AUSTRALIAN PRODUCT INFORMATION – BISOLVON® DRY (DEXTROMETHORPHAN HYDROBROMIDE MONOHYDRATE)

1 NAME OF THE MEDICINE

Dextromethorphan hydrobromide monohydrate

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

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

Bisolvon Dry Pastille is a yellow, round pastilles with a honey lime flavour.

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 Oral Liquid (equivalent to 120 mg dextromethorphan hydrobromide). 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). 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) every 4 - 6 hours when necessary.

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

Children 6 to 11 years:

Slowly suck 1 pastille (10 mg dextromethorphan hydrobromide) every 4 - 6 hours when necessary.

The maximum total daily dose is 6 pastilles (equivalent to 60 mg of dextromethorphan hydrobromide).

If the cough persists for more than 1 week medical advice should be sought.

4.3 CONTRAINDICATIONS

- Dextromethorphan is contraindicated for use in patients with known hypersensitivity or idiosyncratic reaction to dextromethorphan (or any other ingredients in the product – refer to Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) for effects of maltitol and sorbitol).
- 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 depression.
- Respiratory insufficiency.
- Breastfeeding.

Refer to Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS 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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

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.

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.

CYP2D6 inhibitors

Dextromethorphan is metabolized by cytochrome P450 2D6 (CYP2D6). 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 that may exaggerate or prolong the effects of dextromethorphan (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). Slow metabolizers of CYP2D6 inhibitors may experience enhanced effects of dextromethorphan.

Dextromethorphan may increase the risk of serotonin toxicity (serotonin syndrome) particularly if taken with other serotonergic agents, such as MAOIs, SSRIs and CYP2D6 inhibitors. Serotonin syndrome may include mental-status changes (e.g. agitation, excitement, confusion), autonomic instability (e.g. diaphoresis, fever, tachycardia, tachypnea, mydriasis), neuromuscular abnormalities (e.g. tremor, clonus, myoclonus, hyperreflexia, and pyramidal rigidity), and/or gastrointestinal symptoms. Thus, dextromethorphan should not be used with MAOIs (see Section 4.3 CONTRAINDICATIONS) and be used with caution in patients receiving other serotonergic drugs (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

If serotonin syndrome is suspected, treatment with dextromethorphan should be discontinued.

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 and dependence 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 and caregivers should be advised not to exceed the recommended dose and treatment duration.

Use in the elderly

No data available

Paediatric use

Do not use Bisolvon Dry Oral Liquid in children under 6 years of age.

Do not use Bisolvon Dry Pastilles in children under 6 years of age.

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.

Serious adverse events, including neurological disorders, may occur in children in case of overdose.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Dextromethorphan possesses weak serotonergic properties. Thereby dextromethorphan may increase the risk of serotonin toxicity (serotonin syndrome) particularly if taken with other serotonergic 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 (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. Serum levels of dextromethorphan may be increased to levels multifold higher than normal by the concomitant use of potent inhibitors of cytochrome P450 2D6, such as the antiarrhythmics quinidine and amiodarone, antidepressants such as fluoxetine and paroxetine, or other drugs which inhibit cytochrome P450 2D6 such as haloperidol, cimetidine, ritonavir, berberine, bupropion, cinacalcet, flecainide and terbinafine. This increases the patient's risk for toxic effects of dextromethorphan. This effect 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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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

Category A: 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.

High doses of dextromethorphan can cause respiratory depression in neonates even if only administered for a short time.

Medical supervision is recommended for use of dextromethorphan in pregnancy.

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 (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.8 ADVERSE EFFECTS (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.

Cases of dextromethorphan abuse and dependency have been reported (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

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: hallucinations, drug dependence has been reported in individuals abusing dextromethorphan

Nervous system disorders

Very common: dizziness
somnolence

Not known: vertigo, slurred speech and nystagmus, dystonia especially in children

Skin and subcutaneous tissue disorders

Not known: skin reactions such as rash with pruritus

Immune system disorder

Not known: hypersensitivity reactions including anaphylactic reaction, angioedema urticaria, fixed drug eruption, bronchospasm, pruritus, rash and erythema

Gastro-intestinal disorders

Common: nausea, vomiting, constipation and gastrointestinal disorder

General disorders and administration site conditions

Common: fatigue

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Symptoms

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

Management

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

The mainstay of treatment is supportive and symptomatic care. If necessary close intensive care monitoring with symptom-related treatment should be initiated.

For patients who have ingested dextromethorphan and are sedated or comatose, Naloxone in the usual doses for treatment of opioid overdose can be considered. Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Clinical trials

No data available

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

Genotoxicity

No data available.

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Bisolvon Dry Oral Liquid contains methyl hydroxybenzoate, saccharin sodium, maltitol solution, propylene glycol, Vanilla Aroma 33 P 080, apricot aroma 653460, and purified water.

Bisolvon Dry Pastilles contain betadex, acacia, sodium cyclamate, saccharin sodium, quinoline yellow, citric acid, Honey Flavour 8366/001Wild product number 3-183660001, Limette Flavour 18635/02 Wild product number 3-186350002, menthol, maltitol solution, light liquid paraffin, purified water.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Bisolvon Dry Oral Liquid should be stored below 25ºC and protected from direct sunlight.

Bisolvon Dry Pastilles should be stored below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Bisolvon Dry Oral Liquid available in amber glass type III coloured bottles containing 200 mL

Bisolvon Dry Pastilles available in PVC/PVDC/Al blister packs containing 10, 20, 30 and 40 pastilles

Not all pack sizes are distributed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Dextromethorphan hydrobromide monohydrate is a white or almost white crystalline powder, soluble in alcohol and chloroform, sparingly soluble in water, and practically insoluble in ether.

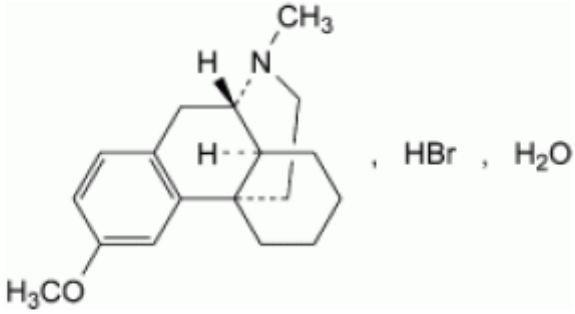
Chemical structure

Chemical name: 3-Methoxy-17-methyl-9α, 13α, 14α -morphinan hydrobromide monohydrate

Molecular formula: $C_{18}H_{25}NO,HBr.\ H_2O$

Molecular weight: 370.3

Structural formula:



CAS number

6700-34-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S2 – Pharmacy Medicine

8 SPONSOR

Sanofi Consumer Healthcare,
87 Yarraman Place, Virginia,
Qld 4014 Australia.
Toll-free: 1800 818 806
Email: medinfo.australia@sanofi.com

Sanofi-Aventis New Zealand Limited,
Auckland, New Zealand.
Toll-free: 0800 283 684

9 DATE OF FIRST APPROVAL

Bisolvon Dry Oral Liquid: 19 March 1999

Bisolvon Dry Pastilles (reformulation): 17 August 2024

10 DATE OF REVISION

17 August 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.1	Removal of beeswax white and update to include purified water per formulation