SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

BENYLIN DRY COUGHS 7.5mg/5ml Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:
Dextromethorphan hydrobromide 7.5 mg

Each 5ml also contains:
Sucrose 1.6 g
Liquid glucose 2.38 g
Sorbitol 325 mg
Ethanol 236 mg
Sodium benzoate 25 mg
Propylene glycol 2.72 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pale brown coloured, peach flavoured syrup.

4.1. Therapeutic indications

This product is indicated as an antitussive, for the relief of an unproductive cough.

4.2 Posology and method of administration

Adults and Children aged 12 years and over:

Posology
10 ml syrup (15 mg dextromethorphan) 4 times a day.
Maximum daily dose: 40 ml syrup (60 mg dextromethorphan)

Children under 12 years:

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

The Elderly (over 65 years)

As for adults above.

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

Method of Administration
For oral use.

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.

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

4.4. Special warnings and precautions for use

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.

There have been no specific studies of this product in renal or hepatic dysfunction. Due to the extensive hepatic metabolism of dextromethorphan, caution should be exercised in the presence of hepatic impairment.

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.

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

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.

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 2.38 g glucose and 1.6 g sucrose per 5 ml. 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 medicine.

This medicine contains 325 mg sorbitol in each 5 ml. 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 25 mg sodium benzoate (E211) in each 5 ml.

This medicine contains 2.72 mg propylene glycol in each 5 ml.

This medicine contains 236 mg of alcohol (ethanol) in each 5 ml. The amount in 5 ml of this medicine is equivalent to less than 6 ml beer or 3 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

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, hallucinations, gross excitation or 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.

4.6 Fertility, pregnancy and lactation

There are no adequate and well-controlled studies in pregnant women. Dextromethorphan 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.

It is not known whether dextromethorphan or its metabolites are excreted 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 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, including isolated reports
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)**
Psychiatric Disorders	Not known Not known Not known Not known	Agitation Confusional state Drug dependence Insomnia
Nervous System Disorders	Not known Not known Not known Not known	Dizziness Psychomotor hyperactivity Seizure Somnolence

Respiratory, thoracic and mediastinal Disorders	Not known	Respiratory depression
Gastrointestinal Disorders	Not known Not known Not known Not known Not known	Abdominal pain Diarrhoea Gastrointestinal disorder Nausea Vomiting
Skin and Subcutaneous Tissue Disorders	Not known Not known Not known Not known	Angioedema Pruritus Rash Urticaria
General disorders and administration site condition	Unknown	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 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 disorders; seizures; clumsiness; dizziness; dysarthria; lethargy; hypertension; serotonin syndrome; tremor; CNS depression; miosis and mydriasis.

Fatal cases of dextromethorphan overdose have been reported very rarely.

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

ATC Code: R05DA09 Pharmacotherapeutic Group: Cough Suppressant, Opium alkaloids and derivatives

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

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. 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. In larger than therapeutic doses, dextrorphan is also an antagonist of N-methyl-D-aspartate (NMDA) receptors.

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 (pre-systemic 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

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.

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.

Carcinogenicity
There are no known reports of animal carcinogenicity studies for Dextromethorphan. The overall weight of evidence for Dextromethorphan and its structural analogues, support the conclusion that this class of phenanthrene-based chemicals, and Dextromethorphan, in particular, are not genotoxic in vitro or in vivo

Teratogenicity
There was no association between dextromethorphan and malformations.

Fertility
Mating, gestation, fertility, littering and lactation were studied in rats at doses up to 50 mg/kg and no adverse effects were found.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid glucose
Sucrose
Sorbitol solution 70% non crystallising
Ethanol 96%
Glycerol
Saccharin sodium
Citric acid monohydrate
Sodium benzoate
Caramel T12
Imitation peach flavour (ethanol, propylene glycol)
Levomenthol
Carbomer
Purified Water

6.2 Incompatibilities

Not applicable

6.3. Shelf-Life

3 Years

6.4. Special Precautions for Storage

Do not store above 30^0C

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 for disposal.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

McNeil Products Limited
50 – 100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 15513/0051

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

16 June 1997

10 DATE OF REVISION OF THE TEXT

08/07/2025