COSINE® EXPECTORANT

(Diphenhydramine 14 mg; Ammonium Chloride 135 mg; Sodium Citrate 57 mg and Menthol 1.1 mg)

SUBMITTED BY: NALIS PHARMACEUTICALS LTD

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SUMMARY OF PRODUCT CHARACTERISTICS

(SmPC).

1 NAME OF THE MEDICINAL PRODUCT:

Cosine Expectorant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:
Diphenhydramine BP……..14 mg
Ammonium Chloride BP……135 mg
Sodium Citrate BP……..57 mg
Menthol BP…… 1.1 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Oral Syrup

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cosine® expectorant is used for the relief of cough and other accompanying symptoms of common cold and allergy in adult such as running nose; sneezing, watery/itchy eyes, nose, throat and nasal congestion.

4.2 Posology and method of administration

For oral administration.

Dosage:
Three times daily:
6 to 12 years - 1 teaspoonful
12years and above - 1 tablespoonful

4.3 Contraindications

Cosine® is contraindicated if any of the following conditions is present:

- **Hypersensitivity to any of the components**
- **Anuria**
- **Azotemia**
- **Hyperkalaemia**
- **Impaired renal function with Oliguria**
- **Angle-closure glaucoma**
- **Severe myocardial damage**
- **Premature or full-term neonates**
- **Prostatic hypertrophy with obstructive uropathy**
- **Acute dehydration**

4.4 Special warnings and precautions for use

Cosine Expectorant may cause drowsiness. Children receiving the product should be carefully supervised in order to avoid accidental mishap. Do not use to make a child sleepy.
Excitability may occur.
Caution should be exercised if moderate to severe renal and/or hepatic impairment is present.
Cosine Expectorant should not be administered to patients with chronic or persistent cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician.
Do not exceed the stated dose.
Do not take with any other cough and cold medicine.
Do not use with any other product containing diphenhydramine, even one used on skin.
Consult a pharmacist or other healthcare professional before use in children aged 6 to 12 years.

Diphenhydramine may enhance the sedative effects of central nervous system depressants including alcohol, sedatives, and tranquilizers. While taking this product, avoid alcoholic beverages and consult a healthcare professional prior to taking with central nervous system depressants.
Patients with the following conditions should be advised to consult a physician before using diphenhydramine and menthol:
- A respiratory condition such as emphysema, chronic bronchitis, or acute or chronic bronchial asthma
- Glaucoma

4.5 Interaction with other medicinal products

This product contains diphenhydramine and therefore may potentiate the effects of alcohol and other CNS depressants.
As diphenhydramine possesses some anticholinergic activity, the effects of anticholinergics (e.g. some psychotropic drugs and atropine) may be potentiated by this product. This may result in tachycardia, mouth dryness, gastrointestinal disturbances (e.g. colic), urinary retention and headache.
MAOIs: Not to be used in patients taking MAOIs or within 14 days of stopping treatment as there is a risk of serotonin syndrome.
There are no known interactions associated with menthol.

4.6 Pregnancy and lactation

This product should not be used during pregnancy or lactation unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

This product may cause drowsiness and patients receiving it should not drive or operate machinery unless it has been shown that their physical and mental capacity remains unaffected.

4.8 Undesirable effects

The following is a list of possible side effects that may occur from the use of cosine® expectorant. These side effects are possible, but do not always occur. Some of the side effects may be rare but serious. Consult your doctor if you observe any of the following side-effects, especially if they do not go away.

- **Nausea and vomiting**
- **Wheezing**
- **Tightness of the chest**

- Urinary retention
- Respiratory depression
- Blurred vision
- Photosensitivity
- Delirium.

4.9 Overdose

Symptoms of overdosage include those due to diphenhydramine or menthol (drowsiness, dizziness, ataxia, anti-cholinergic effects, pyrexia, headaches, convulsions, hallucinations, excitement and respiratory depression).
Treatment consists of gastric lavage and aspiration. Administration of activated charcoal may help. Other symptomatic and supportive measures should be provided.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Diphenhydramine HCl
Pharmacotherapeutic Group: Antihistamines for systemic use, Aminoalkyl ethers

Diphenhydramine is a potent antihistamine and antitussive with concurrent anticholinergic and sedative properties. Experiments have shown that the antitussive action is discrete from H1-receceptor blockade and is located in the brain stem. The duration of activity of diphenhydramine is between 4 and 8 hours. The sedative mechanism for diphenhydramine is thought to result from antagonism of central histamine and cholinergic receptors. The time course for sedation following a 50 mg oral dose was associated with higher plasma concentrations, and was significantly different from placebo during the first three hours following administration. The pharmacodynamics of sedation was correlated with peak concentrations of drug occurring during absorption and the alpha distribution phase.

Menthol
Menthol has mild local anaesthetic and decongestant properties. The mechanism by which menthol may act as an antitussive may be related to a strong stimulant effect on cold receptors in the larynx in the absence of cold air. It has been noted that substances which produce a hot sensation in the airway may stimulate the cough reflex, while menthol, which produces a cold sensation, has the opposite effect.

Sodium Citrate
Sodium citrate has no relevant pharmacodynamic activity other than that caused by its alkalinity (e.g. its gastric acid neutralising capacity).

Ammonium Chloride
Ammonium chloride produces mild irritation of the mucous lining of the stomach and this gastorvagal reflex increases the respiratory tract fluid, relieving dryness and soreness of the respiratory passage.

5.2 Pharmacokinetic properties

Diphenhydramine HCl

Absorption
Diphenhydramine is well absorbed from the gastrointestinal tract, reaching peak plasma concentrations from 47-153 ng/mL between 1.5 and 4 hours after a single 50-mg dose in adults. After multiple oral doses of 50 mg diphenhydramine HCl four times during each day to four subjects, minimum diphenhydramine plasma concentrations at steady state on the third day ranged from 57-150 ng/mL.

Distribution
Diphenhydramine is widely distributed throughout the body, including the CNS. The pharmacokinetics of diphenhydramine follows a two-compartment model in which the distribution or alpha phase is apparent over the first eight to ten hours. The volume of distribution adjusted by body weight is large for diphenhydramine at 14.0 L/kg (38%) for adults, 16.0 (32%) for adolescents, and 19.5 (28%) for children. Diphenhydramine is highly protein bound, with free drug concentrations of 24.0 ± 1.9% ng/mL and 14.8 ± 1.5% ng/mL measured in Asian and Caucasian plasma. In adults with liver disease, protein binding is lower, although the volume of distribution is comparable to healthy adults.

Metabolism
Diphenhydramine undergoes extensive first pass metabolism with an absolute bioavailability of 72% ± 8%. It is extensively metabolized in the liver by demethylation to Ndemethyl diphenhydramine (DMDP), and the extent of DMDP measured in plasma is highly correlated with the clearance of diphenhydramine. DMDP is subsequently demethylated to N,Ndidemethyl diphenhydramine. Because only the latter, minor metabolic pathway of N,Ndidemethylation appears to be mediated by cytochrome P450 2D6, diphenhydramine disposition in humans is not determined by CYP2D6 activity. Rather, clinical pharmacokinetics data suggest that diphenhydramine may be an inhibitor of CYP2D6 without being extensively metabolized by this cytochrome P450 isozyme. N,Ndidemethyl diphenhydramine is further metabolized by oxidative deamination to diphenylmethoxyacetic acid.

Elimination
Mean beta elimination half-life from 8.5 and 11.5 hours in adults have been reported in studies in which blood is sampled up to 24 to 72 hours. The half-life is increased to 13.6 ± 4.2 h in the elderly and to 15.2 ± 1.5 h in adults with liver cirrhosis. Little unchanged drug is excreted in the urine. Mean oral clearances for adults after a 25- and 50-mg dose are 1041 and 1029 mL/min, respectively, having coefficients of variation of 40% and 35%. Oral clearance is about 50% lower in elderly adults. Oral clearance is 691 mL/min (32%) for children ages 2 to 11 years, and is 1251 mL/min (43%) for adolescents' ages 12 to 17 years.

The elderly
Pharmacokinetic studies indicate no major differences in distribution or elimination of dipenhydramine compared to younger adults. Renal dysfunction. The results of a review on the use of diphenhydramine in renal failure suggest that in moderate to severe renal failure, the dose interval should be extended by a period dependent on glomerular filtration rate (GFR).

Hepatic dysfunction
After intravenous administration of 0.8 mg/kg diphenhydramine, a prolonged shelf-life was noted in patients with chronic liver disease which correlated with the severity of the disease. However, the mean plasma clearance and apparent volume of distribution were not significantly affected.

Menthol

Absorption
Menthol is highly lipid soluble and, when taken orally, is rapidly absorbed from the small intestine.

Distribution
There is insufficient data on the distribution of menthol.

Metabolism
In humans, menthol is partially metabolized to menthol glucuronide by rapid conjugation. Animal studies in rats have demonstrated that menthol then undergoes extensive enterohepatic recirculation after being cleaved from the glucuronide conjugate and reabsorbed in the small intestine. The reabsorbed menthol is then subsequently metabolized by oxidative processes in the liver. There is support for this model in humans as well because menthol has been shown to be oxidized by CYP2A6 in human liver microsomes.

Elimination
A study in humans has demonstrated that approximately 50% of a menthol dose is excreted in the urine as menthol glucuronide. Other studies in rats have shown that menthol glucuronide is excreted in both the bile and the urine, but with the bile containing the majority of menthol glucuronide and with the urine also containing various oxidation products.

Sodium Citrate
Sodium citrate is systemically absorbed and renally eliminated, causing metabolic alkalosis and urine alkalisation in sufficient doses.

Ammonium Chloride
Ammonium chloride increases acidity by increasing the amount of hydrogen ion concentrations. Ammonium chloride can be used as an expectorant due to its irritative action on the bronchial mucosa. This effect causes the production of respiratory tract fluid which in order facilitates the effective cough.

Absorption
Completely absorbed within 3–6 h. In healthy persons, absorption of ammonium chloride given by mouth was practically complete. Only 1 to 3% of the dose was recovered in the feces.

Metabolism
Ammonium ion is converted to urea in the liver; chloride ion replaces bicarbonate.

5.3 Preclinical safety data

Mutagenicity
The results of a range of tests suggest that neither diphenhydramine or menthol have mutagenic potential.

Carcinogenicity
There is insufficient information to determine the carcinogenic potential of diphenhydramine or menthol, although such effects have not been associated with these drugs in animal studies.

Teratogenicity
The results of a number of studies suggest that the administration of either diphenhydramine or menthol does not produce any statistically significant teratogenic effects in rats, rabbits and mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium CMC, Propylene Glycol, Methyl Paraben, Propyl Paraben, Glycerine, Citric Acid, Xanthan Gum, Sugar, Strawberry Flavour, Caramel Colour, Sodium Benzoate, Treated Water

6.2 Incompatibilities
None stated except as in 'Interactions with other medicaments'.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30°C.
Keep away from light

6.5 Nature and contents of container
100ml HDPE amber pet bottle with ROPP caps

6.6 Special precautions for disposal and other handling
None

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

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8. DRUG PRODUCT MANUFACTURER

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9. NAFDAC REGISTRATION NUMBER(S)

A11-0788