1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product
TUTOLIN DROP
Diphenhydrmine Hcl
Sodium Citrate

2. Qualitative and quantitative composition
Each 1ml contains
Diphenhydrmine Hcl 3.5mg/1ml
Sodium Citrate 14.25mg/1ml

For excipients see 6.1 below

3. Pharmaceutical form
Oral Syrup
An Orange Viscous syrup with characteristic odour in an amber bottle

4. Clinical particulars
4.1 Therapeutic indications
Tutolin drop is used for the relief of cough and cold symptoms in infants ..

4.2 Posology and method of administration
1-3months 0.4ml 3-4 times daily
4-11 months 1.0ml 3-4 times daily
Also can be taken as directed by the physician.

4.3 Contraindications
Hypersensitivity to the active ingredient or to other ingredients of the product.

4.4 Special warnings and precautions for use
Do not use with any other product containing diphenhydramine, even one used on skin (see Section 4.5). Patients with moderate to severe renal or hepatic dysfunction should exercise caution when using this product (see Section 5.2). Patients with the following conditions should be advised to consult a physician before using Tutolin:
- Acute or chronic bronchial asthma, a persistent or chronic cough such as occurs with smoking, chronic bronchitis or emphysema or where cough is accompanied by excessive secretions
- Narrow angle glaucoma
- Prostatic enlargement (hyperplasia/hypertrophy) with urinary retention

This product may act as a cerebral stimulant in children and occasionally in adults. Symptoms of overdosage include insomnia, nervousness, hyperpyrexia, tremors and epileptiform convulsions. Large doses of antihistamines may precipitate attacks in epilepsy (see Section 4.9). 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

Sodium Citrate should not be administered to patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria. Sodium containing salts should be administered extremely cautiously to patients with heart failure, oedema, renal impairment, hypertension, or aldosteronism. (During treatment of acidosis, frequent monitoring of serum-electrolyte concentrations and acid-base status is essential. Alkalinisation of the urine by bicarbonates or bicarbonate precursors leads to increased renal clearance of acidic drugs.) However, urinary alkalinisation prolongs the half-life of basic drugs and may result in toxicity.
Citrates and Citric Acid enhance intestinal aluminium absorption in renal patients which may lead to increased, harmful serum aluminium levels. It has therefore been suggested that patients with renal failure taking aluminium compounds to control phosphate absorption should not be prescribed citrate or citric acid containing products.

4.5 Interaction with other medicinal products and other forms of interaction
CNS Depressants: This product contains diphenhydramine and therefore may potentiate the effects of alcohol and other central nervous system depressants including opioid analgesics, anticonvulsants, antidepressants, antihistamines, antiemetics, antipsychotics, anxiolytic sedatives and hypnotics.
Antimuscarinic drugs: As diphenhydramine possesses some anticholinergic activity, the effects of anticholinergics (e.g. some psychotropic drugs and atropine) may be potentiated by this product giving rise to tachycardia, mouth dryness, gastrointestinal disturbances (e.g. colic), urinary retention and headache

As with all antacids, sodium citrate may affect the absorption of many drugs.

4.6 Pregnancy and lactation
Although diphenhydramine has been in widespread use for many years without ill consequence, it is known to cross the placenta and has also been detected in breast milk

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
There are no further effects other than those mentioned in Sections 4.3, 4.4, 4.5 and 4.9 of the Summary of Product Characteristics.

4.9 Overdose
Diphenhydramine Mild to Moderate Symptoms: Drowsiness, anticholinergic syndrome (hyperpyrexia, 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 with 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 seizures. Death may occur as a result of respiratory failure or circulatory collapse.

With higher doses, and particularly in children, symptoms of CNS excitation including insomnia, nervousness, tremors and epileptiform convulsions may appear; with massive doses, coma or cardiovascular collapse may follow.

Sodium Citrate
As with all antacids, overdose may produce metabolic alkalosis. The product contains 27mmol of Sodium ions per 30ml and this should be considered. Management of overdose should include monitoring of plasma electrolytes and acid-base status, and general supportive measures.

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.

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

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 ± 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 N-demethyl 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,N-didemethylation 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.

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

5.3 Preclinical safety data
No further data is provided.

6. Pharmaceutical particulars
6.1 List of excipients
Menthol Crystal MethylParaben , Propyl Paraben , Sodium CMC, Sugar, Sunset Yellow , Poncean

6.2 Incompatibilities
Not applicable

6.4 Special precautions for storage
Store below 30°C and protect from light.

6.5 Nature and contents of container

Bottle:	Amber Glass BOOTLE
Closures:	ROPP wadded, tamper evident, with 1ml plastic dropper
Pack Sizes:	15ml.

6.6 Special precautions for disposal and other handling
Keep out of the reach of children.
Shake the bottle well before use.

If a dose of under 5ml is required, the suspension should be administered using an oral dosing device.

7. Marketing authorisation holder
TUYIL PHARMACEUTICAL INDUSTRIES LIMITED

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