PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Valeriana

COMPLEMENTARY MEDICINE

Western Herbal Medicine

This unregistered medicine has not been evaluated by the South African Health Products Regulatory Authority for its quality, safety or intended use.

SCHEDULING STATUS

S0

1 NAME OF THE MEDICINE

A.VOGEL VALERIANA (oral drops)
Western Herbal Medicine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains:

Valeriana officinalis L. (Valerian) ..... 920 mg
[Fresh root, 1:10 extract providing dry plant equivalent: 92 mg herbal drug per ml]

Contains more than 50 % *v/v* alcohol.
Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear, brown liquid with a strong odour of valerian.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A.VOGEL VALERIANA is a herbal medicine with mild sedative action for the supportive treatment of nervous tension, anxiety, restlessness, irritability and sleeplessness.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:
For anxiety and tension:
Take 10 drops 3 times daily.
For sleeplessness:
Take 30 – 50 drops at bedtime.

Special populations
Elderly population:
No dosage adjustment is required for this population.

Paediatric population:
Children 6 – 12 years:
For anxiety and tension:
Take 5 drops 3 times daily.
For sleeplessness:
Take 15 – 25 drops at bedtime.

Method of administration
For oral use only.
Take drops undiluted or diluted in a small volume of water.

4.3 Contraindications

- A.VOGEL VALERIANA should not be used in patients who have a hypersensitivity to *Valeriana officinalis* L. (Valerian) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

- A.VOGEL VALERIANA contains alcohol and should be used with caution by individuals with a sensitivity or intolerance to alcohol.
- If symptoms worsen or do not improve after 2 – 4 weeks during the use of A.VOGEL VALERIANA drops, a doctor, pharmacist or other healthcare provider should be consulted.

Paediatric population

- A.VOGEL VALERIANA, (due to its alcohol content) may impact sensitive individuals during daily activities such as learning ability, physical activities, or affect appetite or sleep patterns.
- A.VOGEL VALERIANA is not recommended for use in children under 6 years of age.

4.5 Interaction with other medicines and other forms of interaction

Valerian should be used with caution when combined with the following:

- Alcohol – possible additive sedative effect when used concomitantly.
- Alprazolam - possible additive sedative effect when used concomitantly.
- CNS depressants - possible additive sedative effect when used concomitantly.
- Glucuronidated medicine– Valerian may weakly inhibit glucuronidations and increase concentrations of medicine metabolised by UGT1A1 and UGT2B7.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
No information available.

Pregnancy
The safety of this product during pregnancy has not been established. In the absence of sufficient data, the use of A.VOGEL VALERIANA during pregnancy is not recommended.

Breastfeeding
The safety of this product during breastfeeding has not been established. In the absence of sufficient data, the use of A.VOGEL VALERIANA during breastfeeding is not recommended.

Fertility
Fertility studies have not been performed.

4.7 Effects on ability to drive and use machines

A.VOGEL VALERIANA may have an effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision in sensitive individuals.

It is not always possible to predict to what extent A.VOGEL VALERIANA may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which A.VOGEL VALERIANA affects them.

A.VOGEL VALERIANA contains alcohol. The effect of valerian preparations may be enhanced by consumption of alcohol.

4.8 Undesirable effects

If symptoms of hypersensitivity occur e.g. rash, urticaria or angioedema of the skin, discontinue use of product, and contact your healthcare professional immediately.

Mild gastrointestinal symptoms (e.g. nausea, abdominal cramps) may occur. The frequency of these symptoms is not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8). Treatment of overdose should be symptomatic and supportive.

Valerian root at a dose of approximately 20 g caused benign symptoms, (fatigue, abdominal cramps, chest tightness, light-headedness, hand tremors and mydriasis), which disappear within 24 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Clinical studies – *Valariana officinalis* L.

Despite inconsistent findings in prior data, systematic reviews and metanalyses, Shinjyo *et al*. (2020) conducted a systematic review and metanalysis on the use of Valerian root for sleep problems, 60 trials (n=6894) were included for review, the authors concluded that valerian could be a safe and effective herb to promote sleep and prevent associated disorders. They suggest that previous inconstancy in the data is likely attributable to variable quality of herbal extracts with more reliable results most likely to be obtained from those extracts derived from the whole root or rhizome and that quality control mechanisms are necessary to counter the negative impact of some of the unstable active constituents.

Valeriana officinalis L. root extract 400 mg resulted in a significant decrease in sleep latency scores ($p<0,05$) and improvements in sleep quality in a placebo controlled trial on 128 participants, the response was particularly evident in the sub-category of participants classified as poor or irregular sleepers ($p<0,05$) (Leathwood *et al*. 1982). A randomised, double-blind, placebo controlled, cross-over study using both objective and subjective measures of sleep efficiency in participants with primary insomnia also concluded that valerian extract had a positive impact on sleep structure and perception of sleep. Slow-wave sleep (SWS) latency was significantly reduced with valerian (21,3 vs. 13,5 min respectively, $p<0,05$) and SWS time in bed was increased with long term treatment compared to baseline (9,8 vs 8,1 % respectively, $p<0,05$) (Donath *et al*. 2000).

5.2 Pharmacokinetic properties

Valariana officinalis L. extract was incubated with rat hepatocytes to quantity the resultant metabolic changes that took place phytochemically and pharmacologically in vitro. Using quantitative HPLC significant metabolic activity were measured with regard to sesquiterpines and iridoids, acetoxyvalerenic acid decreased by 9-fold, whereas hydroxyvalerenic acid increased 9-fold due to O-deacetylation. Valepotriates; didrovaltrate, isovaltrate and valtrate decreased 2,18 and 16-fold respectively. Interestingly binding to GABA (A) receptors was no different between incubated and non-incubated extract, i.e. valerenic acid and valepotriates when tested singularly did not exhibit any binding action, suggesting other constituents or combinations thereof therefore provide the observed inhibitory and allosteric action on GABA (A) receptors (Simmen *et al*. 2005).

Maier-Salamon *et al*. (2009) investigated the hepatic metabolism and transport of valerenic acid (considered to be the main active constituent in valerian) in isolated perfused livers from both Wistar and Mrp2-deficient TR (-) rats, the data confirmed that valerenic acid and its glucuronides were eliminated into bile by the canalicular transporter Mrp2.

The pharmacokinetics of valerenic acid (VA), one of the key constituents and markers for quantitative and qualitative assessment of valerian root extracts was described by Anderson *et al*. (2005). Six healthy adults were administered a 600mg dose of valerian and blood samples collected for 8 hours thereafter, VA levels were determined by LC/MS/MS methods. Maximum serum concentration (C_{max}) was reached within 1-2 hours in the majority of subjects with VA detectible for at least 5 hours post dosing and the determined elimination half-life (T1/2) was 1,1 ± 0,6h, area under the concentration time curve (AUC) was variable (4,80 ± 2,96 ug/ml. h) and did not correlate with age or weight (Anderson et al. 2005). Subsequently the same researchers determined that C_{max}, T_{max} and $T_{1/2}$ or area under the time curve (AUC) were not dissimilar between a single 300 mg dose and that measured after 2 weeks of nightly dosing in elderly women, however C_{max} and AUC decreased, and $T_{1/2}$ was shown to increase with increased body weight (Anderson *et al*. 2010).

5.3 Preclinical safety data

In rodents, ethanolic extracts of valerian root have demonstrated low toxicity in both acute tests and repeated dose experiments over periods of 4-8 weeks. AMES-tests on mutagenicity (dry extracts, 4-7:1 with 40 % ethanol *(v/v)* and 3-6:1 with 70 % ethanol did not yield results of concern. No tests on reproductive toxicity or carcinogenicity are available (ESCOP, 2016).

Rosecrans *et al*. (1961), demonstrated that a 9,5:1 extract of *Valeriana officinalis* L. showed a LD50 of 3,3 g/kg after ip injection in mice, in another study the LD50 of the essential oil was shown to be 15 g/kg in mice (Skramlik, 1959). According to Fehri *et al.* 1991, doses as high as 600 mg/kg of *Valeriana officinalis* in rats over a period of 30 days were shown to have unremarkable adverse effects and in a murine model long term exposure to Valeriana officinalis (30 days) did not result in any oxidative damage to the CNS (Fachinetto *et al.* 2007). Valtrate, didrovaltrate and acevaltrate did not lead to any acute toxicity in rats at oral doses of 4,6 g/kg (Von Eickstedt & Rahman, 1969). In mice, oral doses of 500, 1 000 and 2 000 mg/kg of valerian root extract for 7 days led to increased frequency of micronuclei in polychromatic erythrocytes and decreased the ratio of these to normochromic erythrocytes in the femur, testis chromosomal aberration with spermatozoal abnormality was also detected as well as depleted concentration of nucleic acids in testicular cells. MDA concentrations were also increased, and NP-SH levels decreased in hepatic and testicular cells. Such results may have been due to terpenoids (valepotriates) and flavonoids (6-methylapigenin and 2S(-)-hesperidin found in valerian (Al-Majed *et al*. 2006).

Valerenic acids (valerenic acid, acetoxyvalerenic acid, hydroxyvalerenic acid and methyl valerenate) characteristic of *Valeriana officinalis* were shown to have a low toxicity with IC(50) values between 100 and 200 µM. Valepotriate levels were shown to be of most importance with respect to in vitro toxicity, these however break down over a period of 2 months leading to significant reduction in cytotoxicity (Bos *et al*. 1998).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contains more than 50 % *v/v* alcohol.
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.
Protect from light.
Store in the original package/container.

6.5 Nature and contents of container

Packed in an amber type III glass bottle, with plastic dropper (LDPE) and screw cap (HDPE) with tamper evident seal.

Pack size: 50 ml

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)/REFERENCE NUMBER

U 961 (Act 101/1965)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated.

10 DATE OF REVISION OF TEXT

July 2021