 1993, DE
10) liquid extract (DER 1:7-9), extraction solvent: sweet vine	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	oral liquid 1-several times 30 ml daily 4 weeks	WEU, 1978 DE
11) liquid extract (DER 1:7-9), extraction solvent: sweet vine	Traditional herbal medicinal product for support of mental relaxation.	oral liquid 1-3 x 10 ml daily	TRAD, 1978, DE

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
12) liquid extract (1:21.2), extraction solvent: sweet vine: ethanol 96% (V/V) (39.7:1)	Herbal medicinal product for the relief of mild nervous tension. Herbal medicinal product for the relief of difficulty in falling asleep.	oral liquid (100% liquid extract) 1-3 x40 ml daily	WEU, 1996, DE
13) dry extract (DER 4-7:1), extraction solvent: ethanol 30% m/m	to aid sleep	tablet 500 mg 1 x 1-2 tablets daily	WEU, 1995, BE
14) dry extract (DER 4-5:1), extraction solvent: ethanol 35% (m/m)	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	coated tablet 85.5 mg 3 x 5-7 tablets daily 2 weeks	WEU, 1978, DE
15) dry extract (DER 2.25-3.6:1), extraction solvent: ethanol 36.3% m/m	nervous tension/to aid sleep	tablet 500 mg nervous tension: 3 x 1 tablet daily to aid sleep: 1 x 2 tablets daily	WEU, 1995, BE
16) dry extract (DER 4-7:1), extraction solvent: ethanol 40% (m/m)	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	coated tablet 140 mg 3 x 4 tablets daily 2-4 weeks	WEU, 1978, DE
	Traditionally used for relief of mild symptoms of mental stress and to aid sleep.	coated tablet 70 mg adolescents and adults: 2-3 x 2-3 coated tablets	TRAD, 1978, DE
17) tincture (1:10), extraction solvent: ethanol 56%	Traditionally used for minor nervous tension and temporary insomnia.	adolescents and adults: nervous tension: 0.84 ml, 3-5 times daily insomnia: 0.84 ml drops Not recommended to children.	TRAD, 1978-2008, SE
18) dry extract (DER 2-3:1), extraction solvent: ethanol 60%	Traditionally used for minor nervous tension and temporary insomnia.	tablet 150-225 mg adolescents and adults: nervous tension: 3-4 x 2 tablets daily insomnia: 3-4 tablets Not recommended to	TRAD, 2003-2008, SE

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		children.	
19) dry extract (5.25-7.5:1), extraction solvent: ethanol 60% (V/V)	Herbal medicinal product used in mild nervous tension and sleep disorders.	film-coated tablet 200 mg extract adolescents, adults and elderly: nervous tension: 3 x 1-2 tablets daily insomnia: 2-3 tablets before bedtime; if needed the dose can be increased to 1-3 tablets earlier in the evening max. dose: 10 tablets per day Not recommended to children.	WEU, 1995, SE
20) tincture (1:5), extraction solvent: ethanol 70% (V/V)	Herbal medicinal product for relief of nervousness and sleep disorders.	oral drops, solution adolescents and adults: 1.5 ml 2-3 x daily sleeplessness: 3 ml 0.5 h before bedtime	WEU, 1978-2004, DE
	Used to achieve mild sedation and mental stress reduction, to relief sleep disorders.	oral drops, solution adolescents and adults: 20-30 drops 3-4 x daily	WEU, 1998, LV
21) tincture (1:5), extraction solvent: ethanol 60-80% (V/V)	A herbal remedy traditionally used for symptomatic relief of irritability and tenseness.	oral liquid 2 x 5 ml 3 x daily	TRAD, 1968, UK
22) dry extract (DER 3-6:1), extraction solvent: ethanol 70% (V/V)	Herbal medicinal product for the relief of mild restlessness and sleep disorders.	coated tablet 450 mg adolescents and adults: 3 x 1 tablet daily	WEU, 2002, AT
		coated tablet 300 mg adolescents and adults: 1-2 tablets, when necessary 2 additional tablets	WEU, 2006, AT
		coated tablet 300 mg adolescents and adults: 3 x 1 tablet daily	WEU, 2010, AT
		coated tablet 300 mg adolescents and adults: 1-2 tablets, when necessary 2 additional	WEU, 2010, AT

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		tablets	
		coated tablet 441.35 mg adolescents and adults: 3 x 1-2 tablets daily	WEU, 2010, AT
		tablet 500 mg adolescents and adults: mild nervous tension: 3 x 1 tablet daily sleep disorders: 1-2 tablets in the evening max. 4 tablets daily duration of use: 2-4 weeks	WEU, 2005, FR
	nervous tension/aid sleep	tablet 500 mg nervous tension: 3 x 1 tablet daily to aid sleep: 1 tablet	WEU, since 2000, BE
	temporary mild disturbance of sleep and restlessness	tablet 125 mg for sleep enhancement: 1 x 3-4 tablets, if necessary may be increased to double dose for restlessness: 1-3 x 3-4 tablets	WEU, 2004, FI
	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	coated tablet 125 mg 3 x 4 tablets daily 2 weeks	WEU, 1993, DE
		coated tablet 300 mg sleep: 2 tablets before bedtime nervous tension: 3 x 1 tablet daily	WEU, 2001, UK
23) dry extract (DER 3-6:1), extraction solvent: ethanol 70% (V/V)	Herbal medicinal product for temporary insomnia and minor nervous tension.	tablet 45 mg extract corresponding to 200 mg valerian root adolescents, adults and elderly: nervous tension: 3 x 2-3 tablets daily insomnia: 2-3 tablets before	WEU, 1939, SE

Active substance	Indication	Pharmaceutical form Strength (where relevant) Posology Duration of use	Regulatory Status (date, Member State)
		bedtime; if needed the dose can be increased to 2-3 tablets earlier in the evening followed by 2-3 tablets half an hour before bedtime max. dose: 8 tablets per day Not recommended to children.	
24) dry extract (DER 3-6:1), extraction solvent: ethanol 70% (V/V)	Herbal medicinal product for temporary insomnia and minor nervous tension.	tablet 125 mg extract corresponding to 560 mg valerian root adolescents, adults and elderly: nervous tension: 3 x 1-2 tablets daily insomnia: 1-4 tablets before bedtime; if needed the dose can be increased to 1-4 tablets earlier in the evening followed by 1-4 tablets half an hour before bedtime max. dose: 8 tablets per day Not recommended to children.	WEU, 2005, SE
25) dry extract (DER 6.0-7.4:1), extraction solvent: ethanol 70% (V/V)	Herbal medicinal product for the relief of difficulty in falling asleep.	coated tablet 441.35 mg 1-2 x 1 tablet daily 2-4 weeks	WEU, 1978, DE
26) dry extract (DER 5.5-7.4:1), extraction solvent: ethanol 85% (m/m)	Herbal medicinal product for the relief of mild nervous tension and for the relief of difficulty in falling asleep.	coated tablet 322 mg 3 x 1 tablet daily 2 weeks	WEU, 1978, DE
27) Valerian root oil	Traditional herbal medicinal product for support of mental relaxation.	soft capsule 15 mg 1 capsule in the morning + 1 at noon, 2-3 capsules before bedtime	TRAD, 1978, DE
	for nervous ailments as sleeping disorders and restlessness and excitability	cutaneous use 240-400 mg in 100 l water for a full bath	TRAD, 1978, DE

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

According to the WEU criteria the dry extracts (DER 3-6:1), extraction solvent ethanol 70% (V/V) and (DER 4-7:1), extraction solvent: ethanol 40% (m/m) (equals ethanol 47.4% (V/V)) will be taken up as WEU in the monograph.

Information on relevant combination medicinal products marketed in the EU/EEA
Not applicable

Information on other products marketed in the EU/EEA (where relevant)
Not applicable

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

Valeriana officinalis radix containing preparations and the herbal substance are in use all over the world, since specifications are not available it was decided to skip the information.

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

Therapeutic use of valerian root and its preparations probably goes back to the ancient Greeks and Romans who used a valerian-like herb (‚phu') for treatment of conditions for which therapists would use bitter and aromatic roots today. Dioskurides for example (Materia Medica 50-70 AD) used the dry root or its decoct of a plant called 'phu' or 'wild nard' (not doubtlessly identified as *Valeriana officinalis*) for warming, as a urinary tract remedy, for menstrual cramps and for liver diseases (Madaus, 1976).

The following compilation is restricted to the use of *Valeriana officinalis* L., radix. as monotherapy in the modern phytotherapy going back to the year 1800.

<u>Europe</u>
Hahnemann (1793) describes Katzenbaldrian in his "Apothekerlexikon" as *Valeriana officinalis* effective in epilepsy, chorea minor, chorea huntington (Veitstanz) and other cramps as well as in worm diseases and in hysterical ailments.The preparations he describes are pulverized root, an ethanolic extract, infusion/extract with water. The most concentrated form is valeriana radix aetheroleum.

- Internal use

Chamisso (1781-1831) describes valerian root as antispasmodic, effective against worm diseases and as strengthening. Information on preparations and dose recommendations is not available (according to Benedum *et al.* 2000).

Vietz (1800) recommends valerian root for all spasmodic and convulsive diseases, for epilepsy, hysteric attacks, worm diseases and against nervous fever. Information on preparations and dose recommendations is not available (according to Benedum *et al,.* 2000).

Hager (1873/74) refers to the use of valerian root for cramps, epilepsy, worm diseases and hysterical ailments. Information on preparations and dose recommendations is not available (according to Benedum *et al.,* 2000.

Dragendorff (1967 – reprint of 1898) describes the use of the root as antispasmodic, as remedium nervinum and antihysteric. No details on preparations and dosages are given.

Madaus (1976 – reprint from 1938) recommends the use of the dried root, the powdered herbal substance, tincture or fresh root: trituration.

Dosages according to different therapists cited by the author are:

powdered herbal substance: 0.5-4 g several times/day
powdered herbal substance 0.5-5 g
4.8 g of the herbal substance for cold extract
1-3 tbl. (each corresponding to 0.125 g fresh valerian root) of trituration ‚Teep', for sleeplessness 2 tbl. in the evening

Recommendations for valerian root as single therapy:

for sleeplessness and neurasthenia:
cold extract (1 teaspoon, corresponding to approximately 5 g of the herbal substance, for 24 hours in 1 glass of water, intake in sips over the day, for sleeplessness consumption of the whole extract in the evening)

as enema against worms and cramps in the lower abdomen:
10-12 g of the herbal substance as decoct in 250 ml water

Traditional indications according to several authors cited by Madaus (1976):

aphrodisiac, diuretic, analgesic, emmenagogue, analeptic, stomachic, carminative; against cough, asthma, flatulence, chronic diarrhoea, obstipation, worm infections, anthrax, hysteria, cramps of the neck muscles and paresis due to acute infectious diseases; for internal injuries, after severe typhoid or diphtheria, before salvarsan injection as prophylaxis of a salvarsan-induced shock

Ward (1936) recommends valerian root for use in hysteria, neuralgia and nervous debility.

Preparation/Dosage: an infusion of 1 ounce to 1 pint of boiling water in wineglass doses three or four times daily.

Weiss (1944) emphasizes the following indications for valerian root:

nervous agitation, nervous sleeplessness, nervous palpitations
preparations and dose recommendations:
dried root: tea infusion with two teaspoons / cup
infusion 10.0/15.0, to take in sips
cold maceration with two teaspoons/glass of cold water
tinctura valerianae, single dose ½-2 teaspoons
tinctura valeriana aetherea: to be dosed drop by drop
extractum valerianae fluidum (no dose recommendation for single use given)

The 25th edition of Martindale's Extra Pharmacopoeia (1967) recommends the following uses of herbal preparations made from the dried rhizome and roots:

valerian extract (B.P.C. 1954; soft extract, extraction solvent 60% not less than 18% in the extract), single dose: 60-300 mg
valerian liquid extract (B.P.C.), DER 1:1, extraction solvent: ethanol 60%, single dose: 0.3-1 ml
concentrated valerian infusion (B.P.C.), DER 1:5, prepared by percolation with ethanol (25%), single dose: 15-30 ml
valerian infusion: dilution of 1 vol. of the concentrated infusion to 8 vol. with water
tinct. valerian. simp. (B.P.C. 1949), DER 1:8, prepared by maceration with ethanol (60%), single dose: 4-8 ml
indications: hysteria and other nervous condition, carminative

The BHP (1976) gives the following recommendations:

Indications: hysterical states, excitability, insomnia, hypochondriasis, migraine, cramp, intestinal colic, rheumatic pains, dysmenorrhoea

Preparations/Dose recommendations (three time daily)

dried rhizome and root: 0.3-1 g by infusion or decoction

liquid extract 1:1 (60% ethanol): 0.3-1 ml
tincture simple 1:8 (60% ethanol): 4-8 ml
concentrated infusion 1:5 (25% ethanol): 2-4 ml

List *et al*. (1979) list the following indications for valerian root

mild sedative in nervous exhaustion, sleeplessness, mental overwork, nervous heart ailments, headache, neurasthenia, hysteria; as antispasmodic for stomach cramps, colics etc.

Recommended preparations:

dried herbal substance, dried powdered herbal substance, tincture (extraction solvent ethanol 60%), dose range for single dose is 0.3-1 g, for the total daily dose 2-15 g.

Kommission E monograph "Valerianae radix" (1985)

indications: relief of nervousness and sleep disorders

posology: infusion: 2-3 g herbal substance per cup 1 to several times daily
tincture: 0.5-1 tablespoon (1-3 ml) 1 to several times daily
extracts: corresponding to 2-3 g herbal substance 1 to several times daily.

Standardzulassung Baldrianwurzel (valerian root) (1985)

indications: relief of nervousness and sleep disorders

posology: infusion: 2.5 g herbal substance per cup 1 to several times daily

Standardzulassung Baldriantinktur (valerian tincture) (1986)

preparation: 1:5 (herbal substance:extraction solvent); extraction solvent: ethanol 70% (V/V)

indications: relief of nervousness and sleep disorders

posology: 2-3 x 1.5 ml; in sleeplessness 3 ml 0.5 h before bedtime

Haffner (1991) recommends the following single doses for the use of valerian root preparations:

herbal substance:	2.5 g
extr. fld.	2.0 g
extr. (sicc.)	0.5 g
tinct.	5.0 g
aetheroleum	0.1 g.

- external use (bath additive)

Madaus (1976): headache, reddened and painful eye, wound healing, bath against acute rheumatism

Kommission E monograph "Valerianae radix" (1985, 1990)

indications: relief of nervousness and sleep disorders

posology: 100 g herbal substance for a full bath, preparations corresponding

Standardzulassung Baldrianwurzel (valerian root) (1985)

indications: relief of nervousness and sleep disorders

posology: 100 g herbal substance for a full bath; up to one full bath/day

Kommission B8 monograph Valerian baths (1989)

indications: nervous complaints such as insomnia and general restlessness

posology: min. 0.002 g valerian root oil/l water for a full bath; temp. 34-37°C; duration of bath: 10-20 min

Ammer & Melnizky (1999):

indication: sleeplessness due to fibromyalgia

posology: 20 ml valerian root oil/200 l Water; temp. 36-37°C

Fintelmann & Weiss (2009)

100 g herbal substance in 1 l hot water given into a full bath for restlessness and sleep disorders.

Asia

According to Usmanghani *et al.* (1997), valerian root and rhizomes are used in traditional formulations in Pakistan to relieve disorders of the spinal cord, 'nervous debility', failing reflexes, as hypnotic, for nervous disorders during menopause, for insomnia due to nervous exhaustion and mental overwork, against neurosis, hysteria and epilepsy.

Herbal preparations: only names of traditional preparations are given

Dosage: approximately 3-5 g (it is not specified whether this is a single or a daily dose)

The authors remark that valerian root is described as harmful for kidney function if taken in large doses or for long period.

Due to the lack of information, the plausibility of the Pakistanian tradition cannot be rated. Since the herbal preparations are not common in Europe, no traditional use can be supported in this report vis-à-vis registration in the EU Member States.

USA

Sayre (1917) lists valerian root as a 'gentle nerve stimulant and antispasmodic', employed in hysterical disorders.

Preparations:

Herbal substance (single dose: 1-4 g)

Tincturae Valerianae (20%), single dose: 4-8 ml

Tinctura Valerianae Ammoniata (20%), single dose 2-4 ml

Culbreth (1927) recommends the use of valerian root in the following indications:
hysteria, hypochondria, hemicrania, nervous coughs, whooping-cough, diabetes, delirium tremens, typhoid state, dysmenorrhoea, vertigo, epilepsy, worm convulsions, flatulence, reflex neuralgia

Herbal preparations:

Tinctura Valerianae, single dose: 2-8 ml

Fluidextractum Valerianae (80% ethanol), single dose: 1-4 ml

Culbreth (1927) also mentions unofficial preparations (abstract, extract, infusion, syrup and aqueous extracts).

2.3. Overall conclusions on medicinal use

Table 2: Overview of historical data

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
dried herbal substance	for sleeplessness and neurasthenia as enema against worms and cramps in the lower abdomen	5 g for 24 hours in 1 glass of water (cold extract) intake in sips over the day for sleeplessness consumption of the whole extract in the evening 10-12 g as decoct in 250 ml water	Madaus (1976)

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
dried herbal substance	use in hysteria, neuralgia and nervous debility	infusion 1 ounce to 1 pint of boiling water in wineglass doses three or four times daily	Ward (1936)
dried herbal substance	nervous agitation, nervous sleeplessness, nervous palpitations	tea infusion two teaspoons / cup infusion 10-15 g in 150 ml water, to take in sips up to 3 x 1 tablespoon per day cold maceration two teaspoons/glass of cold water	Weiss (1944)
tinctura valerianae		single dose ½-2 teaspoons	
valerian extract (soft extract, extraction solvent 60% not less than 18% in the extract)	hysteria and other nervous condition, carminative	single dose 60-300 mg	Martindale (1967)
valerian liquid extract, DER 1:1, extraction solvent ethanol 60%		single dose 0.3-1 ml	
concentrated valerian infusion, DER 1:5, prepared by percolation with ethanol (25%)		single dose 15-30 ml	
tinct. valerian. simp., DER 1:8, prepared by maceration with ethanol (60%)		single dose: 4-8 ml	
dried rhizome and root	hysterical states, excitability, insomnia, hypochondriasis, migraine, cramp, intestinal colic, rheumatic pains, dysmenorrhoea	0.3-1 g by infusion or decoction, 3 x daily	BHP (1976)
liquid extract 1:1 (60% ethanol)		0.3-1 ml, 3 x daily	
tincture simple 1:8 (60% ethanol)		4-8 ml, 3 x daily	
concentrated infusion 1:5 (25% ethanol)		2-4 ml, 3 x daily	
dried powdered herbal substance, tincture (extraction solvent	mild sedative in nervous exhaustion, sleeplessness, mental	dose range for single dose is 0.3-1 g, for the total daily dose 2-15 g	List (1979)

Herbal preparation	Documented Use / Traditional Use	Pharmaceutical form Strength (where relevant) Posology Duration of use	Reference
ethanol 60%), fresh/dried herbal substance	overwork, nervous heart ailments, headache, neurasthenia, hysteria; as antispasmodic for stomach cramps, colics etc.		
oral use: infusion, tincture, extracts external use: herbal substance, preparations thereof	relief of nervousness and sleep disorders	oral use: infusion: 2-3 g herbal substance per cup 1 to several times daily tincture: 0.5-1 tablespoon (1-3 ml) 1 to several times daily extracts: corresponding to 2-3 g herbal substance 1 to several times daily external use: 100 g herbal substance for a full bath, preparations corresponding	Kommission E (1985, 1990)
oral use: infusion external use: herbal substance	relief of nervousness and sleep disorders	oral use: infusion: 2.5 g herbal substance per cup 1 to several times daily external use: 100 g herbal substance for a full bath, up to 1 full bath daily	Braun (1996) ("Standardzulassung" since 1985)
tincture (1:5); extraction solvent: ethanol 70% (V/V)	relief of nervousness and sleep disorders	2-3 x 1.5 ml in sleeplessness: 3 ml 0.5 h before bedtime	Braun (2005) ("Standardzulassung" since 1986)
valerian root oil	nervous complaints such as insomnia and general restlessness	min. 0.002 g valerian root oil/l water for a full bath; temp. 34-37°C; duration of bath: 10-20 min	Kommission B8 (1989)
herbal substance extr. fld. extr. (sicc.) tinct. aetheroleum	relief of mild restlessness and sleep disorders	single dose: 2.5 g single dose: 2.0 g single dose: 0.5 g single dose: 5.0 g single dose: 0.1 g	Haffner (1991)
valerian root oil	sleeplessness due to fibromyalgia	20 ml valerian root oil/200 l water; temp. 36-37°C	Ammer & Melnizky (1999)

2.4. Overall conclusions on medicinal use

Rev. 1:
During the revision process data were evaluated again regarding the criteria and the time frames of WEU and traditional use. In spite of all the newly integrated data the classification of the extracts could not be changed. Basically the dry extracts (DER:3-7:1) prepared with ethanol 40-70% (V/V) are covered by data qualifying for well established use. More preparations were added concerning the traditional use or the specification was narrowed.

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

Herbal preparation **Pharmaceutical form**	**Indication**	**Strength** **Posology**	**Period of medicinal use**
oral use:			
dried herbal substance for tea preparation	hysterical states, excitability, insomnia, hypochondriasis, migraine, cramp, intestinal colic, rheumatic pains, dysmenorrhoea relief of nervousness and sleep disorders	3 x 0.3-1 g by infusion or decoction 1-3 x 2-3 g as infusion in sleeplessness: a single dose 0.5-1 h before bedtime and an earlier dose if necessary	BHP (1976) since 1978; Kommission E (1985); Standardzulassung (1985)
dried herbal substance as powder	a) relief of mild nervous tension and for the relief of difficulty in falling asleep b) Traditionally used in the symptomatic treatment of neurotonic conditions of adults and children, notably in cases of mild disorders of sleep.	a) 3 x 2 g daily 760 mg/day b) adults: 2 x 700 mg daily max: 1.75 g daily adolescents: 2 x 350 mg daily	since 1978 since 1978 since 1981
expressed juice from fresh root (1:0.6-0.85)	a) Herbal medicinal product for the relief of mild nervous tension. b) Herbal medicinal product for the relief of difficulty in falling asleep.	a) 1-3 x 10 ml daily b) 1-2 x 10 ml before bedtime	1978-2010

expressed juice from fresh root (1:1.0-1.5)	a) Herbal medicinal product for the relief of mild nervous tension. b) Herbal medicinal product for the relief of difficulty in falling asleep.	a) 3 x 10 ml daily b) 1-2 x 10 ml before bedtime	1978-2010
dry extracts (DER 4-6.1), extraction solvent: water	relief of mild nervous tension and for the relief of difficulty in falling asleep	3 x 420 mg 2 weeks	since 1978
liquid extract (DER 1:4-6) extraction solvent: water	for relief of nervousness and sleep disorders	3 x 20 ml	since 1978
dry extract (DER 5.3-6.6:1), extraction solvent: methanol 45% (m/m)	relief of mild nervous tension and for the relief of difficulty in falling asleep	3 x 380-570 mg daily	1978-2014
dry extract (5.3-6.6:1) extraction solvent: methanol 45% (V/V)	support of mental relaxation and for the relief of difficulty in falling asleep	adolescents and adults: 1-4 times daily 144-288 mg	1978-2008
liquid extract (1:7-9), extraction solvent: sweet wine	for the relief of mild nervous tension and for the relief of difficulty in falling asleep	1-3 x 10 ml	since 1978
dry extract (DER 4-5:1), extraction solvent: ethanol 35% (m/m)	for the relief of mild nervous tension and for the relief of difficulty in falling asleep	3 x 427-599 mg	since 1978
dry extract (DER 4-7:1), extraction solvent: ethanol 40% (m/m)	for the relief of mild nervous tension and for the relief of difficulty in falling asleep	3 x 560 mg 2-3 x 140-210 mg	since 1978 (WEU)
liquid extract (1:1), extraction solvent: ethanol 60% (V/V)	excitability, insomnia	3 x 0.3-1 ml	BHP (1976)
tincture (1:8), extraction solvent: ethanol 60% (V/V)	excitability, insomnia	3 x 4-8 ml	BHP (1976)
tincture (1:10), extraction solvent: ethanol 56%	for minor nervous tension and temporary insomnia	3-5 x 0.84 ml	since 1978
tincture (1:5), extraction solvent: ethanol 70% (V/V)	for relief of nervousness and sleep disorders	2-3 x 1.5 ml; sleeplessness: 3 ml 0.5 h before bedtime	since 1978; Standardzulassung (1986)

tincture (1:5), extraction solvent: ethanol 60-80% (V/V)	symptomatic relief of irritability and tenseness	3 x 10 ml	before 1968
dry extract (DER 3-6:1), extraction solvent: ethanol 70% (V/V)	relief of mild restlessness and sleep disorders	restlessness: 3 x 300-600 mg to aid sleep: 600 mg, if necessary may be increased to double dose	since 1939 (WEU)
dry extract (DER 6.0-7.4:1), extraction solvent: ethanol 70% (V/V)	for the relief of difficulty in falling asleep	1-2 x 441.35 mg	since 1978
dry extract (DER 5.5-7.4:1), extraction solvent: ethanol 85% (m/m)	for the relief of mild nervous tension and for the relief of difficulty in falling asleep	3 x 322 mg	since 1978
valerian root oil	for support of mental relaxation	2 x 15 mg (during the day) + 30-45 mg before bedtime	since 1978
bath additive			
herbal substance	relief of nervousness and sleep disorders	100 g herbal substance for a full bath	Standardzulassung (1985)
valerian root oil	relief of mild restlessness and sleep disorders	240-400 mg for full bath (100 l)	DE 1978

3. Non-Clinical Data

The extracts used in the trials are specified in the comments as far as possible. Unfortunately, in many publications correct specifications of solvent and drug-extract ratio (DER) are missing. In these cases no details can be given, if the extract could not be identified otherwise.

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

3.1.1. Primary pharmacodynamics

GABA (γ-aminobutyric acid) is an inhibitory neurotransmitter of the central nervous system that reduces nerve impulse transmission between neurons through the hyperpolarization of postsynaptic membranes and the reduction of neurotransmitter release into the synapse through presynaptic G-protein coupled receptor inhibition of voltage gattered Ca^{2+}-mechanisms (Jacob *et al*., 2008; Markwardt & Overstreet-Wadiche, 2008). Due to the essential inhibitory functions of GABA, the interest has focused on possible interactions of valerian root with the $GABA_A$-messenger system.

Interaction with neurotransmitter receptors

in vitro

Aqueous and aqueous-ethanolic valerian root extracts

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 [³H] muscimol from synaptic membranes from rat brain cortices (Cavadas *et al*., 1995). For valerenic acid no effect was shown.

In other experiments (Santos, 1994c; Ferreira *et al*., 1996), the effect of different valerian root extracts on the uptake and release of GABA in synaptosomes isolated from rat brain cortex was investigated. While an aqueous and an aqueous-ethanolic extract (no further information) inhibited the uptake and stimulated the release of [^{3}H]-GABA (no concentration given), possibly by reversal of the GABA carrier, this effect was not observed for an ethanolic extract.

These results were confirmed by Ortiz *et al*. (1999). They 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 [^{3}H]-flunitrazepam binding while it was inhibited at higher extract concentrations. These results may point to at least two different biological activities interacting with [^{3}H]-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).

Using [^{3}H]-flunitrazepam binding as an indicator, the interactions of commercial valerian extracts with $GABA_A$ receptors were examined. There was considerable fluctuation among the different extracts, some mildly enhanced [^{3}H]-flunitrazepam binding, others had no effect and others had inhibitory effects, independent of standardization by valerenic acid. Central depression can also be accomplished by a reduction of excitatory transmission. Valerian extracts had modest inhibitory effects on [^{3}H]-MK-801 binding, an indicator of NMDA-Valerian interactions. Spectral analyses (UV region) did not show marked differences among the different extracts. The inhibitory effects of one of the extracts on [^{3}H]-flunitrazepam binding was somewhat stable, while on [^{3}H]-MK-801 binding the inhibitory effects were lost within months (Ortiz *et al*., 2006).

A series of extracts of valerian roots was prepared with solvents of different polarity. Method A:10 g of powdered valerian root, suspended in methanol, treated with ultrasound, was filtered. Combined filtrates concentrated by azeotropical drying through absolute ethanol and ether via evaporation. These methanol extracts were partitioned with a mixture of petroleum ether: diethyl ether 1:1. The remaining water suspensions were extracted again three times with chloroform and three times with n-butanol. The remaining water suspensions were lyophilized. Method B: 10 g of powdered valerian root were extracted 4 times with a mixture of petroleum ether: diethyl ether 1:1. The powder residues were subsequently extracted with 4 solvents (3 x 10 ml solvent each; chloroform; n-butanol; methanol; hot water). Finally they were lyophilized. Extraction method C: extraction with hot water (80°C), then filtration and lyophilisation.
Polar as well as nonpolar extracts were found to interact with adenosine A(1) receptors. While polar extracts activated A(1) receptors (partial agonistic activity), nonpolar extracts showed antagonistic or inverse agonistic activity at A(1) receptors, as demonstrated by GTPγS binding assays at human recombinant A(1) receptors stably expressed in Chinese hamster ovary (CHO) cells (K_i at adenosine A1 receptor (rat): 9-11 µg/ml; GTPγS binding EC_{50} human recombinant A1 receptor: 11-272 µg/ml). Guided by radioligand binding assays, fractionation of a lipophilic petroleum ether:diethyl ether (1:1)

extract led to the isolation of isovaltrate, which was characterized as a potent, highly efficacious inverse agonist at adenosine A(1) receptors ($K_{(i)}$ rat A(1): 2.05 µM). In experiments at rat brain slices measuring post-synaptic potentials (PSPs) in cortical neurons, isovaltrate at least partly reversed the reduction in the PSPs induced by the adenosine A(1) receptor agonist N(6)-cyclopentyladenosine (CPA) (Lacher *et al*., 2007).

The effects of two valerian extracts (extraction solvents: A:H_2O; B: DER 1:10, 70% ethanol w/v) were investigated through [^{3}H]-glutamate and [^{3}H]-fluorowillardine ([^{3}H]-FW) receptor binding assays using rat synaptic membranes in presence of different receptor ligands. In addition, the extract stability was monitored spectrophotometrically. Both extracts demonstrated interaction with ionotropic glutamate receptors. However, the extracts displayed considerable differences in receptor selectivity. The hydroalcoholic extract selectively interacted with quisqualic acid, a group I metabotropic glutamate receptor ligand, while the aqueous extract did not alter the binding of quisqualic acid. The stability of the extracts was examined during several weeks. Freshly prepared extract inhibited 38-60% of [^{3}H]-fluorowillardine binding (AMPA). After 10 days, the aqueous extract inhibited 85% of [^{3}H]-fluorowillardine binding while the hydroalcoholic extract markedly potentiated (200%) [^{3}H]-fluorowillardine binding to AMPA receptors (Del Valle-Mojica *et al*., 2011).

To determine novel mechanisms of action of extracts of valerian root, radioligand binding studies were performed with valerian extracts (100 g dried powdered root at 500 ml of the following extraction solvents: 100% methanol, 50% methanol, dichloromethane [DCM], and petroleum ether [PE] in three steps each) at the melatonin, glutamate, and $GABA_A$ receptors, and 8 serotonin receptor subtypes. Both DCM and PE extracts had strong binding affinity to the 5-HT(5a) receptor, but only weak binding affinity to the 5-HT(2b) and the serotonin transporter. Subsequent binding studies focused on the 5-HT(5a) receptor due to the distribution of this receptor in the suprachiasmatic nucleus of the brain, which is implicated in the sleep-wake cycle. The PE extract inhibited [^{3}H]-lysergic acid diethylamide (LSD) binding to the human 5-HT(5a) receptor (86% at 50 µg/ml) and the DCM extract inhibited LSD binding by 51%. Generation of an IC_{50} curve for the PE extract produced a biphasic curve, thus GTP shift experiments were also performed. In the absence of GTP, the competition curve was biphasic (two affinity sites) with an IC_{50} of 15.7 ng/ml for the high-affinity state and 27.7 µg/ml for the low-affinity state. The addition of GTP (100 µM) resulted in a right-hand shift of the binding curve with an IC_{50} of 11.4 µg/ml. Valerenic acid, the active constituent of both extracts, had an IC_{50} of 17.2 µM (Dietz *et al*., 2005).

The relation between modulation of $GABA_A$ receptors by valerian extracts of different polarity and the content of sesquiterpenic acids (valerenic acid, acetoxyvalerenic acid) are investigated by Trauner *et al.* (2008). All extracts were analysed by HPLC concerning the content of sesquiterpenic acids. $GABA_A$ receptors composed of alpha 1, beta 2 and gamma 2S subunits were expressed in *Xenopus laevis* oocytes and the modulation of chloride currents through $GABA_A$ receptors (IGABA) by valerian extracts was investigated using the two-microelectrode voltage clamp technique. Apolar extracts (DER 95:1 petroleum ether; DER:139:1 ethylacetate) induced a significant enhancement of IGABA, whereas polar extracts (DER 7:1 methanol; DER: 6:1 H_2O) showed no effect. These results were confirmed by fractionating a highly active ethyl acetate extract: again fractions with high contents of valerenic acid exhibited strong receptor activation. In addition, removal of sesquiterpenic acids from the ethyl acetate extract led to a loss of I (GABA) enhancement.

A valerian extract (dried hydroalcoholic extract 100 mg/ml; H_2O) was studied for its metabolic change upon incubation with freshly prepared rat hepatocytes and subsequently analysed phytochemically as well as pharmacologically. Quantitative HPLC analysis revealed considerable metabolic activities with regard to sesquiterpenes and iridoids. The amount of acetoxyvalerenic acid decreased 9-fold after incubation (20 mg extract/10^6 rat hepatocytes; extract concentrations 25-200 µg/ml), while that of

hydroxyvalerenic acid correspondingly increased 9-fold due to O-deacetylation. The valepotriates didrovaltrate, isovaltrate and valtrate decreased 2-, 18- and 16-fold, respectively. However, the binding affinities of the incubated extracts to the benzodiazepine and picrotoxin binding site of the $GABA_A$ receptor were quite similar to those of the non-incubated extracts. Neither valerenic acids nor valepotriates exhibited any significant effect on the two binding sites when tested as single compounds (Simmen *et al*., 2005).

Sesquiterpenoids

Hydroxyvalerenic acid and acetoxyvalerenic acid weakly inhibited the catabolism of GABA at synaptic junctions of the CNS (Riedel *et al*., 1982). Due to the high concentrations of both compounds needed (2-10 nMol) to achieve this effect, the data probably have no clinical relevance.

Neuhaus *et al*. (2008) aimed to obtain blood-brain barrier (BBB) permeability data of compounds from valerian extracts for the first time and to elucidate possible transport pathways across the BBB in vitro model. Transport of valerenic acid, acetoxyvalerenic acid and hydroxyvalerenic acid was compared with the permeability of the $GABA_A$ modulator diazepam, which is known to penetrate into the central nervous system transcellularly by passive diffusion. Experiments were carried out with an established transwell in vitro model based on the human cell line ECV304. Results indicated clearly that all three acids permeated significantly slower than diazepam. The ranking was confirmed in group studies as well as in single-substance studies after normalization to diazepam. Valerenic acid (1.06±0.29 µm/min, factor 0.03 related to diazepam) was the slowest to permeate in the group study, followed by hydroxyvalerenic acid (2.72±0.63 µm/min, factor 0.07 related to diazepam) and acetoxyvalerenic acid (3.54±0.58 µm/min, factor 0.09 related to diazepam). To elucidate the contribution of the paracellular transport, studies were performed at different tightness status of the cell layers reflected by different transendothelial electrical resistance (TEER) values. Results showed an exponential correlation between transport and TEER for all three acids, whereas diazepam permeated TEER independently.

Valerenic acid (3-100 µM) caused an inhibitory effect on muscimol-sensitive NTS neurons which was mediated via $GABA_A$-receptors (Yuan *et al*., 2004).

Lignans

The lignan hydroxypinoresinol, recently found in valerian root, showed a high affinity with IC_{50} of 2.5 µmol/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 & Hoelz, 1997). The kind of action at the receptor (agonistic/antagonistic activity) was not investigated.

An olivil derivate (10^{-6} to 10^{-4} M) was found to be a potent partial agonist at A1 adenosine receptors (Schumacher *et al.*, 2002). Agonistic activity was also shown for valerian root extract (methanol 45%) (Müller *et al.*, 2002). Activation of this receptor type has a sedative effect while antagonists like caffeine have a stimulant effect.

Valepotriates

Benke *et al.* (2009) described a specific binding site on $GABA_A$-receptors with nM affinity for valerenic acid and valerenol. Both agents enhanced the response to GABA at multiple types of recombinant $GABA_A$-receptors. A point mutation in the beta2 or beta3 subunit (N265M) of recombinant receptors strongly reduced the drug response.

in vivo

Aqueous and aqueous-ethanolic valerian root extracts

Valerian tincture (1:5, no further information) reduced spontaneous motility after i.p. administration of the valerian tincture in mice (3.4625 ml/kg bw, corresponding to 0.6925 g herbal substance/kg bw) (Torrent *et al.,* 1972).

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).

An aqueous-ethanolic dry extract (DER 4:1, extraction solvent: ethanol 70% V/V) administered i.p. to male mice, was assessed for possible neuropharmacological activity. At doses of up to 100 mg/kg the extract did not produce sedation nor tranquillization, since no modifications of spontaneous motility, nociception or body temperature and no palpebral ptosis were observed, whereas diazepam at doses of up to 2 mg/kg clearly reduced spontaneous motility, lowered body temperature and produced a weak ptosis. However, the extract showed a significant prolongation of thiopental-induced anaesthesia ($p<0.05$) with 100 mg/kg of extract (Hiller & Zetler, 1996).

Cats with implanted electrodes showed no changes in their EEGs following oral administration of 100 or 250 mg of valerian root extract (no further information) per kg b.w. The muscle tonus was reduced in 30-40% of the animals (Holm *et al*., 1980).

An aqueous-ethanolic (extraction solvent ethanol 70% V/V) valerian root extract had an anxiolytic effect in the elevated plus-maze test in male Spraque Dawley rats after oral administration in the magnitude of ipsapirone, a 5-HT1A-receptor agonist (Hiller & Kato, 1996). After single administration of 5, 25 and 100 mg/kg, the extract showed a distinct anxiolytic-like effect while the observed effect was not significant for 1 mg/kg and lower doses. Remarkably, a moderate anxiolytic-like effect was maintained during subchronic administration over 5 days only for low doses of 1 mg/kg.

The neuroprotective effects of *V. officinalis* against the toxicity induced by amyloid beta peptide 25-35 Abeta(25-35) were evaluated. Cultured rat hippocampal neurons were exposed to Abeta(25-35) (25 µM) for 24-48 h, after which morphological and biochemical properties were evaluated. The neuronal injury evoked by Abeta, which includes a decrease in cell reducing capacity and associated neuronal degeneration, was prevented by valerian extract (DER: 3-6:1; extraction solvent: ethanol 70% w/V; containing 0.52% valerenic acid). Analysis of intracellular free calcium (Ca^{2+}_i) indicated that the neuroprotective mechanisms may involve the inhibition of excess influx of Ca^{2+} following neuronal injury. Moreover, membrane peroxidation in rat hippocampal synaptosomes was evaluated, and the data indicate that valerian extract partially inhibited ascorbate/iron-induced peroxidation (Malva *et al.*, 2004).

In separate experiments, the effects of NG-L-nitro-L-arginine methyl ester (L-NIO), a nitric oxide synthase inhibitor, glibenclamide, an adenosine triphosphate (ATP)-sensitive potassium (K^+) channel blocker, meclofenamate, a nonselective cyclooxygenase (COX) inhibitor, bicuculline, a $GABA_A$-receptor antagonist, and saclofen, a $GABA_B$-antagonist, were investigated on pulmonary arterial responses to various agonists in the feline pulmonary vascular bed. These agonists included valerian root extract (no further specification), muscimol, a $GABA_A$-agonist, SKF-97541 a $GABA_B$-agonist, acetylcholine (ACh), and bradykinin, both inducers of nitric oxide synthase, arachidonic acid, a COX substrate, and pinacidil, an ATP-sensitive K^+ channel activator, during increased tone conditions induced by the thromboxane A2 mimic. Baseline pulmonary tone, responses to the agonists, and responses to the agonists after injections of antagonists were all measured via a pulmonary catheter transducer and recorded. Valerian root extract is a potent smooth muscle dilator in the feline pulmonary vascular bed. The vasodilatory effects of valerian root extract were unchanged after the administration of L-NIO, glibenclamide, and meclofenamate. These effects were ablated, however, by both saclofen and

bicuculline. The ability of saclofen and bicuculline to modulate the dilatory effects of valerian root extract was not statistically different (Fields *et al.*, 2003).

Chronic treatment with classical neuroleptics in humans can produce a serious side effect, known as tardive dyskinesia (TD). The effects of *V. officinalis* (10 g of valerian root in 100 ml ethanol; no further information), were examined in an animal model of orofacial dyskinesia (OD) induced by long-term treatment with haloperidol. Adult male rats were treated during 12 weeks with haloperidol decanoate (38 mg/kg, i.m., each 28 days) and with *V. officinalis* (1% in the drinking water). Vacuous chewing movements (VCMs), locomotor activity and plus maze performance were evaluated. Haloperidol treatment produced VCM in 40% of the treated rats and the concomitant treatment with *V. officinalis* did not alter either prevalence or intensity of VCMs. Haloperidol treatment significantly decreased [^{3}H]-dopamine uptake in striatal slices and *V. officinalis* was not able to prevent this effect. Taken together, the data suggest a mechanism involving the reduction of dopamine transport in the maintenance of chronic vacuous chewing movements (VCMs) in rats. Furthermore, chronic treatment with *V. officinalis* seems not produce any oxidative damage to central nervous system (CNS), but it also seems to be devoid of action to prevent VCM, at least in the dose used in the study (Fachinetto *et al.*, 2007).

Sichardt *et al*. (2007) compared the action of a methanol (M-E; extraction solvent: methanol 45% m/m; valerenic acid 0.332%; concentration 10 mg/ml), ethanol (E-E; extraction solvent: ethanol 62.4% m/m; valerenic acid 0.127%; concentration 10 mg/ml) and an extract (EA-E; marc macerated with ethylacetate; valerenic acid 2.956%; concentration 10 mg/ml) from valerian roots on postsynaptic potentials (PSPs) in cortical neurons. Intracellular recordings were performed in rat brain slice preparations containing pyramidal cells of the cingulate cortex. PSPs were induced by electrical field stimulation. The M-E induced strong inhibition in the concentration range 0.1-15 mg/ml, whereas the E-E (1-10 mg/ml) did not influence significantly the PSPs. The maximum inhibition induced by the M-E was completely antagonized by 1,3-dipropyl-8-cyclopentylxanthine (DPCPX, 0.1 µM), an antagonist on the adenosine A(1) receptor. Contrary to the M-E, the EA-E (10 mg/ml) induced an increase of the PSPs, which were completely blocked by the $GABA_A$ receptor antagonist picrotoxin (100 µm).

The study of Chow *et al*. (2011) investigated the sedative effects of a valerian root extract (DER: 3-6:1; extraction solvent: 70% ethanol; 91% native extract). Locomotor activity and core body temperature were recorded in male mice using radiotelemetry. The extract and some of its single constituents, valerenic acid, linarin, and apigenin, were tested for effects on locomotion and body temperature over 180 min after oral administration. The extract was tested in a dose range of 250-1000 mg/kg, and only the highest dose showed a mild short-term sedative effect with reduced locomotor activity between 66-78 min after administration. Paradoxically, an increased activity was observed after 150 min after gavage. A dose of 1 mg/kg valerenic acid produced an intermittent stimulation of activity. However, a mild short-term sedative effect was found for linarin at 12 mg/kg and apigenin at 1.5 mg/kg. Considering the cumulative locomotor activity over the observation period of 180 min, the authors concluded that neither the extract nor one of the compounds had considerable sedative effects. More precisely, the observed short-term changes in activity pattern indicate that valerian extract as well as the flavonoids linarin and apigenin are rather effective to reduce sleep latency than to act as a sleep-maintaining agent.

The aim of study Pereira *et al*. (2011) of was to investigate the possible preventive effects of a standard Brazilian tincture (no futher information) of *V. officinalis*, which has GABAergic and antioxidant properties, in vacuous chewing movements (VCMs) induced by reserpine in rats. Thus the possible preventive effects of extracts containing *V. officinalis*, which has GABAergic and antioxidant properties, in vacuous chewing movements (VCMs) induced by reserpine in rats was tested. Adult male rats were treated with reserpine (1 mg/kg, s.c.) and/or with a standard Brazilian valerian tincture (1% in drinking water, starting 15 days before the administration of the reserpine). VCMs, locomotor

activity and oxidative stress measurements were evaluated. Furthermore, the identification of valeric acid and gallic acid by HPLC in the tincture was carried out. The data demonstrated that reserpine caused a marked increase on VCMs and the co-treatment with valerian tincture was able to reduce the intensity of VCM.

The purpose of the study from Del Valle-Mojica & Ortíz (2012) was to determine if valerian anxiolytic properties are mediated by metabotropic glutamate receptors (mGluR) such as mGluR (1/5) (mGluR I) and mGluR (2/3) (mGluR II). Adult wild-type zebrafish (*Danio rerio*) prefers the black compartment and avoids the white compartment in the dark/light preference task. Zebrafish exposed to 1 mg/ml of valerian extract (DER lacking; 12.5 g root in 250 ml water) or 0.00117 mg/ml valerenic acid increased their residence time in the white side by 84.61±6.55% and 58.30±8.97%, respectively. LAP3 (mGluR I antagonist) and EGLU (mGluR II antagonist) significantly inhibited the effects of valerian and valerenic acid.

Sesquiterpenoids

The i.p. application of sesquiterpenoid compounds like valerenic acid, valerenal and valeranone isolated from the essential oil of valerian root revealed a sedative and muscle relaxant acitivity. In addition, valerenic acid and valeranone were found to prolong the barbiturate induced sleeping time (Hendriks *et al*., 1981, 1985; Rücker *et al*., 1978; Torrent *et al*., 1972; Hänsel *et al*., 1994).

Flavonoids

6-Methylapigenin, which is a ligand for the benzodiazepine binding site of the $GABA_A$-receptor according to Wasowski *et al.* (2002), produced anxiolytic-like effects in the plus-maze test at a dose of 1 mg/kg i.p. but was devoid of sedative properties. Hesperidin 2 mg/kg i.p. increased the thiopental sleeping time in mice; this effect was markedly potentiated when hesperidin and 6-methylapigenin were combined (Marder *et al.*, 2003).

Linarin at doses of 4 and 7 mg/kg i.p. showed a sedative effect and with 7 mg/kg i.p. a prolonged thiopental sleeping-time in mice. The combination of low doses of linarin (5 mg/kg) and valerenic acid (5 mg/kg) led to a striking increase of thiopental sleeping time while the single administration of each compound in this dosage had no effect at all (Férnandez *et al.,* 2004).

Valepotriates

Valerenic acid and valerenol exerted anxiolytic activity with high potencies in the elevated plus maze and the light/dark choice test in wild type mice. In beta3 (N265M) point-mutated mice the anxiolytic activity of valerenic acid was absent. Thus, neurons expressing beta3 containing $GABA_A$-receptors seems to be a major cellular substrate for the anxiolytic action of valerian extracts (Benke *et al.*, 2009).

Nam *et al*. (2013) investigated the effects of extract from valerian root (DER 4:1; no further information) and its major component, valerenic acid on memory function, cell proliferation, neuroblast differentiation, serum corticosterone, and lipid peroxidation in adult and aged mice. For the aging model, D-galactose (100 mg/kg) was administered s.c. to 6-week-old male mice for 10 weeks. At 13 weeks of age, valerian root extract (100 mg/kg) or valerenic acid (340 µg/kg) were administered orally to control and D-galactose-treated mice for 3 weeks. The dosage of valerenic acid (340 µg/kg) was determined by the content of valerenic acid in valerian root extract (3.401±0.066 mg/g) measured by HPLC. The administration of valerian root extract and valerenic acid significantly improved the preferential exploration of new objects in novel object recognition test and the escape latency, swimming speeds, platform crossings, and spatial preference for the target quadrant in Morris water maze test compared to the D-galactose-treated mice. Cell proliferation and neuroblast differentiation were significantly decreased, while serum corticosterone level and lipid peroxidation in hippocampus were significantly increased in the D-galactose-treated group compared to that in the control group. The administration of valerian root extract significantly ameliorated these changes in the dentate gyrus

of both control and D-galactose-treated groups. In addition, valerenic acid also mitigated the D-galactose-induced reduction of these changes.

Table 4: Overview of the main non-clinical data/conclusions

Herbal preparation tested	Strength Dosage Route of administration	Experimental model In vivo/ In vitro	Reference Year of publication	Main non-clinical conclusions
comparable/similar preparations to preparations of the monograph				
valerian tincture	i.p. tincture (1:5)	mice in vivo	Torrent *et al*., 1972	reduced spontaneous motility
aqueous dry valerian root extract (DER 5-6:1, extraction solvent: water	20 and 200 mg/kg 2 and 200 mg/kg	mice in vivo	Leuschner *et al*., 1993	reduced spontaneous motility increased thiopental-induced sleeping time
ethanolic dry extract (DER 4:1, extraction solvent: ethanol 70% V/V)	100 mg/kg i.p.	male mice in vivo	Hiller & Zetler, 1996	significant prolongation of thiopental-induced anaesthesia
ethanolic extract (extraction solvent: ethanol 70% V/V)	oral 5, 25 and 100 mg/kg	Sprague Dawley rats in vivo	Hiller & Kato, 1996	anxiolytic-like effect
ethanolic dry extract (DER: 3-6:1, extraction solvent: 70% ethanol) native extract: 91%	250-1000 mg/kg	male mice in vivo	Chow *et al.*, 2011	mild short-term sedative effect with reduced locomotor activity at 1000 mg/kg
valerian extract (12.5 g root in 250 ml water) 0.00117 mg/ml valerenic acid	1 mg/ml	Zebrafish in vivo	Del Valle-Mojica & *Ortíz*, 2012	increased residence time in the white side by ~85% and ~58%, respectively
ethanolic dry extract (DER: 3-6:1, extraction solvent: ethanol 70%; containing 0.52% valerenic acids	10-100 ng/ml >1 mg/ml	Cultured rat hippocampal neurons in vitro	Malva *et al.* (2004)	decrease in cell reducing capacity and associated neuronal degeneration evoked by Abeta was prevented by valerian
valerian root extract (DER 4-6:1, extraction solvent: methanol 45% w/w)	K_i A1= 0.15 mg/ml K_i A2 = 2.20 mg/ml	radioligand binding assay at A(1) and A(2A) adenosine receptors (ARs) in vitro	Müller *et al*., 2002	Agonistic activity activation of receptor sedative effect
single substances				
hydroxypinoresinol		in vitro	Hölzl, 1998	IC_{50} of 2.5 µmol/l for the 5-HT1A receptor
6-methylapigenin hesperidin	1 mg/kg i.p. 2 mg/kg i.p.	mice in vivo	Marder *et al.*, 2003	anxiolytic effect increased sleeping time combination potentiates the effect

Herbal preparation tested	Strength Dosage Route of administration	Experimental model In vivo/ In vitro	Reference Year of publication	Main non-clinical conclusions
linarin	4 mg/kg i.p. 7 mg/kg i.p.	mice in vivo	Fernandez *et al*., 2004	sedative action prolonged sleeping time combination of linarin and valerenic acid potentiates the effect
valerenic acid valerenol	10^{-7}-10^{-4} M	mice in vivo plus maze; light/dark choice	Benke *et al*., 2009	$GABA_{A\text{-}r}$eceptor affinity exerted anxiolytic activity with high potencies in the elevated plus maze and the light/dark choice test
valerenic acid	oral 340 µg/kg	male mice in vivo	Nam *et al.*, 2013	significantly improvement of the preferential exploration of new objects in novel object recognition test and the escape latency, swimming speeds, platform crossings, and spatial preference for the target quadrant in Morris water maze test compared to the D-galactose-treated mice; cell proliferation and neuroblast differentiation were significantly decreased, while serum corticosterone level and lipid peroxidation in hippocampus were significantly increased in the D-galactose-treated group compared to that in the control group

3.1.2. Secondary pharmacodynamics

Rezvani *et al.* (2010) studied the effect of valerian extracts on an experimental model of temporal lobe epilepsy (TLE) and the involvement of adenosine system in the actions of aqueous and petroleum ether extract (for both extracts no further information) of valerian was evaluated. Bipolar stimulating and monopolar recording electrodes were implanted stereotaxically in the right basolateral amygdala of male Sprague-Dawley rats. After kindling, the effect of aqueous (200, 500 and 800 mg/kg; i.p.) and petroleum ether (PE; 50 and 100 mg/kg; i.p.) extracts of valerian and cyclopenthyl-1,3-dimethylxanthine (CPT) (selective A(1) receptor antagonist; 10 and 20 µM; intracerebroventricular) on afterdischarge duration (ADD), duration of stage 5 seizure (S5D) and latency to the onset of bilateral forelimb clonuses (S4L) were measured. The effect of CPT (10 µM) on the response of aqueous extract of valerian (500 mg/kg) was also determined. The results showed that aqueous extract of valerian had anticonvulsant effect. However, PE extract and CPT (20 µM) had proconvulsant effect. Administration of CPT (10 µM) before the administration of aqueous extract decreased the anticonvulsant effect of valerian. The results showed significant anticonvulsant effect for aqueous but not PE extract of valerian. Moreover, CPT as a selective adenosine A(1) receptor antagonist decreased the anticonvulsant effect of valerian root aqueous extract.

The effects of *V. officinalis* hydroalcoholic extract were investigated on depression like behavior in ovalbumin sensitized rats. Total of 50 Wistar rats were divided into five groups: Group 1 (control group) received saline. The animals in group 2 (sensitized) were treated by saline and were sensitized using the ovalbumin. Groups 3-5 (Sent - Ext 50), (Sent - Ext 100) and (Sent - Ext 200) were treated by 50, 100 and 200 mg/kg of valerian hydroalcoholic extract (extraction solvent: 70% ethanol; no further information) respectively, during the sensitization protocol. Forced swimming test was performed for all groups and immobility time was recorded. Finally, the animals were placed in the open-field apparatus and the crossing number on peripheral and central areas was observed. The immobility time in the sensitized group was higher than that in the control group ($p<0.01$). The animals in Sent-Ext 100 and Sent-Ext 200 groups had lower immobility times in comparison with sensitized group ($p<0.05$ and $p<0.01$). In the open field test, the crossed number in peripheral by the sensitized group was higher than that of the control one ($p<0.01$) while, the animals of Sent-Ext 50, Sent-Ext 100 and Sent-Ext 200 groups had lower crossing number in peripheral compared with the sensitized group ($p<0.05$ and $p<0.01$ respectively). Furthermore, in the sensitized group, the central crossing number was lower than that of the control group ($p<0.001$). In the animals treated by 200 mg/kg of the extract, the central crossing number was higher than that of the sensitized group ($p<0.05$). The authors (Neamati *et al.,* 2014) concluded that the results of the present study showed that the valerian extract prevented depression like behavior in ovalbumin sensitized rats.

The study of Jacobo-Herrera *et al*. (2006) reports that the EtOAc extract (400 g powdered herbal substance extracted with 2 l ethyl acetate, evaporated to 9 g dried extract) of the underground parts of *V. officinalis* showed inhibitory activity against NF-kappaB at 100 µg/ml in the IL-6/Luc assay on HeLa cells and provided protection against excitotoxicity in primary brain cell cultures at micromolar concentrations. Bioassay-guided fractionation of the EtOAc extract led to the isolation of three known sesquiterpenes: acetylvalerenolic acid (1), valerenal (2) and valerenic acid (3), 1 and 3 were active as inhibitors of NF-kappaB at a concentration of 100 µg/ml. Acetylvalerenolic acid reduced NF-kappaB activity to 4%, whereas valerenic acid reduced NF-kappaB activity to 25%.

Two valerian extracts (100 g dried and powdered root extracted in a Soxhlet apparatus with ethanol 70% for 4 h; 100 g dried and powdered root boiled in 1000 ml water for 30 min) were investigated in comparison with a natural mixture of valepotriates and nifedipine on spontaneous and agonist-induced contractions in non-pregnant human myometrium in vitro. Qualitative and quantitative chemical analysis was used to correlate the chemical composition of extracts with their spasmolytic effects. Myometrial strips were obtained from hysterectomy specimens of premenopausal women. Longitudinal muscle strips were mounted vertically in tissue baths under physiological conditions to record their isometric contraction. The responses of cumulative concentrations of valerian extracts (10-80 µg/ml) on spontaneous contractions in the presence and absence of the beta-adrenoceptor blocker atenolol or the cyclooxygenase inhibitor indometacin, and on agonist-induced contractions, were investigated. Valerian extracts and valepotriates inhibited uterine contractility in a concentration-dependent manner. Pretreatment with either atenolol or indometacin did not affect the uterine responses to valerian extracts. Valerian extracts reduced the maximal contractile response induced by acetylcholine, phenylephrine and histamine independent of the stimulus (Occhiuto *et al.*, 2009).

3.1.3. Safety pharmacology

No information available.

3.1.4. Pharmacodynamic interactions

They were proposed for valerian mainly with drugs influencing vigilance such as codeine, citalopram, and benzodiazepines. A presumable interaction with benzodiazepines, which are positive allosteric modulators on GABA-receptors, is based on in vitro data suggesting GABAergic mechanisms of action of valerian extracts (Trauner *et al.*, 2008; Khom *et al.*, 2007).

In rats an in vivo study was conducted on interactions between valerian root tincture (ethanol 100%, 1:10, not further information, daily therapeutic dose 3,060 mg for an adult human) and haloperidol with respect to impaired liver or kidney functions. Valerian tincture was applied with the drinking water (1%, corresponding to an extract dose of 200-250 mg/kg/d). Haloperidol (38 mg/kg) was applied i.m. once every 4 weeks over 12 weeks beginning after 15 days of treatment with valerian. While renal effects were lacking, in some of the parameters measured in liver homogenates, slight and statistically significant deviations from control values were observed, suggesting an additive effect of haloperidol and valerian. Authors discussed that in humans a possible toxic additive effect would occur only at supratherapeutic doses (Fachinetto *et al.*, 2007).

3.1.5. Conclusions

Preclinical data regarding hydroalcoholic extracts suggest GABAergic properties of these extracts. Low microgram concentrations inhibit uptake and stimulate release of GABA from synaptosomes. However, Cavadas *et al*. (1995) as well as Yuan *et al*. (2004) concluded that this interaction (in vitro) could be caused by the content of GABA in the extracts. This was also supported by other studies. An aqueous extract inhibited the uptake and induced the Ca^{2+}-dependent release of [^{3}H]-GABA possibly due to a homoexchange mechanism since the extract contained 5 mM GABA, which proved to be sufficient to induce this effect (Santos *et al*., 1994a,c). GABA was shown to be absent in an ethanolic extract, correspondingly this extract did not significantly affect GABA release. However, the high content of GABA in certain valerian root extracts cannot explain pharmacodynamic effects in vivo since it does not readily cross the blood-brain barrier. High concentrations of glutamine in aqueous extracts lead to the speculation that GABA-synthesis in vivo may be enhanced due to increased disposal of glutamine in the nerve terminals. In view of the lack of data indicating a central nervous effect of exogenous glutamine, the unclear bioavailability of glutamine in valerian root extract and the fact that glutamine is the most abundant amino acid found in the body while the content in the extract was measured to be only 2 g/l, the clinical relevance of this assumption must be judged critically.

Also isolated constituents have been investigated in several in vitro and in vivo models. Since isolated constituents were used in unphysiological high doses to achieve effects, the clinical relevance of these investigations may be questionable. On the other hand, Marder *et al*. (2003) demonstrated a potentiation of effects by combining flavonoids. These results point to a synergism; the observations for single constituents may not reflect their action in the clinical situation realistically.

As a whole, the results point to both a sedative and an anxiolytic effect, possibly mediated by different constituents, which might contribute to sleep promotion and improvement in nervous state.

The valepotriates, mainly occurring in freshly harvested roots, are very unstable compounds due to their unstable epoxide structure and decompose under different conditions (alkali, acids, storage) into baldrinal and its derivatives, valerianic and isovalerianic acid, and undefined polymers. Dried valerian root has therefore a characteristic malodorous aroma, partly due to the content of isovalerianic acid (Hänsel *et al*., 1999). Since valepotriates are rapidly degraded during storage and their oral bioavailability seems to be very low (Wagner & Jurcic, 1980), in vitro and in vivo effects observed with isolated valepotriates, their degradation products or with valerian root extracts containing valepotriates in vitro or in vivo, must be disregarded in the assessment of valerian root extracts (they are mentioned

for the purpose of completeness). Similarly the baldrinals, the decomposition products of valepotriates, are either not detected or detected only in small quantities.

No studies concerning safety pharmacology were found, however, it is to point out, that from various pharmacodynamic models an influence on CNS functions can be postulated. Here the prolongation of thiopental sleeping time by an aqueous extract in a dose dependent manner in mice must be highlighted.

The deduction of a relevant drug interaction of valerian root and barbiturates under clinical conditions from the cited study is questionable.

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

No data on absorption, distribution, metabolism and excretion are available for the herbal substance or its preparations.

Limited data are available for valerianic acid. An LC-MS/MS assay for the determination of valerianic acid in rat plasma was established and validated. This method was used for pharmacokinetic studies in rats after i.v. (doses: 1, 2 and4 mg/kg) and oral administration (doses: 5, 10 and20 mg/kg). The plasma concentration-time data was analyzed by both non-compartmental and compartmental approaches using WinNonlin software. Following i.v. administration, the disposition of valerianic acid in rat plasma was biphasic, subdivided into a fast distribution and a slow elimination phase. The half-life of the distribution phase was 6-12 min, and that of the terminal elimination phase 6-46 h, indicating a possible large tissue binding. Disposition PK of valerenic acid after oral treatment was also described by a two-compartment model with a clearance (CL/F) of 2-5 $L \bullet h^{-1} \bullet kg^{-1}$ and volume of distribution of (V_d) 17-20 $l \bullet kg^{-1}$. The extent of absorption (F) after oral administration was estimated to be 33.7% with a half-life of 2.7-5 h. Dose proportionality was observed in terms of dose and AUCs, suggesting linear pharmacokinetics at the dose levels studied in rats (Sampath *et al.*, 2012).

Pharmacokinetic interactions

In recent popular publications as well as in widely used information websites directed to cancer patients, valerian is claimed to have a potential of adverse interactions with anticancer drugs. This questions its use as a safe replacement for, for example, benzodiazepines. Seven in vitro studies on six CYP 450 isoenzymes, on p-glycoprotein, and on two UGT isoenzymes were identified. However, the authors concluded that the methodological assessment of these studies did not support their suitability for the prediction of clinically relevant interactions. In addition, clinical studies on various valerian preparations did not reveal any relevant interaction potential concerning CYP 1A2, 2D6, 2E1, and 3A4. Available animal and human pharmacodynamic studies did not verify any interaction potential. The interaction potential of valerian preparations therefore seems to be low and thereby without clinical relevance (Kelber *et al*., 2014a).

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

Experimental data on the toxicological properties of Valerian root extract and its single compounds are limited. For whole extracts or isolated compounds with the exception of valepotriates and their degradation products in various experiments a low order of toxicity was found as shown below.

3.3.1. Single dose toxicity

Table 5: Overview of single dose toxicity values for valerian extracts and constituents thereof (Table cited according to NTP, 2009)

Route **test substance**	**Species (sex and strain)**	**LD_{50}**
i.p. ethanolic extract of valerian root (defatted)	mice (sex and strain n.p.)	3,300 mg/kg
oral valerian oil	rats (sex and strain n.p.)	15,000 mg/kg
oral valeranone	rats and mice (sex and strain n.p.)	>3,160 mg/kg (14.21 mmol/kg)
oral valtrate	mice (sex and strain n.p.)	≥4,600 mg/kg (10.89 mmol/kg)
i.p. valtrate	mice (sex and strain n.p.)	~62 mg/kg (0.15 mmol/kg)

Abbreviations: i.p. = intraperitoneal; LD50 = lethal dose for 50% of test animals; n.p. = not provided

Valerenic acid caused inhibition of spontaneous motility after i.p. administration to mice at a dose of 50 mg/kg, ataxia and temporary immobility at a dose of 100 mg/kg, muscle spasms at doses of 150-200 mg/kg, and severe convulsions and mortality at a dose of 400 mg/kg (6 of 7 animals ad exitum 24 h after administration) (Hendriks *et al*., 1985).

3.3.2. Repeat dose toxicity

An ethanolic valerian root extract (no further information) given to rats at a daily dose of 300 mg/kg and 600 mg/kg p.o. for a period of 30 days did not influence blood pressure, weight of the heart, lungs, liver, spleen, kidneys, bladder, stomach, intestines or testes, haematological parameters (erythrocytes, leukocytes including differential blood count, haematocrit, haemoglobin) or biochemical parameters (blood sugar, urea, SGOT, SGPT and alkaline phosphates). The animals receiving the higher dose had a slightly higher body weight compared to controls (Fehri *et al.*, 1991).

An ethanolic valerian root extract (no further information available) given to rats i.p. at doses of 400-600 mg/kg over a period of 45 days did not result in any significant changes in body weight, blood count or urine status (Rosecrans *et al*., 1961).

Valerian root oil in a dose of 2000-2250 mg/kg p.o. was found to be a tolerated in rats over an experimental period of 8 weeks. With higher doses, loss in body weight, rough and ungroomed coat, apathy and, in some cases, mortality were recorded. At 2500 mg/kg daily, 2/5 of the animals died within 3 weeks (von Skramlik, 1959).

The test of a dietary product with undefined quality in mice showed clear effects on nucleic acid, malondialdehyde and glutathione concentrations in testicular cells and malondialdehyde and glutathione concentrations in hepatic cells. The concentration used was with ~4 g/kg much higher than the recommended dosage in humans (Al-Majed *et al*., 2006).

3.3.3. Genotoxicity

Kelber *et al.* (2014b) 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). 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:

dry extract (3-6:1); extraction solvent: water
dry extract (4-7:1); extraction solvent: ethanol 40% (V/V)
dry extract (3-6:1); extraction solvent: ethanol 70% (V/V)
extract (1:10); extraction solvent: ethanol 96% (V/V) (oily macerate)
extract (167:1); extraction solvent: heptane.
The concentrations were ranging from 100 to 5000 µg/plate. *S. typhimurium* strains TA 98, TA 100, 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.

A Somatic Mutation and Recombination Test (SMART) in *Drosophila melanogaster* showed no genotoxic effects for an infusion of valerian root purchased from a local health food store, raising questions concerning the quality of the herbal substance in relation to pharmaceutical properties. The used dose is not specified, the test procedure is not accepted as a standard method for the investigation of genotoxicity. The data cannot therefore be accepted to show the absence of genotoxic effects of valerian root (Romero-Jiménez *et al*., 2005).

Alkylating, cytotoxic and mutagenic effects have been described for the valepotriates and their degradation products (Bos *et al*., 1997, von der Hude *et al*., 1986) which are not detectable in valerian root extracts or are found only in very low amounts (Bos *et al*., 1997).

The test of a dietary product with undefined quality in mice showed weak genotoxic effects (chromosomal aberrations in bone marrow and in testis) in high doses (Al-Majed *et al*., 2006; Al-Majed, 2007). The dietary complement in form of capsules contained of valerian root and a dry extract of valerian root (not further specified) in a ratio 3.6:1. Assuming an average DER of 6:1 for the dry extract the herbal substance equivalent of 1 g mixture would be ~2.1 g herbal substance.
An aqueous suspension of the product was administrated in mice by gastric administration at 500, 1000 and 2000 mg/kg bw/day (~1.05, 2.1 and 4.2 g herbal substance/kg/day). After 7 days, the dose of 2000 mg/kg bw/day (~4.2 g herbal substance/kg/day) showed an increase (factor 1.5) in the frequency of micronucleated polychromatic erythrocytes and a decrease in the PCE/NCE ratio (polychromatic/normochromatic erythrocytes) in femoral bone marrow (Al-Majed *et al*., 2006). The HED of the highest dosage is 0.34 g/kg. The highest recommended daily dosage (WEU) is 12 g herbal substance/day = 0.24 g/kg (assuming a human body weight of 50 kg).
An aqueous suspension of the product was administrated in mice by gastric administration for 90 days at 125, 250 and 500 mg/kg bw/day (~0.26, 0.52 and 1.05 g herbal substance/kg/day). In the cytogenetic analysis aneuploid effects could be seen with the highest dose tested (500 mg/kg) (1.05 g herbal substance/kg/day) in evaluated testis chromosomes (Al-Majed, 2007). The HED of 1.05 g herbal substance/kg (mice) is 0.085 g/kg. The highest recommended daily dosage (WEU) is 12 g herbal substance/day = 0.24 g/kg (assuming a human body weight of 50 kg).
The effects seen are discussed by the authors as due to the decrease of nucleic acids and nonprotein sulhydryl and an increase of malondialdehyd in the cells and therefore the importance of free radical species for the effects seen.

3.3.4. Carcinogenicity

No information available.

3.3.5. Reproductive and developmental toxicity

There are no relevant published studies on reproductive toxicity of preparations from valerian root.

Mahmoudian *et al*. (2012) determined the effects of valerian consumption in pregnancy on cortical volume and the levels of zinc and copper, two essential elements that affect brain development and

function, in the brain tissues of mouse foeti. Pregnant female mice were treated with either saline or 1.2 g/kg valerian extract (no further information) i.p. daily on gestation days (GD) 7 to 17. On GD 20, mice were sacrificed and their foeti were collected. Fetal brains were dissected, weighed and processed for histological analysis. The volume of cerebral cortex was estimated by the Cavalieri principle. The levels of zinc and copper in the brain tissues were measured by atomic absorption spectroscopy. The results indicated that valerian consumption in pregnancy had no significant effect on brain weight, cerebral cortex volume and copper level in fetal brain. However it significantly decreased the level of zinc in the brain ($p<0.05$).

A test of a dietary supplement in mice revealed the appearance of sperm head morphology abnormalities (amorphous and triangular head abnormalities). The concentration used was with ~4 g/kg (see above) higher than the recommended dosage in humans. A negative influence on male fertility could not be proven due to the unclear quality and dosage of the tested product (Al-Majed *et al*., 2006).

The effects of a valepotriates mixtures on mothers and progeny were evaluated in rats by Tufik *et al*. (1994). A 30-day oral administration of valepotriates (80% dihydrovaltrate, 15% valtrate; 5% acevaltrat; in doses of 6, 12 and 24 mg/kg) did not change the average length of estral cycle, nor the number of estrous phases during this period. Also, there were no changes on the fertility index. Fetotoxicity and external examination studies did not show differences, although internal examination revealed an increase in number of retarded ossification after the highest doses employed (12 and 24 mg/kg). No changes were detected in the development of the offspring after treatment during pregnancy. As for temperature, valepotriates caused a hypothermizant effect after administration by the i.p. route but not after oral administration. Generally, the valepotriates employed induced some alterations after administration by the i.p. route, but doses given orally were innocuous to pregnant rats and their offspring.

3.3.6. Local tolerance

Not applicable

3.3.7. Other special studies

Not applicable

3.3.8. Conclusions

Only incomplete experimental data pointing altogether to a low toxicity of valerian root preparations. Safety assessment is thus mainly based on many years of experience acquired through extensive therapeutic use in man, which indicate valerian root preparations to be safe.

Two publications suggest weak genotoxic effects for an undefined preparation from Valerian radix. Both paper do not provide data on GLP status of the experiments and historical control data. Neither acceptance criteria nor criteria for determining a positive result were defined. A positive control was not included. Most of the effects seen should be discussed as borderline (increase factors). Together with the unclear composition and quality of the product the effects can only be judged as informative value.

A complete set of AMES-test data ("bracketing and matrixing concept") exists. The tests were unequivocally negative for all extracts. These tests allow to prepare a community list entry for all preparations of the monograph with traditional use, except the for essential oil, since HMPC/MLWP

considered the data from the "bracketing and matrixing concept" not sufficient to proof the safety of the essential oil.

There are no experimental investigations concerning reproductive and developmental toxicity. Whether the zinc deficiency in the study of Mahmoudi *et al*. (2012) has been transported through a zinc deficiency in the maternal mice to the foeti remains undiscussed by the authors of the study.

3.4. Overall conclusions on non-clinical data

Results from relevant experimental studies on sedative and an anxiolytic activity support the proposed indications under WEU and support the traditional use as relief of mild symptoms of mental stress and to aid sleep. Specific data on pharmacokinetics and interactions are limited. Non-clinical information on the safety of is scarce. As there is limited information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended. Studies on carcinogenicity are not available.
An AMES-test on mutagenicity for the dry extract (DER 3-6:1, extraction solvent: ethanol 70%) did not give any reason for concern (WEU).
Oral and cutaneous administration of preparations containing valerian root can be regarded as safe at traditionally used doses. AMES-test data for different preparations from Valerian radix, which are guideline conform, allow to prepare a community list entry for all preparations listed under Traditional use, except for the essential oil.

4. Clinical Data

The extracts used in the trials are specified in the comments as far as possible. Unfortunately, in many publications correct specifications of solvent and drug-extract ratio (DER) are missing. In these cases no details can be given, if the extract could not be identified otherwise.

The most widespread human sleep disorders are insomnia, narcolepsy, restless legs syndrome, and sleep apnoea.
Insomnia is the most commonly reported sleep-associated problem, affecting as much as 50% of the adult population periodically and 10-15% chronically (Morin & Benca, 2012). Insomnia is characterized by complaints that include difficulty in falling asleep, frequent awakening from sleep, waking too early and having trouble falling back to sleep, and nonrestorative sleep. These problems occur despite adequate opportunity to sleep and result in daytime sleepiness or fatigue and performance impairment. Insomnia can be characterized in terms of duration (acute or chronic), cause (primary or secondary), type (psychophysiological, paradoxical, inadequate sleep hygiene, comorbid and idiopathic) and timing during the night (initial or onset, middle, late or mixed) (Perlis *et al.*, 2011).

The treatment of non-organic sleep disturbances with synthetic hypnotics/sedatives like benzodiazepines and barbiturates is associated with undesirable effects like adaptation, dependency, hang-over effects, increased sleep apnoea or anterograde amnesia. It induces also undesired changes of sleep patterns. Antihistamines (e.g. promethazine) may cause palpitations, a dry mouth and other disturbing undesirable effects. There is obviously a need for better tolerated alternatives to synthetic sedatives to prevent the manifestation of chronic insomnia. A considerable number of trials underline that valerian root is such an alternative medication that does not exhibit typical undesirable effects observed with conventional treatment of sleep and mood disorders.

4.1. Clinical pharmacology

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

Objective evidence of a mild to moderate sedative or tranquilizing effect of valerian root extract in man is provided by EEG studies in healthy volunteers and in female subjects with sleep disorders, although not all results are consistent and they must not be overemphasized for this reason. For most of such studies see "4.2.2. Clinical studies (case studies and clinical trials)".

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

The pharmacokinetics of valerenic acid was determined in a group of elderly women after receiving a single nightly valerian dose and after 2 weeks of valerian dosing. There was not a statistically significant difference in the average peak concentration: C_{max}: SD 3.3±2.3 (0.7-9.4), T_{max}: SD 1.7±0.9 (0.5-4.0), AUC: SD: 6.54±2.97 (1.61.13.63), $T_{1/2}$ SD: 1.02±0.35 (0.47-1.7) and oral clearance after a single dose compared with multiple dosing. There was considerable inter- and intra-subject variability in the pharmacokinetic parameters. C_{max} and AUC deceased and $T_{1/2}$ increased with increased body weight. The variability between the capsules was extremely low: 2.2%, 1.4% and 1.4%, for hydroxyvalerenic acid, acetoxyvalerenic acid and valerenic acid, respectively. The authors concluded the large variability in the pharmacokinetics of valerenic acid may contribute to the inconsistencies in the effect of valerian as a sleep aid (Anderson *et al.*, 2010).

4.2. Clinical efficacy

An overview of the evaluation and treatment of circadian rhythm sleep disorders (CRSDs) has been published by Sack *et al.* (2007a,b) in two parts. The International Classification of Sleep Disorders (ICSD-2) recognizes namely: 1) *delayed sleep phase type,* 2) *advanced sleep phase type,* 3) *irregular sleep-wake phase type,* 4) *free-running type,* 5) *jet lag type*, and 6) *shift work type*.
The ICSD-2 also recognizes CRSDs *secondary to medical conditions* and *drug or substance abuse*, as well as a general category, CRSD *Not Otherwise Specified (NOS*). The essential feature of CRSDs is a persistent or recurrent pattern of sleep disturbance due primarily to alterations in the circadian timekeeping system or a misalignment between the endogenous circadian rhythm and exogenous factors that affect the timing or duration of sleep. Thus, either exogenous or endogenous factors (and often both) can contribute to the misalignment between the timing of internal circadian rhythms and the desired (from the patient's perspective) or required (from the scheduling demands of society) time for sleep. The interindividual sensitivity of people varies substantially.

Insomnia is the most prevalent sleep disorder in the general population, and is commonly encountered in medical practices. Insomnia is defined as the subjective perception of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep, and that results in some form of daytime impairment. Chronic insomnia is present for at least a month, as opposed to acute or transient insomnia, which may last days to weeks.

4.2.1. Dose response studies

The dose recommendations of the German Kommission E monograph (1985), the WHO monograph (1999) and the ESCOP monograph (1997) on valerian root (single doses of 2–3 g crude herbal substance (ESCOP: 1–3 g) given once or several times daily according to indication or requirements)

are based on broad clinical experience, on EEG-studies and clinical trials comparing valerian root in the mentioned doses to placebo or active comparators. Detailed evidence-based statements on minimal effective dose, safe starting dose, and optimal maintenance dose cannot be made on this basis. The data by Kamm-Kohl *et al*. (1984) (see section 'nervous tension + insomnia') demonstrate that even very low doses of valerian root may achieve clinically relevant results, but most experience confirms the dose regimen mentioned above.

Only one dose-finding trial in short-term clinical use of valerian root has been performed, which showed a dose-dependent effect for the tested doses of 1.3 g and 2.6 g valerian root.

In a double-blind, randomized crossover trial, 7 patients (33-59 years) with problems getting to sleep took either 450 mg (corresponding to 1.3 g of the herbal substance), or 900 mg (corresponding to 2.6 g of the herbal substance) of an aqueous valerian root extract or placebo before bedtime (Leathwood & Chauffard, 1985). Medication was taken in a randomized assignment over three periods of 4 days each with a three day pause in between. During all nights following intake of a test sample, activity was measured by means of a wrist-worn activity meter. In addition, the subjects filled in a questionnaire in the morning with a 9-point scale on: time to fall asleep, quality of sleep and depth of sleep. Sleep latency was decreased significantly with both valerian root extract doses (mean values: placebo = 15.8±5.8 min, 450 mg extract = 9.0±3.9 min, 900 mg extract = 11.4±5.2 min) while total sleep time and total number of movements remained unchanged. With the higher dose patients felt more sleepy the next morning than with placebo.

These results were confirmed in a trial in 10 healthy volunteers (24-44 years), who took placebo, 450 or 900 mg of an aqueous valerian root extract corresponding to 1.2 or 2.4 g of the herbal substance in a crossover schedule. Estimated sleep-latency and wake time after sleep onset were reduced by more than 50% after the higher dose, while the lower dose had a somewhat lower effect (Balderer & Borbely, 1985).

4.2.2. Clinical studies (case studies and clinical trials)

Several controlled clinical trials have been performed, mainly in patients with non-organic insomnia, which confirm a superiority of valerian root versus placebo. In addition, two recent trials must be highlighted demonstrating that efficacy of valerian root is in the same range as that of low-dose oxazepam while valerian root is clearly better tolerated.

- Healthy subjects

In a placebo-controlled, double-blind study a single administration of 400 mg of an aqueous valerian root extract (DER 3:1) did not induce significant changes in the objective measures of sleep (EEG recording in a sleep laboratory) in 10 healthy volunteers (Leathwood & Chauffard, 1982/83). Nevertheless, the results showed tendencies towards a shorter mean sleep latency and an increased mean latency to first awakening. Lack of significance may be due to the small number of volunteers.

Further sleep EEG investigations were performed with the same aqueous extract. Eight subjects without major sleep disorders (4 female, 4 male, average age 22.6 years) spent 5 nights in a sleep laboratory. The first night was without medication, on nights 2 and 3 placebo was administered, on night 4 900 mg of valerian root extract was administered, and on night 5 placebo was administered again. There was no difference between placebo and valerian root extract in the sleep EEG. However, in the subjective assessment of quality of sleep, which was determined by means of a visual analogue scale, the time taken to fall asleep and the time spent awake during the night were reduced under treatment with the valerian root preparation (Balderer & Borbely, 1985).

In a placebo-controlled, double-blind study of crossover design, the effects of a single dose of 1,200 mg valerian root extract (DER 5-7:1, extraction solvent not specified) corresponding to 7.2 g of

the herbal substance on the quantitative EEG of 12 healthy subjects (average age: 53.7±5.6 years) was compared to that of 1 x 10 mg diazepam. Compared to diazepam, an increase in the relative strength of the theta frequency band was observed for the valerian preparations. Under diazepam the power in the theta frequency band decreased while it increased in the beta band. Valerian root extract increased power in the delta and theta bands and decreased power in the beta band (Schulz *et al.,* 1998).

In a double-blind placebo-controlled study the effects of 1 x 100 mg valerian root extract (no further data) (n=12) or 1 x 20 mg propanolol (n=12) or 1 x 100 mg valerian root extract + 20 mg propanolol (n=12) on a stress situation provoked by a mathematical task were investigated 90 or 120 min after administration in 48 young subjects (age 19-29 years) without health disorders. There was no group difference with regard to mathematical performance. Under propanolol, the expected reduction in pulse frequency increase was found in the stress situation; under valerian root a feeling of less marked somatic activation. The authors concluded that these results pointed to a thymoleptic effect of valerian root (Kohnen & Oswald*,* 1988). It is well known that thymoleptic medicinal products may show anxiolytic properties, which may be differentiated from antidepressive effects.

- Non-organic insomnia

In a double-blind, parallel-group trial (verum: n=8, placebo: n=6) in elderly female poor sleepers (average age: 61.6±6.5 years) the patients took 3 x 405 mg/day of an aqueous-ethanolic valerian root extract (DER 5–6:1, extraction solvent: ethanol 70% V/V). After a 1-day treatment, the total sleeping time and slow-wave sleep increased significantly, sleep induction time was reduced and quality of sleep improved. Long-wave sleep (stage 3 and 4) was increased and stage 1 was decreased. After an 8-day treatment, a percentage reduction in sleep stage 1 from 16.4% to 11.9%, an increase in sleeping phase 3 from 6.5% to 10.2%, and an increase in total sleeping phases 3 and 4 from 7.7% to 12.5% (p=0.0273, in each case) occurred under active treatment. Under placebo, these parameters essentially remained unchanged. REM sleep, sleep latency and time awake, as well as the subjective quality of sleep (sleep questionnaire SF-A according to Goertelmeyer, visual analogue scale) did not change under the two medications. The authors concluded that valerian root has a mild tranquilizing instead of a sedating activity that may improve sleep quality under certain conditions (Schulz *et al*., 1994).

In a placebo-controlled crossover study 24 females suffering from sleep disorders received 10 mg diazepam, placebo, 1,200 mg of a valerian root extract (DER 3-7:1, extraction solvent not specified). After intake of valerian root extract the EEG showed an increase in relative power in the delta and theta frequency. There was no increase in the power of the beta frequency range after valerian root extract in contrast to diazepam. The subjectively experienced tiredness increased markedly both after valerian root and diazepam. No absolute values or significance levels were given in the abstract (Schulz & Jobert, 1995).

Diaper & Hindmarch (2004) performed a double-blind placebo-controlled crossover trial in 16 patients (age 50–64 years) with mild sleep-disturbances investigating the effect of a single dose of placebo, 300 mg or 600 mg of an ethanolic valerian root extract (DER 3–6:1, extraction solvent ethanol 70% V/V) corresponding to 1.35 or 2.7 g of the herbal substance. For sleep EEG parameters and several psychometric tests, no group differences were stated; only a tendency to increased drowsiness with the higher valerian root dose was observed.

Donath *et al.* (2000) performed a placebo-controlled, double-blind crossover study in 16 patients with psychophysiological insomnia (International Classification of Sleep Disorders ICSD-Code 1.A.1) with intake of 600 mg of an ethanolic dry valerian root extract (DER 3–7:1, extraction solvent: ethanol 70% V/V), corresponding to 3 g of the herbal substance/day. The study medication was taken each over a fortnight with a wash-out period of 14 days between the treatment phases. Under both verum and

placebo, sleep structure improved significantly; for the main objective efficacy parameter sleep efficiency no difference could be stated. On the other hand, subjective sleep latency decreased significantly only after 14 days of valerian root intake. For valerian root extract a clearly better correlation between objective improvement and subjective perception could be demonstrated than for placebo. The authors concluded that drug effects might have been masked by the effects of general interventions caused by the study design. Valerian root might act by reducing a misperception of sleep and wake phases. They concluded that valerian root has a mild, delayed effect and could be recommended for patients with chronic insomnia in combination with additional non-pharmacological measures but not for patients with acute, reactive sleep disturbances needing rapid relief.

Ziegler *et al*. (2002) demonstrated that the efficacy of valerian root extract in non-organic insomnia is comparable to that of oxazepam: They performed a randomised, double-blind, multi-center study in 186 patients (18-73 years, mean 52±13 years, 125 female, 61 male) with non-organic insomnia (ICD-10, F51.0) who needed a medical treatment.
Over 6 weeks, the patients received once daily in the evening 600 mg of an ethanolic valerian root extract (DER 3–6:1, extraction solvent: ethanol 70% V/V) corresponding to 2.7 g of the herbal substance, or 10 mg oxazepam. The study was designed as a non-inferiority-trial, main efficacy parameter was Goertelmeyer Sleep Questionnaire B (SF-B), item quality of sleep. The other SF-B items, the Clinical Global Impressions Scale (CGI) and a global rating of efficacy and tolerability by investigator and patient were chosen as secondary efficacy parameters. Quality of sleep increased in both groups over the whole treatment period; the one-sided confidence interval was within the limit for non-inferiority (<0.2) for the ITT-population after 2, 4 and 6 weeks of treatment. The other SF-B items (psychic exhaustion in the evening, feeling of refreshment after sleep, psychosomatic symptoms in the sleep phase, duration of sleep) showed comparable improvement with confidence intervals <0.2 as well. 30.4% of patients in the valerian root extract group and 23.6% of patients in the oxazepam group rated their complaints as 'very much improved'. However, in the valerian root extract group more patients did not notice any change (valerian root extract: 13.0% versus oxazepam: 6.7%), while more patients with oxazepam felt at least a minimal improvement (oxazepam: 31.5% versus valerian root extract: 19.6%). Adverse events occurred in 28.4% of patients treated with valerian root extract and in 36% of those, who took oxazepam. Symptoms pointing to possible "hangover" effects occurred in 6 patients of the oxazepam group versus 2 in the valerian root extract group.

The results of Ziegler *et al*. (2002) are confirmed by another randomised, double-blind trial with the same comparators in identical dosages which failed to show a difference between valerian root extract and oxazepam (Dorn, 2000). In this trial, 75 patients, age 52±12 years, with non-organic insomnia (ICD-10, F51.0) received oxazepam 10 mg/day or 600 mg of an aqueous-ethanolic valerian root extract (DER 3-6:1, extraction solvent ethanol 70% V/V) corresponding to 2.7 g of the herbal substance over 4 weeks. The questionnaires included Goertelmeyer SF-B, well-being scale according to von Zerssen (Bf-S), Hamilton Anxiety Scale (HAMA) and sleep-rating by the physician. Both groups improved distinctly in all parameters including the HAMA Scale. The study did not reveal any differences between the treatment groups. In the oxazepam group patients tended to report more often hang-over symptoms.

A placebo controlled, double-blind parallel-group study was carried out in 121 patients (71 female, 50 male, average age 47 years) suffering from non-organic insomnia according to ICD-10 (Vorbach *et al*., 1996). Patients received daily 600 mg of a valerian root extract (DER 3-7:1, extraction solvent: ethanol 70% V/V), corresponding to 3 g of the herbal substance, or placebo over the course of 28 days as a single dose in the evening. The study documentation comprised 3 validated questionnaires (sleeping questionnaire B according to Goertelmeyer, Form B3 (SF-B), von Zerssen's "Befindlichkeits" Mood Scale (Bf-S), the Clinical Global Impression (CGI)) and a global rating of efficacy and tolerability by physician and patient. No main efficacy parameter was defined and the results were clearly rated as

explorative by the authors. The CGI questionnaire improved significantly after 2 weeks; the difference versus placebo further increased until the end of treatment after 4 weeks. The "self-rating scale according to von Zerssen", the "Goertelsmeyer's sleep questionnaire", and other ratings confirmed the positive trend with more pronounced differences between the treatment groups after 4 weeks than after 2 weeks. The change in status after 28-day treatment with valerian root extract therapy was given as "very much better" or "much better" in 55.9% of cases (placebo 25.9%). Although no confirmatory statistical evaluations were performed, the results give quite clear evidence of a therapeutic efficacy of the administered dose of valerian root in insomnia.

A crossover trial comparing an aqueous valerian root extract (400 mg corresponding to 1.2 g of the herbal substance), placebo and a combination of valerian root dry extract (120 mg) + hop strobile dry extract (60 mg) was performed by Leathwood *et al*. (1982) in 166 volunteers, who were partly poor sleepers. DER for the latter preparation is not given. The volunteers took one dose of a total of nine doses (three/preparation) on non-consecutive nights and documented their sleep quality in a questionnaire (not validated). Results were analyzed only for those volunteers, who completed the trial (n=128). On the morning after taking the preparation, time to fall asleep, quality of sleep, natural waking up, dreaming and tiredness in the morning were recorded by means of a questionnaire. Time to fall asleep was reduced in 37% of persons taking the valerian root mono-preparation, in 23% under placebo and in 31% under the combination preparation. The difference between the valerian root mono-preparation and placebo was statistically significant ($p<0.01$). While quality of sleep remained virtually unchanged in habitually good sleepers with all preparations, in habitually poor or irregular sleepers the sleep quality was enhanced and sleep latency was reduced significantly more often with the valerian root 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 the lack 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.

A trial conducted in general practices using a series of randomised "n-of-I" trials (Coxeter *et al*., 2003) revealed a positive trend, but no significant superiority of valerian root versus placebo after three weeks of treatment (only 42/86 = 40% of all randomised patients were included in the analysis). The daily dosage taken was 450 mg of valerian root extract corresponding to 2 g of the herbal substance (extraction solvent not given). The sleep diary consisted of 6 outcome variables (latency to sleep, number of night awakenings, total sleep time, quality of sleep, level of perceived refreshment post-slumber, energy level in the previous day).

- Nervous tension + insomnia

In a placebo-controlled, double-blind study, an aqueous valerian root extract (DER 5-6:1, extraction solvent: water) and placebo were investigated in 78 hospitalised patients (59 female, 19 male, 61-79 years) who were suffering from nervous mood and behavioural disorders. The patients received 3 x 90 mg/day (=270 mg/day) valerian root extract or placebo over a period of 14 days. Assessment of the therapeutic effect was performed before and after treatment using von Zerssen's Mood Scale (Bf-S) and the Nurses' Observation Scale for In-patient Evaluation (NOSIE). In addition, symptoms such as difficulty in falling asleep, problems in sleeping through the night and rapid exhaustion were

assessed on a 4-point scale. The total score on the Bf-S fell by 10.5 points under active treatment and by 4.5 points under placebo ($p<0.01$, t-test). The total score on the NOSIE scale increased by 22.6 and by 6.8 points under placebo ($p<0.01$, t-test). The symptoms "difficulty in falling asleep" and "difficulty in sleeping through the night", which were present in all 78 patients (although no inclusion criterion), improved significantly under active treatment ($p<0.001$ versus placebo in each case); the symptom of rapid exhaustion, about which 63 patients complained, also showed significant improvements in favour of the active treatment ($p<0.02$, Kamm-Kohl *et al*., 1984).

Jacobs *et al*. (2005) performed a completely internet-based, placebo-controlled randomised trial in 391 patients comparing valerian root (daily 6.4 mg of valerenic acids; specification of the extract not available) versus placebo with a treatment duration of 4 weeks. Anxiety was assessed by the State-Trait Anxiety Inventory (STAI-State) questionnaire, a validated 20-item measure of anxiety symptoms; insomnia was assessed by the validated Insomnia Severity Index (ISI). All patient groups improved distinctly with respect to both symptom complexes, but no differences could be demonstrated between the groups after 2 and 4 weeks of treatment. Since no details are available on the actual amount of valerian root taken by the patients, no conclusions can be drawn from these results regarding the common dose of 2-6 g recommended for sleep induction.

In the trial of Oxman *et al.* (2007) participants were recruited through a weekly nationally televised health program in Norway. Enrolment and data collection were over the Internet. 405 participants who were 18 to 75 years old and had insomnia completed a two week diary-keeping run-in period without treatment and were randomised and mailed valerian or placebo tablets for two weeks. All participants and investigators were blind to treatment until after the analysis was completed. For the primary outcome of a minimally important improvement in self-reported sleep quality (>or =0.5 units on a 7 point scale), the difference between the valerian group (29%) and the placebo group (21%) was not statistically significant (difference 7.5%; 95% CI-0.9 to 15.9; p=0.08). On the global self-assessment question at the end of the treatment period 5.5% (95% CI 0.2 to 10.8) more participants in the valerian group perceived their sleep as better or much better (p=0.04). There were similar trends favouring the valerian group for night awakenings (difference =6.0%, 95% CI-0.5 to 12.5) and sleep duration (difference =7.5%, 95% CI-1.0 to 16.1). There were no serious adverse events and no important or statistically significant differences in minor adverse events.

The efficacy of a *Valerian officinalis* supplement for sleep in people with cancer who were undergoing cancer treatment was evaluated by Barton *et al.* (2011). The used Valerian preparation was pure ground raw root from *Valeriana officinalis* standardized to 0.8% valerenic acid. Participants were randomized to receive 450 mg of valerian or placebo orally 1 h before bedtime for 8 weeks. The primary end point was AUC of the overall Pittsburgh Sleep Quality Index (PSQI). Secondary outcomes included the Functional Outcomes of Sleep Questionnaire, the Brief Fatigue Inventory (BFI), and the Profile of Mood States (POMS). Toxicity was evaluated with both self-reported numeric analogue scale questions and the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Questionnaires were completed at baseline and at 4 and 8 weeks. A total of 227 patients were randomized into this study with 119 being evaluable for the primary end point. The AUC over the 8 weeks for valerian was 51.4 (SD=16), while that for placebo was 49.7 (SD=15), with a P value of 0.6957. A supplemental, exploratory analysis revealed that several fatigue end points, as measured by the BFI and POMS, were significantly better for those taking valerian over placebo. Participants also reported less trouble with sleep and less drowsiness on valerian than placebo. There were no significant differences in toxicities as measured by self-report or the CTCAE except for mild alkaline phosphatase increases, which were slightly more common in the placebo group. This study failed to provide data to support the hypothesis that valerian, 450 mg, at bedtime could improve sleep as measured by the PSQI. However, exploratory analyses revealed improvement in some secondary outcomes, such as fatigue.

The objective in the an 8-week pilot double-blind randomized trial was to compare the efficacy of the extract of *Valeriana officinalis* with placebo in the treatment of obsessive-compulsive disorder (OCD). 31 adult outpatients who met the DSM-IV-TR criteria for OCD based on the structured clinical interview participated in the trial. Patients were randomly assigned to receive either capsule of the an extract (7.1:1; extraction solvent: water) (765 mg/day) or placebo (30 mg/day) for 8 weeks. The results showed a significant difference between the extract and placebo regarding Y-BOCS ($p<0.05$). Somnolence was the only significant difference between the two groups in terms of observed side effects ($p=0.02$). The authors conclude that *Valeriana officinalis* has some antiobsessive and compulsive effects. The results showed significant difference between the extract and placebo in the treatment of OCD. There was also no significant difference between the two groups in terms of observed side effects (Pakseresht *et al*., 2011).

Participants in the phase 2 randomized, double-blind, crossover controlled trial (Taibi *et al.*, 2009) were 16 older women (mean age=69.4±8.1 years) with insomnia. Participants took 300 mg of valerian root extract (standardized to 0.8% valerenic acid, further specifications not available) or placebo 30 min before bedtime for 2 weeks. Sleep was assessed in the laboratory by self-report and polysomnography (PSG) at baseline and again at the beginning and end of each treatment phase (total of nine nights in the laboratory) and at home by daily sleep logs and actigraphy. There were no statistically significant differences between valerian and placebo after a single dose or after 2 weeks of nightly dosing on any measure of sleep latency, wake after sleep onset (WASO), sleep efficiency, and self-rated sleep quality. In comparing each treatment to baseline in separate comparisons, WASO significantly increased (+17.7±25.6 min, $p=0.02$) after 2 weeks of nightly valerian, but not after placebo (+6.8±26.4 min, NS). Side effects were minor and did not differ significantly between valerian and placebo.

- Anxiety/stress

The study of Pinheiro *et al*. (2014) evaluated the efficacy of *Valeriana officinalis* for control of anxiety during the third molar surgery. A single oral dose of either Valerian (100 mg) or placebo was randomly administered 1 h before each surgical procedure to 20 volunteers between 17 and 31 years of age. Anxiety level was assessed by physiological parameters (blood pressure and heart rate) and the observation of signs. Descriptive analysis, Chi-square test, Friedman test, Wilcoxon test and effect size test were performed ($p<0.05$) According to the researcher's (80%) and surgeon's (75%) evaluations, the patients treated with Valerian were calmer and more relaxed during surgery. Valerian had a greater effect on the maintenance of systolic blood pressure and heart rate after surgery. Valerian was more effective at controlling anxiety than a placebo when used for the conscious sedation of adult patients submitted to impacted lower third molar surgery.

Cropley *et al*. (2002) performed an open, randomised study comparing the effect of valerian root and an untreated control group in a pressure situation. 44 students completed the colour/interference test with increasing speed of presentation before and after one week intake of 600 mg of an aqueous-ethanolic valerian root extract (DER 3-6:1; extraction solvent: ethanol 70% (V/V)) corresponding to 2.7 g of the herbal substance or no medication. Blood pressure and heart rate were recorded before, during and after the test situation, subjective ratings of pressure before and during the test were documented on a 7-point scale. The increase of systolic blood pressure and the increase of heart rate during test completion was significantly reduced with valerian root extract in contrast to no change without medication. Self-reported pressure immediately before and during the test was decreased significantly with valerian root extract. In all groups task performance was improved in the second test.

These results lead to the assumption that the valerian extract decreases subjective experience of stress (while cognitive performance is not reduced). The significance of the trial is decreased by potential biases due to the lack of blinding and absence of a placebo-group.

- Sleeplessness in patients suffering from fibromyalgia

The study of Ammer & Melnizky (1999) investigates whirl baths with plain water or with water containing valerian have a different influence on pain, disturbed sleep or tender point count. A randomized, comparative and investigator-blinded study was performed. Out-patients with generalized fibromyalgia were randomized. Therapy consisted of either whirl bath with plain water or with the addition of valerian. The baths were carried out 10 times, three times a week. 30 out of 39 patients included in the study were evaluated statistically. After treatment with valerian bath (n=12) well-being and sleep were significantly improved and also the tender point count decreased significantly. Whirl bath in plain water (n=11) reduced general and maximum pain intensity significantly.

- Review on insomnia

The review of Stevinson & Ernst (2000) gave an overview of nine published randomised, clinical trials summarizing the evidence for valerian as inconclusive and demanding rigorous trials to determine its efficacy. The following studies that were not included in the review are included in this assessment report: Coxeter *et al.* (2003); Cropley *et al.* (2002); Diaper Hindmarch (2004); Donath *et al.* (2000); Dorn (2000); Hallam *et al.* (2003); Ziegler *et al.* (2002).

The above-mentioned review evaluates only randomised clinical trials. Valerian root and its preparations belong to the herbal substances and preparations with well-established medicinal use, therefore a larger body of evidence is to be assessed. According to Part II.1 of Annex I to Directive 2001/83/EC as amended on well-established-medicinal use, "…'bibliographic reference' to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy…".

A further problem of the above mentioned review is that the randomised clinical trials (RCTs) were not separately evaluated regarding the different herbal preparations used. Most of the assessed RCTs were performed with aqueous extracts of valerian root with the content mentioned as mg extract without any information on DER, so that the recalculation of the amount of herbal substance used is partly impossible without further information.

Many of the older pharmacodynamic and clinical trials included in the review were done with aqueous extracts of valerian root. Because these data were not convincing to the HMPC, herbal teas and aqueous dry extracts were included in the 'traditional use' part of the monograph. Regarding these extracts, this assessment is concordant with the review of Stevinson & Ernst, 2000. Some pharmacodynamic trials (i.e. Diaper & Hindmarch (2004); Donath et al. (2000); Dorn (2000); Schulz et al. (1994); Vorbach et al. (1996); Ziegler et al (2002)) were also performed using ethanolic extracts of valerian root supporting the inclusion of these herbal preparations in the "well-established use" part of the monograph. Especially the trials published since 2000 are of a better quality, including GCP compliance.

Table 6: Clinical studies on humans (insomnia and nervous tension)

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
ethanolic extracts (DER 3-7:1, extraction solvent 40-70% (V/V))							
Vorbach *et al*., 1996	double-blind placebo-controlled cross-over study; 28 weeks explorative	placebo verum: 600 mg extract/day, corresponding to 1.8-4.2 g of the herbal substance/day oral once daily in the evening	121 patients (71 female, 50 male) average age = 47 years	non-organic insomnia (ICD-10)	3 validated questionnaires: Clinical Global Impression (CGI)) – significant improvement after 2, more pronounced after 4 weeks sleeping questionnaire B according to Goertelmeyer, Form B3 (SF-B) + self-rating scale according to "Zerssen" "Befindlichkeits" Mood Scale (Bf-S) = confirmation of positive trend a global rating of efficacy and tolerability by physician and patient: "very much better" or "much better" in 55.9 % of cases (placebo 25.9 %)	no confirmatory statistical evaluation	explorative study showing a pronounced effect after 4 weeks regarding the sleep quality (SF-B (0-4 wk; $p \leq 0.05$), according to patients and therapists assessment, low number of adverse effects 3/121 patients

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
Donath *et al*., 2000	double-blind randomised placebo-controlled cross-over study; max. 2 week	placebo verum: 600 mg extract/day, corresponding to 3 g of the herbal substance/day oral single and multiple dose	16 patients (4 male, 12 female) median age = 49 years (range: 22-55 years)	psychophysiological insomnia (ICSD-code 1.A.1.)	polysomnographic recordings; sleep efficiency; sleep-stage analysis; arousal index (scored according to ASDA criteria, 1992); subj.: sleep quality, morning feeling, daytime performance, subjectively perceived duration of sleep latency, and sleep period time	slow-wave sleep latency reduced (21.3 vs. 13.5 min respectively, ($p<0.05$)	single dose ineffective; low number of adverse events during the valerian treatment periods (3 vs. 18 in the placebo period)
Dorn, 2000	double-blind randomised study; non-inferiority-trial	reference: 1 x 10 mg oxazepam verum: 600 mg extract, corresponding to 1.8-3.6 g of the herbal substance oral once daily in the evening	75 patients mean age = 52±12 years	non-organic insomnia (ICD-10, F51.0)	main efficacy parameter: Goertelmeyer Sleep Questionnaire B (SF-B) + well-being scale according to von Zerssen (Bf-S) + Hamilton Anxiety Scale (HAMA) = both groups improved distinctly sleep-rating by the physician improved	confirmatory testing with variance analysis for repeated measures (repeated measures ANOVA); one-sided difference α niveau 5%	valerian treatment is not superior to oxazepam treatment; the efficacy seems to be similar according to exploratory analysis

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
Cropley *et al*., 2002	open, randomised study; test before and after one week intake	Placebo verum: 600 mg extract/day, corresponding to 2.7 g herbal substance/day	44 students	healthy subjects in stress situation	colour/interference test with increasing speed of presentation; blood pressure and heart rate increase of systolic blood pressure and increase of heart rate during test completion significantly reduced with valerian extract		supportive for mild tension
Ziegler *et al*., 2002	double-blind randomised multi-center study; non-inferiority-trial 6 weeks	reference: 1 x 10 mg oxazepam verum: 600 mg extract, corresponding to 1.8-3.6 g of the herbal substance oral once daily in the evening	186 patients (125 female, 61 male) mean age = 52 (range:18-73 years)	non-organic insomnia (ICD-10, F51.0)	main efficacy parameter: Goertelmeyer Sleep Questionnaire B (SF-B), (item quality of sleep) = improvement in both groups secondary efficacy parameters: other SF-B items (psychic exhaustion in the evening, feeling of refreshment after sleep, psychosomatic symptoms in the sleep phase, duration of sleep) + Clinical Global Impressions	quality of sleep increased = one-sided confidence interval within the limit for non-inferiority (<0.2) for the ITT-population; other SF-B items comparable improvement (<0.2)	valerian treatment is not inferior to oxazepam treatment with the non-inferiority limit of <0.2

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
					Scale (CGI) = comparable improvement global rating of efficacy and tolerability by investigator and patient: 30.4% in verum-group, 23.6% in oxazepam-group		
Diaper & Hindmarch, 2004	double-blind placebo-controlled crossover trial	single dose verum: 300 mg or 600 mg extract, corresponding to 1.35 or 2.7 g of the herbal substance	16 patients (age 50-64 years)	mild sleep-disturbancies	sleep EEG parameters and several psychometric tests, no group differences were stated	descriptive statistics	single dose, too small to reach significance tendency to increased drowsiness with the higher valerian root dose
other extracts							
aqueous extracts							
Leathwood *et al*., 1982	open	each patient received 3 nights 400 mg aqueous extract/night and 3 nights combination product and 3 nights placebo	128 patients	insomnia	sleep latency; sleep quality; night awakenings; dream recall; somnolence		supportive

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		randomly given oral					
Leathwood & Chauffard, 1982/83	open single dose	400 mg of an aqueous valerian root extract (DER 3:1), corresponding to 1.2 g of the herbal substance	10 healthy subjects	healthy	sleep latencies and night awakenings, and improved sleep quality EEG study shorter mean sleep latency, increased mean latency to first awakening)	not significant	too small, therefore no significance
Kamm-Kohl *et al*., 1984	double-blind placebo-controlled 2 weeks	placebo verum: 3 x 90 mg extract (DER 5-6:1), corresponding to 1.35-1.62 g herbal substance	78 hospitalised patients (59 female, 19 male) age: 61-79 years	nervous mood and behavioural disorders	Zerssen's Mood Scale (Bf-S): total score fell by 10.5 points (valerian) and by 4.5 points (placebo) Nurses' Observation Scale for In-patient Evaluation (NOSIE): total score on increased by 22.6 (valerian) and by 6.8 points (placebo). symptoms "difficulty in falling asleep" and "difficulty in sleeping through the night" improved significantly	p<0.01, t-test) p<0.01, t-test p<0.001	

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					under valerian the symptom of rapid exhaustion showed significant improvements in favour of valerian	$p<0.02$	
Balderer & Borbely, 1985	open	900 mg aqueous extract oral 5 nights in a sleep laboratory: night 1 without medication night 2 and 3 placebo night 4 extract night 5 placebo	8 healthy subjects (4 female, 4 male) in laboratory (average age 22.6 years)	healthy subjects without major sleep disorders	Questionnaires, self-rating scales, night time motor activity; polygraphic sleep recording Sleep EEG Valerian reduced sleep latency and wake time after sleep onset		supportive
Schulz *et al*., 1994	double-blind placebo-controlled parallel-group trial oral 8 days	placebo verum: 3 x 405 mg extract/day, corresponding to 6.075-7.29 g of the herbal substance/day	14 (female) (verum n=8, placebo n=6) average age: 61.6±6.5 years	poor sleepers	polysomnography N0, N1, N2 in weekly intervals; increase in SWS	reduction in sleep stage 1 from 16.4% to 11.9%; increase in sleeping phase 3 from 6.5% to 10.2%; increase in total sleeping phases 3 and 4 from	too small to grant significance, explorative

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
						7.7% to 12.5% (p=0.0273, in each case) under active treatment	
Pakseresht *et al.*, 2011	double-blind randomized study; 8 weeks	placebo verum: 765 mg dry extract (DER: 7.1:1)/day, corresponding to 5.431 g herbal substance/day	31 patients with OCD; 16 Verum	Obsessive compulsive disorder	Y-BOCS	ANOVACI 95%	decrease not clinically relevant; does not support a specific indication
other/undefined preparations –and different indications							
Kohnen & Oswald, 1988	double-blind placebo-controlled study	reference: 1 x 20 mg propanolol (n=12) verum 1: 1 x 100 mg valerian root extract (no further data) (n = 12) verum 2: 1 x 100 mg valerian root extract + 20 mg	48 young subjects (24 female, 24 male); age: 19-29 years	healthy	stress situation provoked by a mathematical task were investigated 90 or 120 min after administration	no statistical significance	supportive for mild tension

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		propranolol					
Schulz & Jobert, 1995	placebo-controlled; crossover study	placebo verum 1: 10 mg diazepam verum 2: 1,200 mg of a valerian root extract (DER 3-7:1, extraction solvent not specified), corresponding to 3.6-8.4 g herbal substance	24 females	sleep disorders	EEG showed an increase in relative power in the delta and theta frequency	no information on statistical methods	supportive
Schulz et al., 1998	double-blind placebo-controlled study; crossover design; single dose	reference: 10 mg diazepam verum: 1,200 mg valerian root extract (DER 5-7:1, extraction solvent not specified) corresponding to 6.0-8.4 g of the herbal substance	12 adult female	healthy	EEG: increase of power in the delta and theta band and a decrease in the beta band		quant. EEG analysis and self-assessment can help to identify mild sedating effects
Coxeter *et al*., 2003	Placebo-controlled randomised "n-of-I"	placebo verum: 450 mg of valerian extract (extraction	42 patients	insomnia	revealed a positive trend, but no significant superiority of valerian root versus placebo of	Student´s t-test Fisher´s exact t-test	undefined extract trial too small revealed a

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	trials 3 weeks	solvent not given), corresponding to 2 g herbal substance			treatment The sleep diary consisted of 6 outcome variables (latency to sleep, number of night awakenings, total sleep time, quality of sleep, level of perceived refreshment post-slumber, energy level in the previous day).	α=0.05 hierarchian Bayesian model 95% CI	positive trend, but no significant superiority of valerian root vs placebo no significant difference between side effects regarding number, distribution and severity
Jacobs *et al.* 2005	double blind randomised placebo-controlled Internet-based study; 4 weeks	placebo verum: valerian root (6.4 mg of valerenic acids/daily; no further specification)	270 patients (135 in each group)	anxiety and insomnia	validated Insomnia Severity Index (ISI): valerian not better than placebo	X^2 test for categorical data ANOVA for continuous data ($p<0.05$)	no significance regarding the treatment groups valerian/ placebo with a standardized unspecified extract
Taibi *et al.,* 2009	double-blind randomised	placebo verum:	16 (female) average age:	insomnia	polysomnography (PSG) + self-report	comparing each treatment to	too small to grant

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
	crossover study; 13 day wash out	1 x 300 mg valerian extract, standardized to 0.8% valerenic acid (no further information) 14 days	69.4±8.1 years		no statistically significant differences on any measure of sleep latency, wake after sleep onset (WASO), sleep efficiency, and self-rated sleep quality	baseline in separate comparisons, WASO significantly increased (+17.7±25.6 min, p=.02) after 2 weeks (placebo = +6.8±26.4 min)	significance, explorative
Barton *et al*., 2011	double blind placebo-controlled randomized study; phase III trial 8 weeks	placebo verum: 450 mg root, standardized to 0.8% valerenic acid; before sleep	119 patients with cancer, receiving therapies	cancer under therapy and insomnia	primary end point: AUC Pittsburg Sleep quality index secondary endpoints: Functional outcomes of sleep questionnaire; BFI; POMS	CI 95%	effects on fatigue symptoms; (main aim) not proven
Pinheiro *et al*., 2014	double-blind randomized study single dose	placebo verum: 1 x 100 mg Valerian root (no further information)	20 volunteers, age: 17-31 years	third molar extraction	dental anxiety scale (DAS)	Wilcoxon; CI 95%	authors assessment: 85% of patients calmer; placebo = 45%; p=0.022

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Outcomes (primary and secondary endpoints)**	**Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score** e.g. Jadad score	**Comments on clinical relevance of results**
Oxman *et al.* 2007	double blind randomised placebo-controlled Internet-based study; 2 weeks	placebo verum: 3.6 g herbal substance one hour before bedtime	328 patients (164 in each group) (male/female) age: 18-75 years	insomnia	primary end point: minimal improvement on 7 point Likert Scale (self-reporting (valerian group=29%, placebo group=21%, not statistically significant); on the global self-assessment questionnaire 5.5% more participants in the valerian group perceived sleep as better or much better (p=0.04); similar trends for night awakenings (difference = 6.0%, 95% CI-0.5 to 12.5) and sleep duration (difference = 7.5%, 95% CI-1.0 to 16.1)	CI 95%	slight improvement not statistically significant

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

No controlled clinical trials have been performed with valerian root in children, and only limited experience in drug monitoring trials has been published.

A drug monitoring trial with an aqueous-ethanolic dry extract (DER 3-6:1, extraction solvent: ethanol 70% V/V) was carried out in 130 children, who suffered from restlessness and/or difficulty in falling asleep due to nervousness (Hintelmann, 2002). Duration of treatment was at least 2 weeks, in 97 patients the treatment continued for more than 4 weeks. 103 children were in the age group of 6-12 years, in this group the mean daily dose was 600 mg corresponding to 1.8-3.6 g of the herbal substance.

starting dose (mg of herbal substance)	300 mg (0.9-1.8 g)	600 mg (1.8-3.6 g)	900 mg (2.7-5.4 g)	1,200 mg (3.6-7.2 g)
n (age 6-12 years)	40 (38.9%)	42 (40.1%)	12 (11.6%)	9 (9.4%)

The dosage was increased in 8.8% of all cases and reduced in 6.9%. Efficacy was rated after 2 and 4 weeks. There was a clear tendency towards better ratings after 4 than after 2 weeks. After 4 weeks, the parents rated efficacy for children with restlessness alone as "good" or "very good" in 89% of the cases, for children with difficulties in falling asleep alone in 100% and for children with both symptoms in 87%. Pre-existing accompanying symptoms like gastrointestinal complaints, tiredness during daytime and fatigue were also improved or disappeared in a high proportion of patients.
Although the treatment results may be due to a placebo effect in a substantial proportion of patients, in view of the positive feedback by parents and physicians the treatment can be considered as a useful alternative to chemically defined compounds in both indications 'relief of sleep disorders' and 'relief of mild nervous tension'.

In an open multicenter observational study n=918 children ≤12 years (n=720 ≥6 years; n=198 <6 years) have been treated with a combination product (coated tablets containing 160 mg valerian root dry extract (DER 4-5:1, extraction solvent: ethanol 70% (V/V) + 80 mg lemon balm dry extract (DER 4-6:1, extraction solvent: 30% ethanol (V/V)) for 4 weeks ±1 week. 80% of the children ≥6 years received the full adult dose without any tolerability problems. The study can be accepted to support the use of valerian root extract as a single active substance in children ≤12 years of age concerning tolerability regarding reduced doses of 2/3 of the adult dose. The indication of restlessness and sleeping problems covers developmental particularities in children, due to which data on efficacy in children of the different age groups ≤12 years are necessary (Müller & Klement, 2006).

As yet, no satisfactory long-term treatment exists for intransigent sleep difficulties in children with an intellectual deficit ID. Five children with varying intellectual deficits and different primary sleep problems underwent 8 continuous weeks of monitoring via sleep diaries, adhering to a double blind, placebo controlled and randomised design with an valerian root extract. Compared to baseline and placebo, valerian treatment led to significant reductions in sleep latencies and nocturnal time awake, lengthened total sleep time and improved sleep quality. The treatment was apparently most effective in children with deficits that involved hyperactivity (Francis & Dempster, 2002).

4.4. Overall conclusions on clinical pharmacology and efficacy

Valerian root and its preparations seems to improve sleep structure with a gradual onset of efficacy rather than to exert a general sedating effect. After single intake valerian root changed mainly

subjective perception of sleep, while sleep EEG changes were more pronounced after several days of intake. These observations are in concordance with clinical experiences showing a gradual improvement of symptoms over 2-4 weeks. Valerian root probably exerts its effects in pathological conditions rather than in healthy volunteers.

For the clinical use of valerian root, a substantial body of general evidence is available from handbooks, expert reports etc. Valerian root has been used for centuries in many countries. Additional evidence results from several randomised, controlled, double-blind clinical trials, partly with EEG-recordings. Taking into account these clinical trials, the indication "relief of sleep disorders" is based on level Ib evidence and the indication "relief of mild nervous tension" on level III evidence.

All together, the evidence available from literature and from clinical trials with valerian root extracts in adults confirms that aqueous-ethanolic extracts of valerian root have a clinical effect in sleep disturbances as assessed by subjective ratings as well as by means of validated psychometric scales and EEG-recordings. These extracts may be more efficacious in elder patients, who consider themselves poor and irregular sleepers. Mild acute sedating effects have been observed in safety trials and sleep laboratory investigations. There is quite strong evidence both from clinical experience and sleep-EEG studies that the treatment effect increases during treatment over several weeks. Important questions remain open concerning for examples optimal dosage and appropriate duration of treatment. Long-term studies have not been performed. It must be pointed out that there is a general discrepancy between the typical duration of use of hypnotics as revealed in epidemiological studies and the typical medication period in clinical trials. No consensus exists that long-term studies should be done with hypnotic medicinal products, since these would carry a hazard for the patients due to the dependency risks for most products (Angst *et al.*, 1995).

The results of the trials of Cropley *et al.* (2002) and Kohnen & Oswald (1988) provide supportive information to the indication 'mild nervous tension´ for which only limited evidence comes from clinical studies in patients.

The clinical trial of Barton *et al.* (2011) does not cast doubt on the efficacy of the valerian extracts due to the difference in between the preparations used and the different clientele.

The trial in elderly women of Taibi *et al.* (2009) without results does not relativize the efficacy of hydroethanolic extracts containing valerian root due to low amounts of the extract given, short duration of the study and lacking information on the manufacturing procedure of the herbal supplement tested, which was standardized to valerenic acid.

The 8-week pilot double-blind randomized trial of Pakseresht *et al.* (2011) is the first clinical trial regarding the efficacy of an aqueous extract of *Valeriana officinalis* on obsessive-compulsive disorder. The daily dosage of 5.46 g herbal substance lies distinctly below most of the traditional posologies. The OCD indication is not acceptable, further studies are needed.

A single oral dose of either Valerian root (100 mg) or placebo was randomly administered 1 h before third molar extraction to 20 volunteers. Anxiety level was assessed by physiological parameters (blood pressure and heart rate) and the observation of signs. The patients treated with Valerian were calmer and more relaxed during surgery. (Pinheiro *et al.*, 2014) These preliminary data with lacking extract specifications need further evaluation.

The meta-analysis from Bent *et al.(*2006) does not differentiate between preparations with valerian root as a single active ingredient and combinations and does not consider the different manufacturing procedures of the preparations. Therefore the review does not contribute to this evaluation of data.

The Cochrane Review from Miyasaka *et al.* (2006) does not consider the different specifications of valerian root containing preparations and focusses on anxiety disorders. The lacking difference

between verum and placebo regarding the changes on HAM-A Score in one included clinical trial does not contribute to this assessment.

Although promising results with use of valerian root extracts in children have been published, the data are still too scarce to justify a general recommendation. A recommendation for use of medicinal products containing valerian root in children below the age of 12 years should be substantiated by specific clinical experience. There is no need for clinical trials or specific warnings for adolescents between 12 to 18 years of age taking into account the excellent tolerability of valerian root and its preparations.

5. Clinical Safety/Pharmacovigilance

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

In view of the assumed sedative effects, several trials with valerian root extracts were undertaken to investigate a possible influence of valerian root extract on the vigilance:

A randomised, controlled, double-blind trial was performed on 102 male and female volunteers to determine whether reaction time, alertness and concentration might be impaired by treatment with a native valerian root extract (VRE). The effect was first examined the morning after a single evening dose of VRE (600 mg, DER 3-6:1, extraction solvent: ethanol 70% (V/V) vs. flunitrazepam (FNZ) (1 mg) and placebo (PL) (trial section A), and then after two weeks of evening administration of VRE vs. PL (trial section B). 99 volunteers were analysed in section A and 91 in section B. The primary criterion was the median of reaction time (MRT) measured with the Vienna Determination Test. Secondary criteria were cognitrones (alertness test), tracking test (two-handed co-ordination), sleep quality (VIS-A, Vis-M), further VDT parameters, and safety criteria. The single administration of VRE did not impair the reaction abilities, concentration and co-ordination. After 14 days of treatment, the equivalence of VRE and PL was proven by confirmative analysis concerning the improvement of MRT (p=0.4481). Evaluation of the secondary criteria were consistent with the results of the primary criterion. The authors concluded that neither single nor repeated evening administrations of 600 mg of VRE have a relevant negative impact on reaction time, alertness and concentration the morning after intake. (Kuhlmann *et al.*, 1999).

In a double-blind trial the authors compared the cognitive and psychomotor effects, in 9 healthy volunteers, of single doses of an ethanolic extract (DER 4:1, extraction solvent: ethanol 70%) corresponding to 1.6 g or 3.2 g valerian root, 0.25 mg triazolam and placebo (Hallam *et al.,* 2003). Several cognitive and computer based attentional tasks revealed that performance was significantly worse with triazolam than with both valerian root doses and placebo, accompanied by a marked increase in mental sedation. No sedation was observed after intake of valerian root.

A double-blind, randomized, crossover, placebo-controlled study was performed to assess the comparative pharmacodynamics of single doses of temazepam (15 and 30 mg), diphenhydramine (50 and 75 mg), and valerian (400 and 800 mg, not further information) in 14 healthy elderly volunteers (mean age: 71.6 years; range: 65-89). Assessments were made at 0, 0.5, 1, 2, 3, 4, 6, and 8 h post-dosing with use of validated measures of subjective sedation and mood (visual analogue scales, Tufts University Benzodiazepine scale) and psychomotor performance (manual tracking and digit symbol substitution tests). Temazepam had dose-dependent effects on sedation and psychomotor ability with a distinct time course. Temazepam 30 mg had the most detrimental effect on psychomotor ability ($p<0.001$ compared with all other treatments). Temazepam 30 mg and both doses of diphenhydramine elicited significantly greater sedation than placebo ($p<0.05$, all), and temazepam had the greatest effect. There was no difference in sedation scores between 50 and 75 mg diphenhydramine. Sedative

effects were slightly lesser with 15 mg temazepam and were not significant in comparison with placebo. Psychomotor impairment was evident after administration of 75 mg diphenhydramine in comparison with placebo on the manual tracking test ($p<0.05$); this was less than the impairment with 30 mg temazepam ($p<0.001$) but similar to that with 15 mg temazepam (NS). No psychomotor impairment was detected with 50 mg diphenhydramine. Valerian was not different from placebo on any measure of psychomotor performance or sedation (Glass *et al*., 2003)

A valerian root extract (not further information) in liquid form was tested with regard to a "hangover" effect (Phase A) as well as with regard to an acute sedative effect (Phase B) in subjects without sleeping disorders. To test the "hangover effect" (Phase A), four groups, each with 20 subjects (age 20-30 years), received 1 x 10 ml = 800 mg of the valerian root preparation (equivalent to 4 g valerian root) or 1 x 1 mg flunitrazepam or 1 x 600 mg of a valerian root-combination preparation (sugar coated tablet) or 1 x placebo at a given time of night. Eight hours after taking the preparation, apparative test diagnostics were performed and subjective feelings were monitored in the laboratory. A mild "hangover" effect on the morning after medication was shown with flunitrazepam for two test parameters. While the usual learning effect occurred under both phytopharmaceuticals and placebo, this effect was not observed under flunitrazepam. With flunitrazepam, the subjects felt tired, unsteady on their legs, unconcentrated, less able to perform, sedated and less well than in the other groups. There was no evidence of a "hangover" effect with the valerian root mono-preparation, the subjects felt more "active" compared to placebo. The subsequent test for a sedative acute effect (Phase B) was performed with three groups each with 12 subjects, who took the test one hour after taking 1 x 800 mg of the liquid valerian root mono-preparation or 1 x 600 mg of the combination preparation or 1 x placebo in the morning. The valerian root mono-preparation led to measurable decreases in vigilance (more erroneous reactions and fewer correct signal detections) ($p<0.05$ vs. placebo) 1-2 h after taking the preparation; with regard to the subjective measures, the subjects had "wobbly legs" and felt less active ($p=0.01$ vs. placebo) (Gerhard *et al.*, 1996).

Table 7: Clinical safety data from clinical trials

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Adverse reactions**	**Comments on clinical relevance of results**
hang over effect Gerhard *et al.,* 1996	placebo-controlled study single dose	800 mg valerian root preparation, corresponding to 4 g herbal substance vs. 1 x 1 mg flunitrazepam vs. 1 x 600 mg of a valerian root-combination preparation	80 volunteers (4 groups á 20)	healthy	none	no evidence of a "hangover" effect with the valerian root mono-preparation
hang-over effect Kuhlmann *et al.,* 1999	double-blind controlled randomised, trial 7 day wash out 14 days	600 mg valerian root extract/day	102 volunteers	healthy	none	reaction time, attention and co-ordination capacity unchanged

Type (aim) and objective(s) of Study Reference	**Study Design and Type of Control Study duration (if available)**	**Test Product(s): herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment**	**Number of Subjects (including age, sex, drop out)**	**Healthy Subjects or Diagnosis of Patients (inclusion criteria)**	**Adverse reactions**	**Comments on clinical relevance of results**
sedation after single dose Hallam *et al.*, 2003	double-blind controlled randomised, trial single dose	ethanolic extract (DER 4:1, extraction solvent: ethanol 70%) corresponding to 1.6 g or 3.2 g herbal substance	9 volunteers	healthy	none	no sedation after valerian
Glass *et al.*, 2003	double-blind placebo-controlled randomized crossover study	valerian root 400/800 mg vs. temazepam 15/30 mg vs. diphenhydramine 50/75 mg	14 elderly volunteers	insomnia	none	valerian root not different from placebo on any measure of psychomotor performance or sedation

5.2. Patient exposure

Summarizing the efficacy studies 667 patients received valerian root preparations. Additionally 130 children participated in an observational study.

Aside from market presence and data from studies, there are no concrete data concerning patient exposure.

If patients with known intolerance to *Valeriana officinalis* are excluded, a traditional use is possible if administration follows the instructions as specified in the monograph.

The sales volumes of one valerian root containing HMP (specification according to WEU) from 2005-2009 for 300 mg coated tablets were worldwide 34,669,620 which cover for 15,868 patient years. The sales volumes of another WEU product with a packaging size of 120 coated tablets cover from 2007-2010 180,921 packages (PSUR data, Germany).

From a valerian root containing HMP (1 coated tablet contains 140 mg dry extract of valerian root, DER 4-6:1, extraction solvent: water) 352,900 packages are sold between 2005-2009 (PSUR data, Germany).

Patients exposure data regarding a valerian oil bath cover 85,714 applications, calculated as 10,000 patients from 2007-2010 (PSUR data, Germany).

5.3. Adverse events, serious adverse events and deaths

A database request in Vigilance Central resulted in 65 case reports connected to medicinal products with one active ingredient containing valerian root. The reported drug reactions range from predominantly suicide attempts with tiredness dizziness and somnolence following a vast cocktail of psychiatric medications due to underlying psychiatric diseases to allergic reactions of the skin. 3 case reports contain nausea and vomiting which might be due to antibiotic co-medication as well.

Three case reports connote a pancreatotoxic risk. One case report (DE-BFARM-07005447) covers a 61-year old women suffering from a Wegener granulomatosis since years. The drug reaction was an acute pancreatitis. She took the following co-medication: folic acid, glimepirid, methotrexatdinatrium, sulfamethoxazol and trimethoprim, decortin, L-thyroxin, amlodipine, hydrochlorothiazide and enalaprilmaleate. Pancreatitis is a listed ADR of sulfamethoxazol and trimethoprim, decortin, and amlodipine in the SmPC, thus these drugs are most likely the trigger of pancreatitis. The patient died from a sepsis due to an intestinal perforation.

Another case (DE-BFARM-06022739) reports an acute pancreatitis for a 36-year old woman, suffering from Crohn´s disease. Co-medication were Pantozol 20 mg/die, MCP, chelidonium extract, *Curcuma xanthorrhiza*, loperamis hydrochloride, *Saccharomyces boulardii*, *Escherichia coli*, desogestrel, ethinylestradiol, metronidazole, tolperisone hydrochloride and mesalazine 500 mg. The pancreatitis started 9 days after the beginning of mesalazine and resolved after disposition of mesalazine. A pancreatitis may be a manifestation of the Morbus Crohn and could be due to the mesalazine treatment (according to SmPC occasionally). Decocq *et al.* (1999) reported 16 cases of mesalazine associated acute pancreatitis from literature, one case with a positive re-challenge.

The third case report (DE-BFARM-07004995) reports an acute pancreatitis for a 77-year old woman with fever, inflammation and increased transaminases. The disease started 22 days after the beginning of a treatment with azathioprine increasing to a dose of 100 mg/day due to an underlying polymyalgia rheumatica. The patient took valerian root 5 once each 6 month. A pancreatitis is listed as occasionally in the SmPC of azathioprine. Co-medication were prednisolone, verapamil hydrochloride, nitroglycerine, ergocalciferole, calcium, torasemide, pantoprazole, nitrendipine, ciprofloxacin

hydrochloride, paracetamole, potassium chloride, metoprolol succinate, MCP, risedronic acid, gabapentine, ASS, latanoprost).

The three reported cases above belong to a case control surveillance study covering all acute pancreatitis patients in 51 Berlin hospitals on more than 200 wards of Internal medicine, Neurology, Psychiatry, Anaesthesiology, Surgery and Orthopedics from 2002 to 2011. 102 patient with acute pancreatitis of unknown origin and 750 control patients were recruited via medical history, clinical data and laboratory data. The statistical analysis of these data showed a positive odds ratio for Valerian root. Therefore a potential risk was postulated as an statistical signal and therefore the case reports are included here (Douros *et al*., 2014*)*.

In the recent review of the clinical efficacy of valerian as a sleep aid for insomnia, results reported in the examined studies indicated that valerian was a safe herb, having only mild neurological and gastrointestinal (GI) symptoms (Taibi *et al.,* 2009). The adverse effects that were reported for ethanolic extracts of valerian included headache, morning hangover, GI complaints such as diarrhea, drowsiness, mental dullness, depression, irritability, dizziness, and nausea. Effects reported with the aqueous extracts included dizziness, significantly increased morning sleepiness with a higher dose (900 mg versus 450 mg), and nausea, while those reported with valepotriate preparations were all GI complaints (indigestion, diarrhea, stomach discomfort, and bitter taste in the mouth) (Taibi *et al*., 2009).

5.4. Laboratory findings

No data available.

5.5. Safety in special populations and situations

5.5.1. Use in children and adolescents

1048 children from 6 to 12 years have been treated with valerian root containing product without safety problems, which can be accepted to cover the safety. However, restlessness and sleep disorders in children of the different age groups can be common symptoms of specific age dependent diseases/conditions (i.e. attention-deficit/hyperactivity disorder (ADHD); developing sleep patterns in toddlers, school problems). They must be differentiated and diagnosed. Therefore general recommendations cannot be given for children below 12 years of age and the following warning is given in the monograph "The use in children below 12 years has not been established due to lack of adequate data."

Adolescents can be treated as adults, they are included into the monograph.

5.5.2. Contraindications

Hypersensitivity to the active substance.

5.5.3. Special Warnings and precautions for use

The use of this product is not recommended in children below the age of 12 years.

For ethanol containing products the appropriate labelling for ethanol, taken from the guideline on excipients, must be included.

5.5.4. Drug interactions and other forms of interaction

The application of valerian root containing preparations may contribute to tiredness dizziness and somnolence when taken in combination with other sedating psychiatric drugs.

Pharmacodynamic interactions of whole extracts or isolated constituents of valerian root with other medicinal products, food or alcohol in man have not been observed. For low-dose valerian root extract (100 mg) and 20 mg propanolol (Kohnen & Oswald, 1988), no interaction could be demonstrated in healthy volunteers. Further interaction studies in humans are not available. Since nonclinical data point to a prolongation of barbiturate sleeping time by co-administration of valerian root, the concomitant intake of synthetic sedatives and valerian root is addressed in the Community herbal monograph under section "4.5 Interactions with other medicinal products and other forms of interactions."

Results of two trials were published recently:

Lefèbre & Foster (2004) investigated interactions of several valerian root preparations available on the U.S. market with CYP3A4 in vitro. The data point to a possible inhibition of CYP3A4-mediated metabolism and P-glycoprotein ATPase activity that could not be correlated to the content of certain constituents.

The influence of an aqueous-ethanolic valerian root extract on the metabolic activity of CYP3A4 and CYP2D6 in humans was investigated in an open crossover trial (Donovan *et al*., 2004). Pharmacokinetic parameters after a single intake of 2 mg alprazolam and 30 mg dextrometorphan (dextrometorphan/dextrorphan ratio) were compared in human volunteers before and after daily intake of 1,000 mg aqueous-ethanolic valerian root dry extract (no further information) over 14 days. The study did not reveal an influence on the CYP2D6 pathway while for CYP3A4 a slight inhibition was shown: C_{max} of alprazolam increased after valerian root extract intake from 25±7 ng/ml to 31±8 vs ($p<0.05$), the AUC at baseline was 88.9% of the AUC after valerian root extract intake (n.s.). The authors rated the magnitude of this moderate increase not as clinically relevant and concluded that valerian root is unlikely to have clinically relevant effects on the disposition of medications primarily dependent on the CYP2D6 or the CYP3A4 pathways.

Gurley *et al.* (2005) confirmed these results in another open crossover trial in 12 young adults for intake of 375 mg/d valerian root extract (DER 4:1, extraction solvent not specified). They found no relevant interaction for CYP1A2, CYP2D6, CAP2E1 and CYP3A4/5.

The results of the well-designed trials by Donovan *et al*. (2004) and Gurley *et al*. (2005) are mentioned in the Community herbal monograph since they give important information on safety of certain co-medications.

The review of Kelber *et al.* (2014a) could not identify studies showing a clinically relevant interaction effect of valerian. This confirms pharmacovigilance reviews of herbal medicinal products, which do not mention valerian at all (Block & Gyllenhaal, 2002*;* Nowack *et al.*, 2011; Paoletti *et al.*, 2011) or claim valerian as safe (Izzo *et al.*, 2012; Steinhoff, 2012).

Additionally Mohamed *et al*. (2010) investigated commonly used herbal supplements including valerian which were screened for their potential to inhibit UGT1A1 activity using human liver microsomes in vitro. The formation of estradiol-3-O-glucuronide, an important glucuronidation enzyme, was used as the index of UGT1A1 activity. The valerian root extract (no further information) showed inhibition of UGT1A1 activity at one or more of the three concentrations tested. A volume per dose index (VDI) was calculated to estimate the volume in which the daily dose should be diluted to obtain an IC_{50}-equivalent concentration. The valerian root extract (Finzelberg) had a VDI value of 1.8 l/dose unit lying below the cut-off point. Further clinical studies are warranted.

5.5.5. Fertility, pregnancy and lactation

In a phase I clinical study, healthy males were administered five tablets of a valerian extract (1 tablet =1 g of dry extract corresponding to 4.4 g of herbal substance, no further information) standardized to 0.43% valerenic acid daily for 10 days (i.e., three times the recommended daily dose). Subjects receiving valerian showed a temporary increase in the percentage of normokinetic spermatozoids and a decrease in diskinetic forms, but these changes had no effect on fertility indices. The fertility parameters measured were the Farris Fertility index, volume of ejaculate, number of spermatozoids in 1 ml of ejaculate, total number of spermatozoids in whole in whole ejaculate, and percentage of normokinetic spermatozoids. In addition, no significant changes in the testicles (i.e., swelling, local hyperemia, dilation of veins, or increase in appendage) were reported (Mkrtchyan *et al.*, 2005).

There is no published evidence for fertility impairment due to valerian root preparations or isolated components. In Australia, valerian root products are classified in category A; this category is applicable for pharmaceuticals, which have been taken by large numbers of pregnant women and women of child-bearing age without an increase in malformations or other direct or indirect teratogenic effects on the foetus being observed (Bos *et al*., 1997).

In a study of all births listed in the Swedish Medical Birth Register from 1995-2004, valerian was one of the most used herbal drugs reported by women during early pregnancy (98 of 811 users) for treatment of insomnia and/or restlessness. No effects were observed on infant characteristics, i.e. prematurity, low birth weight, small for gestational age, large for gestational age, low Apgar scores at 5 min, and congenital malformation (Holst *et al*., 2008)

The text of the monograph under "4.6 Fertility, pregnancy and lactation" is given with "Safety during pregnancy and lactation has not been established. In the absence of sufficient data, the use during pregnancy and lactation is not recommended. No fertility data available."

5.5.6. Overdose

The application of valerian root containing preparations may contribute to tiredness dizziness and somnolence when overdosed.

One case of acute overdose has been reported. An 18-year old student, who took approximately 18.8-23.5 g powdered valerian root (40 to 50 capsules, containing each 470 mg pulverised crude herbal substance) in a suicide attempt, complained of tiredness, abdominal cramps, tightness in the breast, tremor in hands and feet and confusion after 30 min. Three hours after taking valerian root, she was admitted to an emergency out-patient department. The examination showed normal physical findings, apart from a mydriasis and fine hand tremor. ECG, blood count and laboratory parameters including liver values were normal. Tetrahydrocannabinol (THC) was detected in the urine. The patient was treated with active charcoal; the symptoms had completely disappeared after 24 h. The authors ascribed the overdose symptoms to taking valerian root, although the positive proof of THC in the urine could indicate that marihuana abuse also made a contribution. However, THC can often be detected in urine several weeks after last consuming cannabis; the patient denied using cannabis in the previous two weeks (Willey *et al.*, 1995).

As a result of case reports under "4.9 Overdose" in the monograph it is given: "Valerian root at a dose of approximately 20 g caused benign symptoms (fatigue, abdominal cramp, chest tightness, lightheadedness, hand tremor and mydriasis), which disappeared within 24 hours. If symptoms arise, treatment should be supportive."

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

As a result of case reports the text under "4.7 Effects on ability to drive and use machines" is given with "May impair ability to drive and use machines. Affected patients should not drive or operate machinery."

5.5.8. Safety in other special situations

Not applicable.

5.6. Overall conclusions on clinical safety

Approximately 620 patients or subjects received a valerian root extract preparation in the controlled clinical trials (including human pharmacological studies) listed above.

Valerian root preparations were generally well tolerated while in the same studies chemical substances like oxazepam, flunitrazepam, temazepam and diphenhydramine showed typical undesirable effects like drowsiness, fatigue and "hang-over" effects. No typical undesirable effects have been identified for valerian root.

The case report regarding an acute pancreatitis described above does not seem to be related to valerian since the ADR is reported in three SPC´s of the co-medication. Since this case report is part of a case control study a potential pancreatotoxic risk may be observed as a statistical signal, but is not to be entered into the labelling of the monograph due to a lack of sound underlying clinical data.

There is a high exposure to valerian root preparations in the EU Member States: according to data provided by IMS Health, sales in the EU in 2002 exceeded 50 million units. Nearly 50% were sold in Germany. The following adverse events probably linked to the consumption of valerian root have been reported: gastrointestinal symptoms e.g. nausea, abdominal cramps (unknown frequency).

No unequivocal dependencies have been reported. A case of withdrawal symptoms is reported in a 58-year old man with high-output cardiac failure and delirium, who had had a daily consumption of 2.5-10 g valerian root extract over several years. Symptoms improved after application of midazolam (Garges *et al.,* 1998). Another case was reported in a 41-year old woman, who had taken valerian and acetaminophen/hydrocodone "regularly" (Wiener *et al.*, 2003). No details on the preparation and the daily dose are given. In view of the very high consumption of valerian root products worldwide, these case reports are not considered to be a relevant hint for an abuse risk.

No organ toxicities have been observed in connection with valerian root intake.

The case report Willey *et al.* (1995) shows that valerian root is only slightly toxic and the overdose of approximately 20 g valerian root did not lead to any severe clinical symptoms. Many deliberate suicide attempts with similar clinical signs, as mentioned above have been reported since 2006 in Vigilance Central database. Often valerian root containing products are taken in an overdose accompanied by psychiatric medication. Symptomatic treatment leads to a full recovery.

According to the results described above, high doses of valerian root extract may cause a slight sedation during the first few hours after ingestion but in contrast to benzodiazepines valerian root does not reduce vigilance on the next morning when taken in the evening. The corresponding warning (see section "4.7 Effects on ability to drive and use machinery") is recommended in the Community herbal monograph as a general precaution for medicinal products negatively influencing vigilance.

Studies on valerian root as single active substance have not addressed synergistic actions with alcohol. However, data collected for several valerian root combinations, i.e. valerian root and balm (Albrecht *et*

al., 1995), valerian root and hops (Herberg, 1991, Kammerer *et al*., 1996) and valerian root and St. John's wort (Herberg, 1994b), allow to conclude that, unlike synthetic benzodiazepine or barbiturate hypnotics, valerian root does not act synergistically with alcohol.

6. Overall conclusions (benefit-risk assessment)

The herbal substance and its preparations of *Valeriana officinalis* have a positive risk benefit relation due to the minimal adverse events considering the efficacy in WEU. The traditional use is as well to be seen with a positive benefit risk ratio due to minimal risks.

No constituent with known therapeutic activity or active marker can be recognised by the HMPC.

The data on safety are considered sufficient to support a Community list entry for the above mentioned herbal preparations and indications. A Community list entry for all preparations from Valeriana officinalis, radix with traditional use is supported for adolescents over 12 years, adults and elderly for oral and cutaneous use, except for the essential oil, since HMPC/MLWP considered the data from the "bracketing and matrixing concept" not sufficient to proof the safety of the essential oil.

Well-established use:
Data from clinical studies support a well-established-use for

dry extract (DER 3-7:1), extraction solvent ethanol 40-70% (V/V)

Traditional use:
For valerian root and some of its preparations, a tradition within the EU can be claimed for:

a) comminuted herbal substance
b) powdered herbal substance
c) expressed juice from fresh root (1:0.60-0.85)
d) dry extract (DER 4-6:1), extraction solvent: water
e) liquid extract (DER 1:4-6), extraction solvent: water
f) dry extract (DER 4-7:1), extraction solvent: methanol 45% (V/V)
g) dry extract (DER 5.3-6.6:1), extraction solvent: methanol 45% (m/m)
h) liquid extract (DER 1:7-9), extraction solvent: sweet vine
i) dry extract (DER 4-5:1), extraction solvent: ethanol 35% (m/m)
j) liquid extract (DER 1:1), extraction solvent: ethanol 60% (V/V)
k) tincture (ratio of herbal substance to extraction solvent 1:8), extraction solvent: ethanol 60% (V/V)
l) tincture (ratio of herbal substance to extraction solvent 1:10), extraction solvent: ethanol 56%
m) tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 70% (V/V)
n) tincture (ratio of herbal substance to extraction solvent 1:5), extraction solvent: ethanol 60-80% (V/V)
o) dry extract (DER 5.5-7.4:1), extraction solvent: ethanol 70-90% (V/V)
p) essential oil

Indication:

Well-established use:
Herbal medicinal product for the relief of mild nervous tension and sleep disorders.

Traditional use:
Traditional herbal medicinal product for relief of mild symptoms of mental stress and to aid sleep.

The product is a traditional herbal medicinal product for use in the relief of mild symptoms of mental stress and to aid sleep exclusively based upon long-standing use.

Posology:

Well-established use:
Oral use
Adolescents, adults, elderly

single dose: 500-600 mg
For relief of mild nervous tension up to 3 times daily.
For relief of sleep disorders, a single dose half to one hour before bedtime with an earlier dose during the evening if necessary.
maximum daily dose: 4 single doses

Traditional use:

Oral use
Adolescents, adults, elderly (for all preparations)

a) single dose: 0.3-3 g dried valerian root
For relief of mild symptoms of mental stress up to 3 times daily.
To aid sleep, a single dose half to one hour before bedtime with an earlier dose during the evening if necessary.
Herbal tea: 0.3-3 g of the comminuted herbal substance in 150 ml of boiling water as a herbal infusion

b) single dose: 0.76-2.0 g, up to 3 times daily

c) single dose: 10 ml (100% expressed juice)
For relief of mild symptoms of mental stress up to 3 times daily.
To aid sleep, a single dose half to one hour before bedtime with an earlier dose during the evening if necessary.

d) single dose: 420 mg
For relief of mild symptoms of mental stress up to 3 times daily.
To aid sleep, a single dose half to one hour before bedtime with an earlier dose during the evening if necessary.

e) single dose: 20 ml
For relief of mild symptoms of mental stress up to 3 times daily.
To aid sleep, a single dose half to one hour before bedtime.

f) single dose: 144-288 mg
For relief of mild symptoms of mental stress up to 4 times daily.
To aid sleep, a single dose half to one hour before bedtime with an earlier dose during the evening if necessary.

g) single dose: 380-570 mg
For relief of mild symptoms of mental stress up to 3 times daily.
To aid sleep, a single dose half to one hour before bedtime with an earlier dose during the evening if necessary.

h) single dose: 10 ml, up to 3 times daily

i) single dose: 427-599 mg, up to 3 times daily

j) single dose: 0.3-1.0 ml, up to 3 times daily

k) single dose: 4-8 ml, up to 3 times daily

l) single dose: 0.84 ml, 3-5 times daily

m) single dose: 1.5 ml (mental stress); 3 ml (to aid sleep)
For relief of mild symptoms of mental stress up to 3 times daily.
To aid sleep, a single dose half an hour before bedtime.

n) single dose: 10 ml, up to 3 times daily

o) single dose: 322-441.35 mg, up to 3 times daily

p) single dose: 15 mg
For relief of mild symptoms of mental stress up to 3 times daily.
To aid sleep, two single doses half to one hour before bedtime.

Traditional use:

Use as bath additive
Adolescents, adults, elderly (for all preparations)

a) single dose: 100 g for a full bath, up to one bath daily

p) single dose: 240-400 mg for a full bath, up to 3-4 times per week

Annex

List of references