

**BISOLVON<sup>®</sup> DRY ORAL LIQUID**  
**BISOLVON<sup>®</sup> DRY PASTILLES**  
(dextromethorphan hydrobromide monohydrate)

**NAME OF THE MEDICINE**

Dextromethorphan hydrobromide monohydrate is:

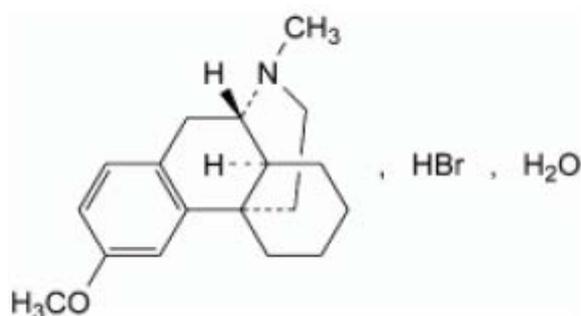
Chemical name: 3-Methoxy-17-methyl-9 $\alpha$ , 13 $\alpha$ , 14 $\alpha$  -morphinan hydrobromide monohydrate

Molecular formula: C<sub>18</sub>H<sub>25</sub>NO, HBr. H<sub>2</sub>O

CAS number: 6700-34-1

Molecular weight: 370.3

Structural formula:



**DESCRIPTION**

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

Each 5 mL of Bisolvon Dry Oral Liquid contains dextromethorphan hydrobromide 10 mg. Other ingredients include methyl hydroxybenzoate, saccharin sodium, maltitol solution, propylene glycol, vanilla aroma 33P080, apricot aroma 653460, and purified water.

Each Bisolvon Dry Pastille contains dextromethorphan hydrobromide monohydrate 10.5 mg (equivalent to dextromethorphan hydrobromide anhydrous 10 mg). Other ingredients include 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, purified water.

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

**PHARMACOLOGY**

**Pharmacodynamics**

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.

## **Pharmacokinetics**

### 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.

## **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.

## **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 ADVERSE EFFECTS for effects of maltitol and sorbitol).

Patients with fructose intolerance should not take Bisolvon Dry Oral Liquid and Bisolvon Dry Pastilles.

Concomitant treatment or treatment within the previous 14 days with monoamine oxidase (MAO) – inhibitors.

Refer to INTERACTIONS WITH OTHER MEDICINES for additional information.

## **PRECAUTIONS**

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

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 INTERACTIONS WITH OTHER MEDICINES).

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 'INTERACTIONS WITH OTHER MEDICINES').

Due to potential histamine release dextromethorphan should be avoided in cases of mastocytosis.

### **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.

### **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.

### **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.

### **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.

### **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.

### **Drug tolerance**

Dextromethorphan has minor addictive potential. Following prolonged use (i.e. exceeding the recommended treatment period) 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.

Cases of dextromethorphan abuse have been reported predominantly in adolescents.

## **INTERACTIONS WITH OTHER MEDICINES**

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 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 CONTRAINDICATIONS (MAO-inhibitors) and PRECAUTIONS).

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.

Serum levels of dextromethorphan may be increased by the concomitant use of 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 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.

## **ADVERSE 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 (refer 'PRECAUTIONS').

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	$\geq 1/10,000 < 1/1,000$
Very Rare	$< 1/10,000$
Not known	cannot be estimated from the data available

#### Psychiatric disorders

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

#### Nervous system disorders

Common: dizziness

Very rare: somnolence

#### Skin and subcutaneous tissue disorders

Not known: fixed drug eruption

#### Immune system disorder

Not known: hypersensitivity reactions including anaphylactic reaction, angioedema, urticaria, pruritus, rash and erythema

#### Gastro-intestinal disorders

Common: nausea, vomiting and gastrointestinal disorder

#### General disorders and administration site conditions

Common: fatigue

### **DOSAGE AND ADMINISTRATION**

The following dosage regimen is recommended:

#### **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). 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 (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.

## **OVERDOSAGE**

In case of overdose, immediately contact the Poisons Information Centre (call 13 11 26) for advice.

### **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, 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.

### **Management**

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia) or 0800 764 766 (New Zealand). The mainstay of treatment is supportive and symptomatic care. If necessary close intensive care monitoring with symptom-related treatment should be initiated. Naloxon can be used as an antagonist.

## **PRESENTATION AND STORAGE CONDITIONS**

Bisolvon Dry Oral Liquid is a clear, colourless, syrupy liquid with an aroma of apricot and vanilla, available in amber-coloured bottles containing 200 mL. Each 5 mL contains 10 mg dextromethorphan hydrobromide.

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

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

Bisolvon Dry Pastilles should be stored below 25°C.

Not all pack sizes are distributed in Australia.

## **NAME AND ADDRESS OF THE SPONSOR**

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

**POISON SCHEDULE OF THE MEDICINE**

S2 – Pharmacy Medicine

**Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)**

Bisolvon Dry Oral Liquid: 19 March 1999

Bisolvon Dry Pastilles: 3 November 2011

**Date of most recent amendment**

15 April 2015