1. NAME OF THE MEDICINAL PRODUCT

Ascorex Expectorant

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 ml contains:	
Salbutamol sulphate BP equivalent to Salbutamol	2 mg
Bromhexine hydrochloride BP	4 mg
Guaifenesin USP	100 mg
Menthol BP	1mg
Flavoured syrup base	q.s.
Colour sunset yellow FCF	

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fixed dose combination expectorant of Salbutamol sulphate, Bromhexine hydrochloride and Guaifenesin is indicated for the symptomatic relief in the treatment of productive cough associated with various respiratory disorders including but not limited to acute bronchitis, Acute Exacerbation of Chronic Bronchitis (AECB), pneumonia and asthmatic bronchitis.

4.2 Posology and Method of Administration

- Adults and Children over 12 years: 10 mL (2 teaspoons) three times a day
- Children from 6 to 12 years: 5 to 10 mL (1-2 teaspoons) three times a day
- Children from 2 to 6 years: 5 mL (1 teaspoon) three times a day

Use in children aged 2 to 6 years only on the advice of a doctor, pharmacist or nurse practitioner, if potential benefits outweigh potential risk.

Children under 2 years: Do not use

4.3 Contraindications

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

Although intravenous salbutamol and occasionally oral salbutamol are used in the management of uncomplicated premature labour, salbutamol presentations should not be used for threatened abortion during the first or second trimester of pregnancy.

4.4 Special Warnings and Precautions for Use

Salbutamol:

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment including lung function testing as patients are at risk of severe attacks and even death. Physicians should consider using oral corticosteroid therapy and/or the maximum recommended dose of inhaled corticosteroid in those patients.

Patients should seek medical advice if treatment becomes less effective.

The dosage or frequency of administration should only be increased on medical advice.

Patients taking salbutamol may also be receiving short-acting inhaled bronchodilators to relieve symptoms.

Increasing use of bronchodilators in particular short-acting inhaled beta$_2$-agonists to relieve symptoms indicates deterioration of asthma control. The patient should be instructed to seek medical advice if short-acting relief bronchodilator treatment becomes less effective or they need more inhalations than usual.

In this situation patients should be reassessed and consideration given to the need for increased anti-inflammatory therapy (eg. Higher doses of inhaled corticosteroids or a course of oral corticosteroid). Severe exacerbations of asthma must be treated in the normal way.

Patients should be warned that if either the usual relief is diminished or the usual duration of action is reduced, they should not increase the dose or its frequency of administration, but should seek medical advice.

Salbutamol causes peripheral vasodilation which may result in reflex tachycardia and increased cardiac output. Caution should be used in patients suffering from angina, severe tachycardia or thyrotoxicosis.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol 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.

Severe exacerbations of asthma must be treated in the usual manner.

Caution should be exercised in its use with anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents.

Salbutamol should not cause difficulty in micturition (urination) because unlike sympathomimetic drugs such as ephedrine, it does not stimulate α-adrenoceptors. However, there have been reports of difficulty in micturition in patients with prostatic enlargement.

Salbutamol should only be used during pregnancy if considered essential by the physician.

Salbutamol does not contain sugars.

This product should not be diluted.

Potentially serious hypokalaemia may result from beta$_2$-agonist therapy mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids. It is recommended that serum potassium levels are monitored is such situations.

In common with other β-adrenoceptor agonists, salbutamol can induce reversible metabolic changes such as increased blood glucose levels. Diabetic patients may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Bromhexine:
Bromhexine should be used with caution in patients with severe liver disease and severe renal failure.

Use with caution in patients with gastric ulceration.

Patients should be advised to expect an increase in the flow of mucus secretions.

There have been very few reports of severe skin lesions such as Stevens Johnson Syndrome and toxic epidermal necrolysis (TEN) in temporal association with the administration of expectorants such as bromhexine hydrochloride. Mostly, these could be explained by the severity of the patient's underlying disease and or concomitant medication. In addition during the early phase of a Stevens Johnson syndrome or TEN a patient may first experience non-specific influenza-like prodomes like e.g. fever, aching body, rhinitis, cough and sore throat. Misled by these non-specific influenza-like prodomes it is possible that a symptomatic treatment is started with a cough and cold medication. Therefore if new skin or mucosal

lesions occur, medical advice should be sought immediately and treatment with bromhexine hydrochloride should be discontinued as a precaution.

Guaifenesin:
Ask a doctor before use if your child suffers from chronic cough, if he/she has asthma or is suffering from an acute asthma attack.

Stop use and ask a healthcare professional if your child's cough lasts for more than 5 days, comes back, or is accompanied by a fever, rash or persistent headache.

Do not give with a cough suppressant.

Caution should be exercised in the presence of severe renal or severe hepatic impairment.

Not more than 4 doses should be given in any 24 hours.

Do not exceed the stated dose.

Do not take with any other cough and cold medicine.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Salbutamol:
Caution should be exercised during use with anaesthetic agents such as chloroform, cyclopropane, halothane and other halogenated agents.

The effects of this product may be altered by guanethidine, reserpine, methyldopa, tricyclic antidepressants.

Salbutamol oral preparations and non-selective beta-blocking drugs, such as propranolol should not usually be prescribed together.

Salbutamol is not contraindicated in patients under treatment with monoamine oxidase inhibitors (MAOIs).

Bromhexine:
No clinically relevant unfavourable interactions with other medicines, such as ampicillin, oxytetracycline or erythromycin, have been reported. Interaction studies with oral anticoagulants or digoxin were not performed.

Guaifenesin:

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

4.6 Fertility, Pregnancy and Lactation

Fertility

Salbutamol:

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals.

Bromhexine:

Based on available pre-clinical experience there are no indications for possible effects of the use of bromhexine on fertility.

Guaifenesin:

There is insufficient information available to determine whether guaifenesin has the potential to impair fertility.

No studies on the effect on human fertility have been conducted with Fixed dose combination expectorant of Salbutamol sulphate, Bromhexine hydrochloride and Guaifenesin.

Pregnancy

Salbutamol:

Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

As with the majority of drugs, there is little published evidence of its safety in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the foetus at very high dose levels.

Bromhexine:

There are limited data from the use of bromhexine in pregnant women.
Pre-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Guaifenesin:

There are no or limited amount of data from the use of Guaifenesin in pregnant women. Animal studies are insufficient with respect to reproductive toxicity.

Lactation

Salbutamol:

As salbutamol is probably secreted in breast milk its use in nursing mothers requires careful consideration.

It is not known whether salbutamol has a harmful effect on the neonate, and so its use should be restricted to situations where it is felt that the expected benefit to the mother is likely to outweigh any potential risk to the neonate.

Bromhexine:
It is unknown whether bromhexine/metabolites are excreted in human milk.
Available pharmacodynamic/toxicological data in pre-clinical studies have shown excretion of bromhexine/metabolites in breast milk. A risk to the breastfed infant cannot be excluded.

Guaifenesin:
Guaifenesin is excreted in breast milk in small amounts. There is insufficient information on the effects of Guaifenesin in breastfed newborns/infants.

The safety of this medicine during pregnancy and lactation has not been established. Fixed dose combination expectorant of Salbutamol sulphate, Bromhexine hydrochloride and Guaifenesin should not be used during pregnancy, in women of childbearing potential not using contraception and breast-feeding.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed with Fixed dose combination expectorant of Salbutamol sulphate, Bromhexine hydrochloride and Guaifenesin.

4.8 Undesirable effects

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 (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000) including isolated reports. Very common and common events were generally determined from clinical trial data. Rare, very rare and unknown events were generally determined from spontaneous data.

Salbutamol:

a) Summary of the safety profile
The most common side effect of salbutamol is fine tremor of the hands, which may interfere with precise manual work. Tension, restlessness and a rapid heartbeat may also occur. There have been very rare reports of muscle cramps. Hypersensitivity reactions such as angioedema, urticaria, bronchospasm, hypotension and collapse have rarely been reported. Potentially serious hypokalaemia may result from β_2-agonist therapy. Occasional headaches have also been reported. As with other drugs in this class rare reports of hyperactivity in children have been reported.

b) Tabulated list of adverse reactions

Immune system disorders	
Very rare:	Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse.
Metabolism and nutrition disorders	
Rare:	Hypokalaemia.
Potentially serious hypokalaemia may result from beta agonist therapy.	
Nervous system disorders	
Very common:	Tremor.
Common:	Headache.
Very rare:	Hyperactivity.
Cardiac disorders	
Common:	Tachycardia, palpitations.
Rare:	Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles
Unknown:	Myocardial ischaemia*
Vascular disorders	
Rare:	Peripheral vasodilatation.
Musculoskeletal and connective tissue disorders	
Common:	Muscle cramps.
Very rare:	Feeling of muscle tension.

* reported spontaneously in post-marketing data therefore frequency regarded as unknown.

Bromhexine:

Immune system disorder: hypersensitivity, anaphylactic reaction, anaphylactic shock

Skin and subcutaneous tissue disorders: angioedema, rash, urticaria, pruritus

Respiratory, mediastinal and thoracic disorders: bronchospasm

Gastro-intestinal disorders: Nausea, vomiting, diarrhoea and abdominal pain upper.

Guaifenesin:

The safety of guaifenesin is based on available data from clinical trials and adverse drug reactions (ADRs) identified during post-marketing experience.

Adverse Drug Reactions Identified during Clinical Trials, Epidemiology studies and Post-Marketing Experience with Guaifenesin. Frequency Category estimated from Clinical Trials or Epidemiology Studies.

Body system (SOC)	**Incidence**	**Adverse Event Preferred Term**

Immune system disorders	Not known	Hypersensitivity reactions (hypersensitivity, pruritus and urticaria) Rash
Gastrointestinal disorders	Not known	Abdominal pain upper Diarrhoea Nausea Vomiting

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Salbutamol:

Symptoms

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events, including tachycardia, tremor, hyperactivity and metabolic effects including hypokalaemia.

Salbutamol overdose may lead to Hypokalaemia (abnormally low potassium concentration in the blood). Serum potassium levels should therefore be monitored.

Lactic acidosis has been reported in association with high therapeutic doses as well as overdoses of short-acting beta-agonist therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

Nausea, vomiting and hyperglycaemia have been reported, predominantly in children and when salbutamol overdose has been taken via the oral route.

Treatment

The preferred antidote for overdose with salbutamol sulphate is a cardioselective beta-blocking agent, which should be used with caution in patients with a history of bronchospasm.

Bromhexine:

No specific overdose symptoms have been reported in humans to date. Based on accidental overdose and/or medication error reports the observed symptoms are consistent with the known side effects of bromhexine at recommended doses.

Guaifenesin:

Symptoms
The effects of acute toxicity from guaifenesin may include gastrointestinal discomfort, nausea and drowsiness. When taken in excess, guaifenesin may cause renal calculi.

Management
Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Salbutamol:
As a beta-adrenergic stimulant for relief of bronchospasm such as occurs with asthma, bronchitis, emphysema. It has a highly selective action on the receptors in bronchial muscle and in therapeutic dosage, little or no action on the cardiac receptors.

Bromhexine:
Bromhexine is a synthetic derivative of the herbal active ingredient vasicine.

Guaifenesin:
Guaifenesin 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. Guaifenesin produces its expectorant action within 24 hours.

5.2 Pharmacokinetic properties

Salbutamol:
Salbutamol is readily absorbed from the gastro-intestinal tract and is subject to first pass metabolism in the liver. Peak plasma concentrations occur within one to four hours after oral administration. After multiple oral doses of salbutamol 4mg four times a day, steady-state plasma concentrations are obtained after 3 days. About half is excreted in the urine as an inactive sulphate conjugate following oral administration. The bioavailability of orally administered salbutamol is about 50%.

Bromhexine:
Following the administration of bromhexine, the antibiotic concentrations of amoxycillin, erythromycin and oxytetracycline in the sputum and bronchopulmonary secretions are increased.

Bromhexine pharmacokinetics are not relevantly affected by co-administration of ampicillin or oxytetracycline. There was also no relevant interaction between bromhexine and

erythromycin according to a historical comparison. The lack of any relevant interaction reports during the long term marketing of the drug suggests no substantial interaction potential with these drugs.

Absorption
Following oral administration, bromhexine shows dose linear pharmacokinetics in the dose range of 8-32 mg. It is rapidly and completely absorbed from the gastrointestinal tract. The bioavailability after oral administration is substantially reduced by an extensive first-pass effect in the range of 70-80%. The absolute bioavailability of bromhexine hydrochloride is about 22.2 ± 8.5 % up to 26.8 ±13.1 % for bromhexine tablets and oral solution, respectively. Concomitant food intake tended to increase bromhexine plasma concentrations probably due to partial inhibition of the first pass-effect.

Distribution
The distribution into lung tissue (bronchial and parenchymal) was investigated after oral administration of 32 mg and 64 mg bromhexine. Lung-tissue concentrations two hours post dose 1.5 - 4.5 times higher in bronchiolo-bronchial tissues and between 2.4 and 5.9 times higher in pulmonary parenchyma compared to plasma concentrations. Unchanged bromhexine is bound to plasma proteins by 95 % (non-restrictive binding).

Metabolism
Bromhexine is almost completely metabolised to a variety of hydroxylated metabolites and to dibromanthranilic acid. All metabolites and bromhexine itself are conjugated most probably in form of N-glucuronides and O-glucuronides. There are no substantial hints for a change of the metabolic pattern by a sulphonamide, oxytetracycline or erythromycin. Thus relevant interactions with CYP 450 2C9 or 3A4 substrates are unlikely.

Elimination
After administration of single oral doses between 8 and 32 mg, the terminal elimination half-life of bromhexine ranged between 6.6 and 31.4 hours. The relevant half-life to predict the multiple dose pharmacokinetics is about 1 hour. No accumulation was observed after multiple dosing (accumulation factor 1.1).

Linearity/Non-linearity
Bromhexine shows dose proportional pharmacokinetics in the range of 8-32 mg following oral administration.

Special populations
There are no data for bromhexine pharmacokinetics in the elderly or in patients with renal or liver insufficiency. Extensive clinical experience did not give rise to relevant safety concerns in these populations

Guaifenesin:
Absorption

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 1.4 ug/ml, with t_{max} occurring approximately 15 minutes after drug administration.

Distribution
No information is available on the distribution of guaifenesin in humans.

Metabolism and elimination
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.

Pharmacokinetics in Renal/Hepatic Impairment
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.

Pharmacokinetics in the Elderly
Not applicable.

5.3 Preclinical safety data

Salbutamol:
In common with other potent selective β_2-agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of foetuses were found to have cleft palate at 2.5mg/kg dose, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50mg/kg/day orally throughout pregnancy resulted in no significant foetal abnormalities. The only toxic effect was an increase in neonatal mortality at the highest dose level as the result of lack of maternal care. Reproductive studies in the rabbit at doses of 50mg/kg/day orally (i.e. much higher than the normal human dose) have shown foetuses with treatment related changes; these included open eyelids (ablepharia), secondary palate clefts (palatoschisis), changes in ossification of the frontal bones of the cranium (cranioschisis) and limb flexure.

In an oral fertility and general reproductive performance study in rats at doses of 2 and 50 mg/kg/day, with the exception of a reduction in number of weanlings surviving to day 21 post-partum at 50 mg/kg/day, there were no adverse effects on fertility, embryofoetal development, litter size, birth weight or growth rate.

Bromhexine:

Preclinically, it has been shown to increase the proportion of serous bronchial secretion. Bromhexine enhances mucus transport by reducing mucus viscosity and by activating the ciliated epithelium (mucociliary clearance). Clinical studies show that bromhexine has a secretolytic and secretomotoric effect in the bronchial tract area, which facilitates expectoration and eases cough.

Guaifenesin:

Mutagenicity/ Carcinogenicity/ Teratogenicity/ Fertility

There is insufficient information available to determine whether guaifenesin has mutagenic potential, carcinogenic potential, teratogenic potential or potential to impair fertility.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Benzoate, Citric acid Monohydrate, Sorbitol Solution 70%, Glycerol, Propylene Glycol, Colour Sunset Yellow FCF, Pineapple Super PH flavor, Black current I.D. 20158, Sorbic Acid, Sugar S/30, Purified water, Celite (Hyflosupercel)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25˚C. Protect from light.

6.5 Nature and contents of container

A printed carton containing a leaflet and amber coloured labeled sealed PET bottle with 10 ml measuring cup, containing a clear, orange coloured, viscous, flavored liquid with sweet taste.

6.6 Special precautions for disposal and other handling

Keep all medicines out of reach of children

7. <APPLICANT/MANUFACTURER>

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