1. NAME OF THE MEDICINAL PRODUCT

Vifazer syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 ml contains:
Salbutamol sulphate BP
Equivalent to Salbutamol……. 1 mg
Bromhexine hydrochloride BP…….2 mg
Guaifenesin BP……50 mg
Excipients……q.s.
In a mentholated flavoured syrup base

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

A light orange coloured syrup with pleasant flavour

4. Clinical particulars

4.1 Therapeutic indications

- Bronchial asthma
- Emphysema atelectasis
- Acute and chronic bronchitis
- Bronchiectasis
- Pulmonary tuberculosis
- Whooping cough
- Pneumonia
- Other broncho-spastic conditions

4.2 Posology and method of administration

Adults: 10 ml (2 teaspoonful) to be taken thrice daily.
Children: 6-12 years- 5-10ml (1-2 teaspoonful) to be taken thrice daily and children below 6 years – 5 ml (1 teaspoonful) to be taken thrice daily.

4.3 Contraindications

- This medicine should not be used in patients hypersensitive to any of components of the formulation.
- Should not be used for threatened abortion during the first or second trimester of pregnancy.

4.4 Special warnings and precautions for use

Salbutamol

- In patients with severe or unstable asthma, bronchodilators should not be the only or main treatment. With severe asthma regular medical assessment is necessary, including lung function testing as patients are at risk of severe attacks or possibly death. For the treatment of such patients, physicians should consider using the maximum

recommended dose of inhaled corticosteroids and/or oral corticosteroids.

- 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.
- Patients may develop serious hypokalemia when salbutamol is given in combination with beta-2 agonist therapy in acute severe asthma. It is important to monitor serum potassium levels in such situations.
- Use with caution in diabetic patients as this product may cause an increase in blood sugar levels. The development of ketoacidosis has been reported as diabetic patients may be unable to compensate for the increase in blood glucose. This effect can be exaggerated by concurrent administration of corticosteroids.
- In such cases medical advice should be sought. Higher doses of inhaled corticosteroids or a course of oral corticosteroids may be considered.

Bromhexine

- Bromhexine should be used with caution in patients with a history of, or existing, peptic ulceration.
- 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 bromhexine hydrochloride. If symptoms or signs of a progressive skin rash (sometimes associated with blisters or mucosal lesions) are present, bromhexine hydrochloride treatment should be discontinued immediately and medical advice should be sought.

Guaifenesin

- Patients with rare hereditary problems of fructose intolerance, glucose-galactose

malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains sodium and sucrose. Hence, to be taken into consideration by patients on a controlled sodium diet and in patients with diabetes mellitus.

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 (MAOI's)

Guaifenesin

- If urine is collected within 24 hours of a dose of the medicinal product, a metabolite of guaifenesin may cause a colour interference with laboratory determinations of urinary 5-hydroxyindoleacetic acid (5-HIAA) and vanillylmandelic acid (VMA).
- Guaifenesin may increase the rate of absorption of paracetamol.

Bromhexine

No clinically relevant unfavourable interactions with other medications have been reported

4.6 Pregnancy and Lactation

Administration of this medicine during pregnancy should be considered only if the expected benefit to mother is greater than any possible risk to the foetus.
This medicine may be secreted in breast milk and hence it should be used when the expected benefit to the mother is likely to outweigh any potential risk to the neonate.

Pregnancy

Salbutamol

Salbutamol should only be used in pregnancy and lactation if considered essential by the physician.
Salbutamol should only be used during pregnancy/lactation if the expected benefits to the mother are greater than any potential risks to the foetus/neonate.
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.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of bromhexine during pregnancy.

Guaifenesin

Guaifenesin has been linked with an increased risk of neural tube defects in a small number of women with febrile illness in the first trimester of pregnancy. The product should be used in pregnancy only if the benefits outweigh this risk.

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 animals have shown excretion of bromhexine/metabolites in breast milk. A risk to the breastfed infant cannot be excluded.

Guaifenesin

There is no information on use in 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

No studies on the effect on human fertility have been conducted with Bromhexine.

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

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 angiodema, 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.

Guaifenesin has occasionally been reported to cause gastrointestinal discomfort, nausea and vomiting, particularly in very high doses. Also, hypersensitivity reactions may occur.

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	Rare	Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse, anaphylactic shock and pruritus
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 extra systoles
	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
Respiratory, thoracic and mediastinal disorders	Unknown	Bronchospasm
Gastrointestinal disorders	Uncommon	Abdominal pain upper, Nausea, Vomiting, Diarrhoea
Skin and subcutaneous tissue disorders	Rare	Rash, Urticaria
	Unknown	Severe cutaneous adverse reactions (including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis)

4.9 Overdose

The most common signs and symptoms of overdose are transient beta agonist pharmacologically mediated events, including tachycardia, tremor, hyperactivity and metabolic effects including hypokalaemia along with nausea, vomiting and hyperglycaemia. Lactic acidosis may also be reported.

Treatment

Patients should be kept under observation and treated symptomatically. Serum potassium levels need to be monitored, along with 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). Further management should be as clinically indicated or as recommended by the national poisons centre, where available.
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

The primary action of Salbutamol is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3′, 5′-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP) in beta-adrenergic cells. The cyclic AMP thus formed mediates the cellular responses. 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. *In vivo* pharmacologic studies have demonstrated that Salbutamol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that a population of beta2- receptors in the human heart exist in a concentration between 10 and 50%. The precise function of these receptors has not been established.
Bromhexine is an expectorant/mucolytic agent which has been investigated in the treatment of respiratory disorders. The drug is a benzylamine derivative (2-amino-3,5-dibromo-N-cyclohexyl N-methylbenzylamine hydrochloride) and also a derivative of vasicine and adhatodic acid, alkaloids obtained from the plant Adhatoda vasica. Following oral administration, Bromhexine increases sputum volume and reduces the viscosity of bronchial secretions in chronic bronchitis patients. The drug has been reported to induce hydrolytic depolymerization of mucoprotein fibers and stimulate activity of the ciliated epithelium.
Guaifenesin is an expectorant which increases respiratory tract fluid secretions and helps to loosen phlegm and bronchial secretions. By reducing the viscosity of secretions, guaifenesin increases the efficiency of the cough reflex and of ciliary action in removing accumulated secretions from the trachea and bronchi.

5.2 Pharmacokinetic properties

Salbutamol

Salbutamol is readily absorbed from the gastrointestinal 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

Absorption

Bromhexine is rapidly and completely absorbed from the gastrointestinal tract.
After oral administration solid and liquid formulations show similar bioavailability. The absolute bioavailability of bromhexine hydrochloride was about 26.8 ± 13.1 % forBromhexine solution, the first pass metabolism amounts to about 75-80%. Concomitant food leads to an increase of bromhexine plasma concentrations.

Distribution
After intravenous administration bromhexine was rapidly and widely distributed throughout the body with a mean volume of distribution (Vss) of up to 1209 ± 206 L (19 L/kg). 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 bronchiolobronchial 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% (nonrestrictive 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 or oxytetracyclin. There is insufficient pharmacokinetic data to evaluate a possible drug-drug interaction between bromhexine and erythromycin.
Elimination
Bromhexine is a high extraction ratio drug after i.v. administration in the range of the hepatic blood flow, 843-1073 mL/min resulting in high inter- and Intraindividual variability (CV > 30 %) After administration of radiolabelled bromhexine about 97.4 ± 1.9
% of the dose were recovered as radioactivity in urine, with less than 1% as parent compound.
Bromhexine plasma concentrations showed a multiexponential decline. After administration of single oral doses between 8 and 32 mg, the terminal elimination half-life ranged between 6.6 and 31.4 hours. The relevant half-life to predict the multiple dose pharmacokinetics is about 1 hour, thus no accumulation was seen after multiple dosing (accumulation factor 1.1).

Bromhexine shows dose proportional pharmacokinetics in the range of 8-32 mg following oral administration. There are no data for bromhexine pharmacokinetics in the elderly or in patients with renal or liver insufficiency.
Bromhexine pharmacokinetics is not relevantly affected by coadministration of ampicillin or oxytetracycline.

Guaifenesin
Guaifenesin is readily absorbed from the gastrointestinal tract and is rapidly metabolized and excreted in the urine. Guaifenesin has a plasma half-life of 1 hour. The major urinary metabolite is B-(2-methoxyphenoxy) lactic acid.

5.3 Preclinical safety data
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.
No preclinical findings of relevance to the Bromhexine and Guaiphenesin have been reported

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Menthol
Citric acid monohydrate
Sodium citrate
Sodium benzoate
Propylene glycol
Glycerol
Liquid glucose
Sucrose
Aspartame
Sorbitol 70%
Raspberry sweet flavor
Sunset yellow colour
Chloroform
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

100 ml syrup is filled in an amber colored Polyethylene Terephthalate (PET) bottle and the bottle is sealed with a cap. One measuring cup is placed on the bottle. Each bottle is packed in a printed carton along with a leaflet

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION

Emcure Nigeria Limited
Plot No. P1 & P2, IT-BT Park, Phase II,
M.I.D.C., Hinjawadi, Pune- 411026, Maharashtra, INDIA.

8. DRUG PRODUCT MANUFACTURER

Emcure Pharmaceuticals Limited
Lane No. 3, Phase-II, SIDCO Industrial Complex
Bari-Brahmana, Jammu (J&K)- 181133, INDIA

9. NAFDAC REGISTRATION NUMBER(S)

B4-5595

10. DATE OF REVISION OF THE TEXT

13.12.2024