

Ventolin™ Syrup **Ventolin™ Tablets 2 mg**

1. Name of the Medicinal Product

Ventolin Syrup

Ventolin Tablets 2 mg

2. Qualitative and Quantitative Composition

Ventolin Syrup: Each 5 ml contains 2 mg Salbutamol (as Sulfate).

Excipient with known effect: Sodium

Ventolin Tablets 2 mg: Each tablet contains 2 mg Salbutamol (as Sulfate).

For the full list of excipients, see section 6.1

3. Pharmaceutical Form

Ventolin Syrup: Syrup

Ventolin Tablets 2 mg: Tablets

Clinical Particulars

4.1 Therapeutic Indications

Ventolin Syrup and Ventolin Tablets are indicated for the relief of bronchospasm in bronchial asthma of all types, chronic bronchitis and emphysema.

4.2 Posology and Method of Administration

Route of administration: oral

Ventolin syrup and Ventolin Tablets are suitable oral therapy for children and adults who are unable to use an inhaler device.

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 values below

60% predicted at baseline with greater than 30% variability, usually not returning entirely to normal after a bronchodilator. These patients will require a 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.

Adults

Ventolin Syrup:

The minimum starting dose is 2 mg three times a day given as 5 ml syrup. The usual effective dose is 4 mg (10 ml syrup) three or four times a day, which may be increased to a maximum of 8 mg (20 ml syrup) three or four times a day if adequate bronchodilation is not obtained.

Ventolin Tablets:

The minimum starting dose is 2 mg three times a day given as 1 tablet. The usual effective dose is 4 mg (2 tablets) three or four times a day, which may be increased to a maximum of 8 mg (4 tablets) three or four times a day if adequate bronchodilation is not obtained.

Elderly

In elderly patients or in those known to be unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with the minimum starting dose.

Paediatric Population

Ventolin Syrup:

2 - 6 years: the minimum starting dose is 1 mg as 2.5 ml of syrup three times daily. This may be increased to 2 mg as 5 ml of syrup three or four times daily.

6 - 12 years: the minimum starting dose is 2 mg as 5 ml syrup three times daily. This may be increased to four times daily.

Over 12 years: the minimum starting dose is 2 mg three times daily given as 5 ml syrup. This may be increased to 4 mg as 10 ml syrup three or four times daily.

Ventolin is well tolerated by children so that, if necessary, these doses may be cautiously increased to the maximum dose.

For lower doses the syrup may be diluted with freshly prepared purified water.

Ventolin Tablets:

6 - 12 years: the minimum starting dose is 2 mg (1 tablet) three times daily. This may be increased to four times daily.

Over 12 years: the minimum starting dose is 2 mg (1 tablet) three times daily. This may be increased to 4 mg (2 tablets) three or four times daily.

4.3 Contra-indications

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

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

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 Ventolin syrup or tablets becomes less effective.

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

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

Increasing use of bronchodilators in particular short-acting inhaled beta₂-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.

Patients should be warned that if either the usual relief with Ventolin oral preparations is diminished or the usual duration of action reduced, they should not increase the dose or its frequency of administration, but should seek medical advice.

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 and diuretics. 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.

Ventolin Syrup:

Ventolin Syrup contains 5.6 mg sodium in each 5 ml of syrup. This should be taken into consideration by patients on a controlled sodium diet. Ventolin syrup is sugar free.

Ventolin Tablets:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with other medicinal products and other forms of interaction

Ventolin syrup or tablets and non-selective beta-blocking drugs, such as propranolol, should not usually be prescribed together.

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.

Breast-feeding

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 known.

4.8 Undesirable Effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ 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

Very rare: Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse.

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.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form

(<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>) or by email (adr@moh.health.gov.il). Additionally, you should also report to GSK Israel (il.safety@gsk.com).

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.

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.

Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Selective beta-2-adrenoreceptor agonists
ATC Code: R03CC02

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.

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. 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%.

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, 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.

Pharmaceutical Particulars

6.1 List of Excipients

Ventolin Syrup:

Citric acid monohydrate
Hydroxypropyl methylcellulose 2910
Sodium benzoate
Sodium citrate
Sodium chloride
Saccharin sodium
Orange flavour IFF 17.42.8187
Purified water

Ventolin Tablets:

Lactose Monohydrate
Maize Starch
Starch Pregelatinised
Magnesium Stearate
Purified Water

6.2 Incompatibilities

Ventolin syrup is sugar free. Dilution of Ventolin syrup with syrup BP or sorbitol solution is not recommended as this may result in the precipitation of the cellulose thickening agent. If dilution is required freshly prepared Purified Water should be used. The diluted mixture must be protected from light and stored below 25°C.

6.3 Shelf Life

The expiry date of the product is indicated on the label and packaging.

6.4 Special Precautions for Storage

Ventolin Syrup and Tablets:

Store below 30°C.

Ventolin Syrup: Protect from light.

Ventolin syrup may be diluted with freshly Purified Water. The diluted mixture must be protected from light and stored below 25°C. Discard after 28 days.

6.5 Nature and Contents of Container

Ventolin Syrup:

Amber glass bottle. Closure: ROPP aluminium. Pack size: 150 ml.

Ventolin Tablets:

Ventolin Tablets are supplied in double-foil blisters packs of 100, 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ventolin Syrup:

Ventolin syrup may be diluted with Purified Water BP (50% v/v). The resulting mixture should be protected from light and used within 28 days. A 50% v/v dilution of Ventolin syrup has been shown to be adequately preserved against microbial contamination. However, to avoid the possibility of introducing excessive microbial contamination, the Purified Water used for dilution should be recently prepared or alternatively it should be boiled and cooled immediately before use.

Admixture of Ventolin syrup with other liquid preparation is not recommended.

7. Manufacturer

Ventolin Syrup: Farmaclair, Herouville-Saint-Clair, France.

Ventolin Tablets: Aspen Bad Oldesloe GmbH, Bad Oldesloe, Germany.

8. License Holder and Importer

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. License Number

Ventolin Syrup: 050-54-24044

Ventolin Tablets: 050-78-24043

Ven Syr-Tab DR v3