

## Ambroxol HCl, Guaiphenesin & Terbutaline sulphate Syrup

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### 1. NAME OF THE MEDICINAL PRODUCT

Ambroxol HCl, Guaiphenesin & Terbutaline sulphate Syrup

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contain

Guaiphenesin IP.....50 mg

Ambroxol hydrochloride IP .....15 mg

Terbutaline sulphate IP .....1.25 mg

Mentholated syrup base..... q.s

### 3. PHARMACEUTICAL FORM

Syrup for oral administration

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic Indications

Ambroxol hydrochloride, Terbutaline sulphate and Guaiphenesin expectorant is indicated for clinical relief of productive cough associated with bronchitis, bronchial asthma, emphysema and other bronchopulmonary disorders where bronchospasm, mucous plugging and problems of expectoration co-exist.

#### 4.2 Posology and Method of Administration

Adults:

10-20 ml thrice daily

Children (6-12 years):

5-10 ml thrice daily

Children (under 6 years):

5 ml thrice daily

#### 4.3 Contraindications

Hypersensitivity to any of the components of the formulation. It should not be used in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease. It is also contraindicated in patients with gastric ulceration.

#### 4.4 Special Warnings and Special Precautions for Use

***Terbutaline:***

As for all beta2-agonists caution should be observed in patients with thyrotoxicosis.

Cardiovascular effects may be seen with sympathomimetic drugs, including terbutaline. There is some evidence from post-marketing data and published literature of myocardial ischaemia associated with beta agonists.

Due to the positive inotropic effect of beta2-agonists, these drugs should not be used in patients with hypertrophic cardiomyopathy.

Tocolysis:

Terbutaline should be used with caution in tocolysis and supervision of cardiorespiratory function, including ECG monitoring, should be considered. Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop. Terbutaline should not be used as a tocolytic agent in patients with significant risk factors for or pre-existing heart disease.

During infusion treatment in pregnant women with beta2-stimulants in combination with corticosteroids a rare complication with a pathological picture resembling pulmonary oedema, has been reported.

Increased tendency to uterine bleeding has been reported in connection with Caesarean section. However, this can be effectively stopped by propranolol 1-2 mg injected intravenously.

Respiratory indications:

Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving Terbutaline 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 hyperglycaemic effects of beta2-agonists, additional blood glucose controls are recommended initially in diabetic patients.

Potentially serious hypokalaemia may result from beta2-agonist therapy. Particular caution is recommended in acute severe asthma as the associated risk may be augmented by hypoxia. The hypokalaemic effect may be potentiated by concomitant treatments. It is recommended that serum potassium levels are monitored in such situations.

If a previously effective dosage regimen no longer gives the same symptomatic relief, the patient should urgently seek further medical advice. Consideration should be given to the requirements for additional therapy (including increased dosages of anti-inflammatory medication). Severe exacerbations of asthma should be treated as an emergency in the usual manner.

**Ambroxol:**

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

**Guaiphenesin:**

Guaiphenesin should be not used for persistent or chronic cough, such as occurs with asthma, or where cough is accompanied by excessive secretions, unless directed by a physician. A persistent cough may be a sign of a serious condition. If cough persists for more than 7 days, tends to recur, or is accompanied by a fever, rash, or persistent headache, a physician should be consulted. Caution should be exercised in the presence of severe renal or severe hepatic impairment. The concomitant use of cough suppressants is not recommended. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Not more than 4 doses should be given in any 24 hours. Avoid with any other cough and cold medicine. Consult a pharmacist or other healthcare professional before use in children under 6 years.

#### **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**

**Terbutaline:**

Beta-blocking agents (including eye drops); 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. Terbutaline should be used with caution in patients receiving other sympathomimetic.

Hypokalaemia may result from beta2-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics.

**Ambroxol:**

No data available

**Guaiphenesin:**

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

**Others**

Ambroxol hydrochloride, Terbutaline sulphate and Guaiphenesin Expectorant should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers.

**4.6 Fertility, Pregnancy and Lactation**

**Pregnancy** However, there are no adequate and well-controlled studies of this combination in pregnant women. Hence this combination should be administered with caution in pregnancy.

**Lactation** It is not known whether this combination is secreted in breast milk. However terbutaline is secreted in breast milk, but effect on the infant is unlikely at therapeutic doses. Therefore this combination should be used with caution nursing mothers.

**4.7 Effects on Ability to Drive and Use Machines**

Most common adverse reactions to terbutaline are tremor, headache, tachycardia, palpitations, muscle spasms and hypokalaemia, this may affect ability to drive and use of machines.

**4.8 Undesirable Effects**

**Terbutaline**

Most of the adverse reactions are characteristic of sympathomimetic amines. The majority of these effects have reversed spontaneously within the first 1-2 weeks of treatment. The frequency of side-effects is low at the recommended doses.

The most common adverse reactions to terbutaline are tremor, headache, tachycardia, palpitations, muscle spasms and hypokalaemia.

Rare cases of arrhythmias e.g. atrial fibrillation, supraventricular tachycardia and extra systoles, myocardial ischaemia, peripheral vasodilation, hypersensitivity reactions including angioedema, bronchospasm, hypotension, collapse, nausea, mouth and throat irritation, sleep disorder, behavioural disturbances such as agitation and restlessness, paradoxical bronchospasm, urticaria and rash.

**Ambroxol**

Under individual hypersensitivity to Ambroxol allergic reactions such as skin rash, nettle-rash, and angioneurotic oedema are possible. Under the prolonged administration in large doses pain in epigastric area, nausea, vomiting can appear.

**Guaiphenesin**

Side effects resulting from guaifenesin administration are very rare. Guaiphenesin has occasionally been reported to cause gastro-intestinal discomfort, nausea and vomiting, particularly in very high doses. Also, hypersensitivity reactions may occur.

## 4.9 Overdose

### **Terbutaline**

Possible symptoms and signs: Headache, anxiety, tremor, nausea, tonic cramp, palpitations, tachycardia, arrhythmia. A fall in blood pressure sometimes occurs.

Laboratory findings; hypokalaemia, hyperglycaemia and lactic acidosis sometimes occur.

### **Treatment:**

Mild and moderate cases: Reduce the dose.

Severe cases: Gastric lavage, administration of activated charcoal. Determination of acid-base balance, blood sugar and electrolytes, particularly serum potassium levels. Monitoring of the heart rate and rhythm and blood pressure. Metabolic changes should be corrected.

A cardioselective beta-blocker (e.g. metoprolol) is recommended for the treatment of arrhythmias causing haemodynamic deterioration. The betablocker should be used with care because of the possibility of inducing bronchoconstriction: use with caution in patients with a history of bronchospasm. If the beta2-mediated reduction in the peripheral vascular resistance significantly contributes to the fall in blood pressure, a volume expander should be given.

Preterm labour: Pulmonary oedema: discontinue administration. A normal dose of loop diuretic (e.g. frusemide) should be given intravenously.

Increased bleeding in connection with Caesarian section: propranolol, 12mg intravenously.

### **Ambroxol**

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, peritonitis. It may even affect behavior/central nervous system (tremor, convulsions, ataxia, and somnolence), respiration (dyspnea, respiratory stimulation), liver, blood (changes if white blood cell count), and urinary system. No data available on chronic potential health effects.

### **Guaiphenesin**

The effects of acute toxicity from guaifenesin may include gastrointestinal discomfort, nausea and drowsiness. The drug is, however, rapidly metabolised and excreted in the urine. Patients should be kept under observation and treated symptomatically.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic Properties

#### **Terbutaline:**

Terbutaline is a selective beta2 - adrenergic causing bronchodilation; increase in mucociliary clearance; suppression of oedema and anti-allergic effects.

The pharmacologic effects of beta-adrenergic agonist drugs, including terbutaline, are at least in part, attributable to stimulation through beta-adrenergic receptors on intracellular adenylyl 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 from mast cells.

#### **Ambroxol:**

Ambroxol (group of benzilamides) belongs to secretolytic and secretomotoric medicinal products. It possesses expressed expectorant effect. Mechanism of action of the medicinal product is stipulated by stimulation of serous cells of tonsils of bronchial tubes' mucous membrane, increasing of mucous secretion content and changing of correlation of serous and mucous components of phlegm, breached under pathological processes in lungs. Under this hydrolyzing ferments activate and releasing of lysosomes from Clark's cells strengthens, that causes decreasing of viscosity of phlegm. Ambroxol increases content of

surfactant in lungs, which is dealt with strengthening of synthesis of the last and secretion in alveolar pneumocytes, and also with breach of its disintegration. The medicinal product increases mucociliar transport of phlegm. It suppresses coughing insignificantly. Ambroxol well penetrates through the placenta barrier, improving synthesis of surfactants during uterine life of foetus, and also it has an ability to warn syndrome of insufficient breathing in newborn. The medicinal product does not cause immense creating of secretion, reduces spastic hyperactivity of bronchial tubes- one of the main factors of developing of bronchial asthma under allergy. Ambroxol is more effective, than its predecessor - Bromhexine; it is non-toxic one and well endured by patients. Action of retard form of Ambroxol is kept in 9-10 hours after administration inside.

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

## **5.2 Pharmacokinetic Properties**

#### **Terbutaline:**

Basic parameters have been evaluated in man after oral administration of therapeutic doses, e.g.

Renal clearance (CLR): 1.925/ml/min (males)

Renal clearance (CLR): 2.32ml/min (females)

Terminal half-life  $T_{1/2}$  has been determined after single and multiple dosing (mean values varied between 16-20 h)

#### **Bioavailability:**

Food reduces bioavailability following oral dosing (10% on average).

Fasting values of 14-15% have been obtained.

#### **Metabolism:**

The main metabolite after oral dosing is the sulphate conjugate and also some glucuronide conjugate can be found in the urine.

#### **Ambroxol:**

##### **Absorption:**

Ambroxol is rapidly absorbed (70-80%) after oral administration. The time to reach peak plasma concentration is approximately 2 hours.

##### **Distribution:**

The distribution half-life of ambroxol is around 1.3 hours.

##### **Metabolism:**

Metabolite is dibromoanthranilic acid (activity unspecified).

##### **Excretion:**

Excretion is primarily via the kidneys. Renal clearance (rate) is approximately 53 ml/minute; approximately 5-6% of a dose is excreted unchanged in the urine. The elimination half-life of ambroxol is biphasic, with an alpha half-life of 1.3 hours and a beta half-life of 8.8 hours.

#### **Guaiphenesin:**

##### **Absorption:**

Guaiphenesin is well absorbed from the gastro-intestinal tract following oral administration, although limited information regarding its pharmacokinetics is available. After the administration of 600 mg Guaiphenesin to healthy adult volunteers, the  $C_{max}$  was approximately 1.4ug/ml, with  $t_{max}$  occurring approximately 15 minutes after drug administration.

Distribution:

No information is available on the distribution of Guaiphenesin in humans.

Metabolism and elimination:

Guaiphenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaiphenesin to 3 healthy male volunteers, the  $t_{1/2}$  was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

**Pharmacokinetics in Renal/Hepatic Impairment:**

There have been no specific studies of Guaiphenesin in subjects with renal or hepatic impairment. Caution is therefore recommended when administering this product to subjects with severe renal or hepatic impairment.

**5.3 Preclinical Safety Data**

**Terbutaline:**

Studies in laboratory animals (mini pigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histological evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

**Guaiphenesin:**

Animal studies to assess the long-term carcinogenic and mutagenic potential or the effect on fertility in animals or humans have not been performed.

**Ambroxol:**

Ambroxol has a low acute toxicity index.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 Shelf-life**

24 months

**6.2 Special Precautions for Storage**

Store in a cool place, Protected from light

**7. MARKETED BY**



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Date of revision: November, 2019