1. NAME OF THE MEDICINAL PRODUCT

Respretol (Terbutaline Sulphate, Ambroxol HCl, Guaifenesin & Menthol syrup).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains Ambroxol hydrochloride 15 mg, Terbutaline sulphate 1.25 mg, Guaifenesin 50 mg, Menthol syrup 1 mg.

{For a full list of excipients, see section 6.1}

3. PHARMACEUTICAL FORM

Liquid – Syrup

4. Clinical particulars

4.1 Therapeutic indications

Respretol Syrup is indicated for clinical relief of 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

Posology

Adults – 10-20ml thrice daily

Children (6-12years) – 10ml thrice daily

Children (under 6years) – 5-10ml thrice daily.

Method of administration

Respretol Syrup is to be administered Orally.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 precautions for use

Guaifenesin

Guaifenesin should not be 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. Stop use and ask a healthcare professional if your cough lasts for more than 5 days, comes back, or is accompanied by a fever, rash, or persistent headache.

Terbutaline Sulphate

As for all beta 2-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. 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. Therefore, terbutaline, like all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

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 seen and could be expected to occur in some patients after use of any beta-adrenergic bronchodilator.

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.

Caution should be taken and with supervision when using terbutaline for patients with tocolysis and **Respretol** should not be used as a tocolytic agent in patients with significant risk for or pre-existing heart disease.

Large doses of intravenous terbutaline have been reported to aggravate preexisting diabetes and ketoacidosis. Due to the hyperglycaemic effects of beta 2-agonists, additional blood glucose controls are recommended initially in diabetic patients.

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

Ambroxol

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

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 sympathomimetics.

Halogenated anesthetics such as the Halothane should be avoided when treating with **Respretol** due to its Terbutaline contents since it increases the risk of cardiac arrhythmias. Other halogenated anesthetics should be used cautiously together with beta 2-agonists.

Owing to the hypokalemic effect of beta-agonists, concurrent administration with terbutaline of serum potassium depleting agents known to aggravate the risk of hypokalemia, such as diuretics, methyl xanthines and corticosteroids, should be administered with caution after a careful evaluation of the benefits and risks. Hypokalemia may result from beta $_2$-agonist therapy and may be potentiated by concomitant treatment with xanthine derivatives, corticosteroids and diuretics.

Terbutaline should be administered with extreme caution to patients being treated with monoamine oxidase 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.

Guaifenesin

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

4.6 Pregnancy and Lactation

Pregnancy

Adequate and well controlled studies of this combination in pregnant women is not available, however caution should be taken when administering **Respretol** to pregnant women.

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 in nursing mothers.

4.7 Effects on ability to drive and use machines

Patients should be cautioned against engaging in activities requiring complete mental alertness, and motor coordination such as operating machinery until their response to **Respretol** Syrup is known.

4.8 Undesirable effects

Terbutaline

The adverse reactions to Terbutaline are similar in nature to those of other sympathomimetic agents and include nervousness and tremor. The frequency of these side effects appears to diminish with continued therapy. Other commonly reported reactions include increased heart rate, palpitations, dizziness, headache, drowsiness, vomiting, nausea, sweating and muscle cramps. These reactions are generally transient and usually do not require treatment.

Guaifenesin

Gastro-intestinal discomfort, nausea and vomiting, gastrointestinal discomfort particularly in very high doses has occasionally been reported with the use of Guaifenesin. Also, hypersensitivity reactions may occur.

Ambroxol

With Ambroxol, gastrointestinal side effects may occur occasionally and a transient rise in serum amino transferase values has been reported.

4.9 Overdose

There is limited experience of overdose with **Respretol** Syrup. Initiate general symptomatic and supportive measures in all cases of over dosages where necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties.

Terbutaline

Terbutaline is a selective beta $_2$- 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 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 from mast cells.

Guaifenesin

Guaifenesin is an expectorant and 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 by reflex 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 centers in the brain, which in turn enhance respiratory fluid flow. Guaifenesin produces its expectorant action within 24 hours.

Ambroxol

Ambroxol is a mucolytic agent. Excessive Nitric oxide (NO) is associated with inflammatory and some other disturbances of airways function. NO enhances the activation of soluble guanylate cyclase and cGMP accumulation. Ambroxol has been shown to inhibit the NO dependent activation of soluble guanylate cyclase. It is also possible that the inhibition of NO-dependent activation of soluble guanylate cyclase can

suppress the excessive mucus secretion; therefore, it lowers the phlegm viscosity and improves the mucociliary transport of bronchial secretions.

Menthol

Menthol has a cooling effect on the throat. It has been suggested that the benefits of menthol may be due to an effect on calcium channels of sensory nerves.

5.2 Pharmacokinetic properties

Terbutaline

Renal clearance (CLR): 1.925/ml/min (males), Renal clearance (CLR): 2.32ml/min (females).
Terminal half-life T½ has been determined after single and multiple dosing (mean values varied between 16-20). Food reduces bioavailability following oral dosing (10% on average). Fasting values of 14-15% have been obtained. The main metabolite after oral dosing is the sulphate conjugate and also some glucoronide conjugate which can be found in the urine.

Ambroxol

Ambroxol is rapidly absorbed (70-80%) after oral administration. The time to reach peak plasma concentration is approximately 2 hours. The distribution half-life of Ambroxol is around 1.3 hours. Metabolite is dibromoanthranilic acid (activity unspecified). 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.

Guaifenesin

Guaifenesin 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 Guaifenesin to healthy adult volunteers, the C_{max} was approximately 1.4ug/ml, with t_{max} occurring approximately 15 minutes after drug administration.

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

Guaifenesin appears to undergo both oxidation and demethylation. Following an oral dose of 600 mg guaifenesin to 3 healthy male volunteers, the t½ was approximately 1 hour and the drug was not detectable in the blood after approximately 8 hours.

There have been no specific studies of Guaifenesin 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

NA

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Methyl paraben

Sodium Propyl paraben

Sodium Benzoate

Glucose Liquid
Sucrose

Citric acid anhydrous

Sucralose

Sodium Chloride

Menthol

Propylene Glycol

Color sunset yellow & Erythrocin

Ess. Orange

Purified Water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30°c,

Keep the medicine out of the reach of children.

6.5 Nature and contents of container

Respretol is packed in 100ml Amber bottle in carton along with package insert.

6.6 Special precautions for disposal

No special requirements.

7. APPLICANT/MANUFACTURER

Imported and distributed by:
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