VENTOLIN® ROTACAPS®

Salbutamol sulfate

1. QUALITATIVE AND QUANTITATIVE COMPOSITION

VENTOLIN ROTACAPS contain a mixture of microfine salbutamol sulfate and larger particle lactose in hard gelatin cartridges. Each Rotacap contains 200 micrograms of salbutamol (as sulfate).

2. PHARMACEUTICAL FORM

Inhalation powder, hard capsule.

3. CLINICAL PARTICULARS

3.1 Indications

Salbutamol is a selective β2 adrenoceptor agonist. At therapeutic doses it acts on the β2 adrenoceptors of bronchial muscle, with little or no action on the β-1 adrenoceptors of the heart. With its fast onset of action, it is particularly suitable for the management and prevention of attack in asthma. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Bronchodilators should not be the only or 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 value below 60% predicted at baseline with greater than 30% variability, usually not returning to normal after bronchodilator. These patients will require high dose inhaled (e.g > 1mg/day beclomethasone dipropionate) or oral corticosteroid therapy.

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 inhaler corticosteroid therapy.

3.2 Dosage and Administration

VENTOLIN has a duration of action of 4 to 6 hours in most patients.

VENTOLIN inhaled formulations are administered by the inhaled route only, to be breathed in through the mouth.

Increasing use of $beta_2$ 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 ROTACAPS capsules are for inhalation use only, using a *VENTOLIN ROTAHALER* inhaler.

RELIEF OF ACUTE BRONCHOSPASM

- **Adults**

200 or 400 micrograms.

- **Children**

200 micrograms.

PREVENTION OF EXERCISE-INDUCED BRONCHOSPASM

- **Adults**

400 micrograms before exertion.

- **Children**

200 micrograms before exertion.

CHRONIC THERAPY

- **Adults**

400 micrograms 3 or 4 times daily.

- **Children**

200 micrograms 3 or 4 times daily.

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

3.3 Contraindications

VENTOLIN is contraindicated in patients with a history of hypersensitivity to any of its components (*see Excipients*). Although i.v. salbutamol and occasionally *VENTOLIN* tablets are used in the management of premature labour uncomplicated by conditions such as placenta praevia, ante-partum haemorrhage or toxaemia of pregnancy, inhaled *VENTOLIN* preparations are not appropriate for managing premature labour. *VENTOLIN* presentations should not be used for threatened abortion.

VENTOLIN dry powder inhaler formulations are contraindicated in patients with severe milk-protein allergy or who have a history of hypersensitivity to salbutamol or any of its formulation components (*see Excipients*).

3.4 Warnings 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 $beta_2$ 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 $beta_2$ agonist therapy mainly from parenteral and nebulised administration.

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

In the event of a previously effective dose of inhaled salbutamol 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.

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. The specific salbutamol presentation should be discontinued, and if necessary a different fast-acting bronchodilator instituted for ongoing use.

3.5 Interactions

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

VENTOLIN is not contra-indicated 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 salbutamol. 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 $beta_2$ 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

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 agonist pharmacologically mediated events (*see Warnings and Precautions and Adverse Reactions*).

Hypokalaemia may occur following overdosage with *VENTOLIN*. 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 Pharmacodynamics

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 to 6 hours) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction.

4.2 Pharmacokinetics

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 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.

Elimination

Salbutamol administered intravenously has a half-life of four to six 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.

4.3 Pre-clinical Safety Data

In common with other potent selective beta$_2$ 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, four 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.

5. PHARMACEUTICAL PARTICULARS

5.1 List of Excipients

Lactose (which contains milk protein).

5.2 Incompatibilities

None reported.

5.3 Shelf Life

36 months.

5.4 Special Precautions for Storage

To keep the Rotacaps in good condition it is important that they are stored in a dry place and where they will not be exposed to extremes of temperature and should be stored below 30°C.

5.5 Nature and Contents of Container

VENTOLIN inhalation powder is contained in a capsule (*ROTACAPS*) each containing 200 micrograms of salbutamol (as sulfate). An inspiration driven inhaler made of plastic (a *ROTAHALER*) is used for administration of medication.

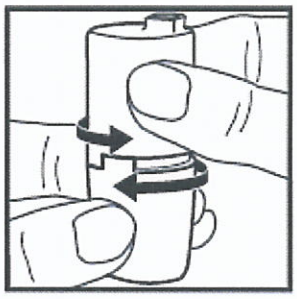
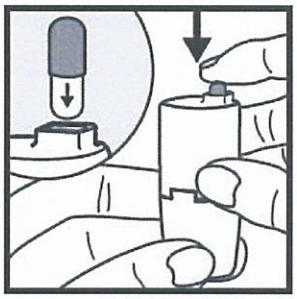
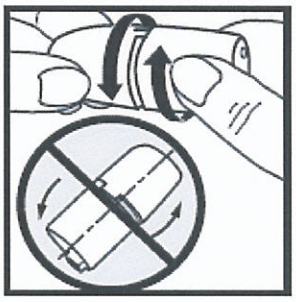
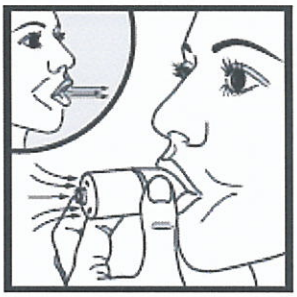
5.6 Instructions for Use/Handling

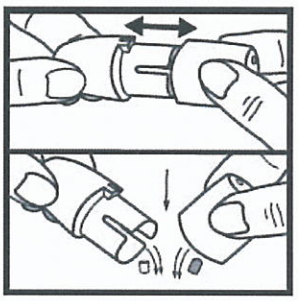
The Rotacaps must only be inserted in to the Rotahaler immediately prior to use. Failure to observe this instruction will affect the delivery of the drug.

Instructions for use

Step-by-step guide to using your *VENTOLIN ROTAHALER*

How to prepare your *VENTOLIN ROTAHALER* for use:	

1	Check that your *ROTAHALER* mouthpiece is clean and dry and free from objects. Hold the white end in one hand and **turn the blue end as far as it will go**.	
2	**Insert the clear end of a *ROTACAPS* capsule into the raised hole at the blue end of your *ROTAHALER*. Push in firmly** until the top of the *ROTACAPS* capsule is level with the top of the hole.	
3	**Hold your *ROTAHALER* horizontally with the moulded line at the top. Turn the blue end back the other way as far as it will go.** This opens the capsule. **Your *ROTAHALER* is now ready for use.**	 Keep your *ROTAHALER* horizontal
How to use your *VENTOLIN ROTAHALER*:		
4	Sit down in a comfortable position. Hold your *ROTAHALER* away from your mouth so you don't blow the powder away. **Breathe out fully.** **Place the mouthpiece (white coloured end) of your *ROTAHALER* in your mouth** between your teeth and lips. **Take one quick, deep breath through the mouthpiece.** Hold this breath for a few seconds or as long as is comfortable. Remove the *ROTAHALER* from your	

	mouth and exhale.	
5	If your doctor has told you to take two capsules, wait about 30 seconds before you take another capsule by repeating steps 2-4 above. At Step 2, when you press the second capsule into the *ROTAHALER*, you will push the shell of the first capsule into the chamber. Pull the 2 halves of the *ROTAHALER* apart and throw away the previously used shell.	

How to clean your *VENTOLIN ROTAHALER*:

Your *ROTAHALER* should be cleaned every 2 weeks. Follow the instructions below to clean your *ROTAHALER*:

6 Pull the two halves apart and throw away the empty *ROTACAPS* shells.

If your *ROTAHALER* needs cleaning: Wash the two halves in warm water and dry thoroughly before reassembling it. Keep your *ROTAHALER* away from excessive heat.

Keep your *ROTAHALER* clean and dry at all times.

Package Quantities and Registration Numbers

Ventolin Rotacaps 200 mcg, box of 1 blister @ 10 rotacaps+Rotahaler-Reg No. xxxxxxxxxxxxxx
Ventolin Rotacaps 200 mcg, box of 10 blisters @ 10 rotacaps+Rotahaler-Reg No. xxxxxxxxxxxxxx
Ventolin Rotacaps 200 mcg, box of 10 blisters @ 10 rotacaps-Reg No. xxxxxxxxxxxxxx
Ventolin Rotacaps 200 mcg, box of 8 blisters @ 16 rotacaps-Reg No. Xxxxxxxxxxxxxx
Ventolin Rotacaps 200 mcg, box of 8 blisters @ 16 rotacaps+Rotahaler Reg No. Xxxxxxxxxxxxxx

HARUS DENGAN RESEP DOKTER

Ventolin Rotacaps
Manufactured by:
GlaxoSmithKline Australia Pty Ltd
Boronia, Australia

Ventolin Rotahaler
Manufactured by:

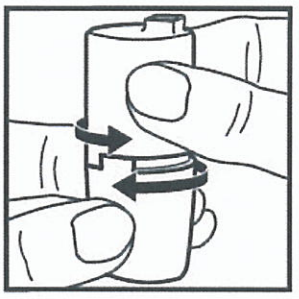
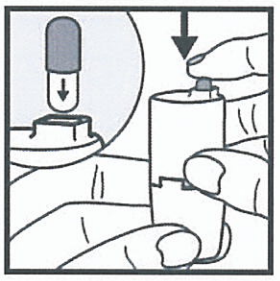
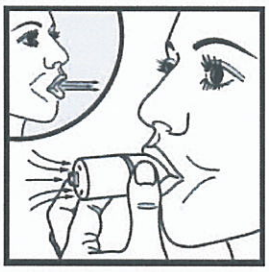
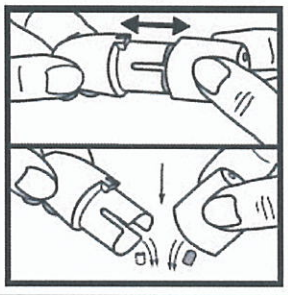
Glaxo Wellcome GmbH & Co.KG
Bad Oldesloe, Germany

Ventolin Rotacaps and Rotahaler
Secondary packed by:
PT. Glaxo Wellcome Indonesia
Jakarta, Indonesia

Imported by:
PT. Glaxo Wellcome Indonesia
Jakarta, Indonesia

PI based on version number : GDS24/IPI02 (21 May 2013)

CARA PAKAI VENTOLIN ROTAHALER

1. Pastikan bagian mulut ROTAHALER bersih, kering dan bebas dari benda apapun. Pegang bagian putih dan putar bagian biru sejauh mungkin.	
2. Masukkan dan tekan kapsul ROTACAPS ke dalam lubang yang menonjol pada bagian belakang Rotahaler yang berwarna biru. Bagian kapsul yang transparan harus masuk terlebih dahulu lalu tekan kapsul ke dalam sampai sejajar dengan bagian atas lubang.	
3. Pegang ROTAHALER horizontal atau mendatar dengan garis cetakan menghadap ke atas. Putar bagian biru sejauh mungkin. Gerakan ini akan membuka kapsul di dalam ROTAHALER. Pastikan posisi ROTAHALER tetap horizontal.	
4. Pegang ROTAHALER menjauh dari mulut. Buang napas. Letakkan bagian ujung PUTIH ROTAHALER di mulut antara gigi dan bibir. Lakukan 1 tarikan napas dengan cepat dan dalam melalui bagian mulut alat. Tahan napas sebisa mungkin sekurang-kurangnya beberapa detik. Keluarkan ROTAHALER dari mulut dan buang napas.	
5. Tarik kedua bagian ROTAHALER sehingga terbuka dan buang kapsul keluar. Pastikan kedua bagian kapsul telah dikeluarkan sebelum menggunakan ROTAHALER kembali. Bila dokter menyarankan untuk memakai 2 kapsul, tunggu sekitar 30 detik sebelum memakai kapsul selanjutnya dengan mengulang langkah 2-4 diatas.	

CARA membersihkan VENTOLIN ROTAHALER

Pastikan ROTAHALER selalu bersih dan kering dan jauhkan dari panas berlebih.

Bersihkan ROTAHALER setiap 2 minggu.

- Tarik dua bagian sehingga terbuka dan buang keluar kapsul ROTACAP yang telah kosong.
- Bersihkan kedua bagian di air hangat dan keringkan sebelum memasangkannya kembali.

Ventolin Rotacaps
Diproduksi oleh:
GlaxoSmithKline Australia Pty Ltd
Boronia, Australia

Ventolin Rotahaler
Diproduksi oleh:
Glaxo Wellcome GmbH & Co.KG
Bad Oldesloe, Germany

Ventolin Rotacaps and Rotahaler
Dikemas sekunder oleh:
PT. Glaxo Wellcome Indonesia
Jakarta, Indonesia

Diimpor oleh:
PT. Glaxo Wellcome Indonesia
Jakarta, Indonesia