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

Ambroxol Hydrochloride, Terbutaline Sulphate and Guaiphenesin Oral Drops
TUSQ® Oral Drops

COMPOSITION
Each ml (approx. 20 drops) contains:
Ambroxol Hydrochloride IP ……..… 7.5 mg
Terbutaline Sulphate IP ……..… 0.25 mg
Guaiphenesin IP ……..… 12.5 mg
Flavoured base …… q.s.

DOSAGE FORM
Oral drops.

INDICATIONS
TUSQ Oral Drops are indicated for symptomatic relief of bronchospasm in bronchial asthma and chronic bronchitis.

DOSE AND METHOD OF ADMINISTRATION
For oral administration. Shake well before use.
Children between 6 months to 2 years of age: 1 ml (approximately 20 drops) to be administered twice daily or 0.5 ml (approximately 10 drops) to be given three times daily.
Do not exceed the stated dose. TUSQ Oral Drops should not be used with other cough and cold medicines.
Or, as prescribed by the physician.

USE IN SPECIAL POPULATIONS
Pregnant Women
This formulation is not intended for use in pregnant woman. For pediatric use only.

Lactating Women
This formulation is not indicated for use in lactating mothers.

Paediatric Patients
TUSQ Oral Drops are not recommended for use in infants below 6 months of age due to lack of safety data. For dosage in children between 6 months to 2 years of age, please refer ‘DOSE AND METHOD OF ADMINISTRATION’ section.

Geriatric Patients

This formulation is not intended for use in the elderly population.

CONTRA-INDICATIONS

TUSQ Oral Drops are contraindicated in the following:

- Hypersensitivity to ambroxol, terbutaline, guaiphenesin, or to any component of the formulation.
- In cardiac disease and in patients with significant risk factors for myocardial ischemia.
- Thyrotoxicosis.

WARNINGS AND PRECAUTIONS

Ambroxol Hydrochloride

Ambroxol should be used with caution in patients with gastric ulceration.

Care to be taken to avoid contact with eye, skin, serious ingestion or inhalation.

In severe renal impairment, accumulation of ambroxol metabolites may occur. Therefore, caution should be exercised in severe renal impairment. Dose should be reduced or the dosing interval extended in severe renal impairment. The secretolytic effect of ambroxol may be supported by adequate fluid intake.

In patients with symptoms of chronic impairment of mucus production and/or clearance, ambroxol should be used with caution. In patients with malignant cilia syndrome, the advantages of mucus liquefaction should be carefully weighed against the risk of a secretory obstruction. The simultaneous administration of antitussives should definitely be avoided due to the risk of secretory obstruction.

There have been very rare reports of severe skin lesions such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN, Lyell's Syndrome) in temporal association with the administration of mucolytic substances such as ambroxol hydrochloride. Mostly these could be explained by the severity of the underlying disease or concomitant medication. During the early phase of a Stevens-Johnson Syndrome or TEN, a patient may first experience nonspecific influenza-like prodromal symptoms e.g., fever, body ache, rhinitis, cough, and sore throat. If new skin or mucosal lesions occur, treatment with ambroxol hydrochloride should be discontinued as a precaution.

Terbutaline Sulphate

Like all other beta 2-agonists, use of terbutaline is contraindicated in patients with thyrotoxicosis.

Immediate hypersensitivity reactions and exacerbation of bronchospasm have been reported after terbutaline administration.

Cardiovascular effects may be seen with sympathomimetic drugs, including terbutaline. There is some evidence from post-marketing data and published literature of myocardial ischemia associated with beta-agonists. Terbutaline, like all other beta-adrenergic agonists, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood

pressure, and/or symptoms. Although such effects are uncommon after administration of terbutaline at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown. Due to the positive inotropic effect of beta 2-agonists, these drugs should not be used in patients with hypertrophic cardiomyopathy. Terbutaline, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension, and cardiac arrhythmias; hyperthyroidism; diabetes mellitus; hypersensitivity to sympathomimetic amines; and convulsive disorders. Significant changes in systolic and diastolic blood pressure have been observed and may be expected to occur in some patients after use of any beta-adrenergic bronchodilators.

Patients with underlying severe heart disease (e.g., ischemic heart disease, arrhythmia or severe heart failure) should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Due to the hyperglycemic effects of beta 2-agonists, additional blood glucose controls are recommended initially in diabetic patients.

Potentially serious hypokalaemia may result from beta 2-agonist therapy. Particular caution is recommended in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalemic effect may be potentiated by concomitant treatments. It is recommended that serum potassium levels be monitored in such situations.

There have been rare reports of seizures in patients receiving terbutaline. Seizures did not recur in these patients after the drug was discontinued.

Guaiphenesin

Caution should be exercised in the presence of severe renal or severe hepatic impairment. The concomitant use of cough suppressants is not recommended. Guaiphenesin should not be administered in patients with rare hereditary problems of fructose intolerance. Guaiphenesin is considered to be unsafe in patients with porphyria.

DRUG INTERACTIONS

Ambroxol Hydrochloride

Antibiotics: After using ambroxol, the concentrations of antibiotics such as amoxycillin, cefuroxime, and erythromycin in bronchial secretions and sputum are increased.

Antitussives: Concomitant administration of antitussives may impair the expectoration of liquefied bronchial mucus due to inhibition of the cough reflex and cause accumulation of secretions.

No clinically relevant interactions with other medications have been reported.

Terbutaline Sulphate

Beta-blockers: Beta-blocking agents (including eye preparations), especially the non-selective ones such as propranolol, may partially or totally inhibit the effect of beta-stimulants. Therefore terbutaline preparations and non-selective beta-blockers should not normally be administered concurrently.

Sympathomimetic agents: Terbutaline should be used with caution in patients receiving other sympathomimetics.

Monoamine oxidase (MAO) inhibitors or tricyclic antidepressants: Terbutaline should be administered with extreme caution to patients being treated with MAO inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, since the action of terbutaline on the vascular system may be potentiated.

Halogenated anesthetics: Halothane anaesthesia should be avoided during beta 2-agonist treatment, since it increases the risk of cardiac arrhythmias. Other halogenated anesthetics should be used cautiously together with beta 2-agonists.

Potassium depleting agents (e.g., diuretics, methyl xanthines, corticosteroids): Owing to the hypokalemic effect of beta-agonists, concurrent administration of terbutaline with serum potassium-depleting agents known to exacerbate the risk of hypokalemia, such as diuretics, methyl xanthines and corticosteroids, should be administered cautiously after careful evaluation of the benefits and risks with special regard to the increased risk of cardiac arrhythmias arising as a result of hypokalaemia. Hypokalaemia also predisposes to digoxin toxicity.

Guaiphenesin

Paracetamol: Guaiphenesin may increase the rate of absorption of paracetamol.

Laboratory tests: If urine is collected within 24 hours of a dose of guaiphenesin, its metabolite may cause a color interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).

UNDESIRABLE EFFECTS

This formulation is generally well tolerated. Adverse events are generally rare, transient, and mild in nature. Following are the adverse effects reported with individual active ingredients of this formulation:

Ambroxol Hydrochloride

Occasional gastrointestinal side effects may occur, but these are normally mild. With prolonged administration in large doses, pain in epigastrium, nausea, vomiting can appear.

Additional adverse effects reported rarely with ambroxol include:

Gastrointestinal disorders: Dyspepsia, nausea, vomiting, diarrhoea, and abdominal pain.

Respiratory, mediastinal, and thoracic disorders: Oral and pharyngeal hypoaesthesia, dry mouth, and dry throat.

Nervous system disorders: Dysgeusia (e.g., changed taste).

Immune system disorders: Anaphylactic reactions including anaphylactic shock.

Skin and subcutaneous tissue disorders: Angioedema, rash, urticaria, pruritus, and other hypersensitivity reactions.
Allergic reactions: In patients having hypersensitivity to ambroxol, skin rash, nettle-rash, and angioneurotic oedema may occur.

Terbutaline Sulphate

The common adverse reactions to terbutaline are tremor, headache, tachycardia, palpitations, muscle spasms, nervousness, somnolence, dizziness, anxiety, insomnia, ventricular extrasystoles, vasodilation, nausea, dry mouth, asthenia, and sweating. Hypokalaemia has also been reported.
The adverse effects reported in less than 1% of patients are hallucinations, rash, paresthesia, hypertonia, muscle cramps, vomiting. There have been rare reports of elevation of liver enzymes and of hypersensitivity vasculitis. Rare cases of arrhythmias (e.g., atrial fibrillation, supraventricular tachycardia, and extrasystoles), myocardial ischemia, peripheral vasodilation, hypersensitivity reactions including angioedema, bronchospasm, hypotension, nausea, mouth and throat irritation, sleep disorder, behavioural disturbances such as agitation and restlessness, paradoxical bronchospasm, urticaria, and rash may occur with terbutaline.

Guaiphenesin

Side effects resulting from guaiphenesin administration are very rare. Guaiphenesin has occasionally been reported to cause gastrointestinal discomfort, nausea and vomiting, particularly in very high doses. Hypersensitivity reactions may occur. Allergic reactions, angioedema, anaphylactic reactions, dyspnoea (reported in association with other symptoms of hypersensitivity), nausea, vomiting, abdominal discomfort, rash, and urticaria have been reported very rarely with the use of guaiphenesin.

OVERDOSE

Ambroxol Hydrochloride

No overdose has been reported with ambroxol in humans. Acute potential health effects include skin irritation, eye irritation, respiratory tract irritation, gastrointestinal tract irritation with decreased motility or constipation, ulceration or bleeding from the stomach or duodenum, and peritonitis. It may even affect behavior/central nervous system (tremor, convulsions, ataxia, and somnolence), respiration (dyspnea, respiratory stimulation), liver, blood (changes in white blood cell count) and urinary system. If overdose occurs, supportive and symptomatic treatment should be provided.

Terbutaline Sulphate

Possible signs and symptoms include headache, anxiety, tremor, nausea, tonic cramps, palpitations, tachycardia, and arrhythmia. A fall in blood pressure may occur. Laboratory findings such as hypokalaemia, hyperglycemia, and lactic acidosis may occur sometimes.

Treatment includes gastric lavage and administration of activated charcoal. Determination of acid-base balance, blood sugar and electrolytes (particularly serum potassium) level is recommended. Monitoring of the heart rate and rhythm and blood pressure is also advised. Metabolic changes should be corrected. A cardioselective beta-blocker (e.g., metoprolol) is recommended for the treatment of arrhythmias causing hemodynamic deterioration. The beta-blocker should be used with care because of the possibility of inducing bronchoconstriction. Caution should be exercised in patients with a history of bronchospasm. If the beta 2-mediated reduction in the peripheral vascular resistance significantly contributes to the fall in blood pressure, a volume expander should be given.

Guaiphenesin

The effects of acute toxicity from guaiphenesin may include gastrointestinal discomfort, nausea, vomiting, and drowsiness. The drug is, however, rapidly metabolized and excreted in the urine. Vomiting would be treated by fluid replacement and monitoring of electrolytes if indicated. Patients should be kept under observation and symptomatic and supportive treatment is advised.

PHARMACODYNAMICS

Ambroxol Hydrochloride

Ambroxol is the active metabolite of bromhexine. Ambroxol is more effective than bromhexine and is non-toxic and well tolerated.

Ambroxol possesses mucolytic, mucokinetic (improvement in mucus transport), and secretolytic properties. It promotes the removal of tenacious secretions from the respiratory tract and reduces mucus stasis (arresting the secretion of mucus). Ambroxol also exhibits anti-oxidant activity. Ambroxol causes an increase of secretion in the respiratory tract. It enhances pulmonary surfactant production and stimulates ciliary activity. These actions result in improved mucus flow and transport (mucociliary clearance). Improvement of mucociliary clearance has been shown in clinical pharmacologic studies. Enhancement of fluid secretion and mucociliary clearance facilitates expectoration and reduces cough.

Terbutaline Sulphate

Terbutaline is a selective beta 2-adrenergic agonist which predominantly stimulates beta 2-receptors, thus producing relaxation of bronchial smooth muscle. Terbutaline sulphate is a direct-acting sympathomimetic agent with mainly beta-adrenergic activity. Terbutaline produces bronchodilation, increase in mucociliary clearance, suppression of oedema, and anti-allergic effects. Due to its bronchodilating properties, terbutaline is given in respiratory disorders such as reversible airway obstruction, as occurs in asthma and in some patients with chronic obstructive pulmonary disease.

The pharmacologic effects of beta-adrenergic agonist drugs, including terbutaline, are in part attributable to beta-adrenergic receptor-based stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine

monophosphate (cyclic AMP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially mast cells.

Guaiphenesin

Guaiphenesin increases the volume of respiratory tract fluid and reduces the viscosity of tenacious secretions and thus, is used as an expectorant. Guaiphenesin is thought to exert its pharmacological action by stimulating receptors in the gastric mucosa. This increases the output from secretory glands of the gastrointestinal system and increases the flow of fluids from glands lining the respiratory tract. The result is an increase in volume and decrease in viscosity of bronchial secretions. Another possible mechanism by which it acts is by increasing the water bonding in the sputum, thereby decreasing its viscosity and leading to an increase in mucokinesis.

Other actions may include stimulation of vagal nerve endings in bronchial secretory glands and stimulating certain centers in the brain, which in turn enhance respiratory fluid flow. Guaiphenesin produces its expectorant action within 24 hours.

PHARMACOKINETICS

Ambroxol Hydrochloride

Ambroxol is absorbed rapidly and almost completely after oral administration. Oral bioavailability is approximately 60% owing to the first-pass effect. Bioavailability of ambroxol hydrochloride is not affected by food. Plasma concentrations are in a linear relationship to the dose. Peak plasma levels are attained after 0.5 to 3 hours.

Plasma protein binding is around 90% in the therapeutic range. After oral, intravenous, and intramuscular administration, ambroxol is distributed swiftly and extensively from the blood into the tissues. The highest active ingredient concentrations have been measured in the lung.

Ambroxol is metabolized in the liver mainly by conjugation. Studies in human liver microsomes showed that CYP3A4 is the predominant isoform for ambroxol metabolism.

Around 30% of an oral dose is eliminated via the first-pass effect. The terminal half-life is about 10 hours. Total clearance is 660 ml/min approximately, and renal clearance is 8% of the total clearance.

Terbutaline Sulphate

Fasting bioavailability after oral doses is reported to be about 14 to 15% and is reduced by food (average 10%). Terbutaline undergoes extensive first-pass metabolism by sulphate (and some glucuronide) conjugation in the liver and the gut wall. It is excreted in the urine and faeces, partly as the inactive sulphate conjugate and partly as unchanged terbutaline, the ratio depending upon the route by which it is given. The terminal half-life after single and multiple dosing is reported to be between 16 and 20 hours.

Guaiphenesin

Guaiphenesin is well absorbed from the gastrointestinal tract following oral administration. However, limited information is available regarding its pharmacokinetics. After the administration of 600 mg guaiphenesin to healthy adult volunteers, the C_{max} was approximately 1.4 mcg/ml, T_{max} occurred approximately 15 minutes after drug administration, t½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours. Guaiphenesin appears to undergo both oxidation and demethylation.

INCOMPATIBILITIES

None known.

SHELF-LIFE

Expiry date as mentioned on the product pack.

PACKAGING INFORMATION

15 ml bottle with dropper.

STORAGE AND HANDLING INSTRUCTIONS

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

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