PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Menoforce

Hot Flush and Night Sweat Remedy

COMPLEMENTARY MEDICINE
Western Herbal Medicine
This unregistered medicine has not been evaluated by the South African Health Product Regulatory Authority for its quality, safety or intended use.

SCHEDULING STATUS:

S0

1 NAME OF THE MEDICINE
A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY (tablets)

Salvia officinalis L. (Sage)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains:
Salvia officinalis L. (Sage) ..... 3400 mg
[Fresh leaves, 1:17 extract providing dry plant equivalent: 200 mg herbal drug per tablet]

Contains sugar: Sucrose ..... 6,6 mg.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Olive-green to yellowish-brown, speckled, oblong biconvex, bevelled tablets with a slightly aromatic odour.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY is a herbal medicine that does not contain oestrogen or have an oestrogen-like action. It is used for the supportive treatment of menopausal syndrome and associated hot flushes and night sweats, and for the supportive treatment of hyperhidrosis (excessive sweating).

A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY has the following therapeutic indications in menopausal women:
- To reduce the frequency and intensity of hot flushes and night sweats.
- To improve sleep quality.
- To improve mental focus (cognitive function) and anxiety.
- To improve fatigue.
- To improve the somato-vegetative symptoms of menopausal syndrome.

4.2 Posology and method of administration
Posology

Adults (18 years and over):
The usual dose is: 1 tablet daily.
The dosage may be increased, on the advice of your healthcare professional to 2 tablets daily (if necessary, for 1 – 2 weeks).

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

Paediatric population:
This product is not indicated in patients younger than 18 years.

Method of administration
For oral use only.

4.3 Contraindications
Do not use in cases of known hypersensitivity to *Salvia officinalis* L. (Sage) preparations or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
If the condition worsens or does not improve after 12 weeks, consult a healthcare practitioner.

Sucrose warning:
A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.
Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY.

4.5 Interaction with other medicines and other forms of interaction
None known.

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 MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY during pregnancy is not recommended.

Breastfeeding
The safety of this product during lactation has not been established. In the absence of sufficient data, the use of A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY during lactation is not recommended.

Fertility
Fertility studies have not been performed.

4.7 Effects on ability to drive and use machines
A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY has no effect on mental and/or physical ability to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects
None 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 professionals 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
None known.
Treatment of overdosage should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
D33.6 Western Herbal Medicine

In both *in vitro* and *in vivo* models A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY (a hydroalcoholic, thujone-free extract from freshly harvested Salvia officinalis leaves) has demonstrated potent modulation of neuro-receptors (involved with thermoregulation and sweating) as well as serotonin transporters with strong binding affinity to, adrenergic α_{2A}, μ-opioid, muscarinic M_3 and serotonin 5-HT_{1A} receptors with IC_{50} values of 15 ug/ml, 20 ug/ml, 25 ug/ml and 19 ug/ml respectively and the highest binding affinity determined to be that from hydroethanolic extracts of the fresh leaves of *Salvia officinalis* (Tober and Schoop 2019).

Both cholinergic and adrenergic nerve terminals are immediately distributed to eccrine sweat glands. The M_3 muscarinic antagonist and adrenergic α_{2A} agonist action of (a hydroalcoholic, thujone-free extract from freshly harvested *Salvia officinalis* leaves) demonstrated in *in vitro* models is suggestive of a peripheral action at the site of sweating and hot flushes since existing muscarinic antagonists such as scopolamine or hyoscyamine are known to inhibit sweating via the M_3 receptor and adrenergic α_{2A} agonistics such as clonidine is known to reduce hot flushes (Tober and Schoop 2019).

In addition to peripheral action on sweating and flushing gained from human recombinant receptors, concurring data from native female hypothalamic receptors suggests additional action on central thermoregulation with all affected receptors being associated with thermoregulation with μ-opioid ligands playing a specific role therein, furthermore muscarinic M_3, α_{2A} adrenergic receptors also being prominently expressed in the thermoregulatory region of the hypothalamus (Tober and Schoop 2019).

In vitro data thus confirms that A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY demonstrated modulation of neurological pathways involved with thermoregulation and modulation which are known therapeutic targets of menopausal syndrome and treatment of menopausal hot flushes (Tober and Schoop 2019), the data convincingly shows that the clinical effects of A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY are at neurotransmitter level and not on oestrogen (Dimpfel *et al.* 2021), this is further supported by Rahte *et al.* (2013) who demonstrated that Bioforce (A.Vogel) *Salvia officinalis* tincture produced by maceration of fresh cut leaves of *Salvia officinalis* in 66 % EtOH (1:17) did not demonstrate any oestrogenic activity *in vitro* in terms of the ERLUX assay.

Efficacy and safety data:

Sixty-nine menopausal women with at least 5 hot flushes daily were treated for 8 weeks with A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY (1 tablet daily i.e. 3400 mg ethanolic extract of fresh *Salvia officinalis* leaves) in an open multicentre clinical trial. Change in intensity and frequency of hot flushes as well as data from the Menopause Rating Scale (MRS) was analysed to evaluate efficacy (Bommer, Klein & Suter 2011).

The following outcomes were noted:
- Total number of hot flushes per day decreased significantly (p=0,0001) – by 29 % after 2 weeks and 48 % after 4 weeks (p=0,0001).
- A significant reduction in number of hot flushes was achieved as early as 2 weeks on treatment.
- Total score of the mean number of intensity rated hot flushes (TSIRHF) reduced by 50 % after 4 weeks and by 64 % after 8 weeks.
- A 50 % reduction in TSIRHF was achieved within four weeks of treatment.
- Moderate, severe and very severe flushes reduced significantly over the 8 weeks of treatment (p=0,0001, p=0,0001 & p<0,05 respectively).
- Significant reduction in global MRS scores and all sub scores of the MRS were noted and 8/11 variables of the MRS reduced significantly, the greatest reduction was noted for 'hot flushes' & 'sleep problems'.

MRS Category	Start	End	% Reduction	P-value
Somato-Vegetative sub-scale (SV-MRS)	7,6	4,3	43 %	P<0,0001
Psychological sub-scale (P-MRS)	5,8	3,1	47 %	P<0,0001
Urogenital sub-scale (UG-MRS)	1,5	1,2	20 %	P<0,01
Total MRS Score	14,9	8,6	43 %	P<0,0001

- In addition to positive effect on hot flushes, MRS Psychological sub-scale scores reduced by 47 % (p<0,0001) (depressive mood, irritability, anxiety and physical/mental exhaustion).

Reported tolerability was 'good/very good' in 90 % of physicians and patients, there were no significant changes in full blood count parameters, AST, ALT, bilirubin, creatinine, glucose or cholesterol (Bommer, Klein & Suter 2011).

In a double-blind, randomised, placebo-controlled trial, 80 women, 48 – 65 years of age who had been menopausal for >12 months, had a Menopausal Rating Scale Score of >10, and experienced at least 5 hot flushes daily or intense hot flushes daily and disturbing sweating (VAS 0-4: >1) were treated with A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY (a tablet daily i.e. 3400 mg ethanolic extract of fresh *Salvia officinalis* leaves) or placebo for 4 weeks. Response to treatment was assessed using the Menopause Rating Scale (MRS), Hot Flush Severity Score (HFS), Profile of Mood State (POMS), SF-B/R sleep quality questionnaire and objectively using quantitative EEG (qEEG) assessments (Dimpfel *et al.* 2021).

The following outcomes were noted:
- MRS scores reduced by 39,2 % from 15,3 ± 6,87 to 9,3 ± 5,75 and significantly in comparison to placebo (p=0,002).
- Significant reduction in the MRS Somato-vegetative (e.g. hot flushes) sub-scale after 4 weeks (p=0,0004).
- Significant reduction in the MRS Psychological sub-scale after 4 weeks (p=0,038).
- Decrease in the HFS score by 55,3 % from 15,9 ± 13,77 to 7,1 ± 7,41 reaching significance from week 3 onward (p=0,028).
- Sleep quality, discontent and fatigue also improved significantly compared to placebo (p<0,05) in terms of SF-B/R and POM data.
- The clinical effects correlated with significant reduction in frontal lobe beta2 wave qEEG intensities compared to placebo, suggestive of less stress induction.
- All brain areas within the 6 distinct frequency bands showed statistically significant spectral power differences versus placebo under test conditions i.e. 'eyes open,' concentration d2-test, memory test, concentration performance test, reaction time test, number identification test and number connection test after 4 weeks, suggesting advanced cognition, the induction of a state of mental activation as well as relaxation.

Reported tolerability was 'very good' in 100 % of cases with no clinically relevant changes in vital signs or laboratory safety parameters (Na+, GOT, GPT, GGT, creatinine, glucose, urine status and sediment) (Bommer *et al.* 2019) (Dimpfel *et al.* 2021).

5.2 Pharmacokinetic properties
Data on pharmacokinetic effects are not available.

5.3 Preclinical safety data
Tests on reproductive toxicity and carcinogenicity have not been performed with A.VOGEL MENOFORCE HOT FLUSH AND NIGHT SWEAT REMEDY.

Genotoxicity data available for the extract of *Salvia officinalis* used in *Salvia off.* tablets demonstrated negative Ames test results. This is supported by other published data and suggests that the risk of genotoxicity or mutagenicity resulting from the use of *Salvia officinalis* extracts is negligible.

Bioforce (A.Vogel) *Salvia officinalis* tincture produced by maceration of fresh cut leaves of Salvia officinalis in 66 % EtOH (1:17) did not demonstrate any oestrogenic activity *in vitro* in terms of the ERLUX assay (Rahte *et al.* 2013).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Colloidal anhydrous silica
Croscarmellose sodium
Glycerol distearate
Microcrystalline cellulose
Sucrose laurate

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months unopened.
Use within 4 months of opening.

6.4 Special precautions for storage
No special storage conditions.
Store at or below 25 °C in a cool, dry place.
Store in the original package/container.

6.5 Nature and contents of container
Amber glass bottles (type III glass), closed with pilfer proof screw caps fitted with a polyethylene liner.

Pack size: 30 tablets

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)

Listing number: 132275

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated.

10 DATE OF REVISION OF TEXT

July 2021