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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

DRAFT

ASSESSMENT REPORT ON *VALERIANA OFFICINALIS* L., RADIX AND *HUMULUS LUPULUS* L., FLOS

DISCUSSION IN WORKING PARTY ON COMMUNITY MONOGRAPHS AND COMMUNITY LIST (MLWP)	January 2008 May 2008 March 2009 May 2009
ADOPTION BY HMPC FOR RELEASE FOR CONSULTATION	14 May 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	15 September 2009

Comments should be provided using this template to hmpc.secretariat@emea.europa.eu
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Note:
This Assessment Report is published to support the release for public consultation of the draft Community herbal monograph on *Valeriana officinalis* L., radix and *Humulus lupulus* L., flos. It should be noted that this document is a working document, not yet fully edited, and which shall be further developed after the release for consultation of the monograph. Interested parties are welcome to submit comments to the HMPC secretariat, which the Rapporteur and the MLWP will take into consideration but no 'overview of comments received during the public consultation' will be prepared in relation to the comments that will be received on this assessment report. The publication of this draft assessment report has been agreed, on an exceptional basis, 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 monograph.

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ASSESSMENT REPORT
FOR HERBAL SUBSTANCE(S), HERBAL PREPARATION(S) OR COMBINATIONS THEREOF WITH WELL-ESTABLISHED USE AND TRADITIONAL USE

BASED ON ARTICLE 10A OF DIRECTIVE 2001/83/EC AS AMENDED

(WELL-ESTABLISHED USE)

BASED ON ARTICLE 16D(1) AND ARTICLE 16F AND 16H OF DIRECTIVE 2001/83/EC AS AMENDED

(TRADITIONAL USE)

Herbal substance(s) (binomial scientific name of the plant, including plant part)	Fixed combinations of *Valeriana officinalis* L., radix (valerian root) and *Humulus lupulus* L., flos (hop strobiles)
Herbal preparation(s)	Dry, liquid and soft extracts
Pharmaceutical forms	Oral administration
Rapporteur	Prof. Dr. A. J. Vlietinck

I. REGULATORY STATUS OVERVIEW[1]

MA: Marketing Authorisation;
TRAD: Traditional Use Registration;
Other TRAD: Other national Traditional systems of registration;
Other: If known, it should be specified or otherwise add 'Not Known'

Member State	Regulatory Status				Comments[2]
Austria	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi
Belgium	☒ MA	☐ TRAD	☒ Other TRAD	☐ Other Specify:	+ Other combi
Bulgaria	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi
Cyprus	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Czech Republic	☒ MA	☒ TRAD	☐ Other TRAD	☒ Other Specify:	+ Other combi
Denmark	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	+ Other combi
Estonia	☐ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	Food suppl.
Finland	☒ MA	☐ TRAD	☐ Other TRAD	☒ Other Specify:	+ Other combi
France	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi
Germany	☒ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi
Greece	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Hungary	☒ MA	☒ TRAD	☒ Other TRAD	☒ Other Specify:	+ Other combi
Iceland	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Ireland	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi
Italy	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	Only food supplements
Latvia	☐ MA	☐ TRAD	☒ Other TRAD	☒ Other Specify:	+ Other combi
Liechtenstein	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Lithuania	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Luxemburg	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Malta	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi
The Netherlands	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Norway	☐ MA	☒ TRAD	☒ Other TRAD	☐ Other Specify:	+ Other combi
Poland	☐ MA	☒ TRAD	☒ Other TRAD	☐ Other Specify:	+ Other combi
Portugal	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Romania	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	
Slovak Republic	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Slovenia	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi
Spain	☐ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	None
Sweden	☐ MA	☒ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi
United Kingdom	☒ MA	☐ TRAD	☐ Other TRAD	☐ Other Specify:	+ Other combi

[1] This regulatory overview is not legally binding and does not necessarily reflect the legal status of the products in the MSs concerned.
[2] Not mandatory field

II. ASSESSMENT REPORT

II.1 INTRODUCTION

II.1.1. Herbal preparations

AUSTRIA

WEU

No	Marketing status	Year	Pharm form	Posology	Indications
1	Aponova Schlaf- und Beruhigungsdragees: 1 coated tablet: 64 mg Valerian extract (3:7:1, ethanol), 40 mg hops extract (6.6-8.4:1, ethanol),	1996	coated tablet	Adults 3 x daily 2-4 tablets, in case to aid sleep 3-5 tablets in the evening	restlessness, anxiety, mild forms of sleep disorders, stage-fright, nervous heart disorders
2	Ardeysedon Dragees: 1 coated tablet: 100 mg Valerian extract (4-7:1, ethanol 70% v/v), 24 mg hops extract (4-8:1, ethanol 40% v/v)	2003	coated tablet	Adults, adolescents and children > 10 years: sleep disorders 2 tablets in the evening; restlessness: max. 3 x daily 2 tablets	restlessness, mild forms of sleep disorders
3	Ardeysedon forte-Dragees: 1 coated tablet: 200 mg Valerian extract (4-7:1, ethanol 70% v/v), 68 mg hops extract (4-8:1, ethanol 40% v/v)	2005	coated tablet	Adults, adolescents and children > 10 years: sleep disorders1 tablets in the evening; restlessness: max. 3 x daily 1 tablet	restlessness, mild forms of sleep disorders
4	Hova Filmtabletten: 1 coated tablet contains: 200.2 mg Valerian extract (4-7:1, ethanol 70% v/v), 45.5 mg hops extract (4-8:1, methanol 40% v/v)	1993	film coated tablet	restlessness: 1-3 times daily 1 tablet; nervous sleep disorders: 2 tablets in the evening (children 6-12 years: 1 tablet)	restlessness, nervous sleep disorders

TU

No	Marketing status	Year	Pharm form	Posology	Indications
1	Bakanasan Baldrian Perlen + Hopfen: 55 mg Valerian extract (3:1, water), 10 mg hops extract (3:1, water)	1991	coated tablet	Sleep disorders 3-5 tablets in the evening; restlessness: 3 x daily 2 tablets	restlessness, mild forms of sleep disorders, nervousness
2	Bakanasan Baldrian-Hopfen-Dragees: 68 mg Valerian extract (3-6:1, ethanol), 16 mg hops extract (4-8:1, water)	2002	coated tablet	Sleep disorders 3 tablets in the evening; restlessness: 3 x daily 2 tablets	to aid sleep, nervousness, restlessness
3	Baldrian Dispert comp. Dragees: 100 mg Valerian extract (ethanol), 24 mg hops extract (ethanol)	1996	coated tablet	2 tablets in the evening	nervous sleep disorders

4	Biogelat Schlafkapseln: 220 mg Valerian extract (6:1, stand. to min. 5% sesquiterpene acids, ethanol), 50 mg hops extract (7.5:1, stand. to min. 0.4% flavonoids, ethanol)	1996	capsule	in the evening 1-2 capsules	nervous sleep disorders
5	Einschlafkapseln Twardy: 100 mg Valerian extract (3-6:1, ethanol), 30 mg hops extract (4-8:1, ethanol)	1993	capsule	3 capsules (children 2 capsules) in the evening	nervous sleep disorders, nervousness
6	Klosterfrau Beruhigungskapseln: 250 mg Valerian extract (), 65 mg hops extract ()	1995	capsule	2-4 times daily 1 capsule, 1 capsule in the evening	restlessness, nervous sleep disorders
7	Luvased Dragees: 75 mg Valerian extract (methanol), 70 mg hops extract (methanol	1994	coated tablet	adults: 1-2 tablets several times; when given in the evenening 2-4 tablets; school children 3 x daily 1 tablet	restlessness, mild forms of sleep disorders, nervousness
8	Sanhelios Einschlaf Kapseln: 100 mg Valerian extract (), 25 mg hops extract ()	1993	capsule	3 x daily 1-2 capsules; or in the evening 2-3 capsules	for sedation, nervous sleep disorders
9	Wellness Baldrian Hopfen forte Kapseln: 220 mg Valerian extract (6:1, stand. to min. 5% sesquiterpene acids, ethanol), 50 mg hops extract (7.5:1, stand. to min. 0.4% flavonoids, ethanol)	1998	capsule	up to 3 x daily 1 capsule, in case of sleep disorders 1-2 capsules in the evening	restlessness, nervous sleep disorders
10	Wellness Baldrian Hopfen Dragees: 60g Valerian extract (4:1), 30g hops extract (5:1)	1990	coated tablet	1-3 x daily 1 tablet; in case of sleep disorders 2-3 tablets in the evening	restlessness, nervous sleep disorders

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

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

Previous documents state a DER of the valerian extract of 5:1 and of the hops extract 5,5:1. It is not clear for me whether the company changed the specification of the extracts recently or they made a correction to the actual conditions in the manufacturing process.

BELGIUM

WEU

No	Marketing status	Year	Pharm form	Posology	Indications
1	Peroben tablets 1 tablet contains 250mg valerian root dry extract(4.5:1, methanol 50%, v/v) and 65 mg hops dry extract (4:1, methanol 50% v/v)	2000	coated	Adults, adolescents>12 years, sleep disorders;1-2 tablets in the evening, restlessness ;1-2 tablets 3x daily	Restlessness, nervous sleep disorders

TU

No	Marketing status	Year	Pharm form	Posology	Indications

BULGARIA

WEU

No	Marketing status	Year	Pharm form	Posology	Indications
1	Valerianae radix extractum siccum (4-6:1); Lupuli strobuli extractum siccum (5-7:1); extraction solvent: methanol 45%	2003	film coated tablets	Adults take two tablets with some liquid one hour before going to bed. Children 6 years and older get half the dosage, i.e. 1 tablet.	Difficulties in falling asleep and sleeping through the night as well as uneasy sleep

TU

No	Marketing status	Year	Pharm form	Posology	Indications

CZECH REPUBLIC

WEU

No	Marketing status	Year	Pharm form	Posology	Indications

TU

No	Marketing status	Year	Pharm form	Posology	Indications
1	Dry extract from Valerian root, DER 4-7 :1, extraction solvent ethanol 70% (V/V) - 200.2 mg/tbl Dry extract from Hop strobiles, DER 4-8 : 1, extraction solvent methanol 40% (V/V) – 45.5 mg/tbl	1999	por tbl flm	for oral use sleep disturbances: adults - two coated tablets (corresponding to 400.4 mg of Valerian extract and 91 mg of Hop extract) ½ hour before bedtime children over 6 years and adolescents - one coated tablets (corresponding to 200.2 mg of Valerian extract and 45.5 mg of Hop extract) ½ hour before bedtime restlessness, nervosity, anxiety: one tablet (corresponding to 200.2 mg of Valerian extract and 45.5 mg of Hop extract) 3 times daily	therapy of sleep disorders due to nervosity; restlessness, nervosity, anxiety
2	Dry extractfrom Valerian root, DER 4-7 :1, extraction solvent ethanol 70% (V/V) – 60 mg/tbl Dry extract from Hop strobiles, DER 11-14 : 1, extraction solvent ethanol 96% (V/V) – 60 mg/tbl	1993	por tbl flm	for oral use adults 2 – 3 coated tablets (corresponding to 120 – 180 mg of Valerian extract and 120 – 180 mg of Hop extract) 1 hour before bedtime children over 6 years 1 – 2 coated tablets (corresponding to 60 -120 mg of Valerian extract and 60 - 120 mg of Hop extract) 1 hour before bed time	sleep disorders due to restlessness, anxiety, excitement and tension

DENMARK

WEU

No	Marketing status	Year	Pharm form	Posology	Indications
1	Extract of Humulus lupulus (4:1) 50 mg Extract of Radix valeriane (4:1) 50 mg	before 1992	Capsules	2-3 capsules before bedtime	Herbal medicinal product for relief of restlessness and difficulty of falling asleep
2	Extract of Humulus lupulus (5.5:1) 16 mg Extract of Radix valeriane (4.5:1) 68 mg	2000 - 2003	Tablets		

TU

No	Marketing status	Year	Pharm form	Posology	Indications

ESTONIA

WEU

No	Marketing status	Year	Pharm form	Posology	Indications
1	BECALM TBL N30 , food supplement	2005	Tablet	Take one tablet twice a day	Anxiety, nervousness, stress.
2	ABO HOP - VALERIAN CAPSULES N60, food supplement	2005	Capsule	Take two capsules 2-3 times a day or two capsules before bedtime	Nervous sleeping disorders and conditions of unrest

TU

No	Marketing status	Year	Pharm form	Posology	Indications

GERMANY

WEU
ES = extraction solvent

No	Marketing status	Year	Pharm form	Posology	Indications
1	dry extract from Valerianae radix (4-6:1), ES water and dry extract from Lupuli flos (3-6:1), ES water	1976	coated tablet	1 coated tablet contains 80 mg dry extract from Valerianae radix and 20 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 3 coated tablets Indication B) 3 coated tablets 1/2 - 1 h before bedtime. If necessary, additionally 3 coated tablets earlier in the evening.	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
2	dry extract from Valerianae radix (6-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (11-14:1), ES ethanol 96% V/V	1976	coated tablet	1 coated tablet contains 225 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication A) 1-3 x daily 1 coated tablet Indication B) 1-2 coated tablets 1/2 - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
3	dry extract from Valerianae radix (4-6.7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4.3-7.7:1), ES ethanol 40% V/V	1976	coated tablet	1 coated tablet contains 100 mg dry extract from Valerianae radix and 24 mg dry extract from Lupuli flos Indication B) 2 coated tablets 1/2 - 1 h before bedtime If necessary, additionally 2 coated tablets earlier in the evening	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
4	dry extract from Valerianae radix (5.5-7.4:1), ES ethanol 85% V/V and dry extract from Lupuli flos (9-11:1), ES ethanol 90% V/V	1976	coated tablet	1 coated tablet contains 77 mg dry extract from Valerianae radix and 18.8 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime. If necessary, additionally 2 coated tablets	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling

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

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

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

17	dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli flos (4-8:1), ES methanol 40% V/V	1976	soft capsule	1 soft capsule contains 100 mg dry extract from Valerianae radix and 25.02 mg dry extract from Lupuli flos Indication A) 1- 3 x daily 2 soft capsules Indication B) 2 soft capsules ½ - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
18	dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1976	soft capsule	1 soft capsule contains 100 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication B) 2 soft capsules 1/2 - 1 h before bedtime	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
19	dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1976	soft capsule	1 soft capsule contains 100 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication B) 2 soft capsules 1/2 - 1 h before bedtime	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
20	dry extract from Valerianae radix (3-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1976	coated tablet	1 coated tablet contains 100 mg dry extract from Valerianae radix and 24 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
21	dry extract from Valerianae radix (5.3-6.6:1), ES methanol 45% m/m and dry extract from Lupuli flos (5.5-6.5:1), ES water	1976	coated tablet	1 coated tablet contains 187 mg dry extract from Valerianae radix and 45 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep

22	dry extract from Valerianae radix (5-8:1), ES methanol 45% m/m and dry extract from Lupuli flos (7-10:1), ES methanol 45% m/m	1976	film-coated tablet	1 film-coated tablet contains 187 mg dry extract from Valerianae radix and 41.88 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 film-coated tablet Indication B) 1 film-coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 film-coated tablet earlier in the evening	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
23	dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1976	soft capsule	1 soft capsule contains 100 mg dry extract from Valerianae radix and 25.02 mg dry extract from Lupuli flos Indication A) 2-3 x daily 2 soft capsules Indication B) 2 soft capsules 1/2 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
24	dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1976	soft capsule	1 soft capsule contains 100 mg dry extract from Valerianae radix and 30 mg dry extract from Lupuli flos Indication B) 2 soft capsules 1/2 - 1 h before bedtime	Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
25	dry extract from Valerianae radix (5.3-6.6:1), ES methanol 45% m/m and dry extract from Lupuli flos (5.5-6.5:1), ES water	1976	coated tablet	1 coated tablet contains 187 mg dry extract from Valerianae radix and 45 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 coated tablet earlier in the evening	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
26	dry extract from Valerianae radix (4-6.7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4.3-7.7:1), ES ethanol 40% V/V	1976	coated tablet	1 coated tablet contains 100 mg dry extract from Valerianae radix and 32 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen"

				before bedtime	Herbal medicinal product for the relief of difficulty in falling asleep
27	dry extract from Valerianae radix (3-6:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1976	coated tablet	1 coated tablet contains 68 mg dry extract from Valerianae radix and 16 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 3 coated tablets Indication B) 3 coated tablets 1/2 - 1 h before bedtime If necessary, additionally 2 x 3 coated tablet earlier in the evening	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
28	dry extract from Valerianae radix (5.3-6.6:1), ES methanol 45% m/m and dry extract from Lupuli flos (5.5-6.5:1), ES water	1976	coated tablet	1 coated tablet contains 187.5 mg dry extract from Valerianae radix and 45 mg dry extract from Lupuli flos Indication A) 1 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
29	dry extract from Valerianae radix (4-7:1), ES methanol 45% V/V and dry extract from Lupuli flos (4-8:1), ES methanol 40% V/V	1976	soft capsule	1 soft capsule contains 100 mg dry extract from Valerianae radix and 25.02 mg dry extract from Lupuli flos Indication A) 1- 3 x daily 2 soft capsules Indication B) 2 soft capsules ½ - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
30	dry extract from Valerianae radix (4-6.7:1), ES methanol 45% V/V and dry extract from Lupuli flos (7.7-9.5:1), ES methanol 45% m/m	1976	soft capsule	1 soft capsule contains 200 mg dry extract from Valerianae radix and 35 mg dry extract from Lupuli flos Indication A) 2 x daily 1 soft capsule Indication B) 1 soft capsule 1/2 - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling

					asleep
31	dry extract from Valerianae radix (4-6.7:1), ES methanol 45% V/V and dry extract from Lupuli flos (4.3-7.7:1), ES methanol 40% V/V	1976	coated tablet	1 coated tablet contains 200 mg dry extract from Valerianae radix and 48 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
32	dry extract from Valerianae radix (4-6:1), ES water and dry extract from Lupuli flos (3-6:1), ES water	1976	coated tablet	1 coated tablet contains 160 mg dry extract from Valerianae radix and 40 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime. If necessary, additionally 2 coated tablets earlier in the evening.	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
33	dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1996	coated tablet	1 coated tablet contains 100 mg dry extract from Valerianae radix and 24 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 2 coated tablets Indication B) 2 coated tablets 1/2 - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
34	dry extract from Valerianae radix (4-5:1), ES methanol 51.25% V/V and dry extract from Lupuli flos (3.4-4.2:1), ES methanol 51.25% V/V	1993	soft capsule	1 soft capsule contains 250 mg dry extract from Valerianae radix and 65 mg dry extract from Lupuli flos Indication A) Up to 2 x daily 1 soft capsule Indication B) 1 soft capsule 1/2 - 1 h before bedtime	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep

35	dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1998	coated tablet	1 coated tablet contains 200 mg dry extract from Valerianae radix and 68 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 coated tablet earlier in the evening	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep
36	dry extract from Valerianae radix (4-7:1), ES ethanol 70% V/V and dry extract from Lupuli flos (4-8:1), ES ethanol 40% V/V	1998	coated tablet	1 coated tablet contains 200 mg dry extract from Valerianae radix and 68 mg dry extract from Lupuli flos Indication A) Up to 3 x daily 1 coated tablet Indication B) 1 coated tablet 1/2 - 1 h before bedtime If necessary, additionally 1 coated tablet earlier in the evening	Indication A) "Unruhezustände" Herbal medicinal product for the relief of mild nervous tension. Indication B) "nervös bedingte Einschlafstörungen" Herbal medicinal product for the relief of difficulty in falling asleep

TU

ES = extraction solvent

No	Marketing status	Year	Pharm form	Posology	Indications
1	dry extract from Valerianae radix (4-6.7:1), ES ethanol 40% V/V and dry extract from Lupuli flos (4.3-7.7:1), ES ethanol 40% V/V	1976	coated tablet	for oral use in adults and adolescents over 12 years 1 coated tablet contains 32 mg dry extract from Valerianae radix and 9 mg dry extract from Lupuli flos 2-3 x daily 1 coated tablet	"Traditionell angewendet zur Besserung des Befindens bei nervlicher Belastung. Diese Angabe beruht ausschließlich auf Überlieferung und langjähriger Erfahrung." Traditional herbal medicinal product for support of mental relaxation. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use
2	liquid extract (1:6.3) from a mixture of Valerianae radix : Lupuli flos (1:1), ES ethanol 40% V/V	1976	oral liquid	for oral use in adults 3 x daily 20 ml containing 12% V/V	"Traditionell angewendet zur Besserung des Befindens bei

				extract	nervlicher Belastung. Diese Angabe beruht ausschließlich auf Überlieferung und langjähriger Erfahrung." Traditional herbal medicinal product for support of mental relaxation. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use
3	soft extract (5-6.7:1) from a mixture of Valerianae radix : Lupuli flos (5.7:1), ES methanol 40% V/V	1976	liquid bath additive	for external use as bath additive in adults and adolescents over 12 years 100 g (= 92.2 ml) bath additive contain 11.7 g soft extract 30 ml liquid bath additive / 120 l water maximal 2 x weekly bath duration 10-20 min bath temperature 34-37ºC	"Traditionell angewendet zur Besserung des Befindens bei nervlicher Belastung. Diese Angabe beruht ausschließlich auf Überlieferung und langjähriger Erfahrung." Traditional herbal medicinal product for support of mental relaxation. The product is a traditional herbal medicinal product for use in specified indications exclusively based on long-standing use

Müller-Limmroth & Ehrenstein (1977)
For the publication the medicinal product “Seda-Kneipp” was used, as referred to in the article. At this time the product was composed as following:
60 mg dry extract of Valeriana (4.5:1); methanol 40% (V/V)
100 mg dry extract from Hop (5:1); methanol 30% (V/V).
Later (1994) the composition was changed. It was now:
77 mg dry extract from Valerian (5.5-7.4:1); ethanol 85% (V/V) 18.8 mg dry extract from Hop (9-11:1); ethanol 90% (V/V).

HUNGARY

WEU

No	Marketing status	Year	Pharm form	Posology	Indications
1	25mg Valeriaenae radix, dry extract ethanolic 70% (V/V), (4-7:1) 100mg Lupuli flos, dry extract methanolic 40% (V/V), (4-8:1) (Hovaletten dragées)	1996	film coated tablet	Adults: Sleeping disorders: 4-5 db film tablets half an hour before going to bed. Restlessness, nervousness, anxiety: 3 x 1-2 film tablets daily	Sleeping disorders based on nervous condition. Restlessness, nervousness, anxiety
2	200.2 mg Valeriaenae radix, dry extract ethanolic 70% (V/V), (4-7:1) 45.5 mg Lupuli flos, dry extract methanolic 40% (V/V), (4-8:1) (Hova filmtabl.)	1999	film coated tablet	Adults: Sleeping disorders: 2 db film tablets half an hour before going to bed. Restlessness, nervousness, anxiety: 1-3 x 1 film tablets daily.	Sleeping disorders based on nervous condition. Restlessness, nervousness, anxiety
3	187.5 mg Valerianae rad. dry extr.methanolic 45% , (5-8:1) 42 mg Lupuli strobuli dry extr.methanolic 45% ,(7-10:1) (Béres Redormin filmtabl.)	2003	film coated tablet	Adults: 2 db film tablets an hour before going to bed. This dosage can be enhanced for 3 filmtablets Children: 6 years or above 1 filmtablet Elderly : the same as adults	Sleeping disorders based on nervous condition

TU

No	Marketing status	Year	Pharm form	Posology	Indications
1	80.00 mg Valerianae radix extr. sicc. (4-6:1) extractant: aqua purificata 20.00 mg Lupuli flos extr. sicc. (3-6:1) extractant: aqua purificata (Cirkulin Valerian with hops mite dragées)	1994	film coated tablet	Adults and elderly: 2-3 x 1-2 dragées	Reduces nervousness, tensions, facilitates getting to sleep
2	160.00 mg Valerianae radicis officinalis extr. aqu..sicc. (4-6:1) 40.00 mg Lupulis flos extr. aqu. sicc. (3-6:1) (Cirkulin Valerian with hops forte dragées)	2002	film coated tablet	Adults and elderly: 1-2 x 1 dragées	Reduces nervousness, tensions, facilitates getting to sleep

Additional information:

Sager Pharma/Gebro Pharma (1996) Hova film coated tablets; 220mg valerian root dry extract (4-7:1, ethanol 70% v/v) and 65.0 mg hops dry ectract (4-8:1, methanol 40% v/v).

Finzelberg/Flachsmann
Hova film tablets ; 200.2 mg valerian root dry extract
and 45.5 mg hops dry extract

ICELAND

No combinations of hop and valerian.

ITALY

No combinations of hop and valerian.

LATVIA

No combinations of hop and valerian.

NORWAY

No combinations of hop and valerian.

POLAND

WEU

No	Marketing status	Year	Pharm form	Posology	Indications

TU

No	Marketing status	Year	Pharm form	Posology	Indications
1	**Hova-** Valerianae radix, extractum siccum (4-7:1) 220mg, extraction solvent – ethanol 70% v/v Lupuli strobilus, extractum siccum (4-8:1) 65mg, extraction solvent methanol 40% v/v	1999	Film-coated tablet	oral use – 1 tablet 1-3 times daily	sleep disorders psychosomatic stomach spasms

ROMANIA

WEU

No	Marketing status	Year	Pharm form	Posology	Indications
1	Redormin; MA: 2004 Composition: 250.0mg Valerianae radix extractum siccum (4-6:1) *Extration solvent:Methanol 45%;Carrier: maltodextrin 25%* *60.0mg* Lupuli flos extractum siccum (5-7:1) *Extraction solvent:Methanol 45%:Carrier: maltodextrin 30%* Excipiens q.s. ad 570mg	2004	Film-coated tablets	Adults: 2 tablets one hour before going to bed. If required, the dose can be increased to 3 tablets. Children over 12 years of age: 1 tablet one hour before going to bed Elderly: as for adults: 2 tablets	Adjuvant in case of difficulties in falling asleep and sleeping through the night as well as uneasy sleep.

TU

No	Marketing status	Year	Pharm form	Posology	Indications

SLOVENIA

WEU

No	Marketing status	Year	Pharm form	Posology	Indications
	1 tablet contains 200.2 mg of Valeriana officinalis L., radix, extractum siccum (5 : 1); extraction solvent: 70 % (V/V) ethanol and 45.5 mg of Humulus lupulus L., flos, extractum siccum (5,5 : 1); extraction solvent: 40 % (V/V) methanol	1999	film-coated tablet	a) Adults and children above 12 years: 2 film-coated tablets half to one hour before bedtime b) Adults and children above 12 years: 1 film-coated tablets up to three times a day	a) Mild insomnia as a consequence of tenseness, restlessness b) mild nervous tension

TU

No	Marketing status	Year	Pharm form	Posology	Indications

SPAIN

Not combination of hop and valerian.

SWEDEN

WEU

No	Marketing status	Year	Pharm form	Posology	Indications

TU

No	Marketing status	Year	Pharm form	Posology	Indications
1	1 ml contains: 460 mg Valeriana officinalis, root, tincture (1:10) and 460 mg Humulus lupulus, strobiles, tincture (1:2.2) 100 ml solution corresponds to 24 g fresh valerian root corresponding to (approx 5 g dried root) and 23 g fresh hops (approx 5 g dried herbal substance).	1978	oral drops	Adults and adolescents: Nervous tension: 40 drops in ½ glass of water 3-5 times daily. Insomnia: 75 drops in ½ glass of water. Not recommended to children	Traditionally used for minor nervous tension and temporary insomnia

Assessor's comments

The herbal preparations with marketing authorizations consist of fixed combinations of dry extracts of valerian root and hop strobiles, prepared with water, methanol/water or ethanol/water. Their pharmaceutical forms are coated tablets, soft capsules or film-coated tablets. These products are marketed in Austria, Belgium, Bulgaria, Czech Republic, Finland, Germany, Hungary, Ireland, Romania, Slovenia and the United Kingdom. In Austria, Czech Republic, Germany, Hungary, Norway, Poland and Sweden several herbal preparations are traditionally used and consist not only of fixed combinations of dry extracts, but also of liquid extracts and/or tinctures. A soft extract of a mixture of both herbal substances is traditionally used as bath additive in Germany.

The dry extracts of valerian root (3-8:1) are prepared with water, methanol/water (methanol 40-51.2%, v/v) or ethanol/water (ethanol 40-80%, v/v). The dry extracts of hop strobiles (3-14:1) are also prepared with water, methanol/water (methanol 25-51.25%, v/v) or ethanol/water (ethanol 40-96%, v/v). These dry extracts are mixed in fixed combinations of valerian root and hop strobile dry extracts varying between 80 mg – 250 mg valerian root dry extract and 14 mg – 68 mg hop strobile dry extract.

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

- 250 mg or 500 mg valerian dry extract (5.3:1, methanol 45% m/m) and 60 mg or 120 mg hop dry extract (6.6:1, methanol 45% m/m)
- 200.2 mg valerian dry extract (5:1, ethanol 70% v/v) and 45.5 mg hop dry extract (5.5:1, methanol 50% v/v)
- 187 mg valerian dry extract (5-8:1, methanol 45% m/m) and 41.9 mg hop dry extract (7-10:1, methanol 45% m/)

(See also under section II.3.2.2)

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

II.1.2. Information on period of medicinal use in the Community regarding the specified indication

Fixed combinations of dry extracts of valerian root and hop strobiles have obtained a marketing authorization in Austria, Belgium, Bulgaria, the Czech Republic, Finland, Germany, Hungary, Ireland, Romania, Slovenia and the United Kingdom, whereas traditional uses of such combinations have been reported by Austria, the Czech Republic, Germany, Hungary, Norway, Poland and Sweden. In most of these countries also other combinations are used for the same indications.

Out of 36 fixed combinations not less than 29 have obtained a marketing authorization in Germany since 1976. Only one fixed combination with marketing authorization is more than 10 years on the market in Hungary, whereas the preparations for traditional use have only been on the market since 1994. One fixed combination consisting of tinctures of valerian root and hop strobile has been traditionally used in Sweden since 1978.

Assessor's comments

Fixed combinations of dry extracts of valerian root and hop strobiles have obtained a marketing authorization in several countries for the same indication as valerian preparations alone, *viz.* relief of mild nervous tension and sleep disorders, for more than 10 years. Several other fixed combinations of dry extracts, liquid extracts or soft extracts are traditionally used for more than 30 years for the same indication as valerian preparations alone, *viz.* to support mental relaxation.

II.2. NON-CLINICAL DATA

The phytochemical composition, the pharmacology (II.2.1.), the pharmacokinetics (II.2.2.) and the toxicology (II.2.3.) of both valerian root and hop strobiles and their preparations have amply been discussed in the assessment reports on valerian root and hop strobiles (EMEA/HMPC/167391/2006 and EMEA/HMPC/513618/2006, respectively).

One pharmacological study has been performed with both a valerian preparation and a fixed valerian-hops preparation. An *in vitro* radioligand binding assay at A_1 and A_{2A} adenosine receptors (ARs) was conducted with a fixed extract combination of valerian and hop (Ze 91019) to investigate a possible mechanism for the pharmacological activity of the extracts. Component extracts of valerian and hop were also individually investigated. The fixed combination as well as the valerian extracts therein exhibited selective affinity to A_1 ARs (K(i) = 0.15-0.37 mg/ml versus [^{3}H]-N^6-cyclopentenyladenosine (CPA). The same extracts exhibited partial agonist activity at the A_1 receptor as indicated by a lower degree of stimulation of [^{35}S]-CTPγS binding in membrane preparations of CHO-hA_1 cells as

compared to full A_1 AR agonist N^6-CPA. In addition valerian extract inhibited c-AMP accumulation in CHO-hA_1 cell membranes. The partial agonistic activity at A_1 ARs may thus play a role in the sleep inducing effect of Ze 91019 and the valerian extract therein (Müller et al., 2002).

Assessor's comments

Orally administered dry extracts of valerian root in the recommended dosage have shown to improve sleep latency and sleep quality. Although these effects cannot be attributed with certainty to any known constituents, several mechanisms of action have been identified for several constituents of valerian root i.e. sesquiterpenes, lignans and flavonoids, including interactions with the GABA-system, agonism at the A1-adenosine receptor and binding to the 5-HT_{1A} receptor (Balduini and Cattabeni, 1989; Mennini et al., 1993; Yuan et al., 2004; Cavadas et al., 1995 and Ortiz et al., 1999).

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

Further studies with a combination of valerian and hops dry extracts have shown interactions with the serotoninergic 5-HT_{4e}, 5-HT_6, 5-HT_7 and melatoninergic ML_1 and ML_2 receptors (Abourashad et al., 2004; Brattström, 2007).

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

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

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

II.3. CLINICAL DATA

II.3.1. Clinical pharmacology

II.3.1.1. *Pharmacodynamics*

Two pharmacological studies have been carried out with a fixed combination of valerian and hop extracts (Ze 91019) to investigate the pharmacodynamic effects in healthy volunteers.
In a first study the fixed combination of valerian and hops was investigated aiming at a demonstration of competition between caffeine and this combination.
Electroencephalographic (EEG) recordings were used to describe the action of caffeine on the central nervous system after oral administration (200 mg) in healthy volunteers. In addition to caffeine, the volunteers (16 in each group) received either placebo or verum (2 and 6 tablets containing the valerian/hop extract).
The EEG responses were recorded every 30 min. The verum medication was capable of reducing (2 tablets) or inhibiting (6 tablets) the arousal induced by caffeine. This pharmacological action was observed 60 minutes after oral administration indicating not only competition between the antagonist caffeine and the partial agonist i.e. the valerian/hop extract but also bioavailability of the compound(s) responsible for the agonistic action. The authors concluded that the valerian/hop extract acts via a central adenosine mechanism, which is possibly the reason for its sleep-inducing and- maintaining activity (Schellenberg et al., 2004).

In a second investigation the pharmacodynamic effects of different dosages of a fixed combination of valerian and hop extracts (Ze 91019) on the quantitative topographical EEG (qEEG) in healthy volunteers were compared to placebo. Two different dosages were applied in two single-blind, cross-over designed observation trials in 12 healthy volunteers (1st dosage : 500 mg valerian and 120 mg hops, versus placebo, first clinical trial ; 2nd dosage : 1500 mg valerian and 360 mg hops, versus placebo, second clinical trial). The qEEG was recorded bipolarly from 17 surface electrodes according to the 10:20 system and analysed using the Fast Fourier Transformation prior to, 1, 2 and 4 hours after drug intake in the recording conditions eyes open, eyes closed and under mental demand. The EEG-spectra were cut into six frequency bands. Both resting conditions (eyes open and eyes closed) were analysed together. After application of the low dosage qEEG power changes remained more or less within placebo range following the normal circadian rhythmics, except for a tendentious reduction of alpha- and beta1-power 4 h after drug intake. The high dosage led to power increases in delta, decreases in alpha and a weak decrease in beta-power. Under mental performance only weak differences to placebo were seen which are not discussed here. In the CPT (completion of complicated

additions and substractions) the concentration and performance capability were hardly influenced. However, a minimal increase of mean answer time and mean OK time (time for correct answers) was observed 4 hours after intake of 2 dragees and 1 hour after 6 dragees of valerian and hops mixture with more pronounced changes after the low dosage than the high one.

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

II.3.1.2. *Pharmacokinetics*

No data available.

II.3.2. Clinical efficacy

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

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

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

II.3.2.1. *Non-controlled clinical studies*

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

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

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

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

In a non-controlled, multicentre study, 480 patients (305 women, 175 men; mean age 49.5 years) suffering from nervous sleep disorders and restlessness were treated for an average of 22 days with a combination preparation containing 225 mg valerian root extract (DER 6-7:1; 70% ethanol) and 30 mg dry extract of hop strobile extract (DER 11-14:1; 96% ethanol) per coated tablet, corresponding to approximately 1500 mg of valerian root respectively 400 mg of hop strobile per tablet. The mean dose

of the combination was 2.6 coated tablets during the day and 1.6 tablets before bedtime in the evening. The mean total daily dose was 3.3 tablets. Main efficacy parameters evaluated were improvement of nervous anxiety and associated psycho-vegetative symptoms (sweating, palpitations, nervous tension) as well as the improvement of sleep disorders. Symptoms were evaluated with a 5-point rating scale (0 = not present to 4 = severe). Therapy with the valerian-hop combination resulted in pronounced improvement of both, anxiety and sleep disorders. The rating of anxiety related symptoms was reduced by 50-57%, symptoms related to sleep parameters were reduced by 58-61%. Global efficacy was assessed as "excellent" or "good" by 24.6% and 57.2% of patients, respectively. No adverse events were reported throughout the study (Wegener, 2003).

II.3.2.2. *Controlled clinical studies*

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

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

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

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

Drug/extract ratios for the latter preparation are not given. The volunteers took one dose of totally nine (three/preparation) on non-consecutive nights and documented their sleep quality in a questionnaire (not validated). Results were analyzed only for those volunteers who completed the trial (n = 128). Of them 52% (n=67) were good sleepers and 48% (n=61) were considered as poor or irregular sleepers.

On the morning after taking the preparation, time to fall asleep, quality of sleep, natural waking up, dreaming and tiredness in the morning were recorded by means of a questionnaire. Time to fall asleep was reduced in 37% of persons taking the valerian root mono-preparation, in 23% under placebo and in 31% under the combination preparation. The difference between the valerian root mono-preparation and placebo was statistically significant ($p<0.01$). While quality of sleep remained virtually unchanged in habitually good sleepers with all preparations, in habitually poor or irregular sleepers the sleep quality was enhanced and sleep latency was reduced significantly more often with the valerian preparation compared to placebo. The combination showed no signfiicant superiority. The quality of sleep was improved in 43% of persons with the valerian root mono-preparation and 25% with placebo ($p<0.05$). No differences in waking up during the night, dreaming and tiredness in the morning were found between valerian root and placebo. With regard to the combination preparation, a stronger effect was found for tiredness in the morning, which was statistically significant compared to both placebo and valerian root mono-preparation. No significant differences were found for the other parameters.
The interpretation of these data is restricted by lacking of a confirmatory analysis. No detailed demographic data are given, no validated questionnaires were used in this trial. It is not clear from the publication whether the medications were taken in a randomized order. Nevertheless, the results are congruent with those of better designed and reported trials.

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

The efficacy of a valerian-hop combination (coated tablets containing 200.2 mg of dry extract of valerian root (DER 5:1, ethanol 70% v/v) and 45.5 mg of dry extract of hop strobiles (DER 5.5:1, methanol 40% v/v); extraction solvents not indicated) was compared to that of 3 mg bromazepam in a two-week reference-controlled, double-blind, randomized clinical parallel group trial with double-dummy technique. 46 patients (37 women, 9 men; mean age 50.3 years) suffering from non-psychiatric sleep disorders were tested for sleep quality, fitness and quality of life by psychometric tests, psychopathologic scales and sleep-questionnaires. All parameters improved in both treatment

groups to a similar extent. During treatment with the herbal combination the percentage of patients subjectively feeling “bad” or “moderate” decreased by 62.6% (from 82.6% to 20%), as compared to a reduction of 32.7% (from 56.5% to 23.8%) in patients treated with bromazepam. Seven adverse events were noted, two of which (one case of gastrointestinal complaints in both treatment arms) were considered to have been caused by the medication. (Schmitz and Jäckel, 1998).

In 2005, Morin et al. evaluated the efficacy and safety of a valerian-hops combination and diphenhydramine for the treatment of mild insomnia. The multicentre, randomized, placebo-controlled, parallel-group study was conducted in 9 sleep disorders centres throughout the US. A total of 184 adults (110 women, 74 men, mean age of 44.3 year) with mild insomnia were treated with two nightly tablets of standardized extracts of valerian (187 mg native extract : 5-8:1, methanol 45% m/m) and hops (41.9 mg native extract : 7-10:1, methanol 45% m/m) combination for 28 days (n = 59) and a placebo for 28 days (n = 65) or 2 tablets of diphenhydramine (25 mg) for 14 days followed by placebo for 14 days (n = 60). Sleep parameters measured by daily diaries and polysomnography, clinical outcome ratings from patients and physicians, and quality of life measures were the outcome measures. Modest improvements of subjective sleep parameters were obtained with both the valerian-hops combination and diphenhydramine, but few comparisons with placebo reached statistical significance. Valerian-hops produced sligtly greater, though nonsignificant, reductions of sleep latency relative to placebo and diphenhydramine at the end of 14 days of treatment and greater reductions than placebo at the end of 28 days of treatments. Diphenhydramine produced significantly greater increases in sleep efficiency and a trend for increased total sleep time relative to placebo during the first 14 days of treatments. There were no significant group differences on any other sleep continuity variables measured by polysomnography.

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

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

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

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

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

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

Table 1 Controlled clinical studies with valerian-hop extracts combinations							
Authors	**Indications**	**Study design**	**Formulation (single dosage)**	**Dose/Duration**	**Test criteria/ Efficacy**	**Safety**	**Comments**
Müller-Limroth and Ehrenstein, 1977	Investigation of sleep quality in sleep disturbed subjects	Double-blind Placebo-controlled n=12	Coated tablets of 60 mg valerian dry extract (4.5:1, methanol 40% v/v) and 100 mg hop dry extract (5:1, methanol 30% v/v) n=12	Study duration: 6 nights Traffic noise during nights 3, 4 and 5 4 Tablets of verum to 6 patients prior to night 2 and to 6 patients prior to night 3 Remaining nights: 4 tablets of placebo	Polysomnography ---------- Reduction of the noise induced disturbance of sleep stage pattern Slow-wave-sleep and stage REM increased	No adverse events	Number of volunteers is too restricted to draw conclusions
Leathwood et al., 1982	Investigation of sleep quality of volunteers	Cross-over trial comparing aqueous valerian dry extract, placebo and a combinaton of valerian and hop extracts n=128 volunteers (67 good and 61 poor sleepers)	400 mg of valerian dry extract (2.8:1, water) Placebo Hova® capsules (Zyma): 60 mg valerian dry extract and 30 mg hop dry extract Preparation unknown	400 mg of valerian aqueous dry extract 2 capsules of 200 mg Hova® One dose of 9 (3 per preparation) on non- consecutive nights	Questionnaire to fill in by the volunteers --- Significant differences between valerian extract and placebo, but not between combination and placebo	Stronger effect for tiredness in the morning for the combination compared to placebo and monopreparation	No confirmatory analysis No validated Question-naire Are medications taken in a randomized order?

Table 1 Controlled clinical studies with valerian-hop extracts combinations (continued)							
Authors	**Indications**	**Study design**	**Formulation (single dosage)**	**Dose/Duration**	**Test criteria/ Efficacy**	**Safety**	**Comments**
Rodenbeck & Hajek, 1998	Non-organic insomnia (DSM-III-R) (ApA, 1987)	Randomized Double-blind Placebo-controlled n=8 (verum) n=7 (placebo)	IVEL®-tablets (Knoll) 250 mg valerian dry extract (5:1) solvent? 60 mg hop dry extract (6:1) solvent?	2 tablets/day 30 min before bedtime 4 weeks (57 days of therapy)	Polysomnography ; Subjective feelings ---------- Decrease of slow-wave-sleep Increase of sleep stage II in the verum group	Placebo n:2 Verum n=4 Gastro-intestinal complaints and headache	Extraction solvent is not given: probably identifical to Ze 91019 and consequently methanol 45% m/m Number of patients is limited; statis-tical significance is doubtful
Schmitz and Jäckel, 1998	Sleep disorders (DSM-IV)	Randomized Double-blind Reference-controlled Lexotanil® (3 mg bromazepam) n=46	Hova® film tablets 200.2 mg valerian dry extract (5:1, ethanol 70% v/v) 45.5 mg hop dry extract (5.5:1, methanol 40% v/v)	2 weeks therapy 1 week cessation of therapy 2 film tablets (verum) and 1 capsule (reference) 30 min before bedtime/day	Psychometric tests Psychopathological scales; Sleep questionnaires ---------- Equivalence of both therapies according to sleep quality, fitness and quality of life	n=1 with stomach complaints in both groups	Extraction solvent is not mentioned in the publication, but corresponds to Hova® No placebo-controlled study, but of good methodologic al quality

Table 1 Controlled clinical studies with valerian-hop extracts combinations (continued)							
Authors	**Indications**	**Study design**	**Formulation (single dosage)**	**Dose/Duration**	**Test criteria/ Efficacy**	**Safety**	**Comments**
Morin et al., 2005	Mild insomnia	Randomized Double-blind Placebo-controlled Multicentre (n=9) Reference-controlled Diphenhydramine: 25 mg/tablet	Tablets of 187 mg of valerian dry extract (5-8:1, methanol 45% m/m) and 41.9 mg of hop dry extract (7-10:1, methanol 45% m/m)	1. 2 nightly tablets of combination for 28 days (n=59) 2. placebo for 28 days (n=65) 3. 2 tablets of diphenhydramine for 14 days followed by placebo for 14 days (n=60)	Sleep parameters measured by daily diairies and poly-somnography, Clinical outcome ratings for patients and physicians and quality of life measures Modest hypnotic effect for valerian-hops combination and diphenhydramine relative to placebo. Sleep improvements with valerian-hops combination are associated with improved quality of life. Both treatments appear safe and did not produce rebound insomnia after discontinuation during this study. Both preparations are useful adjuncts in the treatment of mild insomnia	No serious adverse events	Study of good methodological quality

Table 1 Controlled clinical studies with valerian-hop extracts combinations (continued)							
Authors	**Indications**	**Study design**	**Formulation (single dosage)**	**Dose/Duration**	**Test criteria/ Efficacy**	**Safety**	**Comments**
Koetter et al., 2007	Non-organic sleep disorders (ICD 10, F51.0-51.2)	Randomized Double-blind Placebo-controlled Fixed combination and valerian mono-extract versus placebo n=30 (three arms : n=10 per arm)	Fixed extract combination : Ze 91019 : 500 mg valerian dry extract (5.3:1, methanol 45% m/m) and 120 mg hop dry extract (6.6:1, methanol 45% m/m) Pure valerian extract Ze 911: 500 mg valerian dry extract (5.3:1, methanol 45% m/m)	4 weeks : one dosage/day	Objective sleep parameters determined by means of a transportable home recorder system (QUISI) Clinical global impression scale ---------- Reduction of sleep latency (≥ 30 min) in patients suffering from primary insomnia with combination. Single extract was not superior than placebo	No secondary events	Study of good methodological quality

Assessor's comments

In four non-controlled clinical studies and two randomized placebo-controlled double-blind clinical studies a fixed dry extract combination (Ze 91019) of valerian root and hop strobiles was used to treat patients suffering from non-organic disorders. Both extracts were prepared with 45% methanol m/m with a dry extract ratio of 5.3:1 (valerian) and 6.6:1 (hops), respectively. In only one of these controlled clinical studies (Koetter et al., 2007) the combination product was significantly superior to the placebo. In the other controlled clinical study (Rodenbeck and Hajek, 1998) the number of patients being 15 was too limited to obtain a statistically significant conclusion. Tolerability was very good with the exception of occasional gastro-intestinal discomfort in a small number of patients in four of the abovementioned studies.

In one randomized, reference-controlled (bromazepam as reference) double-blind clinical study by Schmitz and Jäckel (1998) and one randomized, placebo- and reference-controlled (diphenhydramine as reference) double-blind clinical study conducted by Morin et al. (2005) modest hypnotic effects for the fixed valerian-hops combination products were obtained. Equivalence of both reference and combination products according to sleep quality, fitness and quality of life were found. Both clinical studies were of good methodological quality. The composition of the combination products was slightly different from that of Ze 91019 *viz.* valerian dry extract (5.8:1) prepared with ethanol 70% v/v and methanol 45% m/m, respectively and hop dry extract (5.5:1) and (7.10:1) prepared with methanol 40% v/v and methanol 45% m/m, respectively.

In conclusion, preclinical and clinical evidence are sufficient to support a well-established use of several fixed combinations of valerian root dry extract and hops dry extract to treat patients suffering from non-organic sleep disorders.
These fixed preparations should be limited to the ones used in the successful controlled clinical studies *viz*. fixed combinations of 250 mg or 500 mg valerian dry extract (5.3:1, methanol 45% m/m) and 60 mg or 120 mg hop dry extract (6.6:1 methanol 45% m/m) (Ze 91019), 200.2 mg valerian dry extract (5:1, ethanol 70% v/v) and 45.5 mg hop dry extract (5.5:1, methanol 40% v/v) (Hova®) and 187 mg valerian dry extract (5-8:1, methanol 45% m/m) and 41.9 mg hop dry extract (7-10:1, methanol 45% m/m).

II.4. SAFETY

II.4.1. Toxicity

The toxicity of both valerian root and hop strobiles and their preparations have been discussed in the corresponding assessment reports (EMEA/HMPC/167391/2006 and EMEA/HMPC/513618/2006, respectively) of the single ingredients.

II.4.2. Side effects

Gastrointestinal symptoms e.g. nausea, abdominal cramps and headache have been reported during the clinical studies in a small number of patients.

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

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

II.4.3. Contra-indications, warnings

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

II.4.4. Interactions

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

II.4.5. Overdoses

Not known.

Assessor's overall conclusion

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

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

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