PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Echinaforce® Junior

COMPLEMENTARY MEDICINE
Western Herbal Medicines
This unregistered medicine has not been evaluated by the SAHPRA for its quality, safety or intended use.

SCHEDULING STATUS:
S0

1 NAME OF THE MEDICINE
A.VOGEL ECHINAFORCE JUNIOR TABLETS

2 QUALITIVE AND QUANTITIVE COMPOSITION
Each chewable tablet contains:
380 mg of extract (as tincture) from fresh *Echinacea purpurea* (L.) MOENCH herba (Purple coneflower herb)
(1:12-13)
Dry plant equivalent (dpe): 32 mg herbal drug per tablet
Fresh plant equivalent (fpe): 100-200 mg fresh plant per tablet
20 mg of extract (as tincture) from fresh *Echinacea purpurea* (L.) MOENCH radix (Purple coneflower root) (1:11-12)
Dry plant equivalent (dpe): 1,8 mg herbal drug per tablet
Fresh plant equivalent (fpe): 5,6 – 9,8 mg fresh plant per tablet
Contains sugar: Sorbitol 266,2 mg
Sucrose 0,9 mg (in the orange flavouring)

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Flat, round-shaped, speckled, greenish tablets with an aromatic sweetish odour and an aromatic, sweet taste of orange.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
A.VOGEL ECHINAFORCE JUNIOR TABLETS is a herbal medicine for the prophylaxis and treatment of the symptoms of respiratory tract infections (RTI) and recurrent respiratory tract infections and their associated signs and symptoms including rhinitis, pharyngitis, catarrh, cough, pyrexia, malaise and myalgia. Also, for the prevention of RTI complications such as sinusitis, tonsillitis, otitis, bronchitis and pneumonia, to reduce the need for antibiotics in RTI and, by modulating the immune system, to improve resistance in those susceptible to the common cold, flu and recurring RTI.

4.2 Posology and method of administration
Posology
Adults and children over 12 years:
Prophylactic dose: Chew 2 tablets three times daily.
In acute cases: Chew 2 tablets five times daily.
Children 4 – 12 years:
Prophylactic dose: Chew 1 tablets three times daily
In acute cases: Chew 1 tablet five times daily.
Children 2 – 4 years:
Prophylactic dose: Chew 1 tablet two times daily
In acute cases: Chew 1 tablets three to five times daily.

Paediatric population
The use in children below 1 year of age is contraindicated (see 4.3. Contraindications).

Duration of use
For prevention, A.VOGEL ECHINAFORCE JUNIOR TABLETS have been shown in clinical trials to be safe for continuous use of 4 months.

Method of administration
For treatment, start the therapy at first signs of symptoms.
For oral use.
Chewable tablet.

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.
- Children under the age of 1 year.

4.4 Special warnings and precautions for use
- If the symptoms worsen or a high fever occurs during the use of A.VOGEL ECHINAFORCE JUNIOR TABLETS, a doctor, pharmacist or healthcare provider 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.
- *Sucrose warning:*
- This product contains sucrose (in the orange flavouring) which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or saccharose isomaltase deficiency should not take this medicine.
- *Sorbitol warning:*
- Patients with the rare hereditary condition of sorbitol intolerance should not take A.VOGEL ECHINAFORCE JUNIOR TABLETS.

4.5 Interaction with other medicines and other forms of interaction
Do not use with immunosuppressant medicines.

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 a FDA Class 1A Safety Rating.
Non-clinical studies on reproductive toxicity have not been performed.
As a precautionary measure and in the absence of sufficient data, the use during pregnancy and lactation is not recommended unless advised by a doctor.

Breastfeeding
As a precautionary measure and in the absence of sufficient data, the use during pregnancy and lactation is not recommended unless advised by a doctor.

Fertility
No effect on fertility expected.

4.7 Effects on ability to drive and use machines
A.VOGEL ECHINAFORCE JUNIOR 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 professionals are asked to report any suspected adverse reactions to the 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

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 and acts as an immune-modulator: Excessive production of inflammatory cytokines and chemokines are dampened. 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.
Echinaforce exhibits potent antiviral effects, inhibits viral replication and infectiousity of Influenza-, Respiratory Syncytial-, Parainfluenza- and at higher concentrations also of Rhinoviruses. Modulation of inflammatory cytokines was further demonstrated after infection of airway cell lines (A549 or MDCK-1) and organotypic 3D tissue cultures.
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.
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 immunecytochemical staining. This mode of action is similar to that determined in in vitro studies using adult airway epithelium.

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).

Clinical studies
A randomized, placebo-controlled and double-blind clinical study investigated Echinaforce tablets (same drug substances and strengths as in Echinaforce Junior 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).
A comparative clinical study demonstrated Echinaforce drops (same drug substances in same ratio as in Echinaforce Junior tablets) to be as effective as the pressed juice from Echinacea purpurea in the treatment of severe colds (flu).
Echinaforce was safe and effective in randomized, double blind, placebo-controlled clinical study in 755 participants over a time period of 4 months, when used for prophylaxis and acute treatment.
Following a test on its effects on teeth, Echinaforce Junior is allowed to be labeled as "gentle on the teeth", "harmless to teeth" or "friendly to teeth/ tooth friendly".

A randomised, controlled, blinded study compared the long-term prophylactic effect of a fresh plant extract of *Echinacea purpurea* (95 % aerial parts & 5 % roots) (A. Vogel Echinaforce Junior chewable tablets) 3 X 1 daily [400 mg/ tablet total 1200 mg/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. If RTI occurred nasal secretions were analysed to determine respiratory pathogens involved using RT-PCR.
There were 32,5 % fewer cold & flu episodes in those who received Echinaforce Junior 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 Junior group were 173 days (32 %) less than those on Vitamin C control (429 vs 602 [p < 0,001]) and cold & flu episodes were shortened by 1,4 days on Echinaforce Junior compared to those on the vitamin C control. Membranous virus (e.g. influenza, parainfluenza, RSV, corona, metapneumovirus) detections were significantly less in the Echinaforce Junior group vs Vitamin C (28 vs 47 p < 0,05) as were confirmed influenza infections (3 vs 20 respectively p < 0,05) concurring with previous Echinaforce research. [5-7]
Bacterial superinfection and complications of RTI were reduced by 65 % (p < 0,05) with 11 events (affecting 9,7 % of children) in the Echinaforce Junior group and 30 events (affecting 20.4% of children) in the Vitamin C control group.
As a result of this Echinaforce Junior was associated with a significant reduction in need for antibiotics; 6 children (5,8 %) required antibiotic prescriptions in the Echinaforce Junior group compared to 24 (24,5 %) children in the Vitamin C control group which is an equivalent of 76.3% reduction in antibiotic prescriptions (p < 0,001). Antibiotic treatment days were also significantly less in those on Echinaforce Junior vs Vitamin C control i.e. 45 vs 216 days respectively. Echinaforce Junior 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.

Dose response trials
The safety and efficacy of A.Vogel Echinaforce Junior at two dosages in the treatment of acute cold symptoms in children (4 – 12 years) was determined in a multicentred dose response clinical trial. A total of 130 cold episodes in 79 children occured over a 5,3 month observation period; a higher dose of 2000mg of Echinaforce Junior (5 X 1 tablets daily) was compared with a lower dose of 1200mg Echinaforce Junior (3 X 1 tablets daily) when colds occured for a treatment period of 10 days or until symptom resolution. Increasing the therapeutic dose from 1200 mg to 2000 mg per day enhanced the treatment effect by reducing the duration of illness by a further 1,2 days (p=0,046) i.e. from 8,1 days to 6,9 days with respective medians of 7 vs 9 days in the ITT population. Further analysis of the highly compliant population revealed a 1,7 day difference in duration of illness between the two groups (p=0,020) in favour of the higher dosage. An inter-group comparison of 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 2000 mg dose compared to 23,5 % on the 1200 mg dosage (p=0,005). A dosage of 2000 mg per day reduced risk of recurrent infections from 71,9 % to 58,1 % and overall cold incidence from 3,6 episodes to 1,8 episodes in susceptible children (p < 0,001).

Physicians rated tollerability of 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 (identical drug substances in same ratio as in Echinaforce Junior tablets) or tablets (250 mg total weight) both corresponding to a typical daily dose (4 ml / 12 tablets containing 400 mg Echinaforce extract each). 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 drops (27,55 ± 8,94 ng x min/ml) and for the Echinaforce tablets (11,36 ± 2,74 ng x min/ml).
These data show that pharmacologically active constituents in Echinaforce are bioavailable.
Another study demonstrated that Echinaforce tablets (250 mg total weight, 400 mg Echinaforce extract per tablet) and Echinaforce Junior tablets have comparable pharmacokinetic properties. Maximum concentration after oral administration of the Echinaforce tablets and Echinaforce Junior tablets was reached within minutes: 0,22 ± 0,07 ng/ml and 0.22 ± 0,15 ng/ml, respectively. When comparing the two tablet formulations then approximately the same amount of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid-isobutylamide was resorbed since AUCtot or Cmax did not differ considerably.

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; Echinaforce drops contain same drug substances in same ratio as in Echinaforce Junior tablets).
Non-clinical studies on reproductive toxicity have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

B-cyclodextrin
Colloidal silica
Magnesium stearate (vegetable source)
Orange flavour (natural origin)
Sorbitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.
After opening: use within 2 months

6.4 Special precautions for storage

Store at or below 25 °C in a cool, dry place. Protect from light.
Store in the original package/container.

6.5 Nature and contents of container

Amber type III glass bottles with coated aluminium foil sealing and aluminium pilfer proof closure fitted with a polyethylene liner. The bottles are packed in an outer carton.
Pack sizes: 40 tablets and 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

PharmaForce (Pty) Ltd.
130 – 16th Road
Midrand, 1685
Gauteng
+27 (0)10 020 2520
www.avogel.co.za

Manufacturer:

A.Vogel AG
Grünaustrasse 4
CH-9325 Roggwil
Switzerland

8 REGISTRATION NUMBER(S)

Listing number: 420881

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated.

10 DATE OF REVISION OF TEXT

July 2019

13136/PI.07/2019