SUMMARY OF PRODUCT CHARACTERIZATION (SMPC)

FOR

EXOKUF COUGH SYRUP

1. Name of the product

Exokuf Cough Syrup

2. Qualitative & Quantitative composition

Each 5 ml contains

Ammonium Chloride BP 130 mg

Diphenhydramine HCL BP 15mg

Sodium Citrate BP 57mg

Menthol BP 1.1 mg

3. Pharmaceutical Dosage Form

   Oral Syrup.

4. Clinical particulars

   4.1 Therapeutic indications

   4.2 Posology and method of administration

Posology

One to two 5ml to be taken every 4 hours

To aid sleep the patient may start with two 5ml at bedtime followed by two 5ml every 6 hours.

Not suitable for children under 12 years.

Do not take more than 4 doses (1 dose = two 5ml) in 24 hours.

Do not exceed the stated dose.

Method of Administration

Oral

4.3 Contraindications

- Hypersensitivity to any of the ingredients
- Children below 12 years of age
- Patients on monoamine oxidase inhibitor therapy within previous 14 days.

4.4 Special warnings and precautions for use

- Do not combine with other treatments for coughs and colds.
- Exokuf Cough Syrup Oral Solution should be used with caution in patients with the following conditions: prostatic hypertrophy, urinary retention, susceptibility to 'closed angle' glaucoma and hepatic disease.
- Exokuf Cough Syrup Oral Solution may cause drowsiness.
- Seek medical advice when suffering from chronic or persistent cough and when also suffering from asthma, and acute asthmatic attack or where cough is accompanied by excessive secretions Keep out of the reach and sight of children.

Excipient Warnings:

Parahydroxybenzoates may cause allergic reactions (possible delayed).

Sucrose: Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

- Additive CNS depressant effects with alcohol and other CNS depressants including barbiturates, hypnotics, opiod analgesics, anxiolytic sedatives and anti-psychotics.
- Additive anti-muscarinic effects with other drugs of similar properties such as atropine and some anti-depressants.

- Not to be taken in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 of stopping treatment as there is a risk of serotonin syndrome.
- Diphenhydramine can inhibit the oxidative metabolism of some drugs.
- Diphenhydramine may enhance the effects of ephedrine.
- Diphenhydramine may mask the response of the skin to allergenic skin tests and also the ototoxic symptoms associated with certain antibiotics.

4.6 Pregnancy and lactation

Pregnancy

In view of the potential risks versus small benefits, it is recommended that Exokuf Cough Syrup should not be used during pregnancy particularly as the safety of Exokuf Cough Syrup in human pregnancy is not established.

Lactation

In view of the potential risks versus small benefits, it is recommended that Exokuf Cough Syrup should not be used during lactation particularly as the safety of Exokuf Cough Syrup during lactation is not established.

4.7 Effects on ability to drive and use machines

Exokuf Cough Syrup may cause drowsiness. Do not drive or operate machinery. Avoid alcoholic drink.

4.8 Undesirable effects

The overall percentage of treated patients expected to experience adverse reactions is unknown.

Common side effects include:

- CNS effects such as nervous drowsiness (usually diminishes within a few days), paradoxical stimulation, nervous headache, nervous psychomotor impairment.
- Anti-muscarinic effects such as urinary retention, dry mouth, blurred vision, gastrointestinal disturbances and thickened respiratory tract secretions.

Rare side effects include:

Hypotension, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, palpitation, arrhythmia, hypersensitivity reactions, blood disorders and liver dysfunction.

Organ system Class	Common ADRs, >1/100, < 1/10	Uncommon ADRs, >1/1,000, <1/100	Rare ADRs >1/10,000, <1/1000
Blood Lymphatic System Disorder			Blood Disorders NOS
Cardiac Disorder			Palpitation, arrhythmia
Eye Disorders	Blurred vision		
Gastrointestinal Disorder	Dry mouth, gastrointestinal disturbance		
General Disorder	Paradoxical drug reaction		
Hepatobiliary Disorder			Liver Disorder
Immune System Disorders			Hypersensitivity
Nervous System Disorders	Psychomotor skills impairment, drowsiness, headache		Tremor, convulsions, extrapyramidal disorder, dizziness
Psychiatric Disorders			Confusion, depression, sleep disturbances
Renal and Urinary Disorder	Urinary retention		
Respiratory Disorder	Increased upper airway secretion		
Vascular Disorders			Hypotension

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 ATC Code: R06AA52

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-rececptor 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 HCI

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 $\pm$ 1.9% ng/mL and 14.8 $\pm$ 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% $\pm$ 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 $\pm$ 4.2 h in the elderly and to 15.2 $\pm$ 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.

Volume of distribution

Data not found. Protein

binding

Data not found.

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.

Fertility

There is insufficient information to determine whether diphenhydramine has the potential to impair fertility, although a diminished fertility rate has been observed in mice in one study.

6. Pharmaceutical particulars

6.1 List of excipients Sucrose

Propylene Glycol

Sodium Citrate

Methyl paraben

Propyl Paraben

Purified Water.

6.2 Incompatibilities

None

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light. Store in the original package.

6.5 Nature and contents of container

60ml Amber pet Bottles capped with white rop cap.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing authorisation holder

Exodus Pharmacy and Farms Limited

Q5 Bridge Head Market Anambra State