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Evaluation of Medicines for Human Use

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COMMITTEE ON HERBAL MEDICINAL PRODUCTS (HMPC)

ASSESSMENT REPORT ON *VALERIANA OFFICINALIS* L., RADIX

Herbal substance	**well-established use:** *not covered* **traditional use:** - dried valerian root
Herbal preparations	**well-established use:** - extracts prepared with ethanol/water (ethanol 40 - 70 % (V/V)) **traditional use:** - dry extracts prepared with water - valerian tincture - expressed juice from fresh root - valerian root oil
Pharmaceutical forms	solid or liquid dosage forms for oral use
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I INTRODUCTION

This assessment report reviews scientific data available on Valerianae radix (*Valeriana officinalis* L.). This report takes into account the 'Core Data for Valerianae radix' prepared by the EMEA ad hoc Working Group on Herbal Medicinal Products in 1998. Since, several clinical and preclinical trials have been published that supplement valuable information on clinical efficacy and possible modes of action of the herbal substance. This information is reflected in the Community herbal monograph.

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

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.

II NON-CLINICAL STUDIES

Dependent on the extraction technique, valerian root extracts contain differing amounts of monoterpenes (such as bornyl esters, camphene and pinenes), sesquiterpenes (including valerenal and valeranone), and less volatile sesquiterpene carboxylic acids (valerenic acid and derivatives), amino-acids like gamma-aminobutyric acid, glutamine and arginine, alkaloids, flavonoids and lignans (Haensel et al., 1999, Hoelzl, 1998). Valepotriates (nonglycosidic iridoid esters) may be present in the root, but are unstable and unlikely to be present in finished products. The constituents of the volatile oil are very variable due to population differences in genetics and to environmental factors such as sowing method and harvest time.

Among the components listed above, no single or main active ingredient has been identified for valerian root. Various trials with isolated constituents could not fully explain the observed pharmacological activities of valerian root in total. A possible synergistic action of several components is assumed. The whole extract of valerian root must therefore be considered as the active ingredient.

II.1 Pharmacodynamics

II.1.1 Isolated substances

- *Sesquiterpenoids*

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

[1] The herbal substance shall comply with the European Pharmacopoeia monograph: Valerianae radix (ref. 01/2005:0453).

1994). Valerenic acid caused an inhibitory effect on muscimol-sensitive NTS neurons *in vitro* 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 $5\text{-}HT_{1A}$ receptor, which plays a role in sleep induction and anxiety reactions. Affinity for $GABA_A$-, benzodiazepine- and µ-opiate-receptors was distinctly lower (Hoelzl 1998, Bodesheim et al., 1997). The kind of action at the receptor (agonistic/antagonistic activity) was not investigated.

  An olivil derivate was found to be a potent partial agonist at A_1 adenosine receptors *in vitro* (Schumacher et al., 2002). Agonistic activity was also shown for valerian root extract (methanol 45 %, Mueller et al., 2002). Activation of this receptor type has a sedative effect while antagonists like caffeine have a stimulant effect.

- *Flavonoids*

  Marder et al. (2002) isolated 6-methylapigenin and hesperidin from *Valeriana officinalis*. 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.

  The same authors discovered sleep-enhancing properties for linarin (Fernandez et al., 2004). 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.

- *Valepotriates*

  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 et al., 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.

II.1.2 Aqueous and aqueous-ethanolic valerian root extracts

- *Interaction with neurotransmitter receptors in vitro*

  Due to the essential inhibitory functions of GABA, the interest has focused on possible interactions of valerian root with the $GABA_A$-messenger system.
  - Both aqueous-ethanolic (extraction solvent ethanol 60%) 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 *in vitro*. 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 caused an inhibitory effect on muscimol-sensitive NTS neurons *in vitro* 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 *in vitro* an interaction with the $GABA_A$-receptor by displacing [^{3}H] muscimol from synaptic membranes from rat brain cortices (Cavadas et al., 1995). For valerenic

acid no effect was shown. The authors, as well as Yuan et al., concluded that this interaction could be caused by the content of GABA in the extracts.

Further evidence for this conclusion comes from other investigations:

- 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., 1994 a, b). GABA was shown to be absent in an ethanolic extract, correspondingly this extract did not significantly affect GABA release.

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 is only 2 g/l, the clinical relevance of this assumption must be judged critically.

Still, there are data pointing to interaction with the GABA-system via other mechanisms:

- In other experiments by the group of Santos (Santos 1994 c, 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 inhibited the uptake and stimulated the release of [^{3}H]-GABA, 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 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 *in vitro* experiment demonstrated the interaction of a hydroalcoholic extract 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 1989).

- <u>*Animal models*</u>
  - Valerian tincture reduced spontaneous motility after intraperitoneal administration of the valerian tincture in mice (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 4.0 mg/kg. Thus the extract exhibited dose-related sedative activity in mice, however less pronounced than that of diazepam or chlorpromazine (Leuschner et al., 1993).
  - An aqueous-ethanolic dry extract (DER 4:1, extraction solvent ethanol 70 % V/V) administered intraperitoneally 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 and Zetler, 1996).

- Cats with implanted electrodes showed no changes in their EEGs following oral administration of 100 or 250 mg of valerian root extract per kg body weight. 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-HT_{1A}-receptor agonist (Hiller and 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. This feature could be interpreted as a bell-shaped dose-response curve as they are seen for partial agonists. The results of this study deserve to be highlighted since they were achieved with oral administration of doses comparable to those given under clinical conditions.

II.1.3 Conclusion

Aqueous and aqueous-ethanolic extracts from valerian root as well as fractions and isolated individual substances have been investigated in several pharmacological animal models. Since isolated constituents were used in unphysiological high doses to achieve effects, the clinical relevance of these investigations may be discussed. On the other hand, Marder et al. (2003) demonstrated a very strong potentiation of effects by combining flavonoids. These results point to marked synergism; the observations for single constituents may not reflect their action *in vivo* realistically.
As a whole, the results point to both a sedative and an anxiolytic effect, possibly mediated by different constituents, which both might contribute to sleep promotion and improvement in nervous state. These data are consistent with clinical observations. With respect to safety concerns, 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 of course questionable. In view of the fact that there is no information available on experiences with the combination of valerian root and barbiturates in humans, a co-medication of valerian root and barbiturates should be avoided for safety reasons as long as no further data are published.

II.2 Toxicology

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.

II.2.1 Acute Toxicity

- In acute oral toxicity tests the LD_{50} of the sesquiterpene valeranone was greater than 3 g/kg in both rats and mice which corresponds to low toxicity (Rücker et al., 1978).
- The LD_{50} of essential oil of valerian root, 1,500 mg in rats weighing 100 g, was found to be the highest of 27 essential oils tested, including for example, peppermint and anise oils (von Skremlik, 1959).
- The LD_{50} of an ethanolic valerian root extract made from the defatted herbal substance administered intraperitoneally to mice amounted to 3.3 g/kg, a value, which corresponds to a low toxicity (Rosecrans et al., 1961).
- Valerenic acid caused inhibition of spontaneous motility after intraperitoneal 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 hours after administration) (Hendriks et al., 1985).

II.2.2 Sub-acute/Chronic Toxicity

- An ethanolic valerian root extract 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 given to rats intraperitoneally 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).
- In the rat, a dose of 200 – 225 mg valerian root oil per 100 g body weight was found to be a tolerable daily dose p.o. 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 250 mg 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).

II.2.3 Reproductive Toxicity

There are no published studies on reproductive toxicity of preparations from valerian root. 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 much 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).
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., 1998).
Since there are no experimental investigations to date, as stated in the ESCOP- and the WHO-monograph as well as the core-data on valerian root prepared by the EMEA ad hoc Working Group on Herbal Medicinal Products, it is recommended that valerian root preparations should not be taken during pregnancy and lactation; they should not be used without medical advice.

II.2.4 Mutagenicity/Carcinogenicity

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 M et al., 2005).

Alkylating, cytotoxic and mutagenic effects have been described for the valepotriates and their degradation products (Bos et al., 1998, von der Hude, 1986) which are not detectable in valerian root extracts or are found only in very low amounts.

The test of a dietary product with undefined quality in mice showed weak effects on bone marrow micronucleus in high doses. The concentration used was with ~ 4 g/kg much higher than the recommended dosage in humans (Al-Majed et al., 2006).

II.2.5 Conclusion

Only incomplete experimental data pointing altogether to a low toxicity are available on the toxicology 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. Data on genotoxicity are lacking.

III CLINICAL PHARMACOLOGY

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.

III.1 Pharmacodynamics

III.1.1 EEG trials

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.

- *Healthy volunteers*
  - 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 and 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 and 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, 1 x 1,200 mg lavender extract, 1 x 1,200 mg passion flower extract and 1 x 600 mg Kava kava extract. All substances showed individual action profiles. Compared to diazepam, an increase in the relative strength of the theta frequency band was observed for the plant 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).

- *Patients with sleep disturbancies*
  - 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). 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).
  - 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 aqueous-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.
  - 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) or other plant extracts. 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 are given in the abstract (Schulz und Jobert, 1995).
  - Diaper and Hindmarch (2004) performed a double-blind placebo-controlled crossover trial in 16 patients (age 50 – 64 years) with mild sleep-disturbancies investigating the effect of a single dose of placebo, 300 mg or 600 mg of an aqueous-ethanolic valerian root extract (DER 3 – 6:1, extraction solvent ethanol 70 % V/V) corrresponding 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.

Conclusion

Valerian root 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.

III.1.2 Volunteer trials in stress situations

- Cropley et al. (2002) performed an open, randomised study comparing the effect of valerian root, kava-kava 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 corresponding to 2.7 g of the herbal substance, 120 mg kava-kava extract 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 during test completion - with valerian root extract also the increase of heart rate - was significantly reduced with valerian root extract and kava-kava rhizome extract in contrast to no change without medication.
  Self-reported pressure immediately before and during the test was decreased significantly with valerian root extract and kava-kava rhizome extract; the decrease of pressure before start of the test was even more distinct with valerian root extract than with kava-kava rhizome extract. In all 3 groups task performance was improved in the second test.
  These results lead to the assumption that valerian root as well as kava-kava rhizome decreases subjective experience of stress (while cognitive performance is not reduced) which may provide evidence for the clinically established indication “mild nervous tension”. The significance of the trial is decreased by potential biases due to the lack of blinding and absence of a placebo-group. Confirmation of the data in placebo-controlled double-blind trial is desirable.
- 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 minutes or 120 minutes after administration in 48 young subjects (age between 19 and 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 et al., 1988). It is well known that thymoleptic medicinal products may show anxiolytic properties, which may be differentiated from antidepressive effects. The assumption of an anxiolytic effect as a major mode of action of valerian root preparations is confirmed by this trial.

The results of these trials provide supportive information to the indication ‘mild nervous tension´ for which only limited evidence comes from clinical studies in patients.

III.2 Safety Studies

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:

- In a double-blind study with 102 subjects (mean age approximately 40 years), in whom a sleep disorder was excluded, reaction time, attention and co-ordination capacity were determined in an acute test by means of the Vienna Determination Test on the morning after administration of 600 mg of an aqueous-ethanolic valerian root extract (DER 3 – 6:1, extraction solvent ethanol 70 % V/V), 1 mg flunitrazepam or placebo. Subjective assessment of the quality of sleep was based on a visual analogue scale. The reduction in reaction time, as an indication of a learning effect, was significantly smaller with flunitrazepam than in both other groups. No group differences were observed with regard to attention and co-ordination capacity. The quality of sleep and the time taken to fall asleep were assessed as improved in all three groups. A “hangover” effect was observed in 59.4 % of the test persons under flunitrazepam ($p < 0.05$ vs. valerian root extract or placebo), 30.3 % under valerian root extract and 32.4 % under placebo. After a 7-day washout phase, the subjects took 600 mg valerian root extract/day or placebo over 14 days. No difference between therapies was observed in reaction time, attention and co-ordination capacity. A slight improvement in quality of sleep was found in the group treated with valerian root (+7.4 % vs. -4.5 % in the placebo group) (Kuhlmann et al., 1999).
- In a double-blind trial the authors compared the cognitive and psychomotor effects, in nine healthy volunteers, of single doses of an aqueous-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.

- Glass et al. (2003) compared acute effects of placebo, valerian root 400 and 800 mg (probably powdered herbal substance), temazepam 15 and 30 mg, diphenhydramine 50 and 75 mg in 14 elderly volunteers (mean age 71.6 years, range 65 – 89 years). Temazepam and diphenhydramine dose-dependently caused clear sedation and psychomotor impairment in connection with drowsiness and fatigue while for both valerian root doses no differences to placebo were seen.
- A valerian root extract (no details given) 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 between 20 and 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 hours after taking the preparation; with regard to the subjective measures, the subjects had "wobbly legs" and felt less active ($p \leq 0.01$ vs. placebo) (Gerhard et al., 1996).

Conclusion

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

III.3 Pharmacokinetics & bioavailability

III.3.1 Pharmacokinetics

Data on the pharmacokinetic properties of extracts of valerian root or isolated constituents in man are not available. Pharmacokinetic data for valepotriates are not relevant for valerian root extracts.

III.3.2 Bioavailability

Data on the bioavailability of extracts or isolated constituents of valerian root are not available.

III.4 Interactions

III.4.1 Pharmacodynamic interactions

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 et al., 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.

III.4.2 Pharmacokinetic interactions

While no information on possible interactions of valerian root and its preparations was available up to 2004, results of two trials were published recently:

- Lefèbre et al. (2004) investigated interactions of several valerian root preparations available on the US market with CYP 3A4 *in vitro*. The data point to a possible inhibition of CYP 3A4-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 CYP 3A4 and CYP 2D6 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 details given) over 14 days. The study did not reveal an influence on the CYP 2D6 pathway while for CYP 3A4 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 CYP 2D6 or the CYP 3A4 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 by manufacturer). They found no relevant interaction for CYP 1A2, CYP 2D6, CAP 2E1 and CYP 3A4/5.

Conclusion

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

IV CLINICAL EXPERIENCE

IV.1 Efficacy

IV.1.1 Dose-Finding Trials

The dose recommendations of the ESCOP monograph, the German Commission E monograph and the WHO monograph 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 and co-authors (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 1,300 mg and 2,600 mg valerian root.

- In a double-blind, randomized crossover trial, 7 patients (age between 33 and 59 years) with problems getting to sleep took either 450 mg (corresponding to 1,300 mg of the herbal substance), or 900 mg (corresponding to 2600 mg of the herbal substance) of an aqueous valerian root extract or placebo before bedtime (Leathwood and 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 (age between 24 and 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 et al., 1985).

IV.1 2 Controlled 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.

- *Non-organic insomnia*

- 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 (age 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 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 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 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 1,200 mg 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, age between 61 and 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 kava-kava (daily dose 300 mg of kavalactones), 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.

- *Review on insomnia*

  The review of Stevinson and 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 PD et al. (2003); Cropley M et al. (2002); Diaper A et al.(2004); Donath F et al. (2000); Dorn M (2000) Hallam KT et al. (2003); Ziegler G (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 were included in the 'traditional use' part of the monograph. Regarding these extracts, this assessment is concordant with the review of Stevinson and Ernst, 2000. Some pharmacodynamic trials (i.e. Schulz et al. (1994); Vorbach et al. (1996); Donath et al. (2000); Diaper et al. (2004); Dorn (2000); Ziegler (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.

Conclusion

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[2] 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. Valerian root 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).

IV.1.3 Clinical Experience in 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 was 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 2.7 g of the herbal substance.

starting dose (mg of herbal substance)	300 mg (1,350 mg)	600 mg (2,700 mg)	900 mg (4,050 mg)	1,200 mg (5,400 mg)
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’.

[2] As referred to in the HMPC ‘Guideline on the assessment of clinical safety and efficacy in the preparation of Community herbal monographs for well-established and of Community herbal monographs/entries to the Community list for traditional herbal products/substances/preparations’ (EMEA/HMPC/104613/2005)

Müller SF et al (2006) Phytomedicine (article in press):
In an open multicenter observational study n = 918 children ≤12 years (n = 719 ≥ 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.

Conclusion

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. The lack of experience is addressed as a relative contraindication in the Community herbal monograph. 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. General recommendations cannot therefore be given and a treatment should exclusively follow medical advice.
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.

IV.2 TOLERABILITY

Approximately 620 patients or subjects received a valerian root extract preparation in the controlled clinical trials (including human pharmacological studies) listed above.
Valerian root was 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 by the time this report was adopted by the HMPC.

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 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.

One case of acute overdose has been reported. An 18-year old student, who took approximately 18.8 to 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 minutes. 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 hours. 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. The case report 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 (Willey et al., 1995).

IV.3 TRADITIONAL USE

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.

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

IV.3.1 Europe

- *References*
  - 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.).
  - 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.).
  - 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.).
  - Dragendorff (1898) describes the use of the root as antispasmodic, as remedium nervinum and antihysteric. No details on preparations and dosages are given.
  - Madaus (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:
    - 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:

- internal use:
  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 diphteria. Before salvarsan injection as prophylaxis of a salvarsan-induced shock.
- external use:
  headache, reddened and painful eye, wound healing. Bath against acute rheumatism.

For these indications the root was used in most cases, only exceptionally the leaves. Details on herbal preparations and dosages are not given.

- 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 established 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 Hungarian Pharmacopoeia (Edition VI. Volume III. 1967) lists the following valerian root preparations:
  - tinctura valerianae aethera (1:5, ethanol 70 % and aether 7.5:2.5 m/m), single dose 200 – 500 mg
  - tinctura valerianae spirituosa (1:5, ethanol 70 % V/V), single dose 200 – 500 mg
  - valerianae rhizoma et radix, single dose 0,5 – 1 g
- The twenty-fifth 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). 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, prepared by maceration with ethanol (60 %). Single dose: 4 – 8 ml.

  Indications: hysteria and other nervous condition, carminative.
- The British Herbal Pharmacopoeia (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
- Hager's Handbuch (1979) lists 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 powdered herbal substance, tincture (extraction solvent ethanol 60 %), fresh dried herbal substance.

The dose range for the single dose, taken from several pharmacopoeias, is 0.3 – 1 g, for the total daily dose 2 – 15 g.

- Haffner et al. (1991) recommend 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

- *Traditional use in EU countries*

Medicinal products containing aqueous and aqueous-ethanolic extracts, which can be assumed as well-established, combination products and preparations for external use are excluded from the following listing.

Germany

- Several preparations containing pressed juice of the fresh valerian root were traded in the year 1975 and have been fully registered.

  Indications: for nerve calming and sleep disturbances, spasmolytic in general spasmophily, nervous gastrointestinal disorders, nervous cardiac disorders.

  Dose recommendation: 3 x 1 table spoon/day
- A preparation with valerian root oil for oral use with registration as “traditional remedy” has been notified in the year 1978.

  Indication: Traditionally used for improvement of well-being in stress situations.

  Dose recommendation: single dose 15 mg
- Powdered herbal substance for preparation of a tea (tradition proven in cited literature) is registered for the indications “restlessness” and “sleep-induction disturbances due to nervous conditions”.

  Dose recommendation: single dose 2.5 g, once or several times daily.
- Several products containing dry extract with methanol/water (methanol 45 % V/V) have been registered during the last year. Traditional use for at least 30 years is not proven.

France

The French Competent Authority recommends the following traditional use of valerian root preparations:

“Traditionally used in symptomatic treatment of neurotonic conditions of adults and children, particularly in cases of minor sleep disturbances.”

IV.3.2 Asia

According to Usmanghani (1997, Pakistan), valerian root and rhizomes are used in traditional formulations 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 the 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.

IV.3.3 USA

- Sayre's Materia Medica (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 also mentions unofficial preparations (abstract, extract, infusion, syrup and aqueous extracts).

Conclusion

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

- Herbal substance
  - dried valerian root
- Herbal preparations
  - dry extracts prepared with water
  - valerian tincture
  - expressed juice from fresh root
  - valerian root oil

Traditional indications comprise a multitude of conditions, which are only in part comprehensible from a contemporary point of view. Sedative and anxiolytic effects, which have been discussed in detail above, are well reflected in the common indications for valerian root preparations. Besides that, spasmolytic and anticonvulsive properties have been demonstrated in several nonclinical investigations (Ruecker et al., 1978, Hazelhoff et al., 1982, Leuschner et al., 1993, Hiller et al., 1996). These effects are in congruence with the clinical use for dysmenorrhea and gastrointestinal cramps due to nervous conditions which has been outlined in most of the references cited above.

For all other indications, a rational basis is lacking; they are not acceptable in view also of the facts that effective alternatives are available nowadays and that sufficient information on the herbal preparations and dose recommendations are missing.

Recommended dose range for traditional valerian root and its traditional preparations (single dose):
Adolescents over 12 years of age, adults, elderly

Single dose:
- 0.3 to 1 g dried valerian root (e.g. as powdered herbal substance)
- 1 to 3 g dried valerian root for preparation of a tea
- dry extracts prepared with water corresponding to 1 to 3 g of the herbal substance
- valerian tincture corresponding to 0.3 to 1 g of the herbal substance
- 15 ml of expressed juice
- 15 mg of valerian root oil

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.

Maximum daily dose: 4 single doses