1. NAME OF THE MEDICINAL PRODUCT

VALUNIL Cough Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:

Diphenhydramine hydrochloride 14.0 mg

Each 5 ml contains:

Menthol crystal 1.1 mg

Ammonium Chloride 130 mg

Sodium citrate 60 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Syrup.
A clear red syrup

4. Clinical particulars

4.1 Therapeutic indications

VALUNIL Cough Syrup is a combination medicine used to treat cough. It thins the mucus in the nose and windpipe, making it easier to cough out. This medicine also relieves allergic symptoms like runny nose, watery eyes, sneezing, and throat irritation.

4.2 Posology and method of administration

Posology

Adults and Children above 12 years:

One 10 ml dose of syrup 3 times a day.

Maximum daily dose: 30 ml syrup.

Children under 12 years:

Age 2-5 years: 2.5 ml 3 time daily

Age 6-12 years: 5 ml 3 times daily

Method of administration
For oral use

4.3 Contraindications

VALUNIL cough syrup is contraindicated in individuals with known hypersensitivity to Diphenhydramine or menthol crystals or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

This product may cause drowsiness. If affected, individuals should not drive or operate machinery.

This product should not be used to sedate a child.

Diphenhydramine may enhance the sedative effects of central nervous system depressants including alcohol, sedatives, opioid analgesics, antipsychotics and tranquilizers. Alcoholic beverages should be avoided while taking this medicine (see section 4.5).
Do not use with any other product containing diphenhydramine, including topical formulations used on large areas of skin.

Subjects with hepatic disease or moderate to severe renal dysfunction should exercise caution when using this product (see Pharmacokinetics - Renal/Hepatic Dysfunction).

Patients with the following conditions should be advised to consult a physician before using this medicine:

- A chronic or persistent cough such as occurs with chronic bronchitis or emphysema, acute or chronic asthma, or where cough is accompanied by excessive secretions
- Susceptibility to angle-closure glaucoma
- Prostatic hypertrophy and/or urinary retention

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

The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

Diphenhydramine

CNS depressants: may enhance the sedative effects of CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, antipsychotics and alcohol.

Antimuscarinic drugs: may have an additive muscarinic action with other drugs, such as atropine and some antidepressants.

Menthol

There are no known drug interactions associated with menthol.

4.6 Pregnancy and Lactation

This product should not be used during pregnancy or breastfeeding unless the potential benefit of treatment to the mother outweighs the possible risks to the developing fetus or breastfeeding infant.

Diphenhydramine

Pregnancy

Diphenhydramine has been in widespread use for many years without any apparent ill consequence. Diphenhydramine is known to cross the placenta and, therefore, should only be used during pregnancy if

considered essential by a doctor.

4.7 Effects on ability to drive and use machines

This product may cause drowsiness. If affected, the patient should not drive or operate machinery

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with Diphenhydramine are included in the table below by System Organ Class (SOC). The frequencies are provided according to the following convention:

Very common ≥1/10

Common ≥1/100 and < 1/10

Uncommon ≥1/1,000 and <1/100

Rare ≥1/10,000 and <1/1,000

Very rare <1/10,000

Not known cannot be estimated from the available data)

System Organ Class (SOC)	Frequency	Adverse Drug Reaction
Blood and Lymphatic System Disorders	Rare	Blood disorders
Immune System Disorders	Rare	Hypersensitivity reactions
Psychiatric Disorders	Uncommon	Irritability Hallucination Nervousness
	Rare	Confusional state
Nervous System Disorders	Very common	Somnolence (usually diminishes within a few days)
	Common	Dizziness Headache Paradoxical stimulation Psychomotor impairment
	Uncommon	Agitation Paraesthesia Sedation
	Rare	Convulsion Depression Extrapyramidal effects Insomnia Tremor
Respiratory, Thoracic and Mediastinal Disorders	Common	Thickened respiratory tract secretions
	Uncommon	Chest discomfort Nasal dryness
Gastrointestinal Disorders	Common	Dry mouth Nausea Vomiting

4.9 Overdose

Symptoms and signs

Diphenhydramine

Mild to Moderate Symptoms:

Drowsiness, anticholinergic syndrome (mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds), tachycardia, mild hypertension, nausea and vomiting are common after overdose. Agitation, confusion and hallucinations may develop after moderate poisoning.

Severe Symptoms:

Effects may include delirium, psychosis, seizures, coma, hypotension, QRS widening, and ventricular dysrhythmias (including torsades de pointes), but are generally only reported in adults after large ingestions. Rhabdomyolysis and renal failure may rarely develop in patients with prolonged agitation, coma or seizure. Death may occur as a result of respiratory failure or circulatory collapse.

In children, CNS excitation, including hallucinations and convulsions may appear; with larger doses, coma or cardiovascular collapse may follow.

Treatment

Treatment of overdose should be symptomatic and supportive. The benefit of gastric decontamination is uncertain. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) only if the patient presents within 1 hour of ingestion of a potentially toxic amount Seizures may be controlled with Diazepam or Thiopental Sodium. The intravenous use of Physostigmine may be efficacious in antagonising severe antichoinergic symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Diphenhydramine HCl

Diphenhydramine is a potent antihistamine and antitussive with concurrent anticholinergic and sedative properties. Experiments have shown that the antitussive action is discrete from H1- receptor blockage and is located in the brain stem. The sedative mechanism for diphenhydramine is thought to result from antagonism of central histamine and cholinergic receptors. The time course for sedation following a 50mg oral dose was associated with higher plasma concentrations, and was significantly different from place 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.

Sodium citrate

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

Ammonium

Ammonium chloride has an irritant effect on mucous membranes and is considered to have expectorant

properties.

Menthol

Menthol has mild local anaesthetic and decongestant properties.

5.2 Pharmacokinetic properties

Absorption

Diphenhydramine is well absorbed from the gastro intestinal tract, reaching peak plasma concentrations from47 -153ng/mL between 1.5 and 4 hours after a single 50 -mg dose in adults. After multiple oral doses of 50mg diphenhydramine HCl four times during each day to four subjects, minimum diphenhydramine plasma concentrations at steady state on the third day ranged from 57 -150ng/mL

Distribution

Diphenhydramine is widely distributed throughout the body, including the central nervous system. 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 bodyweight is large for diphenhydramine at 14.0L/kg (38%) for adults, 16.0(32%) for adolescents, and19.5 (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 first-pass metabolism with an absolute bioavailability of 72%± 8%. It is extensively metabolized in the liver by demethylation to N-diethyl diphenhydramine (DMDP), and the extent of DMDP measured in plasma is highly correlated with the clearance of diphenhydramine. DMDP is subsequently demethylated to N, N-didemethyl diphenhydramine. Because only the latter, minor metabolic pathway of N, N-didemethylation appears to be mediated bycytochromeP4502D6, diphenhydramine disposition in humans is not determined by CYP2D6 activity. Rather, clinical pharmacokinetics data suggest that diphenhydramine may be aninhibitorofCYP2D6withoutbeingextensively metabolized by this cytochrome P450 isozyme.N,N-didemethyldiphen hydramineis further metabolized by oxidative deamination to diphenyl methoxyacetic acid.

Elimination

Mean beta elimination half-life from 8.5 and 11.5hoursin adults have been reported in studies in which blood is sampled up to 24to 72hours.The half-life is increased to 13.6± 4.2h in the elderly and to15.2± 1.5h in adults with liver cirrhosis. Little un changed drug is excreted in the urine .Mean oral clearances for adults after a 25 – and 50 –mg dose are 1041 and 1029mL/min, respectively, having coefficients of variation of 40% and35%.Oral clearance is about 50% lower in elderly adults. Oral clearance is 691mL/min (32%) for children ages 2 to11years, and is 1251mL/min (43%) for adolescents' ages 12 to 17years.

Sodium citrate

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

Ammonium chloride
Ammonium chloride is effectively absorbed from the gastrointestinal tract. The ammonium ion is converted into urea in the liver; the anion thus liberated into the bloodstream and extracellular fluid causes metabolic acidosis and decreases the pH of the urine, this is followed by a transient diuresis.

Menthol
Menthol is hydroxylated in the liver by microsomal enzymes to p-methane -3,8 diol. This is then conjugated with glucuronide and excreted both in urine and bile as the glucuronide.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Menthol crystal
Ammonium Chloride
Sodium citrate
Ethanol
Methyl Paraben
Propyl Paraben
Glycerin
Sodium CMC
Sorbitol
Sucrose Syrup
Citric Acid
Caramel
Raspberry flavor

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 300C in tight container protected from light and moisture

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Valunill Cough Syrup is packaged and presented in 100ml amber bottles with content total volume of 100ml, capped with a metallic screw cap in chip hardboard containers with a graduated spoon enclosed,

6.6 Special precautions for disposal <and other handling>

Any unused product or waste material should be disposed of in accordance with local requirements.

7. <APPLICANT/MANUFACTURER>

APPLICANT:

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