Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benylin Children's Coughs and Colds 5mg/0.625mg per 5ml Syrup

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains 5 mg Dextromethorphan hydrobromide and 0.625 mg Triprolidine hydrochloride.

Excipients: Each 5ml contains liquid maltitol 4080mg and methyl hydroxybenzoate (E218) 5mg.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Syrup
Clear colourless syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Benylin Children's Coughs & Colds is indicated for the symptomatic relief of dry unproductive cough and rhinorrhoea associated with the common cold and influenza.

4.2 Posology and method of administration

Posology

Adults and children 12 years and over:

Not appropriate.

Children aged 6 to 12 years:

10 ml three or four times daily. Leave at least 4 hours between doses.

Maximum daily dose: 40 ml (4 doses).
Use only when simple measures have failed to provide adequate relief.
Use for more than five consecutive days is not recommended.

Children under 6 years:

Benylin Children's Coughs and Colds Syrup is contraindicated in children under the age of 6 years. [See Section 4.3]

Hepatic Dysfunction

Caution should be exercised when administering this product to patients with hepatic impairment.

Method of administration

For oral use.

4.3 Contraindications

Benylin Children's Coughs and Colds Syrup is contraindicated in individuals with hypersensitivity to dextromethorphan, triprolidine or to any of the excipients listed in section 6.1.

Benylin Children's Coughs and Colds Syrup is contraindicated in patients who are receiving monoamine oxidase inhibitors (MAOIs) or who have received these within the previous 14 days. There is a risk of serotonin syndrome with the concomitant use of dextromethorphan and MAOIs, and the concomitant use of this product and MAOIs may cause a rise in blood pressure or hypertensive crisis (see section 4.5).

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

Use in patients in or at risk of developing respiratory failure.

Use in children under 6 years of age is contraindicated.

4.4 Special warnings and precautions for use

Benylin Children's Coughs and Colds Syrup may cause drowsiness. This product should not be used to sedate a child.

Patients with the following conditions should be advised to consult a physician before using the product:
- Susceptibility to angle closure
- Urinary retention or prostatic enlargement

Triprolidine may enhance the sedative effects of central nervous system depressants including alcohol, sedatives and tranquilisers.

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

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 of psychoactive substances. There is no evidence of drug dependence at therapeutic doses.

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).

Use with caution in hepatic dysfunction.

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

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.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Methylhydroxybenzoate (E218) may cause allergic reactions such as skin rash; this may happen after a few days.

Consult a pharmacist or other healthcare professional before use in children aged 6-12 years.

4.5 Interaction with other medicinal products and other forms of interactions

CNS depressants: Triprolidine may enhance the sedative effects of alcohol and other CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics. Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

Anticholinergic drugs: The effects of anticholinergics, e.g. some psychotropic drugs and atropine, may be potentiated by triprolidine.

MAOIs: Benylin Children's Coughs and Colds Syrup should not be used in patients taking MAOIs or within 14 days of stopping treatment 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.

4.6 Fertility, pregnancy and lactation

This product should not be used during pregnancy or lactation unless the potential benefit of treatment to the mother outweighs the possible risks to the developing foetus or nursing infant.

Fertility

There is no experience of the effect of Benylin Children's Coughs and Colds Syrup on human fertility.

Pregnancy

There are no adequate and well controlled studies available on the effects of administration of this product in pregnant women.
It is not known if dextromethorphan or its active metabolite, dextrorphan cross the placenta.

The available human data on the reproductive effects of dextromethorphan do not demonstrate an increased teratogenic risk.

Results of a controlled study to determine the foetal risk in 184 women exposed to dextromethorphan, 128 exposed in the first trimester of pregnancy, revealed that dextromethorphan use during pregnancy did not increase the rate of major malformations compared to 184 matched controls. Foetal risk was also monitored in a large collaborative study involving 300 women who received dextromethorphan during the first trimester of pregnancy. The study did not support a relationship between the drug and congenital malformations.

Breastfeeding

Triprolidine is excreted in breast milk. It has been estimated that approximately 0.06 to 0.2% of a single 2.5mg dose of triprolidine ingested by a nursing mother will be excreted in the breast milk over 24 hours.

It is not known whether dextromethorphan or its metabolites, are excreted in breast milk.

4.7 Effects on ability to drive and use machines

Benylin Children's Coughs & Colds may cause drowsiness and impair performance in tests of auditory vigilance. Children receiving this product should be carefully supervised in order to avoid accidental mishap.

4.8 Undesirable effects

Placebo controlled studies with sufficient adverse event data are not available for the combination of dextromethorphan and triprolidine.

Adverse drug reactions identified during clinical trials and post- marketing experience with dextromethorphan or triprolidine are listed below by System Organ Class (SOC).

The frequencies are defined 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 is listed as 'Not known'.

System Organ Class (SOC)	**Frequency**	**Adverse Drug Reaction (Preferred Term)**
Blood and Lymphatic System Disorders	Rare	Blood disorder
Immune System Disorders	Rare	Hypersensitivity
Psychiatric Disorders	Rare	Confusional state
	Rare	Depression
	Rare	Sleep disorder
	Not known	Agitation
	Not known	Hallucination
	Not known	Insomnia
Nervous System Disorders	Common	Headache
	Common	Paradoxical drug reaction
	Common	Psychomotor hyperactivity
	Common	Somnolence
	Rare	Dizziness
	Rare	Extrapyramidal disorder
	Rare	Seizure
	Rare	Tremor
	Not known	Paraesthesia
Eye Disorders	Common	Vision blurred
Cardiac Disorders	Rare	Arrhythmia
	Rare	Palpitations
	Not known	Tachycardia
Vascular Disorders	Rare	Hypotension

Respiratory, Thoracic and Mediastinal Disorders	Common	Increased viscosity of bronchial secretion
	Not known	Bronchospasm
	Not known	Dyspnoea
	Not known	Respiratory depression
Gastrointestinal Disorders	Common	Dry mouth
	Common	Gastrointestinal disorder
	Not known	Abdominal pain
	Not known	Diarrhoea
	Not known	Nausea
	Not known	Vomiting
Hepatobiliary Disorders	Rare	Liver disorder
Skin and Subcutaneous Tissue Disorders	Not known	Angioedema
	Not known	Pruritus
	Not known	Rash
	Not known	Urticaria
Renal and Urinary Disorders	Common	Urinary retention
General Disorders and Administration Site Conditions	Not known	Fatigue

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 from Benylin Children's Coughs & Colds may include drowsiness, lethargy, dizziness, ataxia, weakness, hypotonicity, respiratory depression, dryness of the skin and mucous membranes, tachycardia, nystagmus, hyperpyrexia, nausea and vomiting.

Dextromethorphan
It is thought to be of low toxicity, but the effects in overdose will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.
Symptoms of overdose may include:
Psychiatric disorders: agitation; confusional state; conversion disorder; hallucinations, mixed; psychotic disorder.
Nervous system disorders: ataxia; clumsiness; coma; depressed level of consciousness; dizziness; dysarthria; lethargy; nystagmus; seizure; serotonin syndrome; somnolence; tremor
Eye disorders: miosis; mydriasis
Respiratory, thoracic and mediastinal disorders: respiratory depression.
Death may occur as a result of respiratory failure.
Gastrointestinal disorders: nausea; vomiting
Renal and urinary disorders: urinary retention

Triprolidine

Although there have been no reports of convulsions with Triprolidine HCl 2 mg/5 ml, either in therapeutic doses or in overdose, central excitation is a feature of poisoning with antihistamines and can result in convulsions, particularly in infants.

Overdose of an H1 receptor antagonist may result in CNS depression, hyperthermia, anticholinergic syndrome (mydriasis, flushing, fever, dry mouth, urinary retention, decreased bowel sounds), tachycardia, hypotension, hypertension, nausea, vomiting, agitation, confusion, hallucinations, psychosis, seizures, or dysrhythmias. Rhabdomyolysis and renal failure may rarely develop in patients with prolonged agitation, coma, or seizures.

Management

Treatment of overdose should be symptomatic and supportive: Necessary measures should be taken to maintain and support respiration and control convulsions. Gastric lavage should be performed up to 3 hours after ingestion, if indicated.

Naloxone has been used successfully to reverse central or peripheral opioid effects of dextromethorphan in children (0.1 mg/kg body weight).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs: ATC code: N07XX59 dextromethorphan, combinations

Triprolidine

Triprolidine is a potent, competitive H1 receptor antagonist. Being an alkylamine the drug possesses minimal anticholinergic activity. Triprolidine provides symptomatic relief in conditions believed to depend wholly, or partly, upon the triggered release of histamine. After the oral administration of a single dose of 2.5 mg triprolidine to adults, the onset of action, as determined by the ability to antagonize histamine-induced wheals and flares in the skin, was within 1 to 2 hours. Peak effects occurred at about 3 hours, and although activity declines thereafter, significant inhibition of histamine-induced wheals and flares still occurred 8 hours after a single dose.

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.

5.2 Pharmacokinetic properties

Absorption

Triprolidine
Triprolidine is well absorbed from the gut following oral administration.
After the administration of 2.5 mg triprolidine to healthy adult volunteers, the peak plasma concentration (Cmax) of triprolidine was approximately 5.5 - 6.0 ng/ml, occurring at about 2.0 hours (tmax) for the tablet and 1.5 hours for the syrup after drug administration.

Dextromethorphan
Dextromethorphan in well absorbed from the gut following oral administration. Due to individual differences in the metabolism of dextromethorphan [See Metabolism and Elimination], pharmacokinetic values are highly variable. After the administration of a 20mg dose of dextromethorphan to healthy volunteers, the Cmax varied from < 1 mg/l to 8 mg/l, occurring within 2.5 hrs of administration.

Distribution

Triprolidine
Triprolidine 3.75 mg can be detected in plasma within 30 minutes after oral administration. There is approximately 90% of drug bound in plasma. The volume of distribution for 2.5 mg to 5 mg ranges from 5.5 to 8.7 L/kg.

Dextromethorphan
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

Triprolidine
Triprolidine has variable oral bioavailability, possibly due to high first pass hepatic metabolism. The plasma half-life (t½) of triprolidine was approximately 3.2 hours. Animal hepatic microsomal enzyme studies have revealed the presence of several triprolidine metabolites with an oxidized product of the toluene methyl group predominating.

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.

Elimination

Triprolidine
In man, it has been reported that only about 1% of an administered dose is eliminated as unchanged triprolidine over a 24-hour period. The apparent total body clearance of triprolidine (Cl/F) was approximately 30 - 37 ml/min/kg. The elimination rate constant (Kel) was approximately 0.26 hr-1.

Dextromethorphan
Dextromethorphan is primarily excreted via the kidney as unchanged parent drug and its active metabolite, dextrorphan. Dextrorphan and 3- hydroxy-morphinan are further metabolized 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 metabolizers is extremely prolonged, and is in the range of 45 hours. Dextromethorphan syrup and tablets have terminal plasma elimination half -lives (t1/2elβ) of 3.3 ± 0.63 h and 2.7 ± 0.77 h, respectively.

Pharmacokinetics in Renal/Hepatic Impairment

There have been no specific studies of dextromethorphan, triprolidine or Benylin Children's Coughs & Colds in renal or hepatic impairment.

Pharmacokinetics in the Elderly

Not relevant

5.3 Preclinical safety data

Non-clinical studies performed with the combination of actives were not found in the published literature. Since no studies were found, the non-clinical safety data on the individual active ingredients were reviewed.

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Liquid Maltitol
Glycerol
Methyl parahydroxybenzoate (E218)
Sodium benzoate (E211)
Saccharin sodium
Flavour (mixed fruit)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 ^{o}C.

6.5 Nature and contents of container

Amber glass bottles with polypropylene screw caps fitted with PVDC faced wads or a 3 piece plastic child resistant, tamper evident closure fitted with a polyester faced wad or polyethylene/expanded polyethylene laminated wad. Or a two piece plastic child resistant cap fitted with a PVDC wad.

Sizes: 30ml, 100ml, and 125ml.

A polypropylene double ended measuring spoon is supplied with each bottle.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

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
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0823/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 March 1998

Date of last renewal: 20 March 2008

10 DATE OF REVISION OF THE TEXT

December 2018