

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

BENYLIN Dry Coughs Syrup
Diphenhydramine Hydrochloride 14mg/5ml
Dextromethorphan hydrobromide 6.5mg/5ml
Levomenthol 2mg/5ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains diphenhydramine hydrochloride 14 mg, levomenthol 2 mg and dextromethorphan hydrobromide 6.5 mg.

Excipients: Each 5 ml contains liquid glucose 3.49 g, sucrose 1g, ethanol (96%) 0.260 ml and Ponceau 4R (E124) 250 micrograms.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup.
A clear red syrup having a menthol-raspberry flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

BENYLIN Dry Coughs is indicated as an antitussive, for the relief of persistent, dry, irritating cough.

4.2 Posology and method of administration

PosologyAdults and children 12 years and over:
10 ml syrup 3 to 4 times a day.
Maximum daily dose: 40 ml syrup

Children under 12 years:
Benylin Dry Coughs is not recommended. [See section 4.3]

Older people:
Normal adult dosage is appropriate, [See Pharmacokinetics in the older people].

Hepatic Dysfunction:
Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of moderate to severe hepatic impairment, [See Phamacokinetics].

Renal Dysfunction
It may be prudent to increase the dosage interval in subjects with moderate to severe renal failure, [See Pharmacokinetics in Renal Impairment].

Method of administration
For oral use only

4.3 Contraindications

BENYLIN Dry Coughs is contra-indicated in individuals with known hypersensitivity to the product or any of its components.

BENYLIN Dry Coughs is contra-indicated in individuals who are taking, or have taken, monoamine oxidase inhibitors (including the antibacterial agent furazolidone) within the preceding two weeks. The concomitant use of a dextromethorphan-containing product and monoamine oxidase inhibitors, can occasionally result in symptoms such as hyperpyrexia, hallucinations, gross excitation or coma.

Dextromethorphan, in common with other centrally acting antitussive agents, should not be given to subjects in, or at risk of developing respiratory failure.

Benylin Dry Cough is contraindicated for use in children under 12 years of age.

4.4 Special warnings and precautions for use

Do not use with any other product containing diphenhydramine, even one used on skin.

This product may cause drowsiness, (See section 4.8 Undesirable Effects) if affected; individuals should not drive or operate machinery.

Caution should be exercised if moderate to severe renal and/or hepatic impairment is present, [See Pharmacokinetics].

This product may act as a cerebral stimulant in children and occasionally in adults.

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

- Persistent or chronic cough such as occurs with smoking, asthma or emphysema or where cough is accompanied by excessive secretions
- Narrow angle glaucoma.
- Prostate hyperplasia with urinary retention.

If symptoms persist, please consult your doctor.

Patients who are taking other medication and / or under the care of a physician, should consult their doctor / pharmacist before taking this product.

Diphenhydramine may enhance the sedative effects of central nervous system depressants including alcohol, sedatives, and tranquilizers. Patients should be advised while taking this product, to avoid alcoholic beverages and consult a healthcare professional prior to taking with central nervous system depressants (see Section 4.5).

Cases of dextromethorphan abuse have been reported. Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors (see also section 4.5).

This product contains Ponceau 4R (E124) red colouring which may cause allergic reactions.

This product contains 16.7mg sodium per 5ml. This should be taken into consideration by those on a controlled sodium diet.

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

This medicinal product contains 5 vol % ethanol (alcohol), i.e. up to 200 mg per 5ml dose, equivalent to approximately 5 ml beer, 2 ml wine per 5 ml dose. 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 disease or epilepsy.

Do not exceed the recommended dose schedule

4.5 Interaction with other medicinal products and other forms of interaction

Dextromethorphan:

MAOIs: The concomitant use of a dextromethorphan-containing product and monoamine oxidase inhibitors (including the antibacterial agent furazolidone), can occasionally result in serotonin syndrome with symptoms such as hyperpyrexia, hallucinations, gross excitation or coma. See section 4.3

CYP2D6 inhibitors

Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhoea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

Diphenhydramine

Alcohol and CNS Depressants:

This product contains diphenhydramine and therefore may potentiate the effects of alcohol and other CNS depressants such as opioid analgesics, anticonvulsants, antidepressants, antihistamines, antiemetics, antipsychotics, anxiolytics and hypnotics.

Anticholinergic drugs: As diphenhydramine possess 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.

Menthol

None known.

4.6 Fertility, pregnancy and lactation

Both diphenhydramine and dextromethorphan have been in widespread use for many years without apparent ill consequence. There are no adequate and well-controlled studies in pregnant or breast-feeding women. It is not known whether dextromethorphan or its metabolites are excreted in breast milk or cross placenta.

Diphenhydramine is known to cross the placenta and has also been detected in breast milk, but levels have not been reported.

Benylin Dry Coughs should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risk to the developing foetus or nursing infant.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse drug reactions (ADRs) identified during post-marketing experience with Dextromethorphan / Diphenhydramine / Menthol 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).

ADRs are presented by frequency category based on 1) incidence in adequately designed clinical trials or epidemiology studies, if available, or 2) when incidence cannot be estimated, frequency category is listed as ‘Not known’.

Body system (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Immune system disorders	Not known	Angioedema^
Psychiatric Disorders	Uncommon Uncommon Uncommon Uncommon Uncommon Not known	Agitation^* Confusional state^ Insomnia*^ Irritability* Nervousness* Hallucination*
Nervous System Disorders	Very Common Common Not known Not known Not known Not known Not known Not known	Somnolence† Dizziness†^ Convulsion* Coordination abnormal* Headache* Paraesthesia* Psychomotor hyperactivity^ Tremor*
Eye Disorders	Not known	Blurred vision*
Ear and Labyrinth Disorders	Uncommon	Tinnitus*
Cardiac Disorders	Not known Not known	Palpitations* Tachycardia*
Vascular Disorders	Not known	Hypotension*
Respiratory, Thoracic and Mediastinal Disorders	Common Uncommon Uncommon Not known Not known	Dry throat* Bronchospasm^ Dyspnoea^ Chest discomfort* Nasal dryness*

Gastrointestinal Disorders	Common Uncommon Uncommon Uncommon Not known Not known Not known Not known	Dry Mouth† Gastrointestinal disorder*^ Nausea^ Vomiting^ Abdominal pain^ Constipation* Diarrhoea*^ Dyspepsia*
Skin and Subcutaneous Tissue Disorders	Uncommon Not known Not known	Rash* Pruritus*^ Urticaria*^
Renal and Urinary Disorders	Not known Not known	Dysuria* Urinary retention*
General Disorders and Administration site Conditions	Common	Asthenia†

† Frequency category based on clinical trials with single-ingredient Diphenhydramine

* Associated with Diphenhydramine

^ Associated with Dextromethorphan

There have been a few reports of abuse of dextromethorphan, but there is no evidence of drug dependence at therapeutic dosages.

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

Symptoms and signs

The effects of acute toxicity of Benylin Dry Coughs may include hyperpyrexia, lethargy, hyperactivity, nervousness and tremors. With higher doses, and particularly in children, symptoms of cardiovascular collapse and CNS excitation including epileptiform convulsions may appear; large doses of antihistamines may precipitate attacks in epilepsy.

Dextromethorphan

Symptoms of overdose may include:

Eye Disorders: Mydriasis

Nervous System Disorders: CNS depression, CNS excitation, Nystagmus, Serotonin syndrome

Respiratory, Thoracic and Mediastinal Disorders: Respiratory depression, Death may occur as a result of respiratory failure.

Diphenhydramine

Symptoms of overdose may include:

Mild to Moderate Symptoms: Somnolence, anticholinergic syndrome (mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds, agitation, confusion and hallucinations), tachycardia, mild hypertension, nausea and vomiting are common after overdose.

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.

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. The intravenous use of physostigmine may be efficacious in antagonising severe anticholinergic symptoms. Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Dextromethorphan

Dextromethorphan is a non-opioid antitussive drug. It exerts its antitussive activity by acting on the cough centre in the *medulla oblongata*, raising the threshold for the cough reflex. A single oral dose of 10-20 mg dextromethorphan produces its antitussive action within 1 hour and lasts for at least 4 hours.

Diphenhydramine

Diphenhydramine possesses antitussive, antihistaminic, and anticholinergic properties. Experiments have shown that the antitussive effect (resulting from an action on the brain stem) is discrete from its antihistaminic 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

Absorption

Diphenhydramine, dextromethorphan and menthol are well absorbed from the gut following oral administration. Peak serum levels of diphenhydramine following a 50 mg oral dose are reached at between 2 and 2.5 hrs after an oral dose. Due to individual differences in the metabolism of dextromethorphan [See Metabolism & Elimination], pharmacokinetic values are highly variable. After the administration of a 20 mg dose of dextromethorphan to healthy volunteers, the C_{max} varied from < 1 µg/l to 8 µg/l, occurring within 2.5 hrs of administration.

Distribution

Diphenhydramine

Diphenhydramine is widely distributed throughout the body, including the CNS. Following a 50 mg oral dose of diphenhydramine, the volume of distribution is in the range 3.3 - 6.8 L/kg, and it is some 78% bound to plasma proteins.

Dextromethorphan

Due to extensive pre-systemic metabolism by the liver, detailed analysis of the distribution of orally administered dextromethorphan is not possible.

Metabolism and elimination

Diphenhydramine

Diphenhydramine undergoes extensive first pass metabolism. Two successive N-demethylations occur, with the resultant amine being oxidised to a carboxylic acid. Values for plasma clearance of a 50 mg oral dose of diphenhydramine lie in the range 600 - 1300 ml/min and the terminal elimination half-life lies in the range 3.4 - 9.3 hours. Little unchanged drug is excreted in the urine.

Dextromethorphan

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers.

It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrophan (also known as 3-hydroxy-N-methylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.

Dextrophan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.

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.

Pharmacokinetics in Renal Impairment

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 the glomerular filtration rate (GFR).

There have been no specific studies of BENYLIN Dry Coughs or dextromethorphan in renal impairment.

Pharmacokinetics in Hepatic Impairment

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.

There have been no specific studies of BENYLIN Dry Coughs or dextromethorphan in hepatic impairment.

Pharmacokinetics in the Elderly

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

There have been no specific studies of BENYLIN Dry Coughs or dextromethorphan in the elderly.

5.3 Preclinical safety data

Mutagenicity

The results of a range of tests suggest that neither diphenhydramine or menthol have mutagenic potential. There is insufficient information to determine whether dextromethorphan has mutagenic potential.

Carcinogenicity

There is insufficient information to determine the carcinogenic potential of diphenhydramine, dextromethorphan 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. There is insufficient information to determine whether dextromethorphan has teratogenic potential.

Fertility

There is insufficient information to determine whether diphenhydramine or dextromethorphan has the potential to impair fertility, although a diminished fertility rate with diphenhydramine has been observed in mice in one study.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Liquid Glucose
Sucrose
Ethanol (96%)
Glycerol
Sodium citrate
Saccharin sodium
Citric acid monohydrate
Sodium benzoate (E211)
Caramel T12
Raspberry flavour 503.850/T
Ponceau 4R (E124)
Carbomer
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.
Keep bottle tightly closed.

6.5 Nature and contents of container

Amber glass bottle with ROPP aluminium cap or a 3 piece child resistant tamper evident closure fitted with a PE- Alu-PET wad or polyethylene/expanded polyethylene laminated wad or with a HDPE plastic cap fitted with a PE-Alu-PET wad.

Pack size: 125 ml

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Ltd
Airton Road
Tallaght
Dublin 24

8 MARKETING AUTHORISATION NUMBER

PA0823/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 29 September 2007

10 DATE OF REVISION OF THE TEXT

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