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

# Prescribing Information

## 1. Generic Name

Ambroxol Hydrochloride, Terbutaline Sulphate and Guaiphenesin Oral Drops
**(Brand Name: TUSQ ® Oral Drops)**

## 2. Qualitative and Quantitative 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.

## 3. Dosage Form and Strength

Dosage Form: Oral liquid.
Dosage Strength: Ambroxol 7.5 mg, Terbutaline 0.25 mg, and Guaiphenesin 12.5 mg per ml.

## 4. Clinical Particulars

### 4.1 Therapeutic Indication

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

### 4.2Posology 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 administered three times daily.
Do not exceed the stated dose.
Or, as prescribed by the physician.

### 4.3Contraindications

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.

## 4.4 Special Warnings and Precautions for Use

**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 (SJS) 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 SJS 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 is considered to be unsafe in patients with porphyria.

## 4.5Drug 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).

## 4.6 Use in Special Populations

**Pregnant Women**

Ambroxol crosses the placenta. Animal studies do not show either direct or indirect harmful effects on pregnancy, embryofoetal development, parturition or postnatal development. Comprehensive controlled studies in pregnant women after the $28^{th}$ week have not shown any harmful effects on the fetus. Use of ambroxol during the first trimester of pregnancy is not recommended.

No teratogenic effects have been observed with terbutaline in animals or in patients. Transient hypoglycemia has been reported in newborn preterm infants after maternal beta 2-agonist treatment.

Guaiphenesin has been linked with an increased risk of neural tube defects in a small number of women with febrile illness in the first trimester of pregnancy.

TUSQ Oral Drops should not be used during the first trimester of pregnancy. Caution is advised when it is used during second and third trimesters of pregnancy.

**Lactating Women**

Terbutaline and ambroxol are excreted in breast milk. However, their adverse effects on the infant are unlikely at therapeutic doses. Transient hypoglycemia has been reported in newborn preterm infants after maternal beta2-agonist treatment. There is no information regarding effect of guaiphenesin on lactation. Use of TUSQ Oral Drops is not recommended during lactation and thus, 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 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 'Posology and Method of Administration' section.

**Geriatric Patients**

Elderly patients with normal renal and hepatic function may be given the same dose as recommended for adults. Terbutaline is known to be excreted by the kidney, and the 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.

## 4.7Effect on Ability to Drive and Use Machines

No studies have been performed on effect on the ability to drive and use machines. If affected by dizziness following use of this product, patient should be advised not to drive or operate machinery.

## 4.8Undesirable 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 edema 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. Allergic reactions, angioedema, anaphylactic reactions, dyspnoea (reported in association with other symptoms of hypersensitivity), rash, and urticaria have been reported very rarely with the use of guaiphenesin.

## 4.9Overdose

**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 of overdosage 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.

# 5. Pharmacological Properties

## 5.1 Mechanism of Action

**Ambroxol Hydrochloride**

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 sulphate is a direct-acting sympathomimetic agent with mainly beta-adrenergic activity. Terbutaline is a selective beta 2-adrenergic agonist which predominantly stimulates beta 2-receptors, thus producing relaxation of bronchial smooth muscle.

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 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.

## 5.2Pharmacodynamic Properties

**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.

**Terbutaline Sulphate**

Terbutaline produces bronchodilation, increase in mucociliary clearance, suppression of edema, 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 (COPD).

**Guaiphenesin**

Guaiphenesin increases the volume of respiratory tract fluid and reduces the viscosity of tenacious secretions and thus, is used as an expectorant. 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.

## 5.3Pharmacokinetic Properties

**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. 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 through CYP3A4 enzyme.

About 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.

# 6. Nonclinical Properties

## 6.1 Animal Toxicology

**Ambroxol Hydrochloride**

Ambroxol hydrochloride has a low index for acute toxicity. In repeat-dose studies, oral doses of 150 mg/kg/day (mouse, 4 weeks), 50 mg/kg/day (rat, 52 and 78 weeks), 40 mg/kg/day (rabbit, 26 weeks) and 10 mg/kg/day (dog, 52 weeks) were the no-observed adverse effect level (NOAEL). No toxicological target organs were detected. Four week intravenous toxicity studies with ambroxol hydrochloride in rats (4, 16 and 64 mg/kg/day) and in dogs (45, 90 and 120 mg/kg/day - infusion 3 h/day) showed no severe local and systemic toxicity including histopathology. All adverse effects were reversible.

Ambroxol hydrochloride was neither embryotoxic nor teratogenic when tested at oral doses up to 3000 mg/kg/day in rats and up to 200 mg/kg/day in rabbits. The fertility of male and female rats was not affected up to 500 mg/kg/day. The NOAEL in the peri- and post-natal development study was 50 mg/kg/day.

Genotoxicity studies *in vitro* (Ames and chromosome aberration test) and *in vivo* (mouse micronucleus test) did not reveal any mutagenic potential of ambroxol hydrochloride.

Ambroxol hydrochloride did not show any tumorigenic potential in carcinogenicity studies in mice (50, 200 and 800 mg/kg/day) and rats (65, 250 and 1000 mg/kg/day) when treated with a dietary admixture for 105 and 116 weeks, respectively.

**Terbutaline Sulphate**

The effect of repeated daily administration of terbutaline sulfate, subcutaneously and orally, has been studied in rats and dogs. Clinical manifestations of toxicity included hyperemia of mucous membrane and skin, vomiting after initial dosing, and abnormal quietness or irritability. Dose-related increased heart rate was seen in both species. Decreased blood glucose concentrations were observed in an 18 month rat study.

Reproduction and teratology studies have been performed in mice, rats and rabbits. None of these studies revealed any adverse effects on the reproductive performance, or development of fetus, attributable to terbutaline sulfate.

Carcinogenicity studies were conducted in mice and rats. Terbutaline sulfate was given orally at dose levels from 2 to 200 mg/kg/day for 18 months. Results obtained did not suggest carcinogenicity since the number of tumors in control and treated animals were statistically comparable.

**Guaiphenesin**

Early studies of acute toxicity indicate that very large doses are required before significant toxicity is apparent. LD50 values in different species are in the range of 1000 mg/kg and more.
There are no reports on reproductive and developmental toxicity, carcinogenicity, and genotoxicity studies in animals with guaiphenesin.

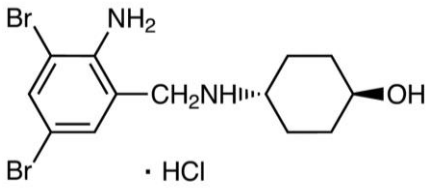
## 7. Description

TUSQ Oral Drops is a clear colourless liquid with vanilla flavour.

Each ml of TUSQ Oral Drops contains 7.5 mg of ambroxol hydrochloride, 0.25 mg of terbutaline sulphate, and 12.5 mg of guaiphenesin for oral administration.

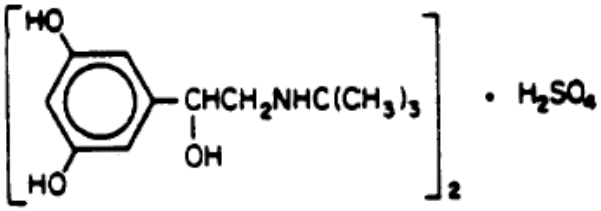
**Ambroxol Hydrochloride**

Ambroxol hydrochloride is slightly soluble in water, white to almost white crystalline powder.
Molecular Formula: C13H19Br2ClN2O.
Molecular Weight: 414.56 g/mol.
Chemical Name: 4-[(2-amino-3,5-dibromophenyl)methylamino]cyclohexan-1-ol;hydrochloride.
Structural Formula:




**Terbutaline Sulphate**

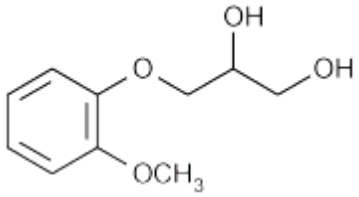
Terbutaline sulfate is water soluble, white to off-white crystalline powder.
Molecular Formula: (C12H19NO3)2.H2SO4.
Molecular Weight: 548.6 g/mol.
Chemical Name: 1-(3,5-dihydroxyphenyl)2-t-butylamino ethanol sulfate.
Structural Formula:




**Guaiphenesin**

Guaiphenesin is water soluble, white to almost white crystalline powder with a bitter taste.
Molecular Formula: C10H14O4.

Molecular Weight: 198.22 g/mol.
Chemical Name: (+)-3-(o-Methoxyphenoxy)-1,2-propanediol.
Structural Formula:




Inactive ingredients (excipients) of TUSQ Oral drops contain Glycerin, Sucralose, Sodium Benzoate, Sodium Citrate, Citric Acid Monohydrate, Propylene Glycol, Flavour Vanilla, and Purified Water.

# 8. Pharmaceutical Particulars

## 8.1 Incompatibilities

None known.

## 8.2 Shelf-life

18 months.

## 8.3 Packaging Information

15 ml bottle with 1 ml calibrated dropper.

## 8.4 Storage and Handling Instructions

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

# 9. Patient Counseling Information

**Administration Instructions**

Instruct patients/caregivers to:

- Ensure the prescribed dose of TUSQ Oral Drops is given as directed.
- Shake well before each use.
- If pregnant or breast-feeding, consult health professional before use. Instruct pregnant women not to take this product in first 3 months of pregnancy. Also instruct lactating women not to use this product while breastfeeding.
- Not to use with other cough and cold relief products (prescription or over-the- counter - OTC) having similar type of ingredients. If users are sure about presence of such ingredients in their medicine, consult a doctor or pharmacist.

## 10. Details of Manufacturer

M/s. Hema Laboratories Pvt. Ltd.
Plot No. 29, Pharmacity, Selaqui Industrial Area,
Dehradun – 248 011, Uttarakhand, India.

## 11. Details of Permission or License Number with Date

DCG(I) NOC Date: 13th October 2016.
Manufacturing License No. 19/UA/2007. Date of Product Permission – 15th September 2017.

## 12. Date of Revision

January 2021.