CHESTON PLUS Syrup (Ambroxol hydrochloride + Terbutaline sulphate + Guaiphenesin)

Composition

Each 5 ml contains:

Ambroxol hydrochloride .... 15 mg
Terbutaline sulphate IP.....1.25 mg
Guaiphenesin IP .....50 mg
Menthol IP.....1 mg
Flavoured syrup base..... q.s.

Dosage Form

Oral Syrup

Pharmacology

Pharmacodynamics

Terbutaline
Terbutaline is a selective beta$_2$-adrenergic stimulant having the following pharmacological effects:-

i. **In the lung:** bronchodilation; increase in mucociliary clearance; suppression of oedema and anti-allergic effects.
ii. **In skeletal muscle:** stimulates Na+/K+transport and also causes depression of subtetanic contractions in slow-contracting muscle.
iii. **In uterine muscle:** inhibition of uterine contractions.
iv. **In the CNS:** low penetration into the blood-brain barrier at therapeutic doses, due to the highly hydrophilic nature of the molecule.
v. **In the CVS:** administration of terbutaline results in cardiovascular effects mediated through beta$_2$-receptors in the peripheral arteries and in the heart e.g. in healthy subjects, 0.25 - 0.5mg injected s.c., is associated with an increase in cardiac output (up to 85% over controls) due to an increase in heart rate and a larger stroke volume. The increase in heart rate is probably due to a combination of a reflex tachycardia via a fall in peripheral resistance and a direct positive chronotropic effect of the drug.

Ambroxol
Ambroxol hydrochloride causes an increase of the 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. Cytokine release from blood but also mononuclear and polymorphonuclear cells was found to be significantly reduced by ambroxolhydrochloride in vitro. The clinical relevance of these findings is still unknown.

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.

Pharmacokinetics

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

I.V. single dose	
Volume distribution (VSS):	114 L
Total body clearance (CL):	213 ml/min
Mean residence time (MRT):	9.0 h
Renal clearance (CLR):	149 ml/min (males)
Oral dose	
renal clearance (CLR):	1.925/ml/min (males)
renal clearance (CLR):	2.32ml/min (females)

The plasma concentration/time curve after IV administration is characterised by a fast distribution phase, an intermediate elimination phase and a late elimination phase.

Terminal half-life T- 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 glucoronide 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 guaifenesin to 3 healthy male volunteers, the 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.

Indications

Cheston Plus Oral 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.

Dosage And Administartion

Adults

10-20 ml thrice daily

Children (6-12 years)

10 ml thrice daily

Children (under 6 years)

5-10 ml thrice daily

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.

Warnings and Precautions

General

Terbutaline
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.

Immediate hypersensitivity reactions and exacerbation of bronchospasm have been reported after terbutaline administration. Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

Large doses of intravenous terbutaline have been reported to aggravate preexisting diabetes and ketoacidosis.

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 beta$_2$-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 $beta_2$-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 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.

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

Ambroxol
In cases of severe renal failure, an accumulation of metabolites formed in the liver must be considered, and a reduction in the maintenance dose or an increase in the dose interval must be performed.
In patients with a tendency for peptic ulcers, the use of ambroxol hydrochloride should be carefully considered. In patients with malignant cilia syndrome, the advantages of secretion 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 (see "Interactions").
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 prodromes like e.g. fever, aching body, rhinitis, cough and sore throat. If new skin or mucosal lesions occur, treatment with ambroxol hydrochloride should be discontinued as a precaution. In acute respiratory indications, medical advice should be sought if symptoms do not improve or worsen during course of therapy.

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.

Others

CHESTON PLUS Oral Syrup should be used with caution in patients with diabetes mellitus, serious cardiovascular disorders, hypertension, hyperthyroidism and peptic ulcers.

Drug Interactions

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.

Hypokalaemia may result from betaM_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.

Ambroxol
By inhibiting the cough reflex, the concomitant use of antitussives may impair the coughing up of the liquefied bronchial mucous and cause a secretory obstruction (see "Warnings and Precautions").

Following the administration of ambroxolhydrochloride antibiotic concentrations of amoxicilline, cefuroxime and erythromycin in the bronchopulmonary secretions and in the sputum are increased.

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).

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 in nursing mothers.

Undesirable Effects

Terbutaline

The intensity of the adverse reactions depends on dosage and route of administration. 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.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100 and <1/10), uncommon (>1/1,000 and <1/100), rare (>1/10,000 and <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Frequency Classification	**Adverse Drug Reaction**	
	System Organ Class (SOC)	**Preferred term (PT)**
Very Common (>1/10)	Nervous System Disorders	Tremor Headache
Common (>1/100,	Cardiac Disorders	Tachycardia Palpitations
	Musculoskeletal and Connective Tissue Disorders #	Muscle spasms
	Metabolism and Nutrition Disorders	Hypokalaemia (See section 4.4)
Not Known ^	Cardiac Disorders	Arrhythmias, e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles Myocardial ischaemia (See section 4.4)
	Vascular Disorders	Peripheral vasodilation
	Immune System Disorders	Hypersensitivity reactions including angioedema, bronchospasm, hypotension and collapse
	Gastrointestinal Disorders	Nausea Mouth and throat irritation
	Psychiatric Disorders	Sleep disorder and Behavioural disturbances, such as agitation and restlessness
	Respiratory, Thoracic and Mediastinal Disorders	Paradoxical bronchospasm *
	Skin and Subcutaneous Tissue Disorders	Urticaria Rash

A few patients feel tense; this is also due to the effects on skeletal muscle and not to direct CNS stimulation.

^ Reported spontaneously in post-marketing data and therefore frequency regarded as unknown

* In rare cases, through unspecified mechanisms, paradoxical bronchospasm may occur, with wheezing immediately after inhalation. This should be immediately treated with a rapid-onset bronchodilator. Bricanyl therapy should be discontinued and after assessment, an alternative therapy initiated.

Ambroxol

Definition of the used frequencies: common (1%), uncommon (0.1%), rare (*Immune system, Skin and subcutaneous tissue disorders*

Rare: rash, urticaria
Frequency not known anaphylactic reactions, including anaphylactic shock angio-oedema, pruritus and other hypersensitivity
Nervous system
Common Dysgeusia (e.g. changed taste)
Gastrointestinal disorders, Respiratory organs
Common nausea, oral and pharyngeal hypoesthesia
Uncommon vomiting, diarrhea, dyspepsia, abdominal pain, dry mouth not known dry throat

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. The frequency of these guaifenesin-related adverse reactions is unknown but based on estimate from post-marketing data are likely to be rare: Allergic reactions, angioedema, anaphylactic reactions, dyspnoea (reported in association with other symptoms of hypersensitivity), nausea, vomiting, abdominal discomfort, rash, urticaria.

Overdosage

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 $beta_2$-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

Based on accidental overdose and/or medication error reports the observed symptoms are consistent with the known side effects. If symptoms of overdosage occur, symptomatic treatment should be provided.

Guaiphenesin

The effects of acute toxicity from guaiphenesin 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.

Packaging Information

CHESTON PLUS: Bottle pack of 100 ml

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