DATA SHEET

1 BISOLVON DRY

BISOLVON DRY Oral Liquid

BISOLVON DRY Pastilles

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL of BISOLVON DRY Oral Liquid contains dextromethorphan hydrobromide monohydrate 10 mg.

Excipients with known effect: methyl hydroxybenzoate, maltitol, saccharin sodium

Each BISOLVON DRY Pastille contains dextromethorphan hydrobromide monohydrate 10.5 mg (equivalent to dextromethorphan hydrobromide anhydrous 10 mg).

Excipients with known effect: maltitol, saccharin sodium

For the full list of excipients, see Section 6.1 List of excipients

3 PHARMACEUTICAL FORM

Oral solution

BISOLVON DRY Oral Liquid is a clear, colourless, syrupy liquid with an aroma of apricot and vanilla.

Pastille

BISOLVON DRY Pastille is a yellow, round pastille with a honey lime flavor.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

BISOLVON DRY Oral Liquid and BISOLVON DRY Pastilles are used for the symptomatic treatment of dry, irritant, unproductive coughs. BISOLVON DRY Pastilles also helps soothe the throat.

4.2 DOSE AND METHOD OF ADMINISTRATION

Bisolvon Dry Oral Liquid and Bisolvon Dry Pastilles are preparations for oral administration.

The following dosage regimen is recommended:

In the case of self treatment, the maximum duration of treatment is 5 days.

BISOLVON DRY Oral Liquid:

Adults and children 12 years and over:
5 – 15 mL of BISOLVON DRY Oral Liquid, every 4 – 6 hours when necessary.

The maximum total daily dose is 60 mL of BISOLVON DRY (equivalent to 120 mg dextromethorphan hydrobromide monohydrate). Do not exceed 4 doses in a 24 hour period.

Children 6 – 11 years:
2.5 – 7.5 mL of BISOLVON DRY Oral Liquid, every 4 – 6 hours when necessary.

The maximum total daily dose is 30 mL of BISOLVON DRY Oral Liquid (equivalent to 60 mg of dextromethorphan hydrobromide monohydrate). Do not exceed 4 doses in a 24 hour period.

BISOLVON DRY Pastilles:

Adults and children 12 years and over:
Slowly suck 1 - 3 pastilles (10 – 30 mg dextromethorphan hydrobromide monohydrate) every 4 - 6 hours when necessary.

The maximum total daily dose is 12 pastilles (equivalent to 120 mg dextromethorphan hydrobromide monohydrate).

Children 6 to 11 years:
Slowly suck 1 pastille (10.5 mg dextromethorphan hydrobromide monohydrate) every 4 - 6 hours when necessary.

4.3 CONTRAINDICATIONS

Dextromethorphan is contraindicated in the following cases:

- hypersensitivity to dextromethorphan or to any of the inactive ingredients in the formulation – refer to Section 4.8 Undesirable effects for the effects of maltitol and sorbitol in patients.
- Patients with fructose intolerance should not take Bisolvon Dry Oral Liquid and Bisolvon Dry Pastilles.
- Children below 6 years of age.

- Patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs in the previous two weeks.
- bronchial asthma
- chronic obstructive pulmonary disease
- pneumonia
- respiratory insufficiency
- respiratory depression
- breastfeeding

Refer to Section4.5 Interaction with other medicines and other forms of interaction for additional information.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Avoid drinking alcoholic beverages while using dextromethorphan. Dextromethorphan potentiates the inhibitory effect of alcohol on the central nervous system.

Dextromethorphan should not be used for chronic persistent cough accompanying a disease state, or for cough associated with excessive secretions.

In cases of productive cough with considerable mucus production (e.g., patients with conditions such as bronchiectasis, cystic fibrosis) or in patients with neurological illness associated with a markedly reduced cough reflex (such as stroke, Parkinson's disease and dementia) antitussive treatment should be administered with particular caution and only after careful benefit-risk assessment (refer to Section 4.5 Interaction with other medicines and other forms of interaction).

Dextromethorphan should not be given to patients with or at risk of developing respiratory failure, e.g. asthma, chronic obstructive airways disease, and pneumonia. Caution is needed in patients with a history of asthma and it should not be given during an acute attack.

Dextromethorphan should be used with caution in patients receiving serotonergic drugs (other than MAO – inhibitors) such as selective serotonin re-uptake inhibitors (SSRI) e.g. fluoxetine, paroxetine or tricyclic antidepressives (refer to Section 4.5 Interaction with other medicines and other forms of interaction and other forms of interaction.).

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor CYP2D6 metabolisers. 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 (refer to Section 4.5 Interaction with other medicines and other forms of interaction)

Due to potential histamine release dextromethorphan should be avoided in patients with the rare disease of mastocytosis. Dextromethorphan can activate mast cells resulting in possible histamine release with associated clinical manifestations.

Paediatric use: Use in children aged 6 – 11 years only on the advice of a doctor, pharmacist or nurse practitioner. Healthcare professional supervision is recommended for use in children 6 to 12 years of age.

Use in patients with hepatic or renal impairment: Information on the use of dextromethorphan in patients with impaired liver or renal function is limited. BISOLVON DRY Oral Liquid and BISOLVON DRY Pastilles should be used with caution in those patients, particularly in patients with severe impairments. Patients with severe renal or liver insufficiency should have their doses lowered or intervals between doses increased.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Dextromethorphan possesses weak serotonergic properties. Thereby dextromethorphan may increase the risk of serotonin toxicity (serotonin syndrome) particularly if taken with otherserotonergic agents, such as MAO-inhibitors or SSRIs. Especially pre-treatment or concomitant treatment with drugs that impair metabolism of serotonin, such as antidepressants of the MAO inhibitor type, may result in the development of a serotonin syndrome with characteristic symptoms like neuromuscular hyperactivity (e.g. tremor, clonus, myoclonus, hyperreflexia, and pyramidal rigidity), autonomic hyperactivity (e.g. diaphoresis, fever, tachycardia, tachypnea, mydriasis) and altered mental status (e.g. agitation, excitement, confusion) (see Section 4.3 Contraindications (MAO-inhibitors) and Section 4.4 Special warnings and precautions for use).

Dextromethorphan should not be used in patients taking monoamine oxidase inhibitors (MAOIs) or who have taken MAOIs within the previous 14 days. The use of dextromethorphan with, or within two weeks of taking MAOIs, may increase the risk of serious side effects such as hypertensive crisis, hyperpyrexia and convulsions.

Dextromethorphan when used with SSRI's (such as fluoxetine) or tricyclic antidepressants (such as clomipramine and imipramine) may result in a "serotonin syndrome" with changes in mental status (e.g agitation, excitement, confusion), hypertension, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering and tremor.

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. The above cited effects may occur if any of these medicines have been administered recently, even if they are no longer being taken.

Concomitant use of dextromethorphan and other CNS depressants (e.g. alcohol, narcotic analgesics and tranquillizers) may increase the CNS depressant effects of these drugs.

If dextromethorphan is used in combination with secretolytics in patients with pre-existing chest disease such as cystic fibrosis and bronchiectasis who are affected by mucus hypersecretion reduced cough reflex can lead to serious accumulation of mucus.

4.6 FERTILITY, PREGNANCY AND LACTATION

Fertility: Based on available non-clinical experience and observations in humans there are no reported harmful effects of the use of dextromethorphan on reproduction or foetal development.

Use in pregnancy: Dextromethorphan has been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed.

BISOLVON DRY Oral Liquid and BISOLVON DRY Pastilles should not be used in the first three months of pregnancy; in later pregnancy periods it should only be taken if clearly needed. Medical supervision is recommended for use of dextromethorphan in pregnancy. High doses of dextromethorphan can cause respiratory depression in neonates even if only administered for a short time.

Use in lactation: The extent of excretion in breast milk is not known; therefore, the use of BISOLVON DRY Oral Liquid and BISOLVON DRY Pastilles is contraindicated during lactation since a respiratory depressive effect on infants cannot be ruled out.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Even when used as recommended this medication may cause mild drowsiness and alter reaction times to the extent that the ability to drive or to operate machinery is impaired. The risk is increased when it is taken in combination with alcohol or with medications that can impair reaction times.

Refer to Section4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

4.8 UNDESIRABLE EFFECTS

Side effects with usual doses are uncommon but may include mild drowsiness, fatigue, dystonias, dizziness and gastrointestinal disturbances (nausea or vomiting, stomach discomfort, or constipation).

Side effects that may occur with high doses (overdosage) include excitation, confusion, psychosis, nervousness, irritability, restlessness, "serotonin syndrome", severe nausea and vomiting, and respiratory depression.

Drug tolerance: Dextromethorphan has addictive potential. Patients may develop tolerance as well as mental and physical dependence. Patients with a tendency towards abuse or dependence should only be given BISOLVON DRY for short periods and under strict medical supervision.

There have been case reports of drug abuse with dextromethorphan, including cases in children and adolescents. The majority of case reports involved patients with a history of drug and/or alcohol abuse and/or psychiatric disorders.

Caution is particularly recommended for use in children, adolescents, young adults and in patients with a history of drug and/or alcohol abuse.

Patients should not exceed the recommended dose and treatment duration.

The maximum adult dose of 60 mL of BISOLVON DRY Oral Liquid contains 28.6 g of maltitol and 4.2 g of sorbitol. The maximum adult dose of BISOLVON DRY Pastilles (12 pastilles) contains 10.2 g of maltitol and 0.8 g of sorbitol. Products containing maltitol and sorbitol may have a laxative effect or cause diarrhea. This is more likely if several products containing maltitol, sorbitol or other related substances are consumed simultaneously.

Patients with the rare hereditary condition of fructose intolerance should not take this medicine as it may cause severe abdominal pain, vomiting and hypoglycaemia due to presence of maltitol and sorbitol.

The frequency of undesirable effects is based on the following categories:

Very Common	≥ 1/10
Common	≥ 1/100 < 1/10
Uncommon	≥ 1/1,000 < 1/100
Rare	≥ 1/10,000 < 1/1,000
Very Rare	< 1/10,000
Not known	cannot be estimated from the data available

Psychiatric disorders:

Common: confusion

Very rare: drug dependence

Frequency not known: hallucinations

Nervous system disorders:

Very common: somnolence, dizziness

Frequency not known: vertigo, slurred speech and nystagmus, dystonia especially in children.

Skin and subcutaneous tissue disorders:

Frequency not known: skin reactions such as rash with pruritis

Immune system disorders:

Frequency not known: hypersensitivity, urticaria, fixed drug eruption, anaphylactic reaction, angioedema, bronchospasm

Gastro-intestinal disorders:

Common: gastrointestinal disorders (nausea, vomiting, constipation)

General disorders and administration site conditions:

Common: fatigue

Reporting suspected adverse reactions is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Management: The mainstay of treatment is supportive and symptomatic care. If necessary close intensive care monitoring with symptom-related treatment should be initiated. Naloxone can be used as an antagonist.

In the event of overdose of dextromethorphan, take all appropriate measures immediately.

Symptoms: In case of overdose known side effects may occur with higher frequency or severity: nausea, vomiting and gastrointestinal disorders, dizziness, fatigue and somnolence and hallucinations. Likewise restlessness and excitability may develop into agitation with increasing overdose. In addition, symptoms such as impaired concentration and consciousness up to coma as a sign of severe intoxication, changes in mood such as dysphoria and euphoria, slurred speech, light-headedness, psychotic disorders like disorientation and delusions up to confusional or paranoid states, increased muscle tone, ataxia, dysarthria, nystagmus and vision disturbance as well as respiratory depression, changes in blood pressure and tachycardia may occur.

Dextromethorphan may increase the risk of serotonin syndrome, and this risk is increased by overdose, particularly if taken with other serotonergic agents.

Cases of fatal outcomes have been reported with combination overdose with dextromethorphan and other drugs (combination poisoning).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Dextromethorphan is a non-opioid cough suppressant. It is the methylated dextrorotatory analogue of levorphanol, a codeine analogue. Dextromethorphan acts centrally on the cough centre in the medulla and nucleus tractus solaris to increase the cough threshold. It does not have classical analgesic, sedative or respiratory depressant effects at usual antitussive doses.

The onset of antitussive effect occurs within an hour and the duration of action is approximately 3 – 6 hours.

5.2 PHARMACOKINETIC PROPERTIES

Absorption:

Dextromethorphan is well absorbed from the gastrointestinal tract after oral administration.

Metabolism:

It is metabolised in the liver, exhibiting polymorphic metabolism involving the cytochrome P450 isoenzyme (CYP 2D6).

Elimination:

It is excreted in the urine as unchanged dextromethorphan and demethylated metabolites, including dextrorphan, which has some cough suppressant activity. The plasma elimination half-life of dextromethorphan is 1.2 to 3.9 hours. However, the rate of metabolism varies between individuals according to phenotype (extensive v poor metabolisers), with half-life being as long as 45 hours in patients who are poor metabolisers.

5.3 PRECLINICAL SAFETY DATA

No information available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

BISOLVON DRY Oral Liquid contains: methyl hydroxybenzoate, saccharin sodium, maltitol solution, propylene glycol, vanilla aroma 33P080, apricot aroma 653460 and purified water.

BISOLVON DRY Pastille contains: betadex, acacia, sodium cyclamate, saccharin sodium, quinoline yellow, citric acid anhydrous, honey flavour 8366/001, limette flavour 18635/02, menthol, maltitol solution, paraffin light liquid, beeswax white and purified water.

6.2 INCOMPATIBILITIES

No information available

6.3 SHELF LIFE

BISOLVON DRY Oral Liquid: 36 months

BISOLVON DRY Pastilles: 36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

BISOLVON DRY Oral Liquid: Store at or below 25°C. Protect from light.

BISOLVON DRY Pastilles: Store at or below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

BISOLVON DRY Oral Liquid is available in amber-coloured bottles containing 200 mL. Each 5 mL contains 10 mg dextromethorphan hydrobromide.

BISOLVON DRY Pastille is available in blister packs containing 10, 20, 30 and 40 pastilles. Each pastille contains 10.5 mg dextromethorphan hydrobromide monohydrate (equivalent to 7.7mg dextromethorphan or 10 mg dextromethorphan hydrobromide anhydrous).

Not all pack sizes are distributed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MEDICINE SCHEDULE

Restricted medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, James and Wells Tower
56 Cawley Street
Ellerslie, Auckland
New Zealand

Toll Free Number (medical information 0800 283 684)

9 DATE OF FIRST APPROVAL

BISOLVON DRY Oral Liquid: 28 April 2016

BISOLVON DRY Pastilles: 10 December 2015

10 DATE OF REVISION OF THE TEXT

05 July 2019

Table 1 - Summary Table of Changes

SECTION	ADDITIONAL TEXT ADDED
7	Medicine Schedule updated to 'Restricted medicine'
2	Update to active ingredient name and excipient information.
4.2	Addition of dose information.
4.2	Update active ingredient name.
4.3	Deletion and update of text for fructose intolerance,
4.3	Clarification of MAOI reference and childrens dosage age
4.4	Addition of reference to alcohol.
4.4	Clarifiaction of text referring to bronchiectasis, cystic fibrosis
4.4	Addition of text regarding Mastocytosis
4.4	"Paediatric Use" section updated
4.4	Addition of hepatic text moved from section 4.6
4.6	Hepatic text removed from this section and added to 4.4.
4.6	"Use in pregnancy" updated
4.7	Reference to Sections 4.4 and 4.5 added.
4.8	Drug tolerance updated
4.8	Text on Drug abuse has been added
4.9	Symptoms has been updated.
4.9	Reference to reported cases of dextromethorphan used with other drugs