Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benylin Dry Coughs Syrup Diphenhydramine hydrochloride 14 mg/5 ml Dextromethorphan hydrobromide 6.5 mg/5 ml Levomenthol 2 mg/5 ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: Each 5ml contains liquid glucose 3.50 g, sucrose 1 g, invert sugar 6.75mg, ethanol (96%) 0.260 ml, sodium benzoate 10 mg, benzyl alcohol 0.48 mg, propylene glycol (E1520) 2.605mg, sodium 16.7mg 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

Posology

Adults 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:
This product is contraindicated in children under the age of 12 years (see section 4.3).

The Elderly:
Normal adult dosage is appropriate, (see section 5.2).

Hepatic Dysfunction:
Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of hepatic impairment. (see section 5.2).

Renal Dysfunction
It may be prudent to increase the dosage interval in subjects with moderate to severe renal impairment, (see section 5.2).

Method of administration
For oral use only.

4.3 Contraindications

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

Benylin Dry Coughs is contraindicated in individuals who are taking, or have taken, monoamine oxidase inhibitors (MAOIs) within the preceding two weeks. There is a risk of serotonin syndrome with the concomitant use of dextromethorphan and MAOIs and the concomitant use of these medications may cause a rise in blood pressure and/or hypertensive crisis (see section 4.5).

This product is contraindicated in patients taking serotonin reuptake inhibitors (SSRIs, see section 4.5).

Dextromethorphan, should not be given to patients in, or at risk of developing respiratory failure.

Benylin Dry Coughs 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.

This product may cause drowsiness. This product should not be used to sedate a child.

Caution should be exercised if moderate to severe renal impairment and/or hepatic impairment is present. (see section 5.2).

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:

- Susceptibility to angle closure.
- Prostate hyperplasia with urinary retention.

Patients with the following conditions should not use this product, unless directed by a physician: acute or chronic asthma, a persistent or chronic cough such as occurs with chronic bronchitis or emphysema, or where cough is accompanied by excessive secretions.

Patients who are taking other medication including cough and cold medicines and / or who are 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.

Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

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

Serotonin Syndrome
Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors. Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, treatment with Benylin Dry Coughs should be discontinued.

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 should be used with caution in atopic children due to histamine release.

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

This product contains 33.4 mg sodium per 10 ml dose, equivalent to 1.67% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains 16.8 mg benzoate salt in each 10 ml dose.

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

This product contains glucose. Patients with rare glucose-galactose malabsorption should not take this medicine.

This product contains invert sugar. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption should not take this medicine.
This should be taken into account in patients with diabetes mellitus.

This medicine contains 392 mg of alcohol (ethanol) in each 10 ml dose. The amount in 10 ml of this medicine is equivalent to less than 10 ml beer or 4 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains 0.96 mg benzyl alcohol per 10ml dose. Benzyl alcohol may cause allergic reactions. Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis"). High volumes should be used with caution and only if necessary, especially in subjects with liver or kidney impairment because of the risk of accumulation and toxicity (metabolic acidosis). Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

This medicine contains 5.21 mg propylene glycol in each 10 ml dose.

4.5 Interaction with other medicinal products and other forms of interaction

Dextromethorphan

Monoamine Oxidase Inhibitors (MAOIs):
Dextromethorphan should not be used concurrently in patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping treatment with MAOIs as there is a risk of serotonin syndrome (pyrexia, hypertension, arrhythmias).

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 SSRIs such as fluoxetine and 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.

Metoprolol:
Metoprolol is a CYP2D6 substrate and metabolism of dextromethorphan has been shown to be prolonged when the two drugs are administered concomitantly.

Isavuconazole:
Isavuconazole is a moderate inhibitor of CYP3A4 and a mild inducer of CYP2B6. When administered concomitantly with dextromethorphan, the AUC and C_{max} of dextromethorphan has been observed to increase by 18% and 17%, respectively.

Alcohol and CNS depressants:
Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

Diphenhydramine

Alcohol and CNS depressants:
Diphenhydramine may enhance the sedative effects of CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, antipsychotics and alcohol.

Antimuscarinic drugs:
Diphenhydramine may have an additive muscarinic action with other drugs, such as atropine and tricyclic antidepressants.

Menthol

None known.

4.6 Fertility, pregnancy and lactation

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.

Both diphenhydramine and dextromethorphan have been in widespread use for many years without any 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 the placenta.

Diphenhydramine is known to cross the placenta and, therefore, should only be used during pregnancy if considered essential by a doctor.
Diphenhydramine is excreted into human breast-milk, but levels have not been reported. Although the levels are not thought to be sufficiently high enough after therapeutic doses to affect the infant, the use of diphenhydramine during breast-feeding is not recommended.

There are no adequate and well-controlled studies in pregnant women for menthol. Menthol is excreted in breast milk; when 100 mg of menthol was ingested, there was up to 5.87 ug/L of menthol in breast milk.

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 clinical trials and 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'.

System Organ Class (SOC)	Frequency	Adverse Drug Reaction (Preferred Term)
Blood and Lymphatic System	Rare	Blood disorder*
Immune system disorders	Rare	Hypersensitivity*
Psychiatric Disorders	Uncommon Uncommon Uncommon Uncommon Uncommon Rare Rare Not known	Agitation^* Confusional state*^ Insomnia*^ Irritability* Nervousness* Depression* Sleep disorder* Hallucinations*
Nervous System Disorders	Very Common Common Common Common Common Rare Rare Rare Not known Not known	Somnolence†^ Dizziness†^ Headache* Paradoxical drug reaction* Psychomotor hyperactivity* Extrapyramidal disorder* Seizure*^ Tremor* Coordination abnormal* Paraesthesia*
Eye Disorders	Common	Blurred vision*
Ear and Labyrinth Disorders	Uncommon	Tinnitus*
Cardiac Disorders	Rare Rare Not known	Arrhythmia* Palpitations* Tachycardia*
Vascular Disorders	Rare	Hypotension*
Respiratory, Thoracic and Mediastinal Disorders	Common Common Uncommon Uncommon Not known Not known Not known	Dry throat* Increased viscosity of bronchial secretion* Bronchospasm^ Dyspnoea^ Chest discomfort* Nasal dryness* Respiratory depression^
Gastrointestinal Disorders	Common Common Uncommon Uncommon Not known Not known Not known	Dry Mouth† Gastrointestinal disorder*^ Nausea^ Vomiting^ Abdominal pain^ Constipation* Diarrhoea*^

	Not known	Dyspepsia*
Hepatobiliary Disorders	Rare	Liver disorder*
Skin and Subcutaneous Tissue Disorders	Uncommon Not known Not known Not known	Rash*^ Angioedema^ Pruritus*^ Urticaria*^
Renal and Urinary Disorders	Common Not known	Urinary retention* Dysuria*
General Disorders and Administration site Conditions	Common	Asthenia†

† Frequency category based on clinical trials with single-ingredient Diphenhydramine
* Associated with Diphenhydramine
^ Associated with Dextromethorphan

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

Dextromethorphan
Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability.

In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.

Dextromethorphan overdose is also associated with conversion disorder; hallucinations, mixed; clumsiness; depressed level of consciousness; dizziness; dysarthria; lethargy; hypertension; serotonin syndrome; tremor; miosis; mydriasis; urinary retention and ischaemic colitis.

Bromide intoxication has been observed during concomitant use with bromide-containing over-the-counter drugs or with overdose of dextromethorphan hydrobromide.

Diphenhydramine
Following overdose in adults, moderate symptoms have been associated with ingestions of greater than 300-500 mg and serious symptoms associated with doses greater than 1 g diphenhydramine.

Young children may be more sensitive to the effects of overdose.

Symptoms of overdose may include:
Mild to Moderate Symptoms: Somnolence, anticholinergic syndrome (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.

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.

Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour. Consider activated charcoal (charcoal dose: 50 g for adults; 1 g/kg for children) only if the patient presents within 1 hour of ingestion of a potentially toxic amount.

For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Naloxone has been used successfully to reverse central or peripheral opioid effects of dextromethorphan in children (0.01 mg/kg bodyweight).

Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.
The intravenous use of physostigmine may be efficacious in antagonising severe anticholinergic symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamics

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 brainstem) is discrete from its antihistaminic effect. The duration of activity of diphenhydramine is between 4 and 8 hours.

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 stimulant action of menthol on mucus production may be beneficial, as bacteria adhere avidly to respiratory tract mucus. Ciliary clearance of mucus is essential in order to prevent infection and therefore any effect of menthol on ciliary activity is of interest.

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 Cmax varied from < 1∞g/l to 8µg/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 dextrorphan (also known as 3-hydroxy-N-methylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine.
Dextrorphan, 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

Glucose syrup
Sucrose
Ethanol (96%)
Glycerol
Sodium citrate
Saccharin sodium
Citric acid monohydrate
Sodium benzoate (E211)
Caramel T12 (containing sucrose, glucose and invert sugar)
Raspberry flavour 503.850/3T (containing propylene glycol (E1520) benzyl alcohol and ethanol)
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 colour glass bottles with ROPP Aluminium caps fitted with PE-Alu-PET Wad.
Pack size: 125 ml

6.6 Special precautions for disposal

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

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