1. NAME OF THE MEDICINAL PRODUCT
Vifex Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml contains:

Salbutamol sulphate BP	
Equivalent to Salbutamol BP	1 mg
Bromhexine hydrochloride BP	2 mg
Guaifenesin BP	50 mg
Flavoured Mentholated syrup base	

3. PHARMACEUTICAL FORM
Syrup

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

Non-i.v. formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion.

4.4 Special warnings and precautions for use

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 with this syrup becomes less effective.

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

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

The management of asthma should normally follow a stepwise programme, and patient response should be monitored clinically and by lung function tests.

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.

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.

Salbutamol should be administered cautiously to patients suffering from thyrotoxicosis.

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, diuretics and by hypoxia. It is recommended that serum potassium levels are monitored in 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 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.

This medicine contains sodium. To be taken into consideration by patients on a controlled sodium diet and it contains sucrose; this should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Salbutamol

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

Bromhexine

No clinically relevant unfavourable interactions with other medications have been reported

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.

4.6 Pregnancy and Lactation

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.

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. 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.

As a precautionary measure, it is preferable to avoid the use of this syrup during pregnancy.

Breast-feeding

This syrup should not be used during 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.

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.

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).

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

Salbutamol

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
Unknown	Anaphylactic reactions including anaphylactic shock[$], angioedema[$] and pruritus[$]
Metabolism and nutrition disorders	
Rare	Hypokalaemia. Potentially serious hypokalaemia may result from beta agonist therapy.
Nervous system disorders	
Very common:	Tremor.
Common:	Headache.
Very rare:	Hyperactivity.
Cardiac disorders	
Common:	Tachycardia, palpitations.
Rare:	Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles
Unknown:	Myocardial ischaemia* (see section 4.4)
Vascular disorders	
Rare:	Peripheral vasodilatation.
Musculoskeletal and connective tissue disorders	
Common:	Muscle cramps.
Very rare:	Feeling of muscle tension.
Respiratory, thoracic and mediastinal disorders	
Unknown	Bronchospasm[$]
Gastrointestinal disorders	
Uncommon	Abdominal pain upper, Nausea, Vomiting, Diarrhoea
Skin and subcutaneous tissue disorders	
Rare	Rash, Urticaria[$]
Unknown	Severe cutaneous adverse reactions (including erythema multi-forme, Stevens-Johnson syndrome/toxic epidermal necrolysis and acute generalized exanthematous pustulosis)

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

[$]This adverse reaction has been observed in post-marketing experience. With 95 % certainty, the frequency category is not greater than rare (3/3,992), but might be lower. A precise frequency estimation is not possible as the adverse drug reaction did not occur in a clinical trial database of 3,992 patients.

4.9 Overdose

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.

Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should 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.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

No specific bromhexine 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 bromhexine at recommended doses and may need symptomatic treatment.
Very large doses may cause nausea and vomiting. The drug is, however, rapidly metabolised and excreted in the urine. Patients should be kept under observation and treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Salbutamol is a selective beta-$_2$ adrenoceptor agonist. At therapeutic doses it acts on the beta-$_2$ adrenoceptors of bronchial muscle providing short acting (4-6 hours) bronchodilation in reversible airways obstruction.
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 administered intravenously has a half-life of 4 to 6 hours and is cleared partly renally and partly by metabolism to the inactive 4' -O-sulfate (phenolic sulfate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. The majority of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.

After oral administration, salbutamol is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulfate. Both unchanged drug and conjugate are excreted primarily in the urine. 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 % for Bromhexine 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).
General
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 β2-agonists, salbutamol has been shown to be teratogenic in mice when given subcutaneously. In a reproductive study, 9.3% of fetuses 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 fetal 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 fetuses 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, embryofetal 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 excipient(s)

Citric acid monohydrate (BP)

Sodium citrate (BP)

Sodium benzoate (BP)

Propylene glycol (BP)

Glycerol (BP)

Liquid glucose (USP)

Sucrose (USP)

Aspartame (USP)

Sorbitol 70% (BP)

Raspberry sweet flavor (In House)

Sunset yellow colour (In House)

Chloroform (BP)

Menthol (USP)

Purified water (BP)

6.2 Incompatibilities

The concomitant use of salbutamol with other oral sympathomimetic agents is not recommended since such combined use may lead to deleterious cardiovascular effects.

6.3 Shelf-life

36 months.

6.4 Special precautions for storage

Store below 30^0C. Protect from light.

6.5 Nature and contents of container

100 ml syrup is filled in an amber coloured Polyethylene Trichloride (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. 40 such cartons are packed in an outer corrugated box.

6.6 Instructions for use and handling

Store in a dry place, below 30°C. Protect from light.

Keep away from the reach of children.

7. MARKETING AUTHORISATION HOLDER

Emcure Pharmaceuticals Limited, Bhosari, India.

8. MARKETING AUTHORISATION NUMBER(S)

Shall be provided when available.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

12.05.2020