PROFESSIONAL INFORMATION
LINCTAGON®-C ADULT COLD AND FLU SYRUP

- Complementary Medicine
- Discipline: D 5.8 Preparations for the common cold including nasal decongestants. Complementary Medicines: Western Herbal Combination Product.
- 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
LINCTAGON®-C ADULT COLD AND FLU SYRUP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients	Per 15 ml syrup	Per 45 ml syrup (max daily dosage)	% NRV# per 45 ml (max daily dosage)
Pelargonium Sidoides DC Dry root extract (DER 4-25:1), extraction solvent ethanol 11% m/m. **Equivalent to 78,4 - 490 mg of dried root.	28 mg**	84 mg	*
Vitamin A (vitamin A retinyl palmitate 250000 IU/ g)	800 IU (240 µg)	2400 IU (720 µg)	80
Vitamin C (ascorbic acid)	330 mg	990 mg	990
MSM (methylsulfonylmethane)	500 mg	1500 mg	*
Zinc (zinc gluconate)	5 mg	15 mg	136,36
Quercetin (quercetin dehydrate)	40 mg	120 mg	*

Nutrient reference values for adults and children older than 4 years, * NRV not established. Linctagon®-C Adult Cold and Flu Syrup contains artificial sweetener: Glycerine 2,62 mg/ 15 ml, Sorbitol 2 mg/ 15 ml, Sucralose 6 mg/ 15 ml, Xylitol 0,3 g/ 15 ml. Linctagon®-C Adult Cold and Flu Syrup contains the preservative potassium sorbate 7,5 mg/ 15 ml.

3. PHARMACEUTICAL FORM
Syrup
Linctagon®-C Adult Cold and Flu Syrup is a caramel-orange liquid with a citrus-mint aroma and flavour.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Linctagon®-C Adult Cold and Flu Syrup is a combination syrup for the relief of symptoms associated with the common cold and flu such as congestion, sneezing, allergies, coughs, muscle aches and with immune support. With added vitamin C.
4.2 Posology and method of administration
The recommended daily dosage is
Adults and children 12 years and older:
Three (3) medicine measures (15 ml) three times a day, after a meal.
Advise patients to use for at least seven (7) days.
Advise the patient to consult a healthcare provider if the symptoms do not improve within one (1) week of the use of this medicinal product.
4.3 Contraindications
- Hypersensitivity to any of the active substances or any other ingredients in Linctagon®-C Adult Cold and Flu Syrup (see 6.1 List of excipients).

4.4 Special warnings and precautions for use
- Hepatotoxicity and hepatitis cases have been reported in association with the administration of products similar to Linctagon®-C Adult Cold and Flu Syrup. Advise patients to discontinue use in the event of signs of hepatotoxicity, and to consult a healthcare provider.
- Use with caution in patients presenting with or prone to iron overload, hemochromatosis, thalassemia and sideroblastic anaemia as Linctagon®-C Adult Cold and Flu contains vitamin C which can increase iron absorption and may worsen these conditions.
- Use with caution in patients with a history of oxalate kidney stones as Linctagon®-C Adult Cold and Flu contains vitamin C which can increase the risk of stone formation.
- Must not be given to patients with the rare hereditary condition of sorbitol/malitol/lactitol intolerance.

Porphyria
Safety has not been established.
4.5 Interaction with other medicinal products and other forms of interaction

Active ingredient	Medicine	Description
Pelargonium sidoides	Anticoagulant medications	Due to the coumarin content, and the similarity thereof to warfarin (Coumadin), there is a theoretical possibility that *Pelargonium sidoides* might exert an anticoagulant effect
Vitamin A	Retinoid compounds	Concomitant use of retinoid compounds and vitamin A supplements can lead to an increased toxicity potential.
Vitamin C	Levothyroxine	Vitamin C may increase the oral absorption of levothyroxine when taken together, possibly due to a reduced pH
Vitamin C	Warfarin	High doses of vitamin C may reduce the response to warfarin, possibly by causing diarrhoea and reducing warfarin absorption.
Quercetin	Diclofenac	Zinc forms insoluble complexes with these antibiotics in the gastrointestinal tract, decreasing their absorption.
Quercetin	Warfarin	Both quercetin and warfarin have the same human serum albumin binding site, with quercetin having a stronger affinity. This could lead to a displacement of warfarin from plasma proteins which could theoretically lead to higher serum levels of warfarin
Zinc	Penicillamine, quinolone antibiotics and tetracycline antibiotics	Zinc forms insoluble complexes with these antibiotics in the gastrointestinal tract, decreasing their absorption.

4.6 Fertility, pregnancy and lactation
Pregnancy
Use during pregnancy is not recommended as safety during pregnancy has not been established.
Breastfeeding
Use is not recommended as safety during lactation has not been established.
Fertility
There are no known effects of Linctagon®-C Adult Cold and Flu Syrup on fertility.
4.7 Effects on the ability to drive and use machines.
Based on the side effect profile, Linctagon®-C Adult Cold and Flu Syrup is not expected to affect the ability to drive or operate machinery.
4.8 Undesirable effects
Advise patients to discontinue use and consult a healthcare provider if they experience any side effects or sensitivity to any of the ingredients.

System Organ Class	Frequency	Adverse Event
Gastrointestinal disorders	frequency unknown	Abdominal discomfort and pain, diarrhoea, dry mouth, dyspepsia, heartburn, indigestion, mouth irritation, nausea, vomiting.
Nervous system disorders	frequency unknown	Headache, paraesthesia
Skin and subcutaneous tissue disorders	frequency unknown	Hypersensitivity reaction (skin rash).
Vascular disorders	Rare	Minor epistaxis.

Advise patient to consult a healthcare provider if symptoms persist, or if any adverse reactions occur.
Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation of the medicinal product 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 Reactions Reporting Form,**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8
4.9 Overdose
Symptoms
See **4.8 Undesirable effects**
In overdose, side effects can be precipitated and/or be of increased severity.
Treatment
If an accidental overdose occurs, treatment is symptomatic and supportive

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: D 5.8 Preparations for the common cold including nasal decongestants. Complementary Medicines: Western Herbal Combination Product.
Pharmacotherapeutic classification: herbal medicinal product for acute bronchitis.
ATC- code: R05CP05 other cough and cold preparations
ATC - code: R05X
Pelargonium sidoides root extract: A study reported the in vitro antiviral activity of *Pelargonium sidoides* extract against influenza viruses. During this study, the abundance of the catechin polymer, prodelphinidin, in the extract resulted in the inhibition of influenza, and the impairment of viral haemagglutination and neuraminidase activity. Polyphenols in *Pelargonium sidoides* (including catechin, gallocatechin, and gallic acid) are theorized to stimulate the release of tumor necrosis factor and interleukins, stimulate interferon activity, and increase the activity of natural killer cells. *Pelargonium* root extracts have also been shown to promote phagocytosis and decrease adhesion of bacteria to tissues.
Vitamin A: Retinol is important for immune function. Retinoic acid is required in maintaining adequate levels of natural killer cells, and preliminary evidence suggests that retinoic acid might increase the production of cytokines, such as interleukin 1 (IL-1). Additionally, B lymphocyte growth, differentiation, and activation are dependent on vitamin A.
Vitamin C: T-lymphocyte activity, phagocyte function, leukocyte mobility, and antibody and interferon production appear to be increased by vitamin C. There is also interest in using ascorbic acid for allergies, such as allergic rhinitis; Evidence suggests that a low levels of ascorbic acid are associated with higher plasma histamine levels
Methylsulfonylmethane: Researchers have suggested that MSM may have anti-inflammatory activity, however, MSM does not decrease inflammatory markers C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). MSM appears to reduce homocysteine levels. Human studies have shown that MSM appears to reduce malondialdehyde (MDA) levels, and improves antioxidant status. This suggests that MSM might reduce lipid peroxidation. *In vitro* studies have shown that MSM possesses anti-inflammatory activity by inhibiting the oxidative function of activated neutrophils and reducing levels of nuclear factor-kappaB (NF-kappaB), interleukin-1, -6 and -8 (IL-1, IL-6, IL-8) and tumor necrosis factor-alpha (TNF-alpha). A clinical trial has shown the benefit of MSM in relieving upper respiratory symptoms in conditions of allergic rhinitis.
Quercetin: Quercetin may influence immune function. The effect of quercetin on nuclear factor-kappa B may reduce the production of interleukin-1beta, tumor necrosis factor alpha, monocyte chemoattractant protein, and macrophage inflammatory protein. The anti-inflammatory activity of quercetin may be attributable to the inhibition of leukotriene and prostaglandin production and activity, as well as the inhibition of histamine release from basophils and mast cells.
Zinc: Zinc is an essential trace element and plays a role in normal immune functioning.
5.2 Pharmacokinetic properties
Pelargonium sidoides root extract:
Absorption: There is currently no information available on the biodistribution of *Pelargonium* extracts or their phytochemical constituents. However, the pharmacokinetics of the coumarin constituent has been investigated in a number of species, including humans, as a standalone pharmacophore. Studies performed on humans have shown that coumarin is completely absorbed from the gastrointestinal tract following oral administration. After absorption, coumarins undergo extensive first-pass metabolism in the liver with only 2 to 6 % reaching systemic circulation unchanged.
Distribution: There is currently no information available on the biodistribution of *Pelargonium* extracts or their phytochemical constituents.
Metabolism: Studies have shown that, in humans, coumarin is metabolised, mainly by hepatic enzyme CYP2A6, to 7-hydroxycoumarin
Excretion: After administration of coumarin, 68-92% of the dose was recovered in the urine as 7-hydroxycoumarin glucuronide and sulfate conjugates. The rapid excretion into the urine suggests that in humans there is very little or no biliary excretion of coumarin metabolites
Vitamin A:
Absorption: 70 – 90 % of preformed vitamin A is absorbed from the intestinal tract. Retinyl esters are metabolised (hydrolysed) by pancreatic and intestinal enzymes where after the unesterified retinol is absorbed directly into intestinal cells by both diffusion and active transport.
Distribution: The liver, through storage and release, narrowly maintains vitamin A concentrations. Vitamin A is bound to retinol-binding protein in the plasma. Vitamin A is stored as retinol, mainly in the liver and to a lesser extent in the retina, kidneys, lungs, adrenal glands and intraperitoneal fat.
Metabolism: Systemically, vitamin A is metabolised to 11-cis-retinoids and acidic retinoids.
Excretion: Vitamin A is primarily excreted through the urine, with a lesser fraction excreted through the faeces and expiration. Biliary excretion increases in conditions of vitamin A excess.
Vitamin C:
Absorption: Orally administered vitamin C is well absorbed; however, absorption decreases as the dose increases. This is due to the saturable sodium-dependent vitamin C transporter responsible for transporting vitamin C from the intestines into the bloodstream.
Excretion: Ascorbic acid, as it is highly hydrophilic, is mainly excreted through the kidneys into the urine.
Methylsulfonylmethane:
Absorption: Pharmacokinetic studies have demonstrated that MSM is absorbed rapidly (within about an hour) from the intestinal tract into the bloodstream with results suggesting near complete bioavailability.
Distribution: Earlier animal studies suggest that MSM is well distributed and completely excreted. MSM can cross the blood-brain barrier and is found in human cerebrospinal fluid in concentrations ranging from 0-25 µmol/L.
Metabolism: MSM is metabolised systemically (forms part of the body's endogenous methanethiol metabolism) and provides sulphur for amino acids cysteine and methionine.
Excretion: Pharmacokinetic studies have suggested that MSM is terminally eliminated from the bloodstream with an approximate half-life of 8 hours.
Quercetin:
Absorption: Quercetin is poorly absorbed from the gastrointestinal tract. Time to maximum plasma concentration is dose dependent; with 8, 20 and 50 mg resulting in Tmax values of 1.9, 2,7, and 4,9 hours respectively. Quercetin absorption appears to be promoted by concomitant intake of dietary fat.
Distribution: Quercetin is extensively plasma protein-bound, this may affect the activity of quercetin. Quercetin is found in the plasma as glucuronides, sulfates, and O-methylated derivatives with only small fractions of the aglycone form present.
Metabolism: After conjugation, quercetin is metabolised in the liver, by method of methylation, to isorhamnetin and tamarixetin. Some research suggests that 23 to 80 % of quercetin is metabolised to carbon dioxide and is eliminated through expired air.
Excretion: Quercetin is excreted in the urine as glucuronide and sulfate conjugates as well as methylated metabolites with half-lives ranging from 6-28 hours.
Zinc:
Absorption: 15 to 40 % of dietary zinc is absorbed from the gastrointestinal tract. Zinc is absorbed primarily in the small intestine.
Distribution: Plasma zinc levels are narrowly regulated at 10 to 15 micromol/L with more than 85 % of the total zinc content in the body being stored in skeletal muscle and bone.
Metabolism: After administration, zinc is rapidly transported to the liver. After oral administration, zinc levels decreased from a maximum of 1.2 % of the administered dose to 0.7 % of the administered dose after 24 hours.
Excretion: Zinc is primarily excreted through the faeces with a small fraction excreted through the urine.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
American peppermint flavour
Glycerine
Menthol liquid
Pelargonium in glycerine
Potassium sorbate
RO water
Sodium carboxymethylcellulose
Sorbitol
Sucralose
Xylitol
6.2 Incompatibilities
None known
6.3 Shelf life
24 Months
6.4 Special precautions for storage
- Store in a dry place at or below 25 °C.
- Protect from light and moisture.
- Keep in original packaging until required for use.

6.5 Nature and contents of container
Linctagon®-C Adult Cold and Flu Syrup is a caramel-orange liquid with a citrus mint aroma and flavour.
Linctagon®-C Adult Cold and Flu Syrup is packed into a 100 ml and 200 ml amber glass container with a white plastic cap, in a unit carton that includes a patient information leaflet.
6.6 Special precautions for disposal and other handling
No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Nativa (Pty) Ltd
260 Cradock Avenue, Lyttelton, Centurion, 0157, Gauteng, South Africa
Tel: +27 (0) 12 664 7110
Customer care line: 0860 628 482
Email: health@nativa.co.za

8. REGISTRATION NUMBER(S)
To be allocated

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
To be allocated

10. DATE OF REVISION OF THE TEXT
July 2022

PPIL307/02