SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ambrokoff syrup.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml contains:

Ambroxol Hydrochloride BP 30mg

Salbutamol Sulfate BP

Eq. To Salbutamol 1mg

Guaifenesin USP 50mg

Menthol USP 0.5mg

Flavour syrupy base Q.S

Ponceau 4R

Excipients of known effect: Propylene glycol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Red colour syrup.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ambroxol+ Menthol+ Salbutamol+ Guaifenesin is used in the treatment of cough & relieves cough associated with bronchitis, bronchial asthma, emphysema and other broncho-pulmonary disorders.

4.2. Posology and method of administration

Although intravenous salbutamol and occasionally salbutamol oral solution 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.

Should not be used in patients hypersensitive to any of the product ingredients,

Hypersensitivity to the active substance or to any of the excipients Flavamed Hustensaft must not be used in children under two years.

4.3. Contraindications

Although intravenous salbutamol and occasionally salbutamol oral solution 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.
Should not be used in patients hypersensitive to any of the product ingredients,
Hypersensitivity to the active substance or to any of the excipients
Flavamed Hustensaft must not be used in children under two years.

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 a risk of severe attacks and even death. Physicians should consider using oral corticosteroid therapy and/or maximum recommended dose of inhaled corticosteroid in those patients.
Patients should seek medical advice if treatment with Salbutamol 2 mg/5 ml oral solution becomes less effective.
The dosage or frequency of administration should only be increased on medical advice.
Patients taking Salbutamol 2 mg/5 ml oral solution 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.
This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per 5ml dose.

Ambroxol:
There have been reports of severe skin reactions such as erythema multiforme, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) associated with the administration of ambroxol. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, ambroxol treatment should be discontinued immediately and medical advice should be sought.Because of a possible build-up of secretion, Flavamed Hustensaft should only be used with caution in disturbed bronchomotor function and large quantities of secretion (e.g. in the rare primary ciliary dyskinesia). Flavamed Hustensaft must only be used with particular caution (i.e. at longer intervals or at a reduced dose) in impaired renal function or a severe hepatic disease. In severe renal insufficiency, an accumulation of the metabolites of ambroxol formed in the liver must be expected. This medicinal product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take Flavamed Hustensaft. Each measuring spoon with 5 ml of oral solution contains sorbitol 1.75 g (= 0.15 bread units). Sorbitol may have a mild laxative effect. The calorific value is 2.6 kcal/g sorbitol. Caution should be exercised in patients with histamine intolerance. Long-term therapy should be avoided in these patients, as ambroxol influences the histamine metabolism and may lead to symptoms of intolerance (e.g. headache, runny nose, itching). Since mucolytics may disrupt the gastric mucosal barrier ambroxol should be used with care in patients with a history of peptic ulcer disease. Paediatric

population Persistent or recurrent cough in children beween 2-4 years requires medical diagnosis before treatment.

Guaiphenesin:
Causes of chronic cough should be excluded if symptoms are persistent. Any accompanying symptoms should be actively sought and appropriately investigated/treated. Stop use and ask a healthcare professional if your cough lasts more than 7 days, comes back or is accompanied by a fever, rash, or persistent headache.
Keep out of the sight and reach of children. Do not exceed recommended dose.
Excipient warnings:
- Patients with rare hereditary problems of fructose intolerance should not take this medicine because this product contains Sorbitol and Maltitol.
- This medicinal product contains 2.7% v/v ethanol (alcohol), up to 214 mg per dose, (equivalent to approx 2 ml wine per dose). Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women and high-risk groups such as patients with liver disease, or epilepsy.

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).

Ambroxol:
On combined use of Flavamed Hustensaft with antitussives (cough-suppressant medicines), a dangerous build-up of secretion may develop due to the impaired cough reflex, meaning that the indication for this combination treatment should be examined particularly carefully.

4.6. Fertility, pregnancy and lactation

Ambroxol:

Pregnancy

There are no sufficient data for the use of ambroxol in pregnant women. This particularly concerns the period up to the 28th week of pregnancy. Ambroxol has shown no teratogenic effects in animal experiment studies (see Section 5.3). Flavamed Hustensaft should only be used in pregnancy after careful benefit/risk evaluation, particularly during the first trimester.

Lactation

Ambroxol crosses into the breast milk in animals. As there is no adequate experience in humans to date, Flavamed Hustensaft should only be used in lactation after careful benefit/risk assessment. Fertility There are no sufficient data about the influence of ambroxol on fertility in humans. In animal experiment studies, ambroxol showed no influence on fertility

Salbutamol:

Pregnancy

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.

Breastfeeding

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.

Fertility

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see section 5.3).

Guaifenesin

Pregnancy

Although adequate and well-controlled studies in pregnant women have not been performed, the Collaborative Perinatal Project monitored 197 mother-child pairs exposed to guaifenesin during the first trimester. An increased occurrence of inguinal hernias was found in the neonates. However, congenital defects were not strongly associated with guaifenesin use during pregnancy in 2 large groups of mother-child pairs.

Breastfeeding

Guaifenesin is excreted in breast milk in small quantities.

Caution should therefore be exercised by balancing the potential benefit of treatment against any possible risks.

4.7. Effects on the ability to drive and use machines

No or negligible influence.

4.8. Undesirable effects

Nausea, Stomach discomfort, Diarrhea, Vomiting, Allergic reaction, Dizziness, Headache, Rash,
Hives, Tremor, Palpitations, Muscle cramp

a) Summary of the safety profile

The most common side effect of Salbutamol 2mg/5ml oral solution is fine tremor of the hands, which may interfere with precise manual work. Tension, restlessness and a rapid heart beat 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

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.

Immune system disorders	
Very rare	Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse.
Metabolism and nutrition disorders	
Rare	Hypokalemia
Potentially serious hypokalemia may result from beta agonist theraapy.	
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* (see section 4.4)
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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

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 (see sections 4.4 and 4.8).

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 hyperglycemia 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 sulfate is a cardioselective beta-blocking agent, which should be used with caution in patients with a history of bronchospasm. Further management should be as clinically indicated or as recommended by the National Poisons Centre, where available.

Ambroxol:

a) Symptoms of an overdose No specific overdose symptoms have been reported in man to date. Based on accidental overdose and/or medication error reports the observed symptoms are consistent with the known side effects of ambroxol at recommended doses and may need symptomatic treatment.

b) Therapeutic measures in overdose Acute measures such as instituting vomiting and gastric lavage are not generally indicated and are to be considered only in extreme overdose. A symptomatic therapy is recommended.

Guaiphenesin:

Signs and Symptoms associated with an overdose of Guaifenesin:

- Nausea and vomiting

Treatment:

Appropriate supportive therapy dependent upon individual response to the preparation.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Ambroxol + Menthol + Salbutamol + Guaifenesin is a combination of four medicines: Ambroxol, Menthol, Salbutamol, and Guaifenesin. Ambroxol is a mucolytic that thins and loosens mucus (phlegm), making it easier to cough out. Menthol is an organic compound which produces a sensation of coolness and relieves minor throat irritation. Salbutamol/albuterol is a bronchodilator which relax the muscles in the airways and widen the airways. Guaifenesin is an expectorant which works by decreasing the stickiness of airway secretions and helps in their removal from the airways. Together, they make breathing easier.

Ambroxol:

Ambroxol, a substituted benzylamine, is a metabolite of bromhexine. It differs from bromhexine by the absence of a methyl group and the introduction of a hydroxyl group in the para-trans position of the cyclohexyl ring. Although its mechanism of action has yet to be completely elucidated, mucolytic and secretomotor effects have been found in various investigations.

Action following oral administration commences after 30 minutes on average and persists for 6 - 12 hours depending on the extent of the single dose.

In preclinical investigations, it increases the proportion of serous bronchial secretion. The transport of mucus is thought to be promoted by the reduction of viscosity and the activation of the ciliated epithelium.

Ambroxol induces activation of the surfactant system by acting directly on the type II pneumocytes of the alveoles and the Clara cells in the region of the small airways.

It promotes the formation and outward transfer of surface-active material in the alveolar and bronchial region of the foetal and adult lungs. These effects have been demonstrated in cell cultures and in vivo on various species.

Following use of ambroxol, concentrations of the antibiotics amoxicillin, cefuroxime, erythromycin and doxycycline in the sputum and in the bronchial secretion are increased. To date, it has not been possible to surmise a clinical relevance from this.

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.

Guaifenesin:

Guaifenesin has an expectorant action which increases the output of respiratory tract fluid by reducing adhesiveness and surface tension. The increased flow of less viscid secretions promotes ciliary action and facilitates the removal of mucus. This changes an unproductive cough to a cough that is more productive and less frequent.

Menthol:

Relieving minor pain caused by conditions such as arthritis, backache, bruising, bursitis, cramping, muscle strains or sprains, and tendonitis.

Menthol is a covalent organic compound made synthetically or obtained from peppermint or other mint oils. It is a waxy, crystalline substance, clear or white in color, which is solid at room temperature and melts slightly above. The main form of menthol occurring in nature is (-)- menthol, which is assigned the (1R,2S,5R) configuration. Menthol has local anesthetic and counterirritant qualities, and it is widely used to relieve minor throat irritation.

5.2. Pharmacokinetic properties

Ambroxol:

Ambroxol is practically completely absorbed following oral administration. Tmax following oral administration is 1 - 3 hours. The absolute bioavailability of ambroxol on oral administration is reduced by approx. one third by a first-pass effect. Renally excreted metabolites (e.g. dibromo anthranilic acid, glucuronides) are formed in the process. Binding to plasma proteins is approx. 85 % (80 - 90 %). The terminal half-life in the plasma is 7 - 12 hours. The plasma half-life of the sum of ambroxol and its metabolites is approx. 22 hours. Ambroxol crosses the placental barrier and passes into the cerebrospinal fluid and breast milk.

Excretion is 90 % renal in the form of metabolites formed in the liver. Unchanged ambroxol accounts for less than 10 % of renal excretion. Due to the high protein binding and the high volume of distribution, as well as the slow redistribution from the tissue to the blood, major elimination of ambroxol through dialysis or forced diuresis is not expected. Clearance of ambroxol is diminished by 20 - 40 % in severe hepatic diseases. In severe renal dysfunction, an accumulation of the metabolites of ambroxol must be expected.

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%.

Guaifenesin :

Guaifenesin is well absorbed from the gastro intestinal tract following oral administration. Guaifenesin has a plasma half-life of approximately 1 hour. It is rapidly hydrolyzed (60% within seven hours) and then excreted in the urine, with beta-(2-methoxyphenoxy)-lactic acid as its major urinary metabolite

Menthol:

Menthol is a covalent organic compound made synthetically or obtained from peppermint or other mint oils. It is a waxy, crystalline substance, clear or white in color, which is solid at room temperature and melts slightly above. The main form of menthol occurring in nature is (-)- menthol, which is assigned the (1R,2S,5R) configuration. Menthol has local anesthetic and counterirritant qualities, and it is widely used to relieve minor throat irritation.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sugar pellets

Sodium methyl paraben

Sodium propyl paraben

Sodium benzoate

Citric acid (Monohydrate)

Xanthan gum transparent

Propylene glycol

Aspartame

Sodium saccharine

Essence of strawberry

Ponceau 4R

Purified water

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C, protected from light and moisture.

6.5. Nature and contents of container

Each carton contains a 100ml amber pet bottle with pack insert.

6.6. Special precautions for disposal and other handling

No special requirements.

7. Marketing authorization holder

Salama Pharmaceuticals Limited
P.O. Box 51665-00200,
Nairobi, Kenya

8. Marketing authorization number(s)

H2024/CTD9187/20277

9. Date of First Authorization

23rd February 2024

10. Date of revision of text

November 2024