HYDRYLLIN DM SYRUP

(Diphenhydramine Hydrochloride/ Dextromethorphan Hydrobromide)

COMPOSITION

Each 5ml contains
Diphenhydramine HCL BP 5mg
Dextromethorphan HBR BP 6.25mg
(Product Complies to Innovator's Specifications)

THERAPEUTIC INDICATIONS

For the symptomatic relief of unproductive cough and congestive symptoms associated with colds.

DOSAGE AND ADMINISTRATION

Adults, the Elderly and Children over 12 years
Patients may start with two 5 ml spoonfuls at bedtime followed by two 5 ml spoonfuls every 6 hours.
Or two 5 ml spoonfuls four times a day.
Do not take more than 4 doses (1 dose = two 5 ml spoonfuls) in 24 hours.
Children under 12 years
Do not give to children under 12 years old.

Method Of Administration

Oral

CONTRAINDICATIONS

Contraindicated in known hypersensitivity to any of the ingredients.
Contraindicated in persons under treatment with monoamine oxidase inhibitors or within 2 weeks of discontinuation of MAOI use.

Contraindicated in persons under treatment with selective serotonin reuptake inhibitors (SSRIs)

Dextromethorphan, in common with other centrally acting antitussive agents, should not be given to patients in, or at risk of developing, respiratory failure.

Dextromethorphan Hydrobromide/Diphenhydramine Hydrochloride should not be used in liver dysfunction. It should not be administered to patients where cough is associated with asthma, or patients with productive cough.

Diphenhydramine has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Do not give to children under 12 years old.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Because of their antimuscarinic properties antihistamines should be used with care in conditions such as closed angle glaucoma, urinary retention, prostatic hyperplasia or pyeloduodenal obstruction. Caution should also be exercised in patients with epilepsy or severe cardiovascular disorders. Caution is needed for the use of dextromethorphan in patients with a history of asthma, or with chronic or persistent cough. This medicine should be used with caution in atopic children due to histamine release.

Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively small doses.

Cases of dextromethorphan abuse and dependence 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 metabolized by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolizers of CYP2D6. Poor metabolizers 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.

If symptoms persist consult doctor.
Keep out of the sight and reach of children.
Do not exceed the stated dose.
Do not take with any other cough and cold medicine

Causes drowsiness which may continue the next day. If affected to not drive or operate machinery.

Avoid alcoholic drink.

Serotonin Syndrome

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.

Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, treatment with Dextromethorphan Hydrobromide/Diphenhydramine Hydrochloride should be discontinued.

Ingredients with specified warnings

To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy. Harmful if suffering from alcoholism.

DRUG INTERACTIONS

Dextromethorphan and diphenhydramine should not be used in persons under treatment with monoamine oxidase inhibitors or within 2 weeks of discontinuation of MAOI use in view of the potential risk of serotonin syndrome and a severe or fatal interaction.

Dextromethorphan-specific interactions

Avoid use of dextromethorphan with moclobemide or other reversible MAO-A inhibitors; rasagiline or other MAO-B inhibitors.

Manufacturer of memantine advises avoid concomitant use with dextromethorphan.

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

Cimetidine inhibits the metabolism of opioid analgesics.

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, diarrhea 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, SSRIs (including 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.

Diphenhydramine-specific interactions

Diphenhydramine as an antihistamine has additive sedative effects with alcohol and other CNS depressants including barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives and antipsychotics. It may also have additive antimuscarinic effects with antimuscarinic drugs such as atropine and some antidepressants.

Diphenhydramine as an antihistamine may theoretically antagonize the effect of histamine and betahistine.

Diphenhydramine inhibits the cytochrome P450 isoenzyme CYP2D6 and may affect the metabolism of some beta blockers and the anti-depressant venlafaxine.

FERTILITY, PREGNANCY AND LACTATION

Although dextromethorphan and diphenhydramine have been in widespread use for many years, insufficient data are available on their use during pregnancy. Use during pregnancy is inadvisable unless there is a clear need. Caution should, therefore, be exercised by balancing the potential benefits of treatment against any possible hazards.

It is not known if dextromethorphan or its metabolites are excreted in human breast milk. Diphenhydramine is excreted in breast milk but the amount has not been quantified. Dextromethorphan Hydrobromide/Diphenhydramine Hydrochloride Night Time Formula is, therefore, best avoided during breast feeding.

EFFECTS ON ABILITY TO DRIVE

Diphenhydramine may cause drowsiness, persons so affected should be advised not to drive or to operate machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. When prescribing this medicine, patients should be told:

• The medicine is likely to affect your ability to drive

• Do not drive until you know how the medicine affects you

• It is an offence to drive while under the influence of this medicine

• However, you would not be committing an offence (called “statutory defence”) if:

° The medicine has been prescribed to treat a medical or dental problem and

° You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and

° It was not affecting your ability to drive safely

ADVERSE DRUG REACTIONS

The following undesirable effects have been reported for use of dextromethorphan or sedating antihistamines including diphenhydramine, and may arise from use of Dextromethorphan Hydrobromide/Diphenhydramine Hydrochloride. The frequency of adverse effects cannot be estimated from available data.

Undesirable effects may be attributable to both dextromethorphan and sedating antihistamines unless otherwise stated.

Blood and the lymphatic system disorders:	Blood disorders including agranulocytosis, leucopenia, haemolytic anaemia, and thrombocytopenia (attributable to sedating antihistamines)
Psychiatric disorders:	Confusion
	Excitation (attributable to dextromethorphan)
	depression (attributable to sedating antihistamines)
Nervous system disorders:	Drowsiness and lowered ability to concentrate, dizziness, convulsions
	Extrapyramidal effects, paradoxical stimulation, headache, psychomotor impairment, tremor, paraesthesias, sleep disturbances (attributable to sedating antihistamines)
Eye disorders:	Blurred vision, angle-closure glaucoma (attributable to sedating antihistamines)
Ear and labyrinth disorders:	Tinnitus (attributable to sedating antihistamines)
Cardiac disorders:	Palpitations, arrhythmias (attributable to sedating antihistamines)
Vascular disorders:	Hypotension (attributable to sedating antihistamines)
Respiratory, thoracic and mediastinal disorders:	Respiratory depression (attributable to dextromethorphan)
	Thickened respiratory tract secretions, Bronchospasm (attributable to sedating antihistamines)
Gastrointestinal disorders:	Gastrointestinal disturbances (including nausea, vomiting, diarrhoea)
	Dry mouth (attributable to sedating antihistamines)
Hepatobiliary disorders:	Liver dysfunction (attributable to sedating antihistamines)
Skin and subcutaneous tissue disorders:	Hypersensitivity reactions including skin rash
	Angioedema, sweating, hair loss (attributable to sedating antihistamines)
Musculoskeletal, connective tissue and bone disorders:	Myalgia (attributable to sedating antihistamines)
Renal and urinary disorders:	Urinary retention (attributable to sedating antihistamines)
General disorders and administration site conditions:	Anaphylaxis (attributable to sedating antihistamines)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 pv@searlecompany.com .

OVERDOSAGE

Acute overdose of dextromethorphan does not usually result in serious signs and symptoms unless very large amounts have been ingested. It is thought to be of low toxicity, but the effects in overdosage will be potentiated by simultaneous ingestion of alcohol and psychotropic drugs. Signs and symptoms of substantial overdose may include nausea and vomiting, CNS disturbances (hyperexcitability, irritability, mental confusion, lethargy, somnolence, ataxia, auditory and visual hallucinations, psychotic disorder), dizziness, slurred speech, nystagmus and respiratory depression.

Symptoms and signs:

Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability.

In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.

Management:

- Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour.

- 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.

Mild cases of diphenhydramine overdose are mainly characterized by prominent antimuscarinic effects including dry mouth, headache, nausea, tachycardia and urinary retention. Larger doses produce depression or stimulation of the CNS. In small children, the stimulatory effects predominate and clinical features include hallucinations and convulsions. Adults usually develop drowsiness first, then convulse and lapse into coma at later stage. Fever and flushing is seen in children but is uncommon in adults.

Gastric lavage should be used if indicated. Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children (0.01mg/kg body weight). Convulsions can be controlled with diazepam. Other treatment is supportive and symptomatic and may include artificial respiration, external cooling for hyperpyrexia and intravenous fluids.

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PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Opium Alkaloids and Derivatives

ATC code: RO5 DA

Pharmacodynamics

Dextromethorphan

Dextromethorphan is a non-opioid, centrally acting cough suppressant. It raises the threshold for the cough reflex in the medulla oblongata. In therapeutic doses, it has no significant analgesic, respiratory depressant, euphoriant or dependence-producing properties. It does not inhibit ciliary function.

Diphenhydramine

Diphenhydramine is an ethanolamine H_1 histamine receptor antagonist. It possesses antitussive, sedative, antimuscarinic and antiemetic properties. Antihistamines, like diphenhydramine, are useful for controlling nasal itching, sneezing and rhinorrhea but are less effective for the relief of nasal congestion.

Pharmacokinetic properties

Dextromethorphan

Dextromethorphan is rapidly absorbed from the gastrointestinal tract following oral administration. It is subject to extensive presystematic metabolism resulting in very low peak plasma concentrations of 1.8ng/ml within 2.5 hours of an oral dose. Peak concentrations of the main metabolite, dextrophan occur 1-2 hours after ingestion. The terminal plasma elimination half-life of dextrophan is about three hours.

It is not known if dextromethorphan or dextrophan is excreted into breast milk or crosses the placenta.

Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (including the cytochrome P450 2D6 isozyme (CYP2D6), which is then conjugated by UDP-glucuronosyl transferases) 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. Unmetabolized dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-Nmethylmorphinan), 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.

Less than 1% of the dose of dextromethorphan is excreted in the feces. Urinary excretion of parent drug and metabolites accounts for up to 50% of the ingested dose over 24 hours.

Diphenhydramine

Diphenhydramine is well absorbed from the gastrointestinal tract but its availability varies between 26 and 60% due to first pass metabolism. Peak plasma concentrations are achieved about 1 to 4 hours after oral administration. The plasma elimination half-life is 3.3 hours.

Diphenhydramine is widely distributed throughout the body including the CNS. It crosses the placenta and has been detected in breast milk. It is highly (85-98%) bound to plasma proteins.

Orientals have lower plasma levels, lower protein binding and a higher volume of distribution and higher plasma clearance, but not half-life, than Caucasians.

Diphenhydramine is extensively metabolized mainly in the liver. It is N-demethylated to monodesmethyldiphenhydramine and didesmethyl-diphenhydramine. The resultant primary amine is oxidatively deaminated to yield the carboxylic acid, diphenylmethoxy acetic acid which may be conjugated with glutamine or glycine.

Diphenhydramine is excreted mainly in the urine with very little excreted as unchanged drug.

Pharmacokinetics in special populations

No data available

PRECLINICAL SAFETY DATA

Dextromethorphan

A 13 weeks dietary study in rats has shown no evidence of toxicity at the 0.1mg/kg dextromethorphan level. Dextromethorphan has been reported to have no mutagenic potential in two species and no effect on perinatal or postnatal mortality in high doses.

Diphenhydramine

In the rat, administration of 12mg/kg i.p. diphenhydramine hydrochloride has been reported to produce foetal mortality and mortality in the offspring up to the tenth day after birth. Doses up to 20 and 25 times the human dose (on a mg/kg basis) exert no teratogenic effects in rats and rabbits.

There is no evidence for diphenhydramine being mutagenic or carcinogenic in man.

PRESENTATION

Hydryllin DM syrup is available in a bottle of 120ml syrup.

INSTRUCTIONS

- Store in cool, dry, dark place away from direct sunlight, heat and moisture.
- Do not store & transport above 30'C.
- Keep the cap tightly closed & store in original packaging.
- Keep out of the reach of the children.
- Do not refrigerate.
- Avoid freezing.

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