Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

TUTOLIN COUGH AND COLD SYRUP
Bromhexine HCL 4mg,
Diphenhydramine hydrochloride 7mg/5ml
Ammonium Chloride 70mg/5ml
Sodium Citrate 29.5mg/5ml
Citric Acid 3mg/5ml
Menthol 0.55mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:

Bromhexine HCL 4mg,
Diphenhydramine hydrochloride 7mg/5ml
Ammonium Chloride 70mg/5ml
Sodium Citrate 29.5mg/5ml
Citric Acid 3mg/5ml
Menthol 0.55mg/5ml

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Syrup
An Orange Viscous syrup with characteristic odour in an amber bottle.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

(a) Properties

Fixed combination of anti-histamine with anti-tussive activity and carminative.

(b) Indications for use

In the symptomatic relief of non-productive cough and of allergic conditions and reactions.

4.2 Posology and method of administration

For oral use.

Adults and children over 12 years:

One or two 5 ml spoonfuls three to four times daily.

4.3 Contraindications

Tutolin Cough Syrup is contraindicated in individuals with hypersensitivity to diphenhydramine, menthol, Bromhexine HCL, Sodium Citrate, Ciitric Acid or to any of the excipients listed in section 6.1.

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 Cough Syrup

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 (see Section 4.5).

This product may cause drowsiness (see Section 4.8).

This medicine contains 1.0g sucrose, 3.5g glucose and 6.75mg invert sugar per 5 ml dose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This should be taken into account in patients with diabetes mellitus.

This product contains Ponceau 4R (E214) red colouring which may cause allergic reactions.

This product contains 16.61mg of sodium per 5ml equivalent to 0.82% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains 197 mg of alcohol (ethanol) in each 5 ml. The amount in 5 ml of this medicine is equivalent to less than 5 ml beer or 2 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects. This

medicine contains 1.05 mg propylene glycol in each 5 ml dose.

This medicine contains 10 mg sodium benzoate in each 5 ml dose.

Bromhexine

Anaphylactic reactions and severe cutaneous adverse reactions (SCARs), including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalised exanthematous pustulosis, have been reported in patients receiving ambroxol. As ambroxol is a metabolite of bromhexine, the risk of anaphylactic and severe cutaneous reactions is considered to apply also to bromhexine. The risk of anaphylactic reactions and SCARs with ambroxol or bromhexine is low. Frequencies of these side effects are unknown. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, bromhexine treatment should be discontinued immediately and medical advice should be sought. Caution is advised when treating patients with haemoptysis because the constituent ingredient bromhexine can lead to rejection of fibrin clots and result in new bleeding

4.5 Interaction with other medicinal products and other forms of interactions

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.

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 Fertility, 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. Menthol is also excreted in breast milk. Benylin Cough Medicine should not be used during pregnancy or lactation unless considered essential by a doctor.

Bromhexine:

Gastrointestinal side effects may occur occasionally with bromhexine and a transient rise in serum aminotransferase values has been reported. Other reported adverse effects include headache, vertigo (dizziness), sweating and allergic reactions including anaphylactic reactions and severe cutaneous adverse reactions (SCARs).

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

Diphenhydramine

Data from several clinical trials are available with a total population of 936 people treated with diphenhydramine where adverse events were assessed. Additionally, adverse events reported during post-marketing experience are included.

Post-marketing Data:
Adverse drug reactions (ADRs) identified during post-marketing experience with Diphenhydramine / Menthol are included in the table below.

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, <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

Adverse Drug Reactions Identified During Post-Marketing Experience with Diphenhydramine / Menthol, Frequency Category Estimated from Clinical Trials or Epidemiology Studies*	
System Organ Classification Frequency category	Adverse Event Preferred Term
Psychiatric Disorders	
Uncommon	Agitation
Uncommon	Confusional state
Uncommon	Insomnia
Uncommon	Irritability
Uncommon	Hallucination
Uncommon	Nervousness
Nervous System Disorders	
Very Common	Somnolence
Common	Dizziness
Uncommon	Coordination abnormal
Uncommon	Convulsion
Uncommon	Headache
Uncommon	Paraesthesia
Uncommon	Sedation

Uncommon	Tremor

Eye Disorders	
Uncommon	Vision blurred
Ear and Labyrinth Disorders	
Uncommon	Tinnitus
Cardiac Disorders	
Uncommon	Palpitations
Uncommon	Tachycardia
Vascular Disorders	
Uncommon	Hypotension
Respiratory, Thoracic and Mediastinal Disorders	
Uncommon	Dry throat
Uncommon	Nasal dryness
Gastrointestinal Disorders	
Common	Dry Mouth
Uncommon	Constipation
Uncommon	Diarrhoea
Uncommon	Dyspepsia
Uncommon	Nausea
Uncommon	Vomiting
Skin and Subcutaneous Tissue Disorders	
Uncommon	Pruritus
Uncommon	Rash
Uncommon	Urticaria
Renal and Urinary Disorders	
Uncommon	Urinary retention
General Disorders and Administration site conditions	
Common	Asthenia§
Uncommon	Chest discomfort

* Frequency category based on clinical trials with single-ingredient diphenhydramine.
§ Adverse drug reaction only reported in one clinical trial.

Menthol

Adverse reactions to menthol at the low concentration present are not anticipated.

Reporting of Suspected Adverse Reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Signs and symptoms

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.

Menthol

Excessive use of menthol may lead to abdominal pain, vomiting, flushed face, dizziness, weakness, tachycardia, stupor, and ataxia.

Management

Treatment of overdose should be symptomatic and supportive. The benefit of gastric decontamination is uncertain. Consider activated charcoal (charcoal dose: 25 - 100 g for adults; 0.5 to 1 g/kg for children) only if the patient presents within 1 hour of ingestions of a potentially toxic amount.

The intravenous use of physostigmine may be efficacious in antagonising severe anticholinergic symptoms.

Bromhexine treatment above 60 mg / day may cause gastric irritation.
Treatment of overdosage with dextromethorphan is essentially symptomatic and supportive. Only in cases of extreme overdosage or individual sensitivity do vital signs including respiration, pulse, blood pressure, temperature and ECG need to be monitored. Activated charcoal orally or by lavage may be given or sodium / magnesium sulfate orally can be used as a cathartic. Attention should be given to the re-establishment of adequate respiratory exchange through provision of a patient airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsion. Acidosis and electrolyte losses should be corrected

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.

Bromhexine hydrochloride is obtained from the plant Adhatoda vasica, Bromhexine creates an environment in the bronchial tree conductive to the removal of sticky mucous from the bronchioles, thus promoting expectoration without excessive straining.
Bromhexine hydrochloride and ammonium chloride maintain the integrity of the mucociliary blanket to bring out the secretion in normal physiological manner.
Ammonium chloride produces mild irritation of the mucus lining of the stomach and this gastro vagal reflex increases the respiratory tract fluid, relieving dryness and soreness of the respiratory passage. Menthol acts as a demulcent and soothing agent.

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.

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.

Bromhexine increases the expectoration of sputum in bronchitis patients, increases the output of water into respiratory tract fluid and depolymerises the mucopolysaccharides in the mucous. It is also claimed to act on bronchial glands, to liberate lysosomal enzymes from the mucous secreting cells which digest the mucopolysaccharide fibers. Thus bromhexine is extremely useful in restoring the mucociliary equilibrium. Besides this, it has been attributed to have mild anti tussive effect. Bromhexine increases sputum volume by stimulating the mucous gland of the respiratory tract and promoting ciliary clearance of sputum. Bromhexine further reduces sputum viscosity by breaking down the tenacious network of mucopolysaccharide fibres in mucoid sputum which are mainly responsible for sputum stickiness
Bromhexine creates an environment in the bronchial tree conducive to the removal of sticky mucus thus promoting expectoration without excessive straining.
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

5.3 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.

Bromhexine is rapidly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the liver. Its oral bioavailability is stated to be only about 20%. It is widely distributed to body tissues and is highly bound to plasma proteins. About 85 to 90% of a dose is excreted in the urine mainly as metabolites. It has a terminal elimination half-life of up to about 12 hours. Bromhexine crosses the blood brain barrier and small amounts cross the placenta. Administration of bromhexine hydrochloride by mouth to healthy subjects produced peak plasma concentrations after about 1 hour. Only small amounts were excreted unchanged in the urine with a half life of about 6.5 hours

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MethylParaben , Propyl Paraben, Sodium CMC1, Sugar, Erythtocine, Sunset Yellow, Ethanol , Raspberry, Sodium Sulphate, Sorbitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C. Keep the medicine tightly closed in the original container.

6.5 Nature and contents of container

Bottle:	Amber PET BOOTLE
Closures:	ROPP wadded, tamper evident, with 10ml measuring cup
Pack Sizes:	100ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

TUYIL PHARMACEUTICAL INDUSTRIES LIMITED

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