PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Nephrosolid

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 NEPHROSOLID (oral drops)
Western Herbal Medicine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains:

Solidago virgaurea L. (Goldenrod) ..... 635 mg
[Fresh aerial parts, 1:8 extract providing dry plant equivalent: 79,4 mg per ml drug product]
Betula pendula ROTH (Silver birch) ..... 166 mg
[Fresh leaves, 1:5,5 extract providing dry plant equivalent: 30,1 mg per ml drug product]
Ononis spinosa L. (Restharrow) ..... 64 mg
[Fresh aerial parts, 1:10 extract providing dry plant equivalent: 6,4 mg per ml drug product]
Equisetum arvense L. (Common horsetail) ..... 55 mg
[Fresh aerial parts, 1:11 extract providing dry plant equivalent: 5 mg per ml drug product]

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 an aromatic odour and an aromatic, bitter taste.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A.VOGEL NEPHROSOLID is a herbal medicine which acts as a tonic to support the function of the kidneys, bladder and urinary tract.

A.VOGEL NEPHROSOLID has the following therapeutic indications:
- As a tonic for the routine maintenance of kidney and urinary tract health.
- For the supportive treatment of the general signs and symptoms of kidney and urinary tract disorder.
- For the supportive treatment of signs and symptoms of kidney and urinary tract infection and inflammation.
- For supportive treatment of mild fluid retention.
- For supportive treatment and prevention of kidney stones.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:
For general kidney, bladder and urinary tract health maintenance:
Take 15 drops once or twice daily.
For acute, supportive treatment of kidney, bladder or urinary tract disorders:
Take 20 – 30 drops three times daily.

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

Paediatric population:
This product is not indicated in patients younger than 12 years.

Method of administration
For oral use only.
Ensure adequate fluid intake during treatment.
Take preferably 30 minutes before meals.
Take drops undiluted or diluted in a small volume of water.

4.3 Contraindications
- A.VOGEL NEPHROSOLID should not be used in patients who have a hypersensitivity to the active substances, plants of the *Asteraceae (Compositae)* family or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
- A.VOGEL NEPHROSOLID contains alcohol and should be used with caution by individuals with a sensitivity or intolerance to alcohol.
- A.VOGEL NEPHROSOLID should be used with caution and under medical supervision in cases of oedema as a result of severe cardiac or renal disease.
- If complaints or symptoms such as fever, dysuria, spasms, or blood in urine occur, a doctor or other healthcare practitioner should be consulted.
- If the condition worsens or does not improve after 4 weeks, consult a healthcare practitioner.

Paediatric population
A.VOGEL NEPHROSOLID is not recommended for use in children under 12 years of age.

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 NEPHROSOLID 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 NEPHROSOLID during breastfeeding is not recommended.

Fertility
Fertility studies have not been performed.

4.7 Effects on ability to drive and use machines
No impairment of the ability to drive or use machines is known.

It is not always possible to predict to what extent A.VOGEL NEPHROSOLID 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 NEPHROSOLID affects them.

A.VOGEL NEPHROSOLID contains alcohol.

4.8 Undesirable effects
If symptoms of hypersensitivity or allergic reactions (itching, rash, urticaria) occur, discontinue use of product, and contact a healthcare professional immediately. The frequency of these symptoms is not known.

Gastrointestinal symptoms (e.g., nausea, vomiting and diarrhoea) may also occur less frequently.

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
No toxic effects are expected.
In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).
Treatment of overdosage should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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The ingredients of A.VOGEL NEPHROSOLID have tonic, anti-inflammatory, antispasmodic, analgesic, antimicrobial, and mild, potassium-sparing diuretic action within the urinary tract.

Solidago virgaurea
European goldenrod has shown diuretic, anti-inflammatory, antimicrobial, antispasmodic and analgesic properties (ESCOP 2018).

In vitro experiments confirm the following actions: (ESCOP 2018)
- Spasmolytic
- Diuretic
- Anti-inflammatory
- Antibacterial action against (*Staphylococcus aureus, Enterobacter faecalis, Escherichia coli* and *Bacillus cereus*)
- Antifungal against various species of Candida (*C. albicans, C. tropicalis, C. krusei, C. parapsilosis, C. pseudo-tropicalis, C. guilliermondi, C. glabrata*) and dermatophytes (T*richophyton mentagrophytes, Microsporum gypseum* and *Microsporum canis*)

In vitro experiments confirm the following actions: (ESCOP 2018)
- Diuretic
- Anti-inflammatory
- Analgesic

Clinical studies *Solidago virgaurea:*
A Swiss group (Brühwiler K, Frater-Scröder M, Kalbermatten R and Tobler M) studied the effect of a fresh Goldenrod tincture on urinary tract inflammation. The diuretic effect on 22 healthy volunteers was first evaluated under double-blind placebo-controlled conditions. A significant rise (30 %) in the amount of secreted urine was observed after a single dose of 100 drops (about 4 ml). Based on this positive result an open trial using 53 patients was initiated. Thirty-six patients had acute urinary tract inflammation, twelve had a chronic history and five exhibited symptomatic bacteriuria associated with pregnancy. Dosage was 100 drops of tincture per day. About 70 % of patients experienced improvement as assessed by the reduction of symptoms such as dysuria, frequency and tenesmus (Brühwiler, Frater-Schröder *et al.* 1992).

The efficacy of a dry extract (5,0 – 7,1:1, ethanol 30 % *m/m*; 3 × 425 mg of extract daily for 4 weeks on average) was investigated in an open, multi-centre, post-marketing study involving a total of 1 487 patients, with subgroups for urinary tract infections, irritable bladder, and urinary calculi/renal gravel. For patients with recurrent urinary tract infections (n=555) the extract alone was as effective as when combined with initial antibiotic treatment (Laszig 1999a, Laszig, Smiszek *et al.* 1999b). In patients suffering from chronic or recurrent irritable bladder symptoms (n=512), incontinence was improved or eliminated in 2 out of 3 cases. The subgroup with "urinary calculi/renal gravel" comprised 427 patients (32 % of whom had additional urinary tract infections and 11 % had additional symptoms of irritable bladder); for the typical symptoms, responder rates of 81 % (feeling of pressure in the region of the bladder) to 98 % (colic) were determined. Global improvement (CGI-scale) under treatment was evaluated by the physicians as "very much or much better" in 79 % of the cases (Laszig, Smiszek *et al.* 1999b).

In a subgroup analysis of the above study of 512 patients with chronic, recurrent irritable bladder conditions (aged 13-96 years, 77 % female) was treated for five weeks with 425 mg of a dry extract (5,0 - 7,1:1) 3 times per day. 96 % of the patients showed improvement recorded by the CGI scale, and in 80 % of patients' estimations, effectiveness was 'good' or 'very good' (Pfannkuch and Stammwitz 2002).

Case reports on 10 patients treated with the above extract during extracorporeal shock wave lithotripsy in hospital and during 4-week after-care indicated a positive spasmolytic effect from treatment with the extract: no colic occurred and additional spasmolytic drugs were unnecessary (Laszig, Smiszek *et al.* 1999b).

Betula pendula
Birch leaf has demonstrated diuretic, anti-inflammatory and antioxidant effects *in vitro*, and diuretic activity in various *in vivo* experiments (ESCOP 2015).

In vitro and *in vivo* experiments:
- Anti-inflammatory properties *in vitro* – 23 % ± 2 % prostaglandin synthesis inhibition and 76 ± 4 % platelet-activating factor (PAF)-exocytosis inhibition (due to high tannin and polyphenol content) (Tunon, Olavsdotter *et al.* 1995).
- Anti-inflammatory effect *in vivo* – of botulin and *Betula pendula* extracts (reduction in oedema) in TPA induced mouse ear inflammation (Dehelean, Şoica *et al.* 2012).
- Xanthine oxidase inhibition – a target for urate lowering drugs in urate kidney stones and urate inducted arthritis (gout), *Betula pendula* ethanolic extract had IC50 (half maximal inhibitory concentration) value of 39,4 ug/mL (due to salicylates and phenolics).
- Antioxidant and free radical scavenging ability (Calliste, Trouillas *et al.* 2001).
- Antimicrobial effect against gram-positive *Staphylococcus aureus in vitro* (Rauha, Remes *et al.* 2000).
- Antibacterial effect against *Staphylococcus aureus* and *Bacillus subtilis* (oleanolic acid compound from extract of *Betula pendula*) (Duric, Kovac-Besovic *et al.* 2013).
- Mild diuretic effect (Major 2002).

Clinical studies on *Betula pendula*:
A field study (n=1066) applied an aqueous extract of Birch leaf for irrigation of the urinary tract for 2 - 4 weeks, achieving symptom resolution in 78 % of patients with urinary tract infection and inflammation, 65 % in those with 'irritable bladder' and 65 % in those with kidney stones (Müller and Schneider 1999).

Birch leaf tea reduced urinary microbial counts by 39 % compared to placebo (18 % reduction) in a randomized, double-blind, placebo-controlled pilot study (n=15) treated lower urinary tract infections with Birch leaf tea (Engesser, Bersch *et al.* 1998).

***Ononis spinosa* (ESCOP 2015)**
Restharow has demonstrated diuretic and analgesic action in various *in vivo* (animal model) experiments anti-inflammatory action *in vitro*.

In vitro experiments:
Ononis extract had high moderate antifungal activity against *Aspergillus flavus*, *Fusarium moniliforme* and *Candida albicans* relative to miconazole nitrate at 40 µg/disc (Mahasneh and El-Oqlah 1999). Further, there was good (>8 mm) pattern of inhibition against both gram-positive and gram-negative bacteria as well as weak to moderate (6 – 8 mm) antifungal activity (Mahasneh and El-Oqlah 1999). Antimicrobial effects of ethanolic extracts *in vitro* of Ononis were also noted against *E.coli* (10 mm inhibition), *S. typhimurium* (10 mm inhibition), *S. aureus* (11 mm inhibition) (Mahasneh and El-Oqlah 1999). In another study, antimicrobial effects were confirmed against *E. coli, P. aeruginosa, S. aureus, C. albicans, C. krusei* (Citoglu and Altanlar 2003).

Equisetum arvense
In vitro and *in vivo* experiments:

Antimicrobial effects:
- Equisetum extract has demonstrated antibacterial action against *Escherichia coli* (Wojnicz, Kucharska *et al.* 2012).
- 5 µg of a hydroalcoholic extract thereof was also shown to be comparable to 30 µg ampicillin or nystatin against *S. aureus*, *K. pneumoniae*, *P. aeruginosa, S. enteritidis, A. niger* and *C. albicans* (Milovanović, Radulović *et al.* 2007).
- The methanolic extract of the aerial parts of *Equisetum arvense* displayed antibacterial activity against *Escherichia coli* at high concentration (1 g/ml) (Aldaas 2011).
- The 1:10 dilution of the essential oil of *Equisetum arvense* possessed a broad spectrum and very strong antimicrobial activity against all the tested bacteria and fungi (*Staphylococcus aureus*, E*scherichia coli*, *Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella enteritidis, Aspergillus niger*) (USLU, ERDOGAN *et al.* 2013).
- The antibacterial activity of ethanolic and aqueous extract of *Equisetum arvense* was screened against selected urinary tract pathogens (*E. coli, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, Staphylococcus saprophyticus* and *Enterococcus faecalis*) using disc diffusion technique. Both the extracts at different concentration exhibited antibacterial activity against all the tested bacterial strains. Ethanolic extract exhibited comparably a high degree of activity than the aqueous extract (Geetha, Lakshmi *et al.* 2011).
- The *in vitro* antibacterial activity of ethanol stem extract (50 – 400 µg/ml) of *Equisetum arvense* was studied against Gram-positive (*Bacillus subtilis* and *Micrococcus luteus*) and Gram-negative (*Escherichia coli, Shigella flexneri*) bacteria. All were found to be very sensitive to plant extract at all concentrations. The mean zone of inhibition for the extract against Gram-positive and Gram-negative bacteria increased with the increasing concentration of the extract. The highest mean zone of inhibition (32 mm) was recorded against *Escherichia coli* (Sinha 2012).
- The 1:10 dilution of the essential oil of *Equisetum arvense* L. was shown to possess a broad spectrum of a very strong antimicrobial activity against all tested strains (*Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella enteritidis*; fungi: *Aspergillus niger* and *Candida albicans in vitro* using the disc diffusion method (Radulović, Stojanović *et al.* 2006).

Anti-inflammatory effects:
- The hydroalcoholic extract of stems from *E. arvense* possesses analgesic effect against chemical models of nociception, the extract also presents a clear anti-inflammatory effect. Flavonoids, sterols, and other compounds (saponins and tannins) can be related, at least in part, to the analgesic and anti-inflammatory effects of hydroalcoholic extract of *E. arvense.* These results indicate that this extract exhibits an antinociceptive effect in chemical models of nociception which is not related to the opioid system, as well as anti-inflammatory properties (Do Monte, dos Santos *et al.* 2004).

Diuretic effect:
- The diuretic action of *equisetum* (without significant change in elimination of electrolytes) has been demonstrated in a double-blind, randomized trial as being superior to placebo (Carneiro, Freire *et al.* 2014).

Antioxidant effect:
- The antioxidant action (Štajner, Popović *et al.* 2006, Mimica-Dukic, Simin *et al.* 2008) have also been demonstrated in various experiments *in vitro* and anti-inflammatory effects demonstrated both in *in vitro* (Gründemann, Lengen *et al.* 2014) and *in vivo* (Do Monte, dos Santos *et al.* 2004).

Effect on bladder:
- *Equisetum arvense* ethanol root extract influences urinary bladder activity by decreasing adenosine triphosphate release, and is, therefore, a potential therapeutic agent against bladder disorder (Zhang, Li *et al.* 2015).

Clinical studies:
E. arvense standardized for silicon content was a suitable and effective treatment for both men and women. It was effective in reducing symptoms of urinary incontinence and overactive bladder including frequency, nocturia, urgency and bladder discomfort (Seipel 2008).

The topical wound healing properties of *equisetum* have also been demonstrated in animal models (Ozay, Ozyurt *et al.* 2010, Ozay, Kasim Cayci *et al.* 2013) and significant improvements in oedema, erythema and pain compared to placebo were demonstrated in a randomized, placebo-controlled double-blind trial applying *equisetum* ointment to episiotomy wounds (Asgharikhatooni, Bani *et al.* 2015).

5.2 Pharmacokinetic properties

***Solidago virgaurea* (ESCOP 2018)**
A 60 % ethanolic extract (100 µg/mL) did not influence the expression of CYP1A2 and the transporter protein MDR1 expression in LS180 cells. However, it did induce a 1,9-fold expression of CYP3A4 gene (Brandin 2007).

After oral administration of leiocarposide and salicin to rats, the glycosides were mostly excreted unchanged in the urine. Hydrolysis of the ester and glycosidic bonds from leiocarposide to leiocarpic acid and saligenin as well as from salicin to saligenin mainly occurred in the caecum and colon. Saligenin was oxidized to salicylic acid in liver, kidney, and lung homogenates. Gentisic acid, a product of further oxidation of salicylic acid, was detected only in liver homogenate (Fötsch 1989a).

Experiments in rats demonstrated that leiocarposide is poorly absorbed after oral administration and is mostly excreted unchanged in the faeces, with less than 10 % of metabolites found in urine. Of the administered dose, 2 % was leiocarpic acid, 3-conjugates (2 %), salicylic acid (0,5 %), 5-conjugates (0,1 %) and salicyluric acid (0,5 %). Salicin was well-absorbed and excreted in the urine as unchanged drug (15 %) and the following metabolites: 0,1 % saligenin, 30 % salicylic acid, 5 % 5-conjugates, 0,1 % salicyluric acid, 2 % gentisic acid and 0,1 % 2,3-dihydroxy-benzoic acid. The different metabolic rates were explained by the high stability of the ester bond of leiocarposide, which is hydrolysed in artificial intestinal fluid only very slowly with a $t_{1/2}$ (half-life) of 41,7 h (Fötsch 1989b).

No information available for *Betula pendula, Ononis spinosa* and *Equisetum arvense (ESCOP 2015, ESCOP 2015, ESCOP 2018)*.

5.3 Preclinical safety data

Solidago virgaurea (ESCOP 2018)
The oral LD_{50} (median lethal dose) of leiocarposide (a phenol diglucoside constituent) in rats was determined as 1,55 g/kg b.w. (Chodera 1985). The mutagenic potential of NaN_3 in Ames assay with Salmonella typhimurium TA1535 was inhibited by a n-hexane extract at 2,5 mg/ml, whereas ethanolic extracts (>5 mg/mL) did not show antimutagenic activity (Kolodziej 2011).

Betula pendula (ESCOP 2015)
An extract of Birch leaf gave a very weak mutagenic response in the Ames test (Göggelmann 1986); no other studies have been performed to confirm this.

Ononis spinosa (ESCOP 2015)
An ethanolic extract (not further defined), administered orally or intraperitoneally at a daily dose corresponding to 2 g/kg b.w. for 14 days to rats or mice did not cause any visible toxic effects (Bolle 1993).

Equisetum arvense (ESCOP 2018)
The subchronic toxicity of powdered equisetum stem administered with the diet to female and male F344 rats was evaluated for 13 weeks. Significant alterations ($p<0,05$) were observed in haematological parameters including increased mean corpuscular haemoglobin (MCH) in males at a dose of 3,8 g as well as increased platelet count (PLT) and decreased MCH in the females at a dose of 7,9 g. Significant decreases ($p<0,01$) in serum calcium concentrations were observed at doses of 7,9 and 24,2 g in males. The intake did not significantly influence macroscopic and histopathological parameters or weight of organs (Tago 2010).

Oral administration of dried equisetum stem at doses of 30, 50 or 100 mg/kg b.w. for 14 days did not cause important changes in the morphology and hepatic function in rats (Baracho 2009).

Wistar rats at the age of 8 weeks (10) and 80 weeks (22) were treated with a hydroalcoholic dry extract (not further specified) at a dose of 50 mg/kg b.w. i.p. for 8 weeks. There was no toxicity observed during treatment (Dos Santos Jr. 2005a).

No information available on reproductive toxicity, genotoxicity, and carcinogenicity.

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
60 months.

6.4 Special precautions for storage
No special storage conditions.
Store at or below 25 °C.
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
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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
To be allocated.

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