Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benylin Dual Action Dry Syrup
Pseudoephedrine 30mg
Dextromethorphan 10mg
Triprolidine 1.25mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml of Benylin Dual Action Dry Syrup contains

Pseudoephedrine Hydrochloride 30 mg
Dextromethorphan Hydrobromide 10 mg
Triprolidine Hydrochloride 1.25 mg

Excipients: contains Sorbitol Solution (70%) 1000.0mg, Sucrose 2835.0mg, sodium Benzoate (E211) 5.0mg, Ponceau 4R (E124) 0.8mg and Ethanol (96% v/v) 201.5mg.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Syrup

A clear, bright red, blackberry-flavoured syrup.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

BENYLIN Dual Action Dry Syrup is indicated for the relief of dry cough and upper respiratory tract congestion such as is associated with the common cold and influenza.

4.2 Posology and method of administration

Posology

Adults and Children 12 years and over:

10 ml every 4-6 hours, up to four times a day

Maximum daily dose: 40ml (80mg dextromethorphan, 240mg pseudoephedrine and 10mg triprolidine).

Children under 12 years:
This medicine is contraindicated in children under the age of 12 years. [See section 4.3]

Use in the elderly
There have been no specific studies of Benylin Dual Action Dry Syrup in the elderly. Experience has indicated that normal adult dosage is appropriate.

Hepatic Dysfunction
Caution should be exercised when administering Benylin Dual Action Dry Syrup to patients with severe hepatic impairment.

Renal Dysfunction
Caution should be exercised when administering Benylin Dual Action Dry Syrup to patients with moderate to severe renal impairment

Method of administration
For oral use.

Do not exceed the stated dose.

4.3 Contraindications

Benylin Dual Action Dry Syrup is contraindicated in individuals with hypersensitivity to dextromethorphan, pseudoephedrine, triprolidine or to any of the excipients listed in section 6.1.

Benylin Dual Action Dry Syrup is contraindicated in patients who are receiving monoamine oxidase inhibitors or who have received these within the previous 14 days. There is a risk of serotonin syndrome with dextromethorphan and the concomitant use of pseudoephedrine and MAOIs may cause a rise in blood pressure or hypertensive crisis (see section 4.5)

Benylin Dual Action Dry Syrup is contraindicated in individuals who are concomitantly taking other sympathomimetic decongestants.

Benylin Dual Action Dry Syrup is contraindicated in individuals who have diabetes mellitus, phaeochromocytoma, hyperthyroidism, closed angle glaucoma or severe renal impairment.

Benylin Dual Action Dry Syrup is contraindicated in patients with cardiovascular disease including hypertension and in those who are taking beta-blockers (see section 4.5).

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

The antibacterial agent, furazolidone, is known to cause a dose-related inhibition of monoamine oxidase. Therefore Benylin Dual Action Dry Syrup should not be administered concurrently with furazolidone.

Benylin Dual Action Dry Syrup is contraindicated in patients at risk of developing respiratory failure.

Benylin Dual Action Dry Syrup is contraindicated in children under the age of 12 years.

4.4 Special warnings and precautions for use

Benylin Dual Action Dry Syrup may cause drowsiness. This product should not be used to sedate a child

If any of the following occur, this product should be stopped:

- Hallucinations
- Restlessness
- Sleep disturbances

Patients with the following conditions should be advised to consult a physician before using this product:

- Susceptibility to angle-closure
- Urinary retention or prostatic enlargement,

- A respiratory condition such as emphysema, chronic bronchitis, or acute or chronic bronchial asthma.

Although pseudoephedrine has virtually no pressor effects in normotensive patients, Benylin Dual Action Dry Syrup should be used with caution in patients taking tricyclic antidepressants, or other sympathomimetic agents (such as appetite suppressants and amphetamine-like psychostimulants). The physician or pharmacist should check that sympathomimetic containing preparations are not simultaneously administered by several routes i.e. orally and topically (nasal, aural and eye preparations).

Pseudoephedrine may act as a cerebral stimulant giving rise to insomnia, nervousness, hyperpyrexia, tremor and epileptiform convulsions.

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 smaller doses.

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 or psychoactive substances.

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).

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.

Benylin Dual Action Dry Syrup should only be used under medical supervision for persistent or chronic cough such as occurs with smoking, asthma or emphysema, or where cough is accompanied by excessive secretions.

If symptoms persist or get worse, stop use and consult your doctor.

Patients who are taking other medication and/or under the care of a physician, should consult their doctor /pharmacist before taking this product.

Use with caution in moderate to severe renal impairment or in hepatic impairment.

Use with caution in occlusive vascular disease.

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

This medicine contains 5% v/v ethanol (alcohol), which is up to 190 mg per ml, equal to 5ml beer or 2ml wine per 5 ml. This can be harmful for those suffering from alcoholism. The ethanol content should be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease and epilepsy.

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

The colouring in this medicine may cause allergic reactions.

Each 5ml of this medicine contains 2.8 g of sucrose per dose. 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.

Not more than 4 doses should be given in any 24 hours. Do not exceed the stated dose.

Do not take with any other cough and cold medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Triprolidine may enhance the sedative effects of alcohol and other central nervous system depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics.

Concomitant use with sympathomimetic agents such as decongestants, tricyclic antidepressants, appetite suppressants and amfetamine-like psychostimulants, may cause a rise in blood pressure.

Pseudoephedrine exerts its vasoconstricting properties by stimulating adrenergic receptors and displacing noradrenaline from neuronal storage sites. Since MAOIs impede the metabolism of sympathomimetic amines and increase the store of releasable noradrenaline in adrenergic nerve endings, MAOIs may potentiate the pressor effect of pseudoephedrine.

MAOIs and/or RIMAs: Benylin Dual Action Dry Syrup should not to be given to patients treated with MAOIs or within 14 days of stopping treatment as there is a risk of hypertensive crisis and serotonin syndrome (pyrexia, hypertension, arrhythmias).

Moclobemide: risk of hypertensive crisis.

Because of its pseudoephedrine content, the product may partially reverse the hypotensive action of antihypertensive drugs which interfere with sympathetic activity including bretylium, betanidine, guanethidine, debrisoquine, methyldopa, adrenergic neurone blockers and beta-blockers.

Furazolidone causes a dose-related inhibition of monoamine oxidase. Although there are no reports to date of hypertensive crisis caused by concurrent use with this product, the combination should be avoided.

Oxytocin: risk of hypertension.

Cardiac glycosides: increased risk of dysrhythmias.

Ergot alkaloids (ergotamine & methysergide): increased risk of ergotism.

Anticholinergic drugs: enhances effects of anticholinergic drugs (such as tricyclic antidepressants and atropine).

Concurrent use with halogenated anaesthetic agents such as chloroform, cyclopropane, halothane, enflurane or isoflurane may provoke or worsen ventricular 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 fluoxetine, 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 Dual Action Dry 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.

Breastfeeding
Pseudoephedrine distributes into and is concentrated in breast milk. In a limited study, three mothers nursing healthy infants were given an antihistamine-decongestant preparation containing 60mg of pseudoephedrine and 2.5 mg of triprolidine. Milk concentrations of pseudoephedrine were higher than plasma levels in all three patients, with peak milk concentrations occurring at 1.0-1.5 hours. The investigators calculated that 1000ml of milk produced during 24 hours would contain approximately 0.5%-0.7% of the maternal dose. However, following a single-blind, crossover study of a single dose of pseudoephedrine 60mg vs. placebo conducted in 8 lactating mothers, and assuming maternal intake of 60mg pseudoephedrine hydrochloride four times daily, the estimated infant dose of pseudoephedrine based on AUC and an estimated milk production rate of 150 ml/kg/day was 4.3% (95% CI, 3.2, 5.4%; range 2.2 to 6.7%) of the weight-adjusted maternal dose.

Triprolidine is excreted in breast milk, it has been estimated that approximately 0.06 to 0.2% of a single 2.5 mg 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

The product may act as a cerebral stimulant in children, and occasionally in adults. Central nervous system depression or excitation may occur, with symptoms such as drowsiness, sleep disturbance and more rarely, hallucinations. Patients receiving it should not drive or operate machinery unless it has been shown that their physical and mental ability remains unaffected.

4.8 Undesirable effects

Placebo controlled studies with sufficient adverse event data were not available for the combination of dextromethorphan, pseudoephedrine and triprolidine.
Adverse drug reactions identified during clinical trials and post-marketing experience with dextromethorphan, pseudoephedrine or the combination of pseudoephedrine and triprolidine or the combination of dextromethorphan and pseudoephedrine are listed below by System Organ Class (SOC). The frequencies are defined in accordance with current guidance, as:

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	Not known Rare	Drug hypersensitivity Hypersensitivity – cross-sensitivity may occur with other sympathomimetics
Psychiatric Disorders	Common Common Rare Rare Rare Not known Not known Not Known Not known Not known Not known Not known	Insomnia Nervousness Confusional state Depression Sleep disorder Agitation Anxiety Delusion Euphoric mood Hallucination Irritability Restlessness
Nervous System Disorders	Very Common Common Common Common Common Rare Rare Rare Not known	Headache Dizziness Paradoxical drug reaction Psychomotor hyperactivity Somnolence Convulsion Extrapyramidal disorder Tremor Paraesthesia
Eye Disorders	Common	Vision blurred
Cardiac Disorders	Rare Rare Not known	Arrhythmia Palpitations Tachycardia
Vascular Disorders	Rare Not known	Hypotension Hypertension
Respiratory, Thoracic and Mediastinal Disorders	Common Not known Not known Not known Not known Not known	Increased viscosity of bronchial secretion Dry Throat Dyspnoea Epistaxis Nasal dryness Respiratory Depression
Gastrointestinal Disorders	Common Common Common Not Known Not Known	Dry mouth Gastrointestinal disorder Nausea Abdominal pain Diarrhoea

	Not Known	Vomiting
Hepatobiliary Disorders	Rare	Liver disorder
Skin and Subcutaneous Tissue Disorders	Not Known Not Known Not Known Not Known	Angioedema Pruritus Rash Urticaria
Renal and Urinary Disorders	Common Not Known	Urinary retention* Dysuria
General Disorders and Administration Site Conditions	Not Known Not Known	Fatigue Feeling Jittery

*in male patients in whom prostatic enlargement could have been an important predisposing factor.

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 Dual Action Dry Syrup may include drowsiness, lethargy, dizziness, ataxia, nystagmus, weakness, hypotonicity, respiratory depression, dryness of the skin and mucous membranes, tachycardia, hypertension, hyperpyrexia, hyperactivity, irritability, convulsions, difficulty with micturition, nausea and vomiting.

Dextromethorphan
It is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs.
Symptoms: These include nausea, vomiting, dizziness and dysarthria (slurred speech).
Overdose may also result in mydriasis, CNS depression, CNS excitation, nystagmus, somnolence (drowsiness) , mental confusion, psychotic disorder (psychosis), serotonin syndrome and respiratory depression

Pseudoephedrine
Overdosage may result in:

Metabolism and nutrition disorders: hyperglycaemia, hypokalaemia.

Psychiatric disorders: CNS stimulation, insomnia; irritability, restlessness, anxiety, agitation; confusion, delirium, hallucinations, psychoses.

Nervous system disorders: convulsions, tremor, intracranial haemorrhage including intracerebral haemorrhage, drowsiness in children.

Eye disorders: mydriasis.

Cardiac disorders: palpitations, tachycardia, reflex bradycardia, supraventricular and ventricular arrhythmias, dysrhythmias, myocardial infarction.

Vascular disorders: hypertension, hypertensive crisis.

Gastrointestinal disorders: nausea, vomiting, ischaemic bowel infarction.

Musculoskeletal and connective tissue disorders: rhabdomyolysis.

Renal and urinary disorders: acute renal failure, difficulty in micturition

Triprolidine
Overdosage 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. Catheterisation of the bladder may be necessary. If desired, the elimination of pseudoephedrine can be accelerated by acid diuresis or by dialysis.

Naloxone has been used successfully to reverse central or peripheral opioid effects of dextromethorphan in childrsn (0.01 mg/kg body weight).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pseudoephedrine has a direct and indirect sympathomimetic activity and is an orally effective upper respiratory decongestant. Pseudoephedrine is substantially less potent than ephedrine in producing both tachycardia and elevation of systolic blood pressure and considerably less potent in causing stimulation of the central nervous system. Pseudoephedrine produces its decongestant effect within 30 minutes, persisting for at least 4 hours.

Dextromethorphan has an antitussive action. It controls coughs by depressing the medullary cough centre. A single oral dose of 10 - 20 mg dextromethorphan produces its antitussive action within 1 hour and lasts for at least 4 hours.

Triprolidine provides antihistamine activity by antagonising H_1-receptors. After oral administration of a single dose of 2.5 mg triprolidine to adults the onset of action, as determined by the ability to antagonise histamine-induced weals and flares in the skin, is within 1 to 2 hours. Peak effects occur at about 3 hours and, although activity declines thereafter, significant inhibition of histamine-induced weals and flares still occurs 8 hours after the dose.

5.2 Pharmacokinetic properties

After the administration of 2.5 mg triprolidine hydrochloride and 60 mg pseudoephedrine hydrochloride to healthy adult volunteers, the peak plasma concentration (C_{max}) of triprolidine is approximately 5.5 ng/ml - 6.0 ng/ml occurring at about 1.5 - 2.0 hours (T_{max}) after drug administration. Its plasma half-life is approximately 3.2 hours. The C_{max} of pseudoephedrine is approximately 180 ng/ml with T_{max} approximately 1.5 - 2.0 hours after drug administration. The plasma half-life is approximately 5.5 hours (urine pH maintained between 5.0 - 7.0). The plasma half-life of pseudoephedrine is increased in subjects with alkaline urine and decreased in subjects with acid urine.

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.

5.3 Preclinical safety data

It has been estimated that 0.5 to 0.7% of a single dose of pseudoephedrine ingested by a mother will be excreted in the breast milk over 24 hours.

In rats and rabbits, systemic administration of triprolidine up to 75 times the human daily dosage did not produce teratogenic effects.

Systemic administration of pseudoephedrine up to 50 times the human daily dosage in rats, and up to 35 times the human daily dosage in rabbits did not produce teratogenic effects.

There is insufficient information available to determine whether dextromethorphan has teratogenic potential.

No studies have been conducted in animals to determine whether pseudoephedrine, dextromethorphan or triprolidine have the potential to impair fertility.

The active ingredients of BENYLIN Dual Action Dry Syrup are well-known constituents of medicinal products and their safety profiles are well documented. The results of pre-clinical studies do not add anything of relevance for therapeutic purposes.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol solution (70%)
Sucrose
Sodium benzoate (E211)
Methyl parahydroxybenzoate (E218)
Ponceau 4R (E124)
Ethanol
Blackberry flavour
Levomenthol
Vanillin
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate. Keep the bottle in the outer carton.

6.5 Nature and contents of container

Benylin Dual Action Dry Syrup is stored in 30ml, 40ml, 50ml, 100ml and 200ml amber glass bottles closed with metal roll-on closures or HDPE screw caps fitted with saran - or steran (PVDC)-faced wads.

Alternatively the product is available in amber glass bottles with a three piece plastic child resistant tamper evident closure fitted with a polyvinylidine chloride (PVDC) faced wad or polyethylene expanded polyethylene laminated wad.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McNeil Healthcare (Ireland) Ltd.
Airton Road
Tallaght
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0823/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15th March 1984
Date of last renewal: 15th March 2009

10 DATE OF REVISION OF THE TEXT

December 2016