Professional information for BENYLIN® DRY COUGH

SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE:

BENYLIN® Dry Cough syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 5 mL syrup contains:

Dextromethorphan hydrobromide	15 mg

Excipients with known effect:

Preservative:	Sodium benzoate	0,5 % *m/v*

Contains sweetener: Each 5 mL contains 20 mg sodium cyclamate and 1,5 mg saccharin sodium.

Contains sugar alcohol: Each 5 mL contains 2,5 g sorbitol.

Sugar free.

Alcohol free.

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM:

Syrup.

Dark brown syrup with a faint odour of menthol and raspberries.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

BENYLIN® Dry Cough is indicated for the symptomatic relief of non-productive cough.

4.2 Posology and method of administration:

Do not exceed the recommended dose.

For oral use only.

Shake the bottle before use.

Adults: One medicine measure (5 mL) every four hours, or two medicine measures (10 mL) every six to eight hours.

Children 5 to 12 years: Half to one medicine measure (2,5 mL – 5 mL) every six to eight hours.

Children below 5 years of age: Not recommended (see section 4.3).

4.3 Contraindications:

- Hypersensitivity to dextromethorphan or to any of the other ingredients in BENYLIN® Dry Cough (see section 6.1).
- Patients taking monoamine oxidase inhibitors (MAOIs), or for 2 weeks after stopping the MAOI medicine. There is risk of serotonin syndrome with the concomitant use of BENYLIN® Dry Cough and MAOIs and the concomitant use of these medicines may cause a rise in blood pressure and/or hypertensive crisis (see section 4.5).
- Patients with asthma and hepatic dysfunction.
- Children under 5 years of age.

4.4 Special warnings and precautions for use:

BENYLIN® Dry Cough should not be taken for a persistent respiratory condition, which occurs with smoking, bronchial asthma, emphysema, chronic bronchitis or where cough is accompanied by excessive secretions, except under the advice and supervision of a doctor. A persistent cough

may be a sign of a serious condition. If cough persists for more than one week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a doctor.
Persistent coughs should be investigated by a doctor for the possible underlying cause.

Cases of dextromethorphan abuse and associated dependence have been reported. Caution with BENYLIN® Dry Cough is particularly recommended for adolescents and young adults, as well as in patients with a history of drug abuse or use of 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 with BENYLIN® Dry Cough should therefore be exercised in patients who are slow metabolisers of CYP2D6 or use CYP2D6 inhibitors (see section 4.5).
If a patient is a known slow metaboliser of CYP2D6, or is using any other medicines (such as serotonergic medicines, including selective serotonin re-uptake inhibitors (SSRIs), medicines which impair the metabolism of serotonin (including MAOIs - see section 4.3) or CYP2D6 inhibitors), a doctor or pharmacist should be consulted prior to taking BENYLIN® Dry Cough.
Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic medicines.

Sodium benzoate:

BENYLIN® Dry Cough contains sodium benzoate. An increase in bilirubinaemia following its displacement from albumin may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

4.5 Interaction with other medicines and other forms of interaction:

Monoamine oxidase inhibitors (MAOIs):

BENYLIN® Dry Cough should not be used concurrently in patients taking MAOIs, or within 14 days of stopping treatment with MAOIs, as there is a risk of serotonin syndrome. Concurrent use with monoamine oxidase inhibitors may cause excitation, hypertension and hyperpyrexia.

Central nervous system (CNS) depressants:

Concomitant administration with central nervous system depressants may potentiate central nervous system depressant effects.

CYP450 interactions:

CYP2D6 inhibitors:

BENYLIN® Dry Cough is metabolised by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body. This increases the risk of the patient 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 increases the CNS adverse effects of the medicine. 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 BENYLIN® Dry Cough is necessary, the patient should be monitored and the BENYLIN® Dry Cough dose may need to be reduced.

Isavuconazole:

Isavuconazole is a moderate inhibitor of CYP3A4 and a mild inducer of CYP2B6. When administered concomitantly with dextromethorphan, the area under the curve (AUC) and C_{max} of dextromethorphan has been observed to increase by 18 % and 17 %, respectively.

Selective serotonin reuptake inhibitors (SSRIs):

Concomitant use of BENYLIN® Dry Cough with SSRI medicines may lead to serotonin syndrome.

4.6 Fertility, pregnancy and lactation:

Safety in pregnancy and lactation has not been established.

Pregnancy:

BENYLIN® Dry Cough is not recommended in pregnancy.

Lactation:

BENYLIN® Dry Cough should not be used by nursing mothers, as there is no information to support the secretion of dextromethorphan into breast milk.

4.7 Effects on ability to drive and use machines:

BENYLIN® Dry Cough can cause side effects, such as somnolence and dizziness. Caution is advised before driving a vehicle or operating machinery until the effects of BENYLIN® Dry Cough are known.

4.8 Undesirable effects:

Immune system disorders:

Less frequent: angioedema

Psychiatric disorders:

Less frequent: insomnia

Nervous system disorders:

Less frequent: dizziness, psychomotor hyperactivity, somnolence

Gastrointestinal disorders:

Less frequent: gastrointestinal disturbances, abdominal pain, diarrhoea, nausea, vomiting

Skin and subcutaneous tissue disorders:

Less frequent: pruritus, rash, urticaria

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of BENYLIN® Dry Cough is important. It allows continued monitoring of the benefit/risk balance of BENYLIN® Dry Cough. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions
Reporting Form", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8.
For further information, please contact the Johnson & Johnson call centre on 0860 410032 (landline).

4.9 Overdose

Symptoms of overdose may include: excitation, agitation, confusional state, conversion disorder, mixed hallucinations, ataxia, clumsiness, coma, depressed levels of consciousness, dysarthria, dystonia, lethargy, nystagmus, seizure, serotonin syndrome, tremor, miosis, mydriasis, respiratory depression, urinary retention, tachycardia, ischaemic colitis, and hypertension. Bromide intoxication has been observed during concomitant use with bromide-containing over-the-counter medicines or with overdose of dextromethorphan hydrobromide.

Treatment:

Symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Category and class: A: 10.1 Antitussives and Expectorants

Pharmacotherapeutic group: Cough Suppressant, Opium alkaloids and derivatives

ATC code: R05DA09

Dextromethorphan is the dextrorotatory isomer of 3-methoxy-*N*-methylmorphinan. 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 centrally acting cough suppressant. It acts by elevating the threshold for coughing.

The major metabolite of dextromethorphan, dextrorphan, binds with high affinity to σ-receptors to produce the 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 has 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 whether 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.

Elimination:

Dextromethorphan is primarily excreted via the kidney as unchanged parent compound and its active metabolite, dextrorphan. Dextrorphan and 3-hydroxymorphinan 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 and that of dextrorphan is between 3,4 to 5,6 hours. The half-life of dextromethorphan in poor metabolisers is extremely prolonged, and is in the range of 45 hours. Dextromethorphan syrup has a terminal plasma elimination half-lives of 3,3 ± 0,63 h.

5.3 Preclinical safety data:

Preclinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity, carcinogenicity and toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

citric acid hydrous (E330),

D&C YELLOW NO. 10,

FD&C BLUE NO. 1 (E133),

FD&C RED NO. 40 (E129),

glycerine (E422),

menthol (flavourant),

propylene glycol (E1520),

raspberry flavour,

saccharin sodium (E954),

sodium benzoate (E211),

sodium carboxymethylcellulose (E466),

sodium citrate hydrous (E331),

sodium cyclamate (E952),

sorbitol (E420),

purified water.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

24 months.

Store at or below 25 ˚C.

6.4 Special precautions for storage:

Store in a cool place.

Keep tightly closed.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container:

Amber glass bottles containing 100 mL and 200 mL, with a plastic measuring cup.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Johnson & Johnson (Pty) Ltd.

241 Main Road

Retreat

7945

South Africa

8. REGISTRATION NUMBER:

Z/10.1/5

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

02 March 2012

10. DATE OF REVISION OF THE TEXT:

21 December 2021.

EXPORT REGISTRATION DETAILS:

Botswana:	BOT9800287 S3
Kenya:	H2001/0370
Malawi:	PMPB/PL 353/5
Mauritius:	R3646/02/14
Nigeria:	NAFDAC Reg. No.: B4-7111
Namibia:	04/10.1/1520 NS1
Tanzania:	TAN 00,927 R05F WAR
Uganda:	1651/25/97
Zambia:	082/047 P
Zimbabwe:	2000/22.2.5/3769 P