Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benylin Non-Drowsy Dry Coughs, Syrup Dextromethorphan hydrobromide 7.5 mg/5 ml

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BENYLIN Non-Drowsy Dry Coughs, Syrup contains dextromethorphan hydrobromide 7.5 mg in each 5 ml.

Each 5 ml of BENYLIN Non-Drowsy Dry Coughs, Syrup also contains:

Sorbitol solution (70%) E420	325 mg
Sucrose	1625 mg
Glucose	2380 mg
Sodium	4.4 mg
Ethanol	236 mg
Sodium benzoate	25 mg
Propylene glycol	2.7 mg
Invert sugar	6.7mg

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Syrup
A clear amber coloured syrup with a characteristic smell of peaches.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BENYLIN Non-Drowsy Dry Coughs, Syrup is indicated for the relief of non-productive irritating cough.

4.2 Posology and method of administration

Adults and children 12 years and over:
Oral. 15 mg (10 ml syrup) 3-4 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).

Hepatic dysfunction
Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of hepatic impairment (See sections 4.4 and 5.2).

4.3 Contraindications

This product is contraindicated in individuals with known hypersensitivity to dextromethorphan or to any of the excipients listed in section 6.1.

Dextromethorphan should not be used in patients taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOI treatment (see section 4.5). 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 Non-Drowsy Dry Coughs, Syrup is contraindicated for use in children under 12 years of age.

4.4 Special warnings and precautions for use

Use with caution in patients with hepatic dysfunction.

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.

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.

Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses. While taking this product, patients should be advised to avoid alcoholic drinks and consult a healthcare professional prior to taking with central nervous system depressants.

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 Non-Drowsy Dry Coughs, Syrup 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.

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.

Excipients:

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

Sorbitol: This medicine contains 650 mg sorbitol in each 10 ml dose. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

This medicine contains 472 mg of alcohol (ethanol) in each 10 ml dose. The amount in a 10 ml dose of this medicine is equivalent to less than 12 ml beer or 5 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicine contains 42 mg benzoate salt in each 10 ml dose.

This medicine contains 5.43 mg propylene glycol in each 10 ml dose.

This medicine contains less than 1 mmol sodium (23 mg) per 10 ml dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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

4.6 Fertility, pregnancy and lactation

Although dextromethorphan has been in widespread use for many years without apparent ill consequence, there is insufficient information on the effects of administration during human pregnancy. In addition, it is not known whether dextromethorphan or its metabolites are excreted in breast milk.

BENYLIN Non-Drowsy Dry Coughs, Syrup should therefore only be used when the potential benefit of treatment to the mother exceeds any possible hazards to the developing foetus or nursing infant.

4.7 Effects on ability to drive and use machines

Although the overall data do not support that dextromethorphan impacts driving, due to its potential for somnolence and dizziness, caution should be used when driving a motor vehicle or operating machinery.

4.8 Undesirable effects

Post-marketing Data:
Adverse drug reactions (ADRs) identified during clinical trials and post-marketing experience with Dextromethorphan are listed 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, <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 category	Adverse Drug Reaction (Preferred Term)
Psychiatric Disorders	Rare	Confusional state
	Not known	Agitation
	Not known	Insomnia
Nervous System Disorders	Not known	Dizziness
	Not known	Psychomotor hyperactivity
	Not known	Seizure
	Not known	Somnolence
Respiratory, Thoracic and Mediastinal Disorders	Rare	Bronchoconstriction
	Rare	Dyspnoea
	Not known	Respiratory depression
Gastrointestinal Disorders	Not known	Abdominal pain
	Not known	Diarrhoea
	Not known	Nausea
	Not known	Vomiting
Skin and Subcutaneous Tissue Disorders	Not known	Angioedema
	Not known	Pruritus
	Not known	Rash
	Not known	Urticaria

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

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.

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.

Fatal cases of dextromethorphan overdose have been reported.

Management

Treatment of overdose should be symptomatic and supportive.

Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cough suppressant
ATC code: R05DA09

Dextromethorphan is the dextrorotatory isomer of 3-methoxy-N-methyl-morphinan. It is a synthetic morphine derivative that, in contrast to its levoisomer, has no significant analgesic, respiratory depressant or physical dependency properties at recommended doses.

Dextromethorphan is a cough suppressant and acts centrally on the cough centre in the medulla oblongata to elevate the threshold for coughing.

The onset of antitussive effects are realised within 15 to 30 minutes of oral administration, lasting for approximately 3 to 6 hours.

The major metabolite of dextromethorphan, dextrorphan, binds with high affinity to σ-receptors to produce its antitussive activity without exhibiting the classic opiate effects that occur from binding into μ- and δ-receptors. Dextrorphan also exhibits binding activity at serotonergic receptors and was shown to enhance serotonin activity by inhibiting the reuptake of serotonin.

5.2 Pharmacokinetic properties

Absorption
Dextromethorphan is rapidly absorbed from the gastrointestinal tract with peak plasma concentrations reached in approximately 2 to 2.5 hours. The low plasma levels of dextromethorphan suggest low oral bioavailability secondary to extensive first-pass (presystemic metabolism) in the liver. The maximum clinical effects occur 5 to 6 hours after ingestion of dextromethorphan.

Distribution
Dextromethorphan is widely distributed in the human body. Dextromethorphan and its active metabolite, dextrorphan, are actively taken up and concentrated in brain tissue. It is not known if dextromethorphan or dextrorphan are excreted in breast milk or cross the placenta.

Metabolism
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.

Excretion
Dextromethorphan is primarily excreted via the kidney as unchanged parent drug and its active metabolite, dextrorphan. Dextrorphan and 3-hydroxy-morphinan are further metabolised by glucuronidation and are eliminated via the kidneys.

The elimination half-life of the parent compound is between 1.4 to 3.9 hours; dextrorphan is between 3.4 to 5.6 hours. The half-life of dextromethorphan in poor metabolisers is extremely prolonged, in the range of 45 hours.

5.3 Preclinical safety data

5.3.1. General Toxicology

Acute oral toxicity studies conducted with Dextromethorphan report the following LD_{50} values (mg/kg): mouse, 210 and rat, 116. Acute subcutaneous toxicity with Dextromethorphan reports the LD_{50} value (mg/kg): mouse, 112. Acute intravenous toxicity with Dextromethorphan reports the LD_{50} value (mg/kg): rat, 16.3.

Repeat dose toxicity studies conducted in rats for 13 weeks duration at doses up to 100 mg/kg and 27 weeks at 10 mg/kg, and of 14 weeks in dogs by oral gavage at doses up to 4 mg/kg on five days per week. The only effect recorded was of reduced body weight gain in the rat 13-week study at the highest dose.

5.3.2. Genetic Toxicology

Dextromethorphan hydrobromide was negative in the bacterial reverse mutation assay (Ames test). Dextromethorphan 39 mg/kg is reported to be negative in *in-vivo* mouse micronucleus test and comet assay. Dextromethorphan was reported to be negative in *in vitro* chromosome aberration assay tested up to 200 µg/ml.

5.3.3. Carcinogenicity

There are no known reports of animal carcinogenicity studies for Dextromethorphan. There is no evidence of a carcinogenic risk to humans.
The overall weight of evidence for Dextromethorphan and its structural analogues, supports the conclusion that this class of phenanthrene-based chemicals, and Dextromethorphan, in particular, are not genotoxic *in vitro* or *in vivo*, and do not represent a carcinogenic risk to patients.

5.3.4. Teratogenicity

There was no association between dextromethorphan and malformations. Dextromethorphan is generally considered safe to use during pregnancy.

5.3.5. Fertility

Mating, gestation, fertility, littering and lactation were studied in rats at doses up to 50 mg/kg and no adverse effects were found. There is no evidence of a fertility impairment risk to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Levomenthol
Sodium benzoate (E211)
Sucrose
Glycerol
Liquid Glucose
Sorbitol solution (70%) (E420)
Saccharin sodium
Citric acid monohydrate
Ethanol 96% vol (alcohol)
Caramel T12 (containing sucrose, glucose and invert sugar)
Imitation peach flavour (containing ethanol and propylene glycol (E1520))
Carbomer
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C. Keep the bottle tightly closed in order to protect from light and moisture.

6.5 Nature and contents of container

30 ml, 125 ml and 300 ml round amber glass bottles with ROPP aluminium caps or 3-piece child resistant, tamper evident closures fitted with a PE-Alu-PET or polyethylene/expanded polyethylene laminated wad or with a HDPE plastic cap fitted with a PE-Alu-PET wad.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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