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

Dextromethorphan HBr, Chlorpheniramine Maleate & Phenylephrine HCl Syrup
TUSQ®-Dx Liquid

COMPOSITION
TUSQ-Dx Liquid
Each 5 ml contains:
Dextromethorphan Hydrobromide IP ……..…15 mg.
Chlorpheniramine Maleate IP ……..… 2 mg.
Phenylephrine Hydrochloride IP ……...… 5 mg.
Flavoured Mentholated Syrupy Base ……...… q.s.

TUSQ-Dx Liquid (Sugar Free)
Each 5 ml contains:
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Chlorpheniramine Maleate IP ……..… 2 mg.
Phenylephrine Hydrochloride IP ……...… 5 mg.
Flavoured Mentholated Base ……..……...… q.s.

DOSAGE FORM
Oral liquid.

INDICATIONS
TUSQ-Dx Liquid is indicated for the relief of dry cough and other symptoms associated with upper respiratory tract infections (e.g., common cold) or upper respiratory allergies.

DOSE AND METHOD OF ADMINISTRATION
For oral administration.

1. **Dosage Recommendation in Children:**
   - 2 to 6 years: 2.5 ml to be administered 3 to 4 times a day.
   - 6 to 12 years: 5 ml to be administered 3 to 4 times a day.
2. **Dosage Recommendation in Adults and Children above 12 Years of Age:** 10 ml to be administered 3 to 4 times a day.

Or, as prescribed by the physician.

Maximum recommended daily dose of each ingredient of this formulation in adults:

- Dextromethorphan: 120 mg.
- Chlorpheniramine Maleate: 24 mg.
- Phenylephrine: 60 mg.

Maximum daily dose should not be exceeded for any component of the formulation.

USE IN SPECIAL POPULATIONS

Pregnant Women

Pregnancy Category: Dextromethorphan - C, Chlorpheniramine Maleate - B, Phenylephrine - C.
It is not known whether components of TUSQ-Dx Liquid (dextromethorphan, chlorpheniramine maleate, and phenylephrine) can cause fetal harm when administered to a pregnant woman. Use of chlorpheniramine during the third trimester of pregnancy may result in reactions in the newborn or premature neonates. Thus, TUSQ-Dx Liquid should not be used during pregnancy unless considered mandatory by a physician.

Lactating Women

It is not known whether dextromethorphan or its metabolites are excreted in human milk. Phenylephrine is excreted in breast milk, but not in a clinically significant amount. Chlorpheniramine maleate may inhibit lactation and may be secreted in breast milk. Because of higher risk of intolerance of antihistamines in newborns and infants, TUSQ-Dx Liquid should not be administered to a nursing mother.

Paediatric Patients

Safety and efficacy of this formulation in neonates and children below 2 years of age has not been established. Thus, TUSQ-Dx Liquid is not recommended for use in paediatric patients below 2 years of age. For dosage in children above 2 years of age, please refer ‘DOSE AND METHOD OF ADMINISTRATION’ section.

Geriatric Patients

Usually, no dose adjustment is considered necessary in elderly patients with normal renal and hepatic function. Risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Renal Impairment Patients

Dextromethorphan, chlorpheniramine maleate, and phenylephrine are primarily excreted by the kidney. Impaired renal function could potentially lead to the risk of decreased clearance and thereby increased plasma levels of these drugs. TUSQ-Dx Liquid should be used with caution in patients with severe impairment of renal function, and patients should be monitored closely for signs of toxicity.

Hepatic Impairment Patients

Due to the extensive hepatic metabolism of dextromethorphan, chlorpheniramine maleate, and phenylephrine caution should be exercised in the presence of moderate to severe hepatic impairment.

CONTRAINDICATIONS

TUSQ-Dx Liquid is contraindicated for use in the following:

- Hypersensitivity to dextromethorphan, chlorpheniramine maleate, phenylephrine or to any component of this formulation.
- In patients who have been treated with monoamine oxidase (MAO) inhibitors within the last 14 days.
- In patients who are currently receiving other sympathomimetic drugs.
- Cardiovascular disorders.
- In patients with hypertension, peripheral vascular insufficiency, and hyperthyroidism.
- In patients with glaucoma or urinary retention.
- Pheochromocytoma.
- Dextromethorphan-containing preparations should not be given to subjects having or at risk of developing respiratory failure.
- In patients taking serotonin reuptake inhibitors (SSRIs).

WARNINGS AND PRECAUTIONS

Dextromethorphan Hydrobromide

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 poor metabolisers 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.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take dextromethorphan-containing preparations.

Cases of drug abuse have been reported with higher doses of dextromethorphan. Thus, caution is recommended in patients with a history of drug abuse or psychoactive substances.

Chlorpheniramine Maleate

Chlorpheniramine maleate may cause drowsiness and may have additive CNS effects with alcohol or other CNS depressants (e.g., hypnotics, sedatives, tranquilizers).

Antihistamines should be used with caution in patients with peptic ulcer, pyloroduodenal obstruction, and urinary bladder obstruction due to symptomatic prostatic hypertrophy and narrowing of the bladder neck.
Chlorpheniramine, in common with other drugs having anticholinergic effects, should be used with caution in the following conditions: Epilepsy; raised intra-ocular pressure including glaucoma; severe hypertension or cardiovascular disease; bronchitis, bronchiectasis or asthma; hepatic impairment. Children and the elderly are more likely to experience the neurological anticholinergic effects and paradoxical excitation (e.g., increased energy, restlessness, nervousness).
Chlorpheniramine should not be used with other antihistamine-containing products.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take chlorpheniramine-containing preparations.

Phenylephrine Hydrochloride
Sympathomimetic amines should be used with caution in patients with hypertension, diabetes mellitus, heart disease (angina), peripheral vascular disease, increased intraocular pressure, hyperthyroidism, or prostatic hypertrophy.
Phenylephrine should not be used with other sympathomimetics (such as decongestants, appetite suppressants, and amphetamine-like psychostimulants).
Sympathomimetic-containing products may act as cerebral stimulants giving rise to insomnia, nervousness, hyperpyrexia, tremor, and epileptiform convulsions.

Effects on Ability to Drive and Use Machines
Phenylephrine has no adverse effects on the patient’s ability to drive and to use machines. Dextromethorphan may impair cognitive function and can affect a patient's ability to drive safely. Also, the anticholinergic properties of chlorpheniramine may cause drowsiness, dizziness, blurred vision, and psychomotor impairment, which can seriously hamper the patients' ability to drive and use machinery. Patients should be advised not to drive or operate machinery if affected by dizziness.

DRUG INTERACTIONS
Dextromethorphan Hydrobromide
MAO Inhibitors: Patients may develop hyperpyrexia, hypotension, nausea, myoclonic leg 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 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. 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.

Chlorpheniramine Maleate

Alcohol, Hypnotics, Anxiolytics, Sedatives, Opioid Analgesics, and Neuroleptics: Concurrent use of chlorpheniramine maleate with any of these drugs may enhance the sedative effect.

Phenytoin: Chlorpheniramine maleate inhibits phenytoin metabolism and can lead to phenytoin toxicity.

MAO Inhibitors and Tricyclic Antidepressants: The antimuscarinic effects of chlorpheniramine are enhanced by other antimuscarinic drugs and both antimuscarinic and sedative effects are enhanced by MAO inhibitors (concurrent therapy is contraindicated) and tricyclic antidepressants.

Phenylephrine Hydrochloride

MAO Inhibitors: Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and MAO inhibitors, thus concomitant use is contraindicated.

Sympathomimetic Amines: Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.

Beta-Blockers and Other Antihypertensives (Including Debrisoquine, Guanethidine, Reserpine, and Methyldopa): Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased.

Tricyclic Antidepressants (Amitriptyline): Concomitant use of phenylephrine with amitriptyline may increase the risk of cardiovascular side effects.

Ergot Alkaloids (Ergotamine and Methylsergide): Concomitant use of phenylephrine with these drugs increases risk of ergotism.

Digoxin and Cardiac Glycosides: Co-administration of phenylephrine with these drugs increases risk of irregular heartbeat or heart attack.

UNDESIRABLE EFFECTS

The most common adverse effects associated with this formulation (combination product) include drowsiness, sedation, decreased mental alertness, dryness of mucous membranes, dry mouth, and gastrointestinal disturbances. Serious side effects with oral antitussives, antihistamines, and sympathomimetics have been rare.

Other adverse events that may occur with this formulation include:

- **Dermatologic:** Urticaria, drug rash, photosensitivity, allergic reactions, skin rashes including exfoliative dermatitis, pruritus, tingling, and coolness of the skin.
- **Gastrointestinal:** Epigastric discomfort, anorexia, nausea, vomiting, diarrhea, constipation.
- **Cardiovascular:** Hypotension, hypertension, cardiac arrhythmias (tachycardia or reflex bradycardia), chest pain, palpitations.
- **Central Nervous System:** Disturbed coordination, extrapyramidal effects, decreased mental/physical ability, tremor, irritability, insomnia, lassitude, visual disturbances, blurred vision, weakness, nervousness, convulsion, headache, euphoria, and dysphoria. Paradoxical CNS stimulation may occur especially in children or after high doses of chlorpheniramine maleate.
- **Genitourinary:** Urinary frequency, difficult urination, urinary retention.
- **Respiratory:** Tightness of the chest and wheezing, shortness of breath.
- **Hematologic:** Hemolytic anemia, thrombocytopenia, agranulocytosis.
- **Other:** Sweating, liver dysfunction, including hepatitis and jaundice, myalgia, paraesthesia, tinnitus.

OVERDOSE

Dextromethorphan Hydrobromide

Symptoms: Overdose symptoms include nausea and vomiting, CNS depression, dizziness, dysarthria (slurred speech), nystagmus, somnolence/drowsiness, excitation, mental confusion, psychosis, and respiratory depression.

Management: 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.

Chlorpheniramine Maleate

Symptoms: The estimated lethal dose of chlorpheniramine is 25 to 50 mg/kg body weight. Overdose with chlorpheniramine is associated with antimuscarinic, extrapyramidal, gastrointestinal, and CNS effects. In children, CNS stimulation predominates over CNS depression, causing ataxia, excitement, tremors, psychosis, hallucinations, and convulsions. Hyperpyrexia may also occur. Other symptoms of overdose in children include dilated pupils, dry mouth, facial flushing. In adults, CNS depression is more common with drowsiness, coma and convulsions, progressing to respiratory failure or possibly cardiovascular collapse including arrhythmias.

Treatment: In severe overdose the stomach should be emptied. If overdose is by the oral route, treatment with activated charcoal should be considered (treatment is most effective if given within an hour of ingestion). Convulsions may be controlled with intravenous diazepam or phenytoin, although it has been suggested that CNS depressants should be avoided. Other

treatment is supportive and symptomatic and may include artificial respiration, external cooling for hyperpyrexia, and intravenous fluids. Vasopressors such as noradrenaline or phenylephrine may be used to counteract hypotension. Forced diuresis, peritoneal dialysis or haemodialysis appear to be of limited benefit. Haemoperfusion may be used in severe cases.

Phenylephrine Hydrochloride

Symptoms: Overdose symptoms may include hypertension and possibly reflex bradycardia. In severe cases confusion, hallucinations, seizures, and arrhythmias may occur.

Treatment: Treatment measures include early gastric lavage and symptomatic and supportive measures. The hypertensive effects may be treated with an α-receptor blocking agent (such as phentolamine mesylate, 6 to 10 mg) given intravenously, and the bradycardia treated with atropine, preferably only after the pressure has been controlled.

PHARMACODYNAMIC

Dextromethorphan Hydrobromide - Cough Suppressant/Antitussive.

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. Dextromethorphan is a non-opioid antitussive (cough suppressant) drug. It exerts its antitussive activity by acting on the cough centre in the medulla oblongata, raising the threshold for the cough reflex. It is reported that dextromethorphan has similar efficacy to codeine in depressing cough reflex. In therapeutic dosage dextromethorphan does not inhibit ciliary activity.

Chlorpheniramine Maleate – Antihistamine.

Chlorpheniramine is an antihistamine drug (H_1 receptor antagonist) that also possesses anticholinergic activity. Antihistamines diminish or abolish the actions of histamine in the body by competitive (reversible) blockade of histamine H_1 receptor sites on tissues. Chlorpheniramine prevents released histamine from dilating capillaries and causing edema of the respiratory mucosa.

Phenylephrine Hydrochloride - Sympathomimetic Nasal Decongestant.

Phenylephrine is an orally active sympathomimetic amine and exerts a decongestant action on the nasal mucosa. Phenylephrine is a nasal decongestant with a potent postsynaptic α-receptor agonist activity. Dilated blood vessels can cause nasal blocks or stuffy nose. Phenylephrine shrinks blood vessels in the nasal passages and thus, reduces nasal congestion. A direct action at the receptors accounts for the greater part of its effects, whereas only a small part of effect is due to its ability to release norepinephrine.

Sympathomimetic amines, such as phenylephrine, act on α-adrenergic receptors of the respiratory tract to produce vasoconstriction effect. This result in temporarily reduction of swelling associated with inflammation of the mucous membranes lining the nasal and sinus

passages. This allows the free drainage of the sinusoidal fluid from the sinuses. In addition to reducing mucosal lining swelling, phenylephrine also suppresses the production of mucous, therefore preventing a buildup of fluid within the nasal cavities.

PHARMACOKINETICS

Dextromethorphan Hydrobromide

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 such as 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.

Chlorpheniramine Maleate

Absorption: Chlorpheniramine maleate is almost completely absorbed after administration by mouth, peak plasma concentrations occurring at about 2.5 to 6 hours.

Distribution: The drug is widely distributed including passage into the CNS, with a volume of distribution of between 1 and 10l/kg. About 70% of chlorpheniramine in the circulation is protein-bound.

Metabolism and Excretion: Chlorpheniramine undergoes some first pass metabolism and enterohepatic recycling. Chlorpheniramine is extensively metabolised, principally to inactive desmethylated metabolites which are excreted primarily in the urine, together with about 35% unchanged drug. Only trace amounts are excreted in the faeces. The mean elimination half-life has been reported to be about 30 hours, with mean values ranging from 2 to 43 hours.

Phenylephrine Hydrochloride

Absorption: Phenylephrine hydrochloride is rapidly absorbed from the gastrointestinal tract and undergoes first-pass metabolism by MAO in the gut and liver. As a consequence, systemic bioavailability of oral route is only about 40%. Following oral administration, peak plasma concentration is achieved in 1 to 2 hours.
Distribution: Penetration into the brain appears to be minimal.
Metabolism and Excretion: Following absorption, the drug is extensively metabolised in the liver as the sulphate conjugate. Both phenylephrine and its metabolites are excreted in the urine. The mean plasma half-life is in the range 2 to 3 hours.

INCOMPATIBILITIES
None known.

SHELF-LIFE
Expiry date as mentioned on the product pack.

PACKAGING INFORMATION
100 ml bottle with a measuring cup.

STORAGE AND HANDLING INSTRUCTIONS
Store at a temperature not exceeding 30°C. Protect from light.
Keep out of reach of children.

Last updated: March 2020.