

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 7 mg and Levomenthol 0.55 mg in each 5 ml.

Excipients

5ml contains:

Sorbitol 2.525 g

Sodium 17 mg

Ethanol 96% 0.260 ml

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 known hypersensitivity to the product or any of its components.

Benylin Children's Dry Coughs is contraindicated in children under 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 section 5.2).

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

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

This medicinal product contains 5 vol % ethanol (alcohol), i.e. up to 200mg per 5ml equivalent to 5ml beer, 2ml wine per 5ml. This can be harmful for those suffering from alcoholism. The ethanol content should be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver or kidney disease or epilepsy.

This medicinal product contains 16.47 mg sodium per 5ml. This should be taken into consideration by those on a controlled sodium diet.

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.

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 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 Post-Marketing Experience with Diphenhydramine/ Menthol
Frequency Category Estimated from Clinical Trials or Epidemiology Studies*

Body system	Incidence	Reported adverse event
Psychiatric disorders	Not known	Confusional state
		Irritability
		Hallucination
Nervous system disorders	Not known	Nervousness
		Somnolence
		Dizziness
Eye disorders	Not known	Agitation
		Coordination abnormal
		Convulsion
Ear and labyrinth disorders	Not known	Headache
		Insomnia
		Paraesthesia
Cardiac disorders	Not known	Sedation
		Tremor
		Vision blurred
Respiratory, thoracic and mediastinal disorders	Not known	Tinnitus
		Hypotension
		Palpitations
Gastrointestinal disorders	Not known	Tachycardia
		Chest discomfort
		Dry throat
Skin and subcutaneous tissue disorders	Not known	Nasal dryness
		Dry mouth
		Constipation
		Diarrhoea
		Dyspepsia
		Nausea
		Vomiting
		Pruritus
		Rash
		Urticaria

Renal and urinary disorders	Not known	Urinary retention
General disorders and administration site conditions	Common	Asthenia

(*) 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

Diphenhydramine

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

Severe Symptoms: Effects may include delirium, psychosis, seizures, coma, hypotension, QRS widening, and ventricular dysrhythmias (including torsades de pointe), 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.

Treatment

Treatment of overdose should be symptomatic and supportive. Measures to promote rapid gastric emptying (with syrup of ipecac-induced emesis or gastric lavage) and, in cases of acute poisoning, the use of activated charcoal, may be useful.

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-receptor 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 $24.0 \pm 1.9\%$ 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 first-pass metabolism with an absolute bioavailability of $72\% \pm 8\%$. 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
Citric acid monohydrate
Sodium citrate
Saccharin sodium
Carmellose sodium
Glycerol
Sorbitol 70 % (Non crystalline)
Concentrated raspberry essence (Double strength)
Ethanol 96%
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

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

McNeil Healthcare (Ireland) Ltd.
Airton Road
Tallaght
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0823/021/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th August 1992

Date of last renewal: 24th August 2007

10 DATE OF REVISION OF THE TEXT

July 2015