SUMMARY OF PRODUCT CHARACTERISTICS:
BONAIR HFA INHALER
(Salbutamol Pressurised Inhalation BP)

1. NAME OF THE MEDICINAL PRODUCT
BONAIR HFA INHALER (Salbutamol Pressurised Inhalation BP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
BONAIR HFA INHALER is a pressurised metered-dose inhaler delivering 100 micrograms of salbutamol (as Salbutamol Sulfate BP) per actuation. BONAIR HFA INHALER contains a new propellant (HFA 134a) and does not contain any chlorofluorocarbons.

3. PHARMACEUTICAL FORM
Aerosol

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
BONAIR HFA INHALER is indicated in adults, adolescents and children aged 4 to 11 years. For babies and children under 4 years of age, see sections 4.2 and 5.1.

BONAIR HFA INHALER provides short-acting (4 to 6 hour) bronchodilation with fast onset (within 5 minutes) in reversible airways obstruction.

It is particularly suitable for the relief and prevention of asthma symptoms. It should be used to relieve symptoms when they occur, and to prevent them in those circumstances recognised by the patient to precipitate an asthma attack (e.g. before exercise or unavoidable allergen exposure).

BONAIR HFA INHALER is particularly valuable as relief medication in mild, moderate or severe asthma, provided that reliance on it does not delay the introduction and use of regular inhaled corticosteroid therapy.

4.2 Posology and method of administration
BONAIR HFA INHALER is for oral inhalation use only.

<u>Adults (including the elderly):</u>

For the relief of acute asthma symptoms including bronchospasm, one inhalation (100 micrograms) may be administered as a single minimum starting dose. This may be increased to two inhalations if necessary. To prevent allergen- or exercise-induced symptoms, two inhalations should be taken 10-15 minutes before challenge.

For chronic therapy, two inhalations up to four times a day.

Paediatric Population

Relief of acute bronchospasm

The usual dosage for children under the age of 12 years: one inhalation (100 micrograms). The dose may be increased to two inhalations if required.

Children aged 12 years and over: Dose as per adult population.

Prevention of allergen or exercise-induced bronchospasm

The usual dosage for children under the age of 12 years: one inhalation (100 micrograms) before challenge or exertion. The dose may be increased to two inhalations if required.

Children aged 12 years and over: Dose as per adult population.

Chronic therapy

The usual dosage for children under the age of 12 years: up to two inhalations 4 times daily.

Children aged 12 years and over: Dose as per adult population.

4.3 Contraindications

Bonair HFA Inhaler (Salbutamol Pressurised Inhalation BP) is contraindicated in patients with hypersensitivity to any of the active substances or to the excipient.

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

4.4 Special warnings and precautions

Patients inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of drug to the lungs. Patients should be warned that they may experience a different taste upon inhalation compared to their previous inhaler

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 the maximum recommended dose of inhaled corticosteroid and/or oral corticosteroid therapy in these patients

The dosage or frequency of administration should only be increased on medical advice. If a previously effective dose of inhaled salbutamol fails to give relief lasting at least three hours, the patient should be advised to seek medical advice.

Increasing use of bronchodilators, in particular short-acting inhaled β_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 more inhalations than usual are required. In this situation the patient should be assessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroid 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 with thyrotoxicosis.

Potentially serious hypokalaemia may result from β_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 and diuretics. Serum potassium levels should be monitored in such situations.

As with other inhalation therapy, paradoxical bronchospasm may occur, with increased wheezing immediately after administration. Should this occur, the preparation should be immediately discontinued and replaced by alternative treatment.

4.5 Interaction with other medicinal products and other form of interactions:

Salbutamol and non-selective β-receptor blocking drugs should not usually be prescribed together.

4.6 Pregnancy and Lactation

Pregnancy

Studies in animals have shown reproductive toxicity. Safety in pregnant women has not been established. Salbutamol should not be used during pregnancy unless clearly necessary. Rare reports of various congenital anomalies following intrauterine exposure to salbutamol (including cleft palate, limb defects and cardiac disorders) have been received. Some of the mothers were taking multiple medications during their pregnancies. This medication should not be used during pregnancy unless clearly necessary.

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).

4.7 Effects on Ability to Drive and Use Machines

None reported.

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 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <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:	Hypokalaemia. Potentially serious hypokalaemia may result from *beta*$_2$ agonist therapy.
Nervous system disorders	
Common:	Tremor, headache.
Very rare:	Hyperactivity.
Cardiac disorders	
Common:	Tachycardia.
Uncommon:	Palpitations.
Very rare:	Cardiac arrhythmias (including atrial fibrillation, supraventricular tachycardia and extrasystoles).
Unknown:	Myocardial ischaemia* (see section 4.4)
Vascular disorders	
Rare:	Peripheral vasodilatation.
Respiratory, thoracic and mediastinal disorders	
Very rare:	Paradoxical bronchospasm.
Gastrointestinal disorders	

Uncommon:	Mouth and throat irritation.
Musculoskeletal and connective tissue disorders	
Uncommon:	Muscle cramps.

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

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 (see sections 4.4 and 4.8).

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.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Andrenergics, inhalants. Selective beta-2-andrenoreceptor agonists

ATC code: R03AC02

Salbutamol is a selective β_2-adrenoceptor agonist. At therapeutic doses it acts on the β_2-adrenoceptors of bronchial muscle providing short acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

5.2 Pharmacokinetic properties:

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.

After administration by the inhaled route between 10 and 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and circulation, but is not metabolised by the lung. On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as the phenolic sulfate.

The swallowed portion of an inhaled dose 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. Most 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%.

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 fetuses were found to have cleft palate at 2.5mg/kg 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. Reformulation of the Bonair HFA Inhaler has not altered the known toxicological profile of salbutamol.

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.

The non-CFC propellant, HFA 134a, has been shown to have no toxic effect at very high vapour concentrations, far in excess of those likely to be experienced by patients, in a wide range of animal species exposed daily for periods of two years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Propellant HFA 134a

Ethanol

Oleic acid

6.2 Incompatibilities

None reported.

6.3 Shelf Life

36 month

6.4 Special precaution for storage

Pressurised canister. Do not puncture or burn even when apparently empty. Keep away from sunlight and heat. Store below 30°C, protected from moisture. Keep away from eyes. Keep out of reach of children.

Bonair HFA Inhaler (Salbutamol Pressurised Inhalation BP) should be stored horizontal or in an inverted position, with the mouthpiece pointing downwards.

6.5 Nature and content of container

Pressurised metered-dose preparation for inhalation filled in Aluminium canister crimped with suitable metered-dose valve, labelled with product label, assembled with polypropylene adaptor packed in a folding carton along with Patient Information leaflet

6.6 Special precautions for disposal and other handling

Not applicable

7. MARKETING AUTHORIZATION HOLDER

Bliss GVS Pharma Ltd

102, Hyde Park, Saki Vihar Road, Andheri –East, Mumbai -400 072, India