PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Boldocynara

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 BOLDOCYNARA (oral drops)
Western Herbal Medicine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains:

Cynara scolymus L. (Artichoke) ..... 414 mg
[Fresh leaves, 1:30 extract providing dry plant equivalent: 14 mg herbal drug per ml]

Taraxacum officinalis WEB. (Dandelion) ..... 414 mg
[Fresh root and herb, 1:17 extract providing dry plant equivalent: 24 mg herbal drug per ml]

Peumus boldus MOLINA. (Boldo) ..... 64 mg
[Dried leaves, 1:10 extract providing dry plant equivalent: 6 mg herbal drug per ml]

Mentha x piperita L. (Peppermint) ..... 28 mg
[Fresh herb, 1:18 extract providing dry plant equivalent: 1,6 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 an aromatic odour and an aromatic, bitter taste.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

A.VOGEL BOLDOCYNARA is a herbal medicine which acts as a tonic to support the function of the liver and gallbladder. The ingredients promote liver function, production and flow of bile, support digestion, and have an antispasmodic action. Suggested as a general liver tonic to support liver detoxification and treatment of symptoms caused by liver and/or gallbladder dysfunction e.g. nausea, indigestion, raised cholesterol and skin problems.

4.2 Posology and method of administration

Posology

Adults and children over 12 years:
Treatment:
Take 10 – 15 drops 3 times daily.
Maintenance (for good general liver and digestive health):
Take 15 drops once or twice 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.
Take preferably 30 minutes before meals.
Take drops undiluted or diluted in a small volume of water.

4.3 Contraindications

- A.VOGEL BOLDOCYNARA should not be used in patients who have a hypersensitivity to the active substances, plants of the *Asteraceae (Compositae)* family, to menthol or to any of the excipients listed in section 6.1.
- Do not use in cases of bile duct obstruction or serious disorders warranting medical supervision or advice such as active peptic ulcers, cholangitis, gallstones, liver cancer or other serious liver disease.

4.4 Special warnings and precautions for use

- A.VOGEL BOLDOCYNARA contains alcohol and should be used with caution by individuals with a sensitivity or intolerance to alcohol.
- Due to *Taraxacum officinale* content - avoid use in persons at risk of hyperkalaemia and those on potassium restricted diets.
- Due to *Mentha x piperita* content - use with caution in patients with gastroesophageal reflux disease, and due to the menthol content, use with caution in epilepsy, asthma, persistent or chronic cough, or other chronic lung conditions.
- Due to *Peumus boldus* content – contains camphor, therefore use with caution in patients with epilepsy or chronic lung conditions.
- If the condition worsens or does not improve after 2 weeks, consult a healthcare practitioner.

Paediatric population
Digestive disorders in children below 12 years of age need to be medically evaluated. A.VOGEL BOLDOCYNARA therefore should not be used in these instances without medical recommendation.

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 BOLDOCYNARA 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 BOLDOCYNARA 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 BOLDOCYNARA 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 BOLDOCYNARA affects them.

A.VOGEL BOLDOCYNARA 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.

Mild gastrointestinal symptoms (e.g. slight diarrhoea, flatulence, abdominal spasm, hyperacidity and epigastric complaints like discomfort, nausea, and heartburn) may also 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Cynara scolymus

Cynara scolymus has choleretic, diuretic and hypocholesterolemic properties (Bone & Mills, 2013) and well-established use as a traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia with a sensation of fullness, bloating and flatulence (EMA, 2018).

In vitro and *in vivo* experiments:

Oral administration of *Cynara scolymus* led to a significant increase in bile flow after acute and repeated administration with effects similar to the reference compound dehydrocholic acid (DHCA). Further, the total bile acid concentration increased significantly in response to *Cynara scolymus* (Saénz Rodriguez *et al*. 2002).

Cynara scolymus extract significantly increased bile production and secretion of bile in pigs compared to control and Silymarin demonstrating and confirming its choleretic and cholagogue effects (Martínez *et al*. 2018).

Cynara scolymus extracts have demonstrated lipid-lowering effect in animal studies:

- Hypercholesterolemic rats treated with various doses of *Cynara scolymus* or simvastatin once per day for 30 days along with hypercaloric diet. Rats treated with extract of *C. scolymus* (150, 300, or 600 mg/kg) and simvastatin showed significant decreases in serum levels of total cholesterol (−46,9 %, −51,9 %, −44 %, and −41,9 %, respectively) and low-density lipoprotein-cholesterol (LDL-C; −52,1 %, −54,8 %, −51,9 %, and −46,7 %, respectively), compared with control (p<0,005) (Mocelin *et al*. 2016).
- While high-density lipoprotein-cholesterol (HDL-C) increased significantly, triglyceride and triglyceride/HDL-C ratio decreased significantly in atherogenic rats treated with *Cynara scolymus* compared to control (Bogavac-Stanojevic *et al*. 2018).
- *Cynara scolymus* leaf extract resulted in a significant reduction in plasma total cholesterol (18,1 %), triglyceride (60,5 %) LDL-C (37,8 %) in diabetic induced rats (Ben Salem *et al*. 2017).

Clinical studies on *Cynara scolymus:*

305 patients with functional dyspepsia treated with a commercial herbal product comprising *Cynara scolymus*, *Taraxacum officinalis*, Inulin, *Curcuma longa* and *Rosmarinus officinalis* for 60 days. Statistically significant improvement in symptom severity was observed at 30 days and further improvement at 60 days. There was a minimum of 50 % improvement in global symptom scores in 38 % of patients at 30 days and 79 % at 60 days. LDL and total cholesterol decreased by 6-8 % (p≤0,0001) and a reduction in Aspartate transaminase (AST), Alanine transaminase (ALT) and Gamma-glutamyltransferase (GGT) by 13-20 U/L (P<0,01) (Sannia 2010).

A subset of 208 adults with irritable bowel syndrome (IBS) and concomitant dyspepsia were treated with artichoke leaf extract for 2 months; IBS incidence reduced by 26,4 % (p<0,001) and a significant shift in bowel pattern from 'alternating constipation/diarrhoea' to 'normal' (p<0,001). Nepean Dyspepsia Index (NDI) score decreased by 41 % (p<0,001) and there was a 20 % improvement in NDI total quality of life after treatment (Bundy *et al*. 2008).

A Cochrane review sourced three randomized controlled trials (RCT) applying artichoke leaf in hypercholesterolaemia, all three trials reported statistically significant reductions in cholesterol levels; the review concluded that artichoke leaf has potential to lower cholesterol levels, but the evidence is, as yet, not convincing (Wider *et al*. 2009).

In a double-blind, randomised, placebo controlled trial (n=92) on overweight patients with mild hypercholesterolaemia, artichoke leaf extract resulted in significant increase in mean HDL-C (p<0,001) and in mean change in HDL-C (p=0,004). A significantly decreased difference was also found for the mean change in total cholesterol (p=0,033), LDL-C (p<0,001), total cholesterol/HDL ratio (p<0,001) and LDL/HDL ratio (p<0,001) compared with placebo. Results support the potential role of artichoke leaf extract in treating mild hypercholesterolaemia, specifically increasing HDL-C, decreasing total cholesterol and LDL-C (Rondanelli *et al*. 2013).

In a double-blind placebo-controlled clinical trial, 80 patients with metabolic syndrome were randomized to receive artichoke leaf extract (1800 mg per day as four tablets) or matching placebo for 12 weeks resulting in decreased serum triglyceride level compared to placebo (−10 % vs. −2 %, p=0,01). The subgroup analysis showed that in males with the Taq IB-B1B1 gene, LDL-C levels also significantly decreased (-15 % vs. 9 %, p=0,004) (Rezazadeh *et al*. 2018).

In a randomized, double-blind, clinical trial of 60 patients with non-alcoholic steatohepatitis, 2700 mg of *Cynara scolymus* extract for two months resulted in a significant reduction in mean weight, triglycerides, LDL, AST, ALT and cholesterol levels (Rangboo *et al*. 2016).

Artichoke dry extract 1800 mg/day for 6 weeks was compared to placebo in the treatment of hyperlipoproteinemia in 143 adult patients in a double-blind, randomized, placebo-controlled, multi-centre clinical trial. Changes of total cholesterol and LDL-C from baseline to the end of treatment showed a statistically significant superiority (p=0,0001) of artichoke dry extract over placebo. The decrease of total cholesterol was 18,5 % compared with 8,6 % in the placebo group and LDL decrease 22,9 % and 6,3 % respectively. LDL/HDL ratio also showed a decreased of 20,2 % in the artichoke group CY450 and 7,2 % in the placebo group (Englisch *et al*. 2000).

A standardised artichoke extract in a randomised, placebo-controlled trial (n=54) resulted in a statistically significant average lowering of cholesterol in all test patients with of 16,8 % compared to 10,0 % with placebo as well as a reduction LDL/HDL-quotient (Schmiedel 2002).

Taraxacum officinalis

Well established use as a traditional herbal medicinal product for the relief of symptoms related to mild digestive disorders (such as feeling of abdominal fullness, flatulence, and slow digestion) and temporary loss of appetite (EMA, 2019).

In vitro and *in vivo* experiments:

Dandelion leaf extract inhibited hepatic lipid accumulation, reduce insulin resistance and lipid mediators in rats fed a high-fat diet, suggesting its use in prevention and treatment of obesity-related non-alcoholic fatty liver disease (NAFLD) (Davaatseren *et al*. 2013).

Taraxacum officinalis and *Silibum marinum* extracts administered to rats at a dose of 100 mg/kg/day exerted a hepatorenal protective effect against carbon tetrachloride oxidative kidney injury in rats with lower serum ALP and GGT and lower malondialdehyde (MDA) in kidney tissue and higher glutathione (GSH) and glutathione S-transferases (GST) enzyme activity (Karakuş *et al*. 2017).

In a rodent model, *Taraxacum officinale* significantly decreased the pancreatic weight/body weight ratio in cholecystokinin octapeptide induced acute pancreatitis, increased the pancreatic levels of heat shock proteins (HSP60 and HSP72) and decreased the secretion of interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) confirming a protective and anti-inflammatory action in this context (Seo *et al*. 2005).

Dandelion root extract normalized Hepatic Cu/Zn superoxide dismutase (SOD) activity, in addition, metallothionein-I and -II (MT I/II) immunopositivity was strongly reduced as were hepatic fibrinous deposits with restoration of histological architecture in rats with carbon tetrachloride induced hepatic fibrosis. Dandelion extract led to inactivation of hepatic stellate cells and the enhancement of hepatic regenerative capabilities supporting the traditional use thereof in hepatic disorders (Domitrović *et al*. 2010). Similar hepato-protective effects against carbon tetrachloride liver cell injury were subsequently reported confirming the hepatoprotective effect in this context (Al-Malki *et al*. 2013).

Taraxacum officinale displayed hepatoprotective action against alcoholic liver damage in both *in vitro* and *in vivo* animal models. HepG2/2E1 cells treated with hot water *Taraxacum officinale* root extract did not experience any cell damage in response to 300 nM ethanol. In mice treated with Taraxacum officinale, alcohol-induced hepatotoxicity was prevented (reductions of serum AST, ALT, alkaline phosphatase, and lactate dehydrogenase activities) compared to ethanol-alone administered mice. These mice also experienced significant increases in hepatic antioxidant activity (catalase, GST, glutathione peroxidase, glutathione reductase, and GSH), as well as resolution of MDA levels (You, *et al*. 2010).

Taraxacum officinale contains anti-angiogenic, anti-inflammatory, and anti-nociceptive activities through its inhibition of nitric oxide (NO) production and cyclooxygenase-2 (COX-2) expression and/or its antioxidative activity using various *in vitro* and *in vivo* models. Scavenging activity in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay, a diminishing effect on intracellular reactive oxygen species (ROS) level, and anti-angiogenic activity in the chicken chorioallantoic (CAM) assay were demonstrated. In lipopolysaccharides (LPS) stimulated macrophages, *Taraxacum officinale* suppressed the production of NO and expression of inducible nitric oxide synthase (iNOS) and COX-2. Further, in the carrageenan-induced air pouch model, it inhibited the production of exudate, and significantly diminished NO and leukocyte levels in the exudate. Acetic acid-induced vascular permeability was inhibited and treatment with *Taraxacum officinale* caused a dose-dependent inhibition on acetic acid-induced abdominal writhing in mice (Jeon *et al*. 2008).

Clinical studies on *Taraxacum officinale*

A hydroethanolic extract of *Taraxacum officinale* 8 ml three times daily in a pilot study (n=17) resulted in a significant increase in the frequency of urination (p<0,05) in the 5 hours following the first dose and significant increase in the excretion ratio in the 5 hours following the second dose, confirming its diuretic action in humans and the traditional use thereof in this context (Clare *et al*. 2009).

Peumus boldus
A traditional herbal medicinal product used for symptomatic relief of dyspepsia and mild spasmodic disorders of the gastrointestinal tract (EMA, 2016). Traditionally also used as a choleretic and cholagogue (Bone & Mills, 2013).

In vitro and *in vivo* studies:
A dried hydro-alcoholic extract of *Peumus boldus* exerted a significant hepatoprotective effect in tert-butyl hydroperoxide-induced hepatotoxicity in isolated rat hepatocytes (*in vitro* technique) by reducing the lipid peroxidation and the enzymatic leakage of lactate dehydrogenase (LDH); this *in vitro* efficacy was reinforced by a significant hepatoprotection on CCl4-induced hepatotoxicity in mice (*in vivo* technique), the plant extract reducing the enzymatic leakage of ALT, boldine, the main alkaloid of P. *boldus* appears to be implicated in this hepatoprotective activity (Lanhers *et al*. 1991).

Pre-treatment with boldo leaf infusion significantly diminished ($p<0,05$) lipoperoxidation induced by cisplatin compared to untreated animals. The results suggest that the boldo infusion acts as a protector with respect to the oxidative hepatic damage caused by cisplatin likely due to the natural antioxidants boldine and principally catechin suggesting the potential use of the infusion as a chemoprotector (Fernández *et al*. 2009).

The proliferative index of hepatocytes, assessed by the immunoexpression of Ki-67 positive cells, was significantly increased in rats pre-treated with *Peumus boldus* aqueous extract suggesting a possible trophic effect of the extract on the damaged liver tissue (EMA, 2016).

Mentha piperita
A traditional herbal medicinal product for the symptomatic relief of digestive disorders such as dyspepsia and flatulence (EMA, 2017).

In vitro and *in vivo* studies:
Mentha leaf extract pre- and post-treatment resulted in a significant decline in acyl carrier protein (ACP), alkaline phosphatase (ALP), serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT) and lactoperoxidase (LPO) content was observed in arsenic-induced hepatopathy in mice compared to controls i.e. significantly altering biochemical parameters in the liver and reducing the side effects of arsenic-induced hepatopathy (Sharma *et al*. 2007).

Peppermint oil inhibited contraction induced by carbachol, confirming its antispasmodic activity on rat tracheal smooth muscle involving prostaglandins and nitric oxide synthase (de Sousa *et al*. 2010).

The anti-ulcerogenic property of *Mentha piperita* was determined using various ulcer models in rats and concluded to be due to its anti-secretory action along with antioxidative and cytoprotective action through prostaglandin mediated mechanisms (Al-Mofleh *et al*. 2006).

Clinical studies on *Mentha piperita*:
In a double-blind crossover trial on 30 infants, *Mentha piperita* was compared with simethicone for the treatment of infantile colic. Daily episodes of colic decreased from 3,9 (± 1,1) to 1,6 (± 0,6) and the crying duration decreased from 192 (± 51,6) minutes to 111 (± 28) minutes, with no differences between the two interventions confirming that *Mentha piperita* may be used to control infantile colic (Alves *et al*. 2012).

The most comprehensive meta-analysis to date (12 RCTs including 835 patients) on the impact of peppermint oil on IBS concluded that peppermint oil was shown to be safe and effective for pain and global symptoms of IBS in adults (Alammar *et al*. 2019).

A review of the use of peppermint oil in IBS reported on 3 trials in which peppermint oil was compared with anticholinergic drugs, in these trials smooth muscle relaxants did not show superiority over peppermint oil suggesting equivalence of treatments (Grigoleit & Grigoleit 2005).

Clinical studies – A.VOGEL BOLDOCYNARA
A multicentre, open clinical trial determined the tolerability and efficacy of *A.Vogel Boldocynara tablets* (a tableted version of A.VOGEL BOLDOCYNARA comprising 3 of the 4 constituents found in Boldocynara liquid (i.e. *Cynara scolymus*, *Peumus boldus* and Taraxacum officinale) to 75 patients (18-70 years) suffering from functional digestive disorders. There was a statistically significant decrease of sum score and single scores of frequency of dyspepsia ($p<0,0001$) and interference of dyspepsia with normal activities of all symptoms of the Short-Form Leeds Dyspepsia Questionnaire (SF-LDQ) (dyspepsia, heartburn, regurgitation and nausea) ($p<0,0001$) after 6 weeks. Further, there was a statistically significant decrease of sum score and single scores of the frequency ($p<0,0001$) and interference with daily activities ($p<0,0001$) of all other assessed gastrointestinal symptoms (fat intolerance, upper abdominal pain, epigastric discomfort, abdominal bloating, postprandial fullness, flatulence, abdominal cramps, constipation, diarrhoea and stool irregularities) after 6 weeks. Quality of life also improved with a statistically significant decrease in all 12 items assessed via the QoL-SF-12. The evaluation of the laboratory parameters demonstrated a high degree of safety. No clinically relevant change in the mean of leucocyte counts, erythrocyte counts, haemoglobin, haematocrit, MCV, MCH, MCHC, ESR/erythrocyte sedimentation rates, thrombocyte counts, ALT (GPT), AAT (GOT), bilirubin, creatinine, glucose and cholesterol was observed (Bommer *et al*. 2013).

5.2 Pharmacokinetic properties
No pharmacokinetic data available.

5.3 Preclinical safety data
Adequate tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed for *Cynara scolymus*, *Taraxacum officinale* and *Mentha piperita* (EMA, 2016, EMA, 2017, EMA, 2018).

For *Peumus boldus*, tests on reproductive toxicity have been performed with a dry ethanolic extract of boldo leaf and boldine administered orally to pregnant rats. Results showed anatomical alterations in the foetus and a few cases of abortion at high doses.
Tests on genotoxicity and carcinogenicity have not been performed (EMA, 2019).

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 unopened.
Use within 5 months of opening.

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

U 876 (Act 101/1965)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated.

10 DATE OF REVISION OF TEXT

July 2021