PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Echinaforce®
Tablets

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 ECHINAFORCE® TABLETS
Echinacea purpurea (L.) MOENCH

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains:
Echinacea purpurea (L.) MOENCH (Purple cone-flower) .....380 mg
[Fresh aerial parts, 1:12 extract providing dry plant equivalent: 32 mg herbal drug per tablet]
Echinacea purpurea (L.) MOENCH (Purple cone-flower) .....20 mg
[Fresh root, 1:11 extract providing dry plant equivalent: 1,8 mg herbal drug per tablet]

Contains sugar: Lactose ..... 232,6 mg

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Round-shaped, biconvex, bevelled, greenish tablets with an aromatic odour and an aromatic, sweet and anaesthetising taste.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
A.VOGEL ECHINAFORCE® TABLETS, a herbal medicine for the prophylaxis and treatment of the symptoms of colds, flu, respiratory tract infections (RTI) and recurrent respiratory tract infections and their associated signs and symptoms including rhinitis, pharyngitis, catarrh, cough, pyrexia, malaise and myalgia.
A.VOGEL ECHINAFORCE® TABLETS improve resistance in those susceptible to the common cold, flu and recurring RTI and prevent complications of RTI such as sinusitis, tonsillitis, otitis, bronchitis and pneumonia.
A.VOGEL ECHINAFORCE® TABETS modulate and support the immune system in paediatrics and adults, and reduce the need for antibiotics (paediatric patients with RTI) and the need for analgesic and decongestant medication (adults with RTI).

4.2 Posology and method of administration
Posology
Adults and children over 12 years:
Prophylactic dose:
Take 3 tablets up to twice a day.
In acute cases:
Take 3 tablets three times daily.

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

Paediatric population:
Children 6 – 12 years:
Prophylactic dose:
Take 1 tablet up to three times daily.
In acute cases:
Take 1 tablet five times daily.

For children aged 2 – 6 years, A.VOGEL ECHINAFORCE® JUNIOR chewable tablets or A.VOGEL ECHINAFORCE® drops are recommended.

Prophylactic (prevention) dose: During times of increased infection risk.
Acute (treatment) dose: Start therapy at the first signs of symptoms.

Method of administration
For oral use only.
To be taken with some water before meals or melt in the mouth.

4.3 Contraindications
- Do not use in cases of known hypersensitivity to the active substance, to plants of the *Asteraceae (Compositae)* family or to any of the excipients listed in section 6.1.
- Because of their immunomodulatory activity, *Echinacea* extracts must not be used in cases of progressive systemic disorders, autoimmune diseases, immunosuppression and diseases of the white blood cell system.
- Concomitant use with immunosuppressant medicines.

4.4 Special warnings and precautions for use
- If severe symptoms persist for more than 10 days or symptoms worsen or high fever occurs during the use of A.VOGEL ECHINAFORCE® TABLETS, a doctor, pharmacist or other healthcare professional should be consulted.
- There is a possible risk of anaphylactic reactions in atopic patients. Atopic patients should consult their doctor before using products made of *Echinacea*.

Lactose warning:
- A.VOGEL ECHINAFORCE® TABLETS contain lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take A.VOGEL ECHINAFORCE® TABLETS.

4.5 Interaction with other medicines and other forms of interaction
There is no evidence from limited interaction studies that *Echinacea* extracts will interact with other medicinal products.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential/Contraception in males and females
No information available.

Pregnancy
Data on a limited number (several hundreds) of exposed pregnancies indicate no adverse effects of *Echinacea* extracts on pregnancy or on the health of the foetus/new-born child.

Echinacea extracts carry an FDA Class A Pregnancy Safety Rating.
"Adequate and well-controlled studies have failed to demonstrate a risk to the foetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)."

As a precautionary measure and in the absence of additional data, the use during pregnancy should be done under supervision of and on recommendation of a doctor.

Non-clinical studies on reproductive toxicity have not been performed.

Breastfeeding
Although there is a low level of evidence based on expert opinion of the safety of oral *Echinacea* in recommended doses during lactation, as a precautionary measure and in the absence of additional data, the use during lactation should be done under the supervision of and on recommendation of a doctor.

Fertility
No effect on fertility expected.

4.7 Effects on ability to drive and use machines
A.VOGEL ECHINAFORCE® TABLETS have no or negligible influence on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects
Adverse reactions are grouped into the following frequency classifications: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), not known (cannot be assessed from the available data)

Tabulated list of adverse reactions

Body System	**Undesirable effect** (Frequency not known)
Immune system disorders:	Hypersensitivity reactions (rash, urticaria, Stevens-Johnson Syndrome, angioedema of the skin, Quincke oedema, bronchospasm with obstruction, asthma and anaphylactic shock) may occur. *Echinacea* can trigger allergic reactions in atopic patients.

a. Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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
None known.
Treatment of overdosage should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
D33.6 Western Herbal Medicine.
Pharmacotherapeutic group and ATC code:
Immunomodulators of plant origin / L03AW05
Other preparations for respiratory system / R07AX

In vitro
Symptoms following cold and flu-like episodes are primarily a cause of inflammatory mediators (cytokines) produced by the epithelium and the immune system when encountering an infectious particle. Echinaforce® potently regulates the expression of cytokines like TNF-α, IL-6 and IL-8, and acts as an immune-modulator: Excessive production of inflammatory cytokines and chemokines are dampened (Ritchie *et al*. 2011). Alkylamides in Echinaforce® were shown to be key players in the process of immune modulation via acting on CB-2 receptors on immune cells. Interaction with CB-2 receptor was confirmed by computer modelling techniques (Gertsch *et al*. 2004).

Echinaforce® exhibits potent antiviral effects, inhibits viral replication and infectiousity of Influenza-, Respiratory Syncytial-, Parainfluenza- and at higher concentrations also of Rhinoviruses (Sharma *et al*. 2009 & Pleschka *et al*. 2009). Modulation of inflammatory cytokines was further demonstrated after infection of airway cell lines (A549 or MDCK-1) and organotypic 3D tissue cultures (Sharma *et al*. 2010).

Echinaforce® induced phagocytotic capacity in human granulocytes by 56 % when comparing to control.

Anti-oxidative effects were attributed to Echinaforce®: Cyclooxygenase and Lipoxygenase enzymes were inhibited by 44,7 ± 15,3 % and 93 ± 7 %, respectively.

Direct and indirect antiviral activity by secretion of interferon was demonstrated for *Echinacea purpurea*. Also, *Echinacea* extract inhibited the receptor-binding activity of viruses, suggesting that the extract interfered with the viral entry into cells (Pleschka *et al*. 2009).

The anti-viral properties of A.VOGEL ECHINAFORCE® have been confirmed against major viruses *in vitro* including highly pathogenic forms of Influenza virus (Avian, H5N1, H7N7 and swine H1N1) (Pleschka *et al*. 2009) as well as Influenza A & B (Vimalanathan *et al*. 2013 & Vimalanathan *et al*. 2017) , rhinovirus (Sharma *et al*. 2010) as well as herpes simplex (Sharma *et al*. 2009) confirming its viricidal action specifically against enveloped viruses (Sharma *et al*. 2009).

A.VOGEL ECHINAFORCE® is also viricidal *in vitro* against various human coronaviruses including SARS-CoV-1 (responsible for the original SARS outbreak in 2002), MERS-CoV (responsible for the MERS outbreak in 2012), Coronavirus 229E (causing the common cold) and the latest novel coronavirus, the SARS-CoV-2, responsible for the COVID-19 pandemic (Signer, Jonsdottir *et al*. 2020). Various *in vitro* experiments confirm that incubation of these strains of coronavirus with Echinaforce® inactivated all strains of coronavirus including the SARS-CoV-2 virus i.e. the viruses were inactivated, and their replication blocked when they made direct contact with Echinaforce® for SARS-CoV-2 this was achieved at concentrations below 50 µg/ml, a dose exceeded by a factor of 100 by a single Echinaforce® (400 mg tablet). The data suggests the potential prophylactic role A.VOGEL ECHINAFORCE® may play against all the coronaviruses tested (Signer, Jonsdottir *et al*. 2020).

Echinaforce® demonstrated strong bactericidal action against *S. pyogenes, H. influenzae* and *L. pneumophilia* as well as the ability to reverse respective cellular pro-inflammatory responses induced by these bacteria and a partial bactericidal effect *S. aureus* (MRSA & MSSA) and *Mycobacterium smegmatis* but complete reversal of their respective pro-inflammatory responses *in vitro* (Sharma *et al*. 2010).

In vitro studies have confirmed that when human bronchial epithelial cells are infected with Influenza virus A (H3N2), bacterial ligands such as ICAM-1 (intracellular adhesion molecule 1), fibronectin and platelet-activating factor receptors (PAFr) are stimulated allowing for subsequent attachment of bacteria such as *Haemophilus influenzae* and *Staphylococcus aureus* and the onset of secondary bacterial infection. In this context Echinaforce® has demonstrated the ability to reverse the expression of these bacterial ligands, thus preventing the likelihood of secondary bacterial attachment. Further, in the same context, the significant Influenza A driven inflammatory cytokine expression (cytokine storm) was prevented by Echinaforce® by suppressing the expression of Toll-Like Receptor 4 (TLR-4) and NF-κB (nuclear factor kappa). The study concluded that Echinaforce® has the potential to reduce respiratory complications by inhibiting virus-induced bacterial attachment, and the inflammatory cytokine storm caused by Influenza A (Vimalanathan *et al*. 2017).

Similarly, post-infective treatment with Echinaforce® was shown *in vitro* to significantly reduce *S. pneumoniae* adherence to juvenile airway epithelium infected with influenza virus or RSV; the mode of action being the down regulation of the ICAM-1 receptor confirmed by immunocytochemical staining. This mode of action is similar to that determined in *in vitro* studies using adult airway epithelium (Vimalanathan *et al*. 2018).

Ex vivo
Leukocytes isolated from Echinaforce®-treated volunteers showed modulated activity. Expression of cytokines (IL-8 and TNF-α) was inhibited under *ex vivo* stimulation with LPS. These results were confirmed in a clinical study with 30 subjects treated for 8 days with Echinaforce®. Daily blood samples were *ex vivo* stimulated with SEB/LPS and a panel of cytokines was measured. During treatment with Echinaforce® TNF-α and IL-1 were reduced and IL-10 increased under concomitant induction of chemokines (MCP-1 and IL-8) (Ritchie *et al*. 2011).

Clinical studies
In an open, phase 4, multicentre, controlled trial on 80 athletes Echinaforce® (Forte) was effective for the prevention and treatment of the common cold with 'good' to 'very good' tolerability, 71 % reporting no cold episodes (Schoop *et al*. 2006).

A randomized, placebo-controlled and double-blind clinical study investigated Echinaforce® tablets in 246 subjects with a common cold. Cold-related symptoms were reduced by 62,7 % in comparison to placebo by 29,3 % (p=0,02) (Brinkeborn *et al*. 1999).

A comparative clinical study demonstrated Echinaforce® drops to be as effective as the pressed juice from *Echinacea purpurea* in the treatment of severe colds (flu).

Echinaforce® was safe and effective in a randomized, double-blind, placebo-controlled clinical study in 755 participants over a time period of 4 months, when used for prophylaxis and acute treatment of the common cold. In this trial Echinaforce® reduced the total number of cold episodes, cumulated episode days and the need for RTI related analgesic and decongestant medication, and was particularly effective in preventing infections from enveloped viruses (p<0,05) i.e. Corona, Influenza, Parainfluenza, Respiratory Syncytial and Metapneumovirus i.e. pooled data from all detected enveloped virus infections revealed 47 cases in the placebo and 24 in the Echinaforce® group (p=0,0114). Prophylactic action of Echinaforce® was specifically demonstrated in population subsets considered to be more susceptible to RTI i.e. stressed subjects, those with recurrent RTI, poor sleepers and smokers (Jawad *et al*. 2012 & Schapowal, 2013).

A randomised, controlled, blinded study compared the long-term prophylactic effect A.VOGEL ECHINAFORCE® JUNIOR chewable tablets 3 X 1 daily [providing Echinaforce® 400 mg/tablet and total 1200 mg/day equivalent to ≈ 3 X A.VOGEL ECHINAFORCE® Tablets/day] with 3 X 1 vitamin C 50 mg [total 150 mg vitamin C daily] against respiratory tract infections in 203 children aged between 4 and 12 years (average age was 8 and 40 % were < 6yrs) over 4 months during the Swiss winter (Ogal *et al*. 2021).

The findings are summarised as follows:
- 32,5 % fewer cold & flu episodes in those who received Echinaforce® than those on the vitamin C control (OR=0,52 [95 % CI, 0,30-0,91] p=0,021).
- Cumulated sick days in the Echinaforce® group were 173 days (32 %) less than those on vitamin C control (429 vs 602 [p<0,001]).
- Cold & flu episodes were shortened by 1,4 days on Echinaforce® compared to those on the vitamin C control.
- Membranous virus (e.g. influenza, parainfluenza, RSV, corona, metapneumovirus) detections were significantly less in the Echinaforce® group vs vitamin C (28 vs 47 p<0,05).
- Confirmed influenza infections (3 vs 20 respectively p<0,05) concurring with previous Echinaforce® research.
- Bacterial superinfection and complications of RTI were reduced by 65 % (p<0,05).
- Echinaforce® was associated with 76,3 % reduction in antibiotic prescriptions (p<0,001).
- Echinaforce® use was further associated with significantly less average number of days with fever per group i.e. 1,6 days (SD 4,34) vs 4,9 days (SD 6,61) the difference being 3,3 days (p<0,001) equivalent to 67,3 % reduction.

Paediatric dose-response trials (Weishaupt *et al.* 2020):
The safety and efficacy of A.VOGEL ECHINAFORCE® at two dosages (Echinaforce® 1200 mg/day [equivalent of ≈ 3 X A.VOGEL ECHINAFORCE® TABLETS] vs 2 000 mg/day, 5 X A.VOGEL ECHINAFORCE® TABLETS/day] in the treatment of acute cold symptoms in children (4 – 12 years) was determined in a multicentred dose-response clinical trial with the following outcomes:
- Echinaforce® treated cold episodes lasted 7,5 days on average, with nine out of 10 episodes being fully resolved after 10 days.
- Children treated with Echinaforce® experienced an average of 1,9 cold episodes which was significantly less than the season average of 3,1 episodes (p<0.001)
- The higher dose regime enhanced the treatment effect by reducing the duration of illness by a further 1,2 days (p=0,046).
- In the highly compliant sub-population, a 1,7-day difference in duration of illness between the two groups (p=0,020) in favour of the higher dosage was found (further analysis of the highly complaint population).
- Cumulated sick days per subject revealed a significant difference of 2,9 days between groups (p=0,048) and after 10 days of treatment 8,7 % of cases remained unresolved in the 2 000 mg dose compared to 23,5 % on the 1 200 mg dosage (p=0,005).
- Effective symptom resolution finally contributed to a low antibiotic prescription rate in this study of 4.6 %.
- Physicians rated tolerability of A.VOGEL ECHINAFORCE® JUNIOR as 'good – very good' in 98,5 % of cases with no significant difference between the respective dosage groups and parents concurred rating tolerability as 'good-very good' in 99,2 % of cases.

5.2 Pharmacokinetic properties
Pharmacokinetic studies on Echinaforce® were performed over 4 hours in volunteers after ingesting oral drops (same drug substances in identical ratio as in ECHINAFORCE® TABLETS (Woelkart *et al.* 2006). For the oral drops a peak serum-level of 0,40 ng/ml dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide was detected after 30 minutes. For the tablets (250 mg total weight) after 45 min 0,12 ng/ml of the compound was measured. A total amount of bioavailable dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamide was expressed as area-under-curve for Echinaforce® oral drops (27,55 +/- 8,94 ng x min/ml) and for the Echinaforce® tablets (11,36 +/- 2,74 ng x min/ml).

Additional pharmacokinetic studies were performed with other Echinaforce® products (tablets and sore-throat spray). Isobutylamides (alkylamides) were resorbed from all formulations and bioavailability was comparable between the different Echinaforce® products. These data show that pharmacologically active constituents in Echinaforce® are bioavailable, while exhibiting a fast absorption.

5.3 Preclinical safety data
Echinacea purpurea showed no toxicity in single-dose toxicity (rodents), repeated-dose toxicity (rodents) and genotoxicity/carcinogenicity studies.

No mutagenic effects of Echinaforce® extract were detected in Ames' test (with or without metabolic activation).

Non-clinical studies on reproductive toxicity have not been performed.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose
Magnesium stearate
Pregelatinised starch

Contains sugar:
Lactose ..... 232,6 mg

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months unopened
After opening: use within 3 months.

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 sizes: 60 or 120 tablets.

Not all pack sizes may be marketed.

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/REFERENCE NUMBER(S)
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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
To be allocated.

10 DATE OF REVISION OF TEXT
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