Ventolin™ Inhaler CFC Free
Salbutamol

1. QUALITATIVE AND QUANTITATIVE COMPOSITION
Ventolin Inhaler is a pressurised metered-dose inhaler which delivers 100 micrograms salbutamol (as sulphate) per actuation, into the mouthpiece of a specially designed actuator. The inhaler also contains the CFC-free propellant HFA 134a. Each canister contains at least 200 actuations.

2. PHARMACEUTICAL FORM
Pressurised inhalation, solution

3. CLINICAL PARTICULARS
3.1 Therapeutic Indications
Salbutamol is a selective beta₂ adrenoceptor agonist. At therapeutic doses it acts on the beta₂ adrenoceptors of bronchial muscle, with little or no action on the beta₁ adrenoceptors of the heart. With its fast onset of action, it is particularly suitable for the management and prevention of attack in asthma.

Bronchodilators should not be the only or the main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment as death may occur. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity, and PEF values below 60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require high dose inhaled (e.g >1mg/day beclomethasone dipropionate) or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

VENTOLIN 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.

3.2 Dosage and Administration
VENTOLIN has a duration of action of 4 to 6 hours in most patients.

Increasing use of beta₂ agonists may be a sign of worsening asthma. Under these conditions a reassessment of the patient's therapy plan may be required and concomitant glucocorticosteroid therapy should be considered.

As there may be adverse effects associated with excessive dosing, the dosage or frequency of administration should only be increased on medical advice.

VENTOLIN Inhaler is administered by the oral inhaled route only.

In patients who find co-ordination of a pressurised metered-dose inhaler difficult a spacer may be used with VENTOLIN Inhaler.

Babies and young children using the VENTOLIN Inhaler may benefit from the use of a paediatric spacer device with a face mask (for example the BABYHALER™). (See Clinical Studies).

RELIEF OF ACUTE BRONCHOSPASM
- Adults: 100 or 200 micrograms.
- Children: 100 micrograms, the dose may be increased to 200 micrograms if required.

PREVENTION OF ALLERGEN OR EXERCISE-INDUCED BRONCHOSPASM
- Adults: 200 micrograms before challenge or exertion.
• Children: 100 micrograms before challenge or exertion. The dose may be increased to 200 micrograms if required.

**CHRONIC THERAPY**

- **Adults:** Up to 200 micrograms four times daily.
- **Children:** Up to 200 micrograms four times daily.

On demand use of **VENTOLIN** should not exceed four times daily. Reliance on such supplementary use or sudden increase in dose indicates deteriorating asthma (see **Warnings and Precautions**).

**3.3 Contra-indications**

VENTOLIN is contra-indicated in patients with a history of hypersensitivity to any of its components (see Excipients). Non-i.v. formulations of VENTOLIN must not be used to arrest uncomplicated premature labour or threatened abortion.

**3.4 Warning and Precautions**

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 short-acting bronchodilators, in particular beta2 agonists to relieve symptoms indicates deterioration of asthma control. Under these conditions, the patient's therapy plan should be reassessed.

Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to starting or increasing corticosteroid therapy. In patients considered at risk, daily peak flow monitoring may be instituted.

VENTOLIN should be administered cautiously to patients with thyrotoxicosis.

Potentially serious hypokalaemia may result from beta2 agonist therapy mainly from parenteral and nebulised administration.

Particular caution is advised in acute severe asthma as this effect may be potentiated by concomitant treatment with xanthine derivatives, steroids, diuretics and by hypoxia. It is recommended that serum potassium levels are monitored in such situations.

As with other inhalation therapy, paradoxical bronchospasm may occur, resulting in an immediate increase in wheezing after dosing. This should be treated immediately with an alternative presentation or a different fast-acting inhaled bronchodilator, if immediately available. VENTOLIN Inhaler should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.

In the event of a previously effective dose of inhaled VENTOLIN failing to give relief for at least three hours, the patient should be advised to seek medical advice in order that any necessary additional steps may be taken.

The patient’s inhaler technique should be checked to make sure that aerosol actuation is synchronised with inspiration of breath for optimum delivery of the drug to the lungs.

**3.5 Interaction**

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

VENTOLIN is not contraindicated in patients under treatment with monoamine oxidase inhibitors (MAOIs).
3.6 Pregnancy and Lactation

Fertility
There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see Pre-clinical Safety Data).

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.

During worldwide marketing experience, rare cases of various congenital anomalies, including cleft palate and limb defects have been reported in the offspring of patients being treated with VENTOLIN. Some of the mothers were taking multiple medications during their pregnancies. As no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2 to 3%, a relationship with salbutamol use cannot be established.

Lactation
As salbutamol is probably secreted in breast milk, its use in nursing mothers is not recommended unless the expected benefits outweigh any potential risk. It is not known whether salbutamol in breast milk has a harmful effect on the neonate.

3.7 Effects on Ability to Drive and Use Machines
None reported.

3.8 Adverse Reactions
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 and very rare 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 beta2 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

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
3.9 Overdose
The most common signs and symptoms of overdose with VENTOLIN are transient beta agonis pharmacologically mediated events (see Warnings and Precautions and Adverse Event).

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.

4 PHARMACOLOGICAL PROPERTIES
4.1 Pharmacodynamic
Salbutamol is a selective beta2-adrenoceptor agonist. At therapeutic doses it acts on the beta2-adrenoceptors of bronchial muscle providing short acting (4 to 6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

4.2 Pharmacokinetic
Absorption
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.

Distribution
Salbutamol is bound to plasma proteins to the extent of 10%.

Metabolism
On reaching the systemic circulation, salbutamol becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as the phenolic sulphate.

The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulphate. Both unchanged drug and conjugate are excreted primarily in the urine.

Elimination
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-sulphate (phenolic sulphate) 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.

4.3 Clinical Studies
Special Patient Populations
Children < 4 years of age
Paediatric clinical studies conducted at the recommended dose (SB020001, SB030001, SB030002), in patients < 4 years with bronchospasm associated with reversible obstructive airways disease, show that the Ventolin inhaler has a safety profile comparable to that in children ≥ 4 years, adolescents and adults.

4.4 Preclinical Safety Data
In common with other potent selective beta2-receptor 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 2.5 mg/kg, 4 times the maximum human oral dose. In rats, treatment at the levels of 0.5, 2.32, 10.75 and 50 mg/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. A reproductive study in rabbits revealed cranial malformations in 37% of foetuses at 50 mg/kg/day, 78 times the maximum human oral dose.
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.

HFA 134a has been shown to be non-toxic 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.

5 PHARMACEUTICAL PARTICULARS
5.1 List of Excipients
1,1,1,2-tetrafluoroethane (also known as HFA 134a or norflurane).

5.2 Incompatibilities
None reported.

5.3 Shelf Life
24 months.

5.4 Special Precautions for Storage
Replace the mouthpiece cover firmly and snap it into position.
VENTOLIN Inhaler should be stored below 30°C. Protected from frost and direct sunlight.

As with most inhaled medications in aerosol canisters, the therapeutic effects of this medication may decrease when the canister is cold. The canister should not be broken, punctured or burnt, even when apparently empty.

5.5 Nature and Contents of Container
VENTOLIN Inhaler comprises a suspension of salbutamol sulphate in the propellant HFA 134a. The suspension is contained in an aluminium alloy can, sealed with a metering valve. Each canister is fitted with plastic actuator incorporating an atomising nozzle and fitted with duscap. VENTOLIN Inhaler delivers 100 micrograms of salbutamol (as sulphate) per actuation. Each canister contains at least 200 actuations.

5.6 Instructions for Use/Handling
Testing your inhaler
Before using for the first time, remove the mouthpiece cover by gently squeezing the sides of the cover, shake the inhaler well, and release two puffs into the air to make sure that it works. If it has not been used for 5 days or more, shake it well and release 2 puffs into the air to make sure that it works.

Using your inhaler
1. Remove the mouthpiece cover by gently squeezing the sides of the cover. As shown at picture 1.
2. Check inside and outside of the inhaler including the mouthpiece for the presence of loose objects.
3. Shake the inhaler well to ensure that any loose objects are removed and that the contents of the inhaler are evenly mixed.
4. Hold the inhaler upright between fingers and thumb with thumb on the base, below the mouthpiece as shown at picture 2.
5. Breathe out as far as is comfortable and then place the mouthpiece in your mouth between your teeth and close your lips around it but do not bite it as shown at picture 3.
6. Just after starting to breathe in through your mouth press down on the top of the inhaler to release VENTOLIN while still breathing in steadily and deeply as shown at picture 4.
7. While holding your breath, take the inhaler from mouth and take your finger from the top of the inhaler. Continue holding your breath for as long as is comfortable (picture 5).
8. If you are to take further puffs keep the inhaler upright and wait about half a minute before repeating steps three to seven.
9. Replace the mouthpiece cover is replaced by firmly pushing and snapping the cap into position.

1. Remove the metal canister from the plastic casing of the inhaler and remove the mouthpiece cover.
2. Rinse the actuator thoroughly under warm running water.
3. Dry the actuator THOROUGHLY inside and out.
4. Replace the metal and mouthpiece cover.

DO NOT PUT THE METAL CANISTER INTO WATER.

Package Quantity and Registration Number
Each canister of Ventolin Inhaler CFC Free provides 200 inhalations.
Ventolin Inhaler CFC Free 100 mcg/actuation
Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Manufactured by
Glaxo Wellicome S.A
Aranda, Spain

Packed by
PT SmithKline Beecham Pharmaceuticals
Jakarta, Indonesia
For
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Jakarta, Indonesia

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