SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Benylin Dry Coughs Night Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:	
Diphenhydramine hydrochloride	14 mg
Dextromethorphan hydrobromide	6.5 mg
Levomenthol	2 mg

Each 5 ml also contains:	
Ethanol	196 mg
Glucose	3.5 g
Sucrose	1 g
Ponceau 4R (E124)	0.25 mg
Sodium	16.7 mg
Benzyl alcohol	0.48 mg
Propylene glycol	2.61 mg
Sodium benzoate (E211)	10 mg

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Clear red syrup, darkening on ageing to brown syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This product is indicated as an antitussive, for the night time relief of persistent, dry, irritating cough, and aiding restful sleep.

4.2 Posology and method of administration

Posology
Adults and children aged 12 years and over:
Patients may start with two 5 ml spoonfuls at bedtime followed by two 5 ml spoonfuls every 6 hours.

Or two 5 ml spoonfuls four times a day.

Do not take more than 4 doses (1 dose = two 5 ml spoonfuls) in 24 hours.

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 Pharmacokinetics in the Elderly].

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
Caution should be exercised in the presence of moderate to severe renal impairment (see section 5.2).

Method of administration
For oral use

4.3 Contraindications

This medicine is contraindicated in individuals with known hypersensitivity to diphenhydramine, dextromethorphan, levomenthol 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.

Not to be used in children under the age of 12 years.

4.4 Special warnings and precautions for use

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

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.

Diphenhydramine should be used with caution by individuals with susceptibility to angle-closure or with prostatic hypertrophy, urinary retention. Subjects with moderate to severe renal impairment or hepatic dysfunction should exercise caution when using this product (see section 5.2).

Drug dependence, tolerance and potential for abuse
For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Drug withdrawal syndrome
The drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

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 this medicine should be discontinued.

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

Diphenhydramine may enhance the sedative effects of central nervous system depressants including alcohol, opioid analgesics, antipsychotics, sedatives, and tranquilizers.

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.

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.

Do not use with any other product containing diphenhydramine including topical formulations used on large areas of skin.

This product should not be taken with any other cough and cold medicines.

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

This product contains 16.7 mg sodium per 5 ml, equivalent to 0.835 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This product contains 3.5 g glucose and 1 g sucrose per 5 ml. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. This should be taken into account in patients with diabetes mellitus.

This medicine contains 10 mg sodium benzoate (E211) in each 5 ml.

This medicine contains 2.61 mg propylene glycol in each 5 ml.

This medicine contains 0.48 mg benzyl alcohol in each 5 ml. 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).

This medicine contains 196 mg of alcohol (ethanol) in each 5 ml. The amount in 5 ml of this medicine is equivalent to less than 5 ml beer or 2 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

4.5 Interaction with other medicinal products and other forms of interaction

Dextromethorphan and Diphenhydramine

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, hallucination, gross excitability, coma, 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.

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

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. This may result in tachycardia, mouth dryness, gastrointestinal disturbances (e.g. colic), urinary retention and headache.

4.6 Fertility, pregnancy and lactation

This medicine 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 breastfeeding 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 medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When taking this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
  - The medicine has been taken to treat a medical or dental problem and
  - You have taken it according to the information provided with the medicine and
  - It was not affecting your ability to drive safely.

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

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 Rare Rare Not known Not known Not known	Confusional state Insomnia Irritability Nervousness Depression Sleep disorder Agitation Drug dependence (see section 4.4) Hallucination

Nervous System Disorders	Very Common Common Common Common Common Rare Rare Rare Not known	Somnolence Dizziness Headache Paradoxical stimulation Psychomotor impairment Extrapyramidal disorder Seizure Tremor 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 Not known Not known Not known	Increased viscosity of bronchial secretion Chest discomfort Nasal dryness Respiratory depression
Gastrointestinal Disorders	Common Common Not known Not known Not known Not known	Dry Mouth Gastrointestinal disorder Abdominal pain Diarrhoea Nausea Vomiting
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 Not known	Asthenia Drug withdrawal syndrome

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms

Dextromethorphan
Dextromethorphan is thought to be of low toxicity, but the effects in overdose will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.
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 hallucinations mixed, psychotic disorder, seizure, clumsiness, dizziness, CNS depression, dysarthria, lethargy, hypertension, serotonin syndrome tremor, miosis and mydriasis.

Fatal cases of dextromethorphan overdose have been reported very rarely.

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. Convulsions may be controlled with diazepam and thiopental sodium.

5.1 Pharmacodynamic properties

There is no available information on the pharmacodynamic properties for the combination of dextromethorphan, diphenhydramine and menthol in humans. The information presented below describes the pharmacodynamic properties of the single active ingredients.

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, 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

Menthol has mild local anaesthetic and decongestant properties.
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, but there are no reports of *in-vivo* studies in human subjects on the effects of menthol on ciliary clearance.

5.2 Pharmacokinetic properties

There is no available information on the pharmacokinetic properties for the combination of dextromethorphan, diphenhydramine and menthol in humans. The information presented below describes the pharmacokinetic properties of the single active ingredients.

Absorption
Diphenhydramine, dextromethorphan and menthol are well absorbed from the gut following oral administration.

Diphenhydramine
Peak serum levels of diphenhydramine following a 50 mg oral dose are reached at between 2 and 2.5 hrs after an oral dose.

Dextromethorphan
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 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 this medicine 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 this medicine 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 this medicine or dextromethorphan in the elderly.

5.3 Preclinical safety data

The active ingredients of this medicine are well-known constituents of medical products and their safety profiles are well documented. The results of pre-clinical studies do not add anything of relevance for therapeutic purposes.

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 503.850/3T (benzyl alcohol, propylene glycol, ethanol)
Carbomer
Ponceau 4R (E124)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years
Discard the bottle 4 months after first opening.

6.4 Special precautions for storage

Do not store above 30^{o}C. Store in the original container.

6.5 Nature and contents of container

125 or 150 ml amber glass bottles with a 2 piece or a 3 piece plastic child resistant, tamper evident closure fitted with a polyterephtalate ethylene faced aluminium/expanded polyethylene laminated wad

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

McNeil Products Limited
1 Station Hill Square
Station Hill
Reading
RG1 1LN
UK

8 MARKETING AUTHORISATION NUMBER

PL 15513/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/02/2009

10 DATE OF REVISION OF THE TEXT

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