Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benylin Children's Dry Coughs Syrup Diphenhydramine Hydrochloride 7mg/5ml Levomenthol 0.55mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains Diphenhydramine Hydrochloride 7mg and Levomenthol 0.55mg in each 5ml.

Excipient(s) with known effect: Each 5 ml contains:
Sorbitol 2.525g
Sodium 16.47mg
Ethanol 197mg
Sodium Benzoate (E211) 25mg
Propylene glycol (E1520) 1.07mg

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Syrup
Clear, colourless syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Children aged 6 years and over:
Oral. 10 ml syrup 3 or 4 times a day.
Maximum daily dose: 40 ml syrup
Use only when simple measures have failed to provide adequate relief.
Use for more than five consecutive days is not recommended.

Children under 6 years:
Benylin Children's Dry Coughs is not suitable for administration to children under 6 years of age. [See Section 4.3]

The Elderly:
Not applicable

Hepatic & Renal dysfunction
It may be prudent to increase the dosage interval in subjects with moderate to severe hepatic and/or renal dysfunction, [See Pharmacokinetics].

4.3 Contraindications

Benylin Children's Dry Coughs is contraindicated in individuals with hypersensitivity to diphenhydramine, levomenthol or to any of the excipients listed in section 6.1.

Benylin Children's Dry Coughs is contraindicated in patients taking Monoamine inhibitors (MAOIs) or within 14 days of stopping treatment (see section 4.5)

Benylin Children's Dry Coughs should not be used in children under the age of 6 years.

4.4 Special warnings and precautions for use

Benylin Children's Dry Coughs 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 [See Pharmacokinetics].

Benylin Children's Dry Coughs 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.

Not more than 4 doses should be given in any 24 hours. 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

This medicine contains 2.525g sorbitol in each 5ml dose. Patients with hereditary problems of fructose intolerance (HFI) should not take this medicine. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

A dose of 10 ml of this medicine administered to a child 6 years of age and weighing 21 kg would result in exposure to 18.8 mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about 3.13 mg/100 ml.
For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml.

The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in younger children, for example feeling sleepy.

Co-administration with medicines containing e.g., propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity.

This medicinal product contains 16.47 mg sodium per 5ml, equivalent to 0.82% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains 1.07 mg propylene glycol in each 5ml dose.

This medicine contains 25mg sodium benzoate per 5ml dose.

4.5 Interaction with other medicinal products and other forms of interaction

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 Fertility, 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

Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with diphenhydramine and menthol are included in Table 1.

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, including isolated reports
Not known (cannot be estimated from the available data)

Table 1 Adverse Drug Reactions Identified During Clinical Trials and Post-Marketing Experience with Diphenhydramine/ Menthol

Frequency Category Estimated from Clinical Trials or Epidemiology Studies*

Body system	**Incidence**	**Reported adverse event**
Psychiatric disorders	Uncommon	Agitation Confusional state Insomnia Irritability Hallucination Nervousness
Nervous system disorders	Very common	Somnolence
	Common	Dizziness
	Uncommon	Coordination abnormal Convulsion Headache Paraesthesia Sedation Tremor
Eye disorders	Uncommon	Vision blurred
Ear and labyrinth disorders	Uncommon	Tinnitus
Cardiac disorders	Uncommon	Palpitations Tachycardia
Vascular disorders	Uncommon	Hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dry throat Nasal dryness
Gastrointestinal disorders	Common	Dry mouth
	Uncommon	Constipation Diarrhoea Dyspepsia

		Nausea Vomiting
Skin and subcutaneous tissue disorders	Uncommon	Pruritus Rash 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.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Signs and Symptoms

Diphenhydramine

Mild to Moderate Symptoms: Somnolence, anticholinergic syndrome (hyperpyrexia, mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds), tachycardia, mild hypertension, nausea and vomiting are common after overdose. Cerebral stimulation in children and occasionally in adults, insomnia, nervousness, tremors, epileptiform convulsions may occur. 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.

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.
In the event of overdose please consult with the local poison treatment guidance.
The intravenous use of physostigmine may be efficacious in antagonising severe anticholinergic symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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-rececptor blockade 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 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

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.

The duration of activity of diphenhydramine is between 4 and 8 hours.

Menthol has mild local anaesthetic and decongestant properties.

5.2 Pharmacokinetic properties

Diphenhydramine

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 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 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 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,N-didemethyl 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,N-didemethyl 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.

Pharmacokinetics in the Elderly

Pharmacokinetic studies indicate no major differences in distribution or elimination of diphenhydramine compared to younger adults.

Pharmacokinetics in 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).

Pharmacokinetics in Hepatic Dysfunction
After intravenous administration of 0.8 mg/kg diphenhydramine, a prolonged half-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.

5.3 Preclinical safety data

Mutagenicity
The results of a range of tests suggest that for diphenhydramine or menthol potential mutagenic risk has not been established.

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. There is no evidence of adverse effects with menthol on fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium benzoate (E211)

Citric acid monohydrate
Sodium citrate
Saccharin sodium
Carmellose sodium
Glycerol
Sorbitol 70 % (Non crystalline)
Concentrated raspberry essence (Double strength) (containing ethanol and propylene glycol (E1520))
Ethanol 96%
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening of the container – 4 Months.

6.4 Special precautions for storage

Do not store above 30°C.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

125 ml amber glass bottle with ROPP aluminium cap containing Melinex faced pulpboard wad or with a 3 piece plastic child resistant tamper evident closure fitted with a polyester faced wad or polyethylene/expanded polyethylene laminated wad.

Or a 2 piece child resistant cap consisting of an external white plastic cap in Polypropylene or an inner plastic cap including a tamper evident ring in High Density Polyethylene. The CRC cap is fitted with a PET wad.

A spoon with a 5 ml and 2.5 ml measure is supplied with the pack.

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

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