For the use of only a Registered Medical Practitioner or a Hospital or a Laboratory

Not to be sold by retail without the prescription of a Registered Medical Practitioner

Prescribing Information

1. Generic Name

Dextromethorphan HBr and Amylmetacresol Lozenges
(Brand Name: TUSQ®-D Cough Lozenges)

2. Qualitative and Quantitative Composition

TUSQ-D Cough Lozenges (Orange flavor)
Each lozenge contains:
Dextromethorphan Hydrobromide IP ……..…5 mg.
Amylmetacresol BP …… 0.6 mg.
Mentholated sugar base …….. q.s.
Colour : Sunset Yellow FCF
Lozenges are flavoured

TUSQ-D Cough Lozenges (Orange flavor – Sugar Free)
Each lozenge contains:
Dextromethorphan Hydrobromide IP ……..…5 mg.
Amylmetacresol BP …… 0.6 mg.
Mentholated sugar free base …….. q.s.
Colour : Sunset Yellow FCF
Lozenges are flavoured

TUSQ-D Cough Lozenges (Honey Lemon flavor)
Each lozenge contains:
Dextromethorphan Hydrobromide IP ……..…5 mg.
Amylmetacresol BP …… 0.6 mg.
Mentholated sugar base …….. q.s.
Colour : Tartrazine
Lozenges are flavoured

3. Dosage Form and Strength

Dosage Form: Lozenges.
Dosage Strength: Dextromethorphan hydrobromide 5 mg and amylmetacresol 0.6 mg per lozenges.

4. Clinical Particulars

4.1 Therapeutic Indication

TUSQ-D Cough Lozenges are indicated for the relief of dry cough associated with sore throat (pharyngitis).

The action of sucking the lozenge allows its ingredients to work locally in the area of discomfort and also helps lubricate and soothe the painful area. This helps relieve the soreness and discomfort of mouth and throat.

4.2Posology and Method of Administration

For oral administration. To be sucked and dissolved slowly in the mouth.

- **Children between 6 to 12 years:** 1 lozenge to be sucked slowly in the mouth every 4 hours; a maximum of 6 lozenges in 24 hours.
- **Adults and children over 12 years:** 1 lozenge to be sucked slowly in the mouth every 4 hours; a maximum of 12 lozenges in 24 hours.

Do not exceed the stated dose. Or, as prescribed by the physician.

4.3Contraindications

TUSQ-D Cough Lozenges are contraindicated in the following:

- Hypersensitivity to dextromethorphan or to amylmetacresol or to any component of this formulation.
- In patients who have been treated with monoamine oxidase (MAO) inhibitors within the last 14 days.

4.4Special Warnings and Precautions for Use

Dextromethorphan Hydrobromide

Dextromethorphan should not be given to patients at risk of developing respiratory failure. Caution is advised in patients with a history of asthma and it should not be given during an acute attack. Care is also advisable in patients with bronchitis, emphysema, or in other conditions where chronic or persistent cough occurs.

Administration of dextromethorphan may be accompanied by histamine release and should be used with caution in children with atopic dermatitis.

Use of dextromethorphan with alcohol or other central nervous system (CNS) depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population is a poor metaboliser of CYP2D6. 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.

Dextromethorphan-containing preparations should not be administered in patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

Dextromethorphan may impair cognitive function and can affect a patient's ability to drive safely. Patients should be advised not to drive or operate machinery if affected by dizziness.

Amylmetacresol

Amylmetacresol-containing products are not to be given to children under 6 years of age. Care is advisable in children because they can choke on lozenges.

If symptoms persist, have not improved, or have worsened after 3 days, consult a physician. Prolonged use is not recommended.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltose insufficiency should not take amylmetacresol-containing products.

4.5Drug Interactions

Dextromethorphan Hydrobromide

MAO Inhibitors: Patients may develop hyperpyrexia, hypotension, nausea, myoclonic jerks, and coma following co-administration of MAO inhibitors and dextromethorphan. Thus, concomitant administration of dextromethorphan and MAO inhibitors should be avoided.

CYP2D6 Inhibitors (Fluoxetine, Paroxetine, Quinidine, Terbinafine): 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 multi-fold 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. 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. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

Alcohol, Antihistamines, Psychotropics, and Other CNS Depressant Drugs: Dextromethorphan might exhibit additive CNS depressant effects when co-administered with these drugs.

Amylmetacresol

For amylmetacresol, no clinically significant interactions are known.

4.6Use in Special Populations

Pregnant Women

Dextromethorphan is pregnancy category C drug. There are no data available on use of this product in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of TUSQ-D Cough Lozenges during pregnancy.

Lactating Women

There is insufficient information on the excretion of dextromethorphan and amylmetacresol metabolites in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made

whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric Patients
TUSQ-D Cough Lozenges are not recommended for use in children below 6 years of age.

Geriatric Patients
Dosage can be administered as like adults. There is no need for dosage modification in the elderly population.

4.7Effect on Ability to Drive and Use Machines
Dextromethorphan may impair cognitive function and can affect a patient's ability to drive safely. If affected, patients are advised not to operate machinery or drive a motor vehicle after ingestion of this medicine.

4.8Undesirable Effects
Adverse effects with these lozenges appear to be rare and may include dizziness, occasional hypersensitivity reactions, glossodynia, oral discomfort, and soreness of the tongue.

4.9Overdose
Dextromethorphan Hydrobromide
Overdose-related symptoms include nausea and vomiting, CNS depression, dizziness, dysarthria (slurred speech), nystagmus, somnolence/drowsiness, excitation, mental confusion, psychosis, and respiratory depression.
Treatment of overdose should be symptomatic and supportive. Gastric lavage may be of use. Naloxone has been used successfully as a specific antagonist to dextromethorphan toxicity in children.

Amylmetacresol
Mild overdose may result in gastrointestinal discomfort. Treatment should be symptomatic. In cases of severe overdose, empty the stomach by gastric lavage. Administer a saline laxative and activated charcoal by mouth.

5. Pharmacological Properties
5.1 Mechanism of Action
Dextromethorphan Hydrobromide - Cough Suppressant (antitussive)
Dextromethorphan produces antitussive effect by acting on the cough center which is located in the medulla oblongata part of the brain. Dextromethorphan crosses the blood-brain-barrier and activates sigma opioid receptors on the cough center in the CNS, thereby suppressing the cough reflex. Dextromethorphan raises the threshold for the cough reflex, thereby produces cough suppressant effect.

Amylmetacresol - Antiseptic

Amylmetacresol is mild antiseptic that kills the bacteria and/or viruses associated with mouth and throat infections. Sucking of the lozenge allows amylmetacresol to produce antiseptic effect directly on the sore areas of the mouth and throat.

5.2Pharmacodynamic Properties

Dextromethorphan Hydrobromide

Dextromethorphan is a non-opioid antitussive (cough suppressant) drug. Dextromethorphan is the dextrorotatory isomer of 3-methoxy-N-methyl-morphinan. It is a synthetic morphine derivative that, in contrast to its levorotatory isomer, has no significant analgesic, respiratory depressant or physical dependency properties at recommended doses. It is reported that dextromethorphan has similar efficacy to codeine in depressing cough reflex. In therapeutic dosage dextromethorphan does not inhibit ciliary activity.

Amylmetacresol

Amylmetacresol works locally in the mouth and throat areas. Amylmetacresol is having antiseptic properties in a soothing base. The lozenges help to lubricate and soothe the painful throat area.

5.3Pharmacokinetic Properties

Dextromethorphan Hydrobromide

Pharmacokinetic studies of dextromethorphan use in lozenge form are not available. However, following kinetic parameters have been reported when dextromethorphan is administered orally.

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.

Metabolism: Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Unmetabolised dextromethorphan, together with the three demethylated metabolites namely, 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.

Excretion: Dextromethorphan is primarily excreted via the kidney as unchanged parent drug and its active metabolite, dextrorphan. Dextrorphan and 3-hydroxy-morphinan are further metabolised by glucuronidation and are eliminated via the kidneys. The elimination half-life of the dextromethorphan is between 1.4 to 3.9 hours, while half-life of dextrorphan, the main metabolite, is between 3.4 to 5.6 hours. The half-life of dextromethorphan in poor metabolisers is extremely prolonged, in the range of 45 hours.

Amylmetacresol

There is rapid release of amylmetacresol into the saliva with peak levels achieved within 3 to 4 minutes of sucking the lozenge. A doubling of saliva volume was observed within minutes and levels above baseline were maintained, while the lozenge dissolved over approximately 5 to 6 minutes.

6. Nonclinical Properties

6.1 Animal Toxicology

Dextromethorphan Hydrobromide

Toxicity: LD50 values reported for dextromethorphan was 210 mg/kg in mouse and 116 mg/kg in rat. Acute subcutaneous toxicity with dextromethorphan reports the LD50 value of 112 mg/kg in mouse. Acute intravenous toxicity with dextromethorphan reports the LD50 value of 16.3 mg/kg in rat.

Repeat dose toxicity studies conducted in rats for 13 weeks duration at doses up to 100 mg/kg and 27 weeks at 10 mg/kg, and of 14 weeks in dogs by oral gavage at doses up to 4 mg/kg on 5 days per week. The only effect recorded was of reduced body weight gain in the rat 13-week study at the highest dose.

Mutagenicity: Dextromethorphan hydrobromide was negative in the bacterial reverse mutation assay (Ames test). Dextromethorphan 39 mg/kg is reported to be negative in *in-vivo* mouse micronucleus test and comet assay. Dextromethorphan was reported to be negative in *in- vitro* chromosome aberration assay tested up to 200 µg/ml.

Amylmetacresol

Oral LD50 value for amylmetacresol in rat is 1500 mg/kg. No specific data is available on other toxicological parameters.

7. Description

TUSQ-D Cough Lozenges (Orange Flavour) are Orange coloured circular lozenge without any entrapped air bubbles, moulding crackers or any other defects.

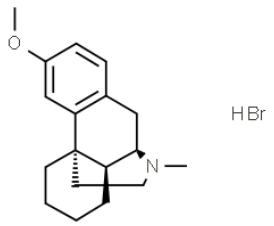
TUSQ-D Cough Lozenges (Sugar Free - Orange Flavour) are Orange coloured circular lozenge without any entrapped air bubbles, moulding crackers or any other defects.

TUSQ-D Cough Lozenges (Honey Lemon flavor) are Light yellow clear coloured transparent, smooth without any entrapped air bubbles, moulding crackers or any other defects.

Each lozenge of TUSQ-D contains 5 mg of dextromethorphan hydrobromide and 0.6 mg of amylmetacresol for oral administration (sucking) in adults and children above 6 years of age.

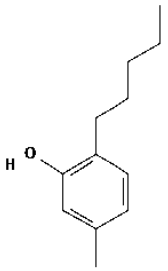
Dextromethorphan Hydrobromide

Dextromethorphan hydrobromide is a white to slightly yellow crystalline powder, odourlss, and insoluble in water.
Molecular Weight: 271.4 g/mol.
Molecular Formula: C18H26BrNO.
Chemical Name: (1S,9S,10S)-4-methoxy-17-methyl-17-azatetracyclo[7.5.3.0^{1,10}.0^{2,7}] heptadeca-2(7),3,5-triene; hydrobromide.
Structural Formula:



Amylmetacresol

Amylmetacresol is a phenol having the structure of m-cresol substituted at the 6-position with an amyl group. It has a role as an antiseptic drug.
Molecular Weight: 178.27 g/mol.
Molecular Formula: C12H18O.
Chemical Name: 5-methyl-2-pentylphenol.
Structural Formula:



Inactive ingredients : TUSQ-D Cough Lozenges (Orange Flavour) : Sugar, Liquid Glucose, Purified Water, Orange Flavour, Colour Sunset Yellow, Citric Acid & Menthol.

Inactive ingredients: TUSQ-D Cough Lozenges (Sugar Free - Orange Flavour): Isomalt, Sucralose, Purified Water, Orange Flavour, Colour Sunset Yellow, Citric Acid & Menthol.

Inactive ingredients: TUSQ-D Cough Lozenges (Honey Lemon flavor) : Sugar, Liquid Glucose, Purified Water, Flavour Honey – Dew Melon, Flavour Lemon Lime, Colour Tartrazine, Citric Acid & Menthol.

8. Pharmaceutical Particulars

8.1 Incompatibilities

None known.

8.2Shelf-life

24 Months

8.3Packaging Information

Six lozenges per strip.

8.4Storage and Handling Instructions

Store protected from light and moisture at a temperature not exceeding 30°C.
Keep out of the reach of children.

9. Patient Counseling Information

Instructions to Patients:

- Instruct patients to take the prescribed dose of TUSQ-D Cough Lozenge as directed. Do not exceed the dose or duration of treatment.
- Instruct patients not to take this product during pregnancy and lactation unless advised by their doctor.
- Consult your doctor before use of this lozenge with other cough and cold relief products (prescription or over-the- counter - OTC) because they might have similar type of ingredients. If users are not sure about presence of such ingredients in their medicine, consult a doctor or pharmacist.
- Protect the lozenges from humidity by keeping in a dry place.
- Lozenges are not recommended for use in children below 6 years of age.
- If affected by dizziness, patients are advised not to operate machinery or drive a motor vehicle after ingestion of this medicine.

10. Details of Manufacturer

Blue Cross Laboratories Pvt. Ltd.
B- 6 Kanchan Pharma House, NH – 8, Aslali Ahmedabad, Gujrat.
Mfg at - Leamak Healthcare Pvt. Ltd.
Sarkhej Bavla Highway, Matoda – 382 213, Ahmedabad.

11. Details of Permission or License Number with Date

TUSQ-D Cough Lozenges (Orange flavor) - Mfg. Lic. No. : G/25A/3151-A Date of FDA Product Permission: 10/03/2004.

TUSQ-D Cough Lozenges (Orange flavor – Sugar Free) - Mfg. Lic. No. : G/25A/3151-A Date of FDA Product Permission: 30/11/2006.

TUSQ-D Cough Lozenges (Honey Lemon flavor) - Mfg. Lic. No. : G/25A/3151-A Date of FDA Product Permission: 10/03/2004.

12. Date of Revision

March 2021.

MADE IN INDIA BY
BLUE CROSS LABORATORIES PVT LTD.
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