Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ventolin 500 micrograms/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 500 micrograms salbutamol as salbutamol sulphate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. (Injection)
A colourless to pale straw coloured sterile aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ventolin Injection is indicated in adults and adolescents (children aged 12 years and over).

Ventolin Injection should be administered under the direction of a physician. It is indicated for two distinct clinical situations:
1. For the management of severe bronchospasm. It provides short acting bronchodilation in reversible airways obstruction due to asthma and chronic obstructive pulmonary disease (COPD) such as chronic bronchitis and emphysema.
2. For the short-term management of uncomplicated premature labour. To arrest labour between 22 and 37 weeks of gestation in patients with no medical or obstetric contraindication to tocolytic therapy.

4.2 Posology and method of administration

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

Ventolin parenteral preparations are to be used under direction of a physician.

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 parenteral preparations should not be administered in the same syringe or infusion as any other medication.

Adults and Adolescents (children aged 12 years and over):-
In bronchospasm and status asthmaticus:

Subcutaneous Route:- 500 micrograms (8 mcg/kg bodyweight) and repeated every four hours as required.

Intramuscular Route:- 500 micrograms (8 mcg/kg bodyweight) and repeated every four hours as required.

Intravenous Route:- 250 micrograms (4 mcg/kg bodyweight) injected slowly. If necessary the dose may be repeated. A solution of 250 micrograms in 5ml is ordinarily used.

In the short term management of uncomplicated premature labour.
Treatment with Ventolin Injection should only be initiated by obstetricians/physicians experienced in the use of tocolytic agents. It should be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetus health status.

Duration of treatment should not exceed 48 hours as data show that the main effect of tocolytic therapy is a delay in delivery of up to 48 hours; no statistically significant effect on perinatal mortality or morbidity has been observed in randomised, controlled trials. This short term delay may be used to administer glucocorticoids or to implement other measures known to improve perinatal health.

Ventolin Injection should be administered as early as possible after the diagnosis of premature labour, and after evaluation of the patient to eliminate any contra-indications to the use of salbutamol (see section 4.3). This should include an adequate assessment of the patient's cardiovascular status with supervision of cardiorespiratory function and ECG monitoring throughout treatment (see section 4.4).

Ventolin Injection may be administered as a single injection by the intravenous route. The usual recommended dose is 100 to 250 micrograms of salbutamol.

Special cautions for infusion: The dose must be individually titrated. Careful attention should be given to cardio-respiratory function, including increases in pulse rate and changes in blood pressure, electrolytes, glucose and lactate levels and fluid balance monitoring. These parameters should be carefully monitored during treatment. A maximum maternal heart rate of 120 beats per min should not be exceeded.

Careful control of the level of hydration is essential to avoid the risk of maternal pulmonary oedema (see section 4.4). The volume of fluid in which the drug is administered should thus be kept to a minimum. A controlled infusion device should be used, preferably a syringe pump.

Treatment should be discontinued should signs of pulmonary oedema or myocardial ischaemiadevelop. (see section 4.4 and section 4.8)

Paediatric Population:
The safety and efficacy of Ventolin Injection in children under the age of 12 years has not been established. From the available data no recommendation on posology can be made.

4.3 Contraindications

Ventolin parenteral preparations are contraindicated in patients with a history of hypersensitivity to any of their components.

Ventolin Injectionis contra-indicated in the following conditions:

- Any condition at a gestational age < 22 weeks
- as a tocolytic agent in patients with pre-existing ischaemic heart disease or those patients with significant risk factors for ischaemic heart disease
- threatened abortion during the 1st and 2nd trimester
- any condition of the mother or foetus in which prolongation of the pregnancy is hazardous, e.g. severe toxaemia, intrauterine infection, vaginal bleeding resulting from placenta praevia, eclampsia or severe preeclampsia, placental abruption, or cord compression.
- intrauterine foetal death, known lethal congenital or lethal chromosomal malformation.

Ventolin Injection is also contraindicated in any pre-existing medical conditions with which a beta-mimetic would have an untoward effect e.g., pulmonary hypertension and cardiac disorders such as hypertrophic obstructive cardiomyopathy or any type of obstruction of the left ventricular outflow tract, e.g. aortic stenosis.

4.4 Special warnings and precautions for use

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

Bronchodilators should not be the only or main treatment in patients with persistent asthma. In patients with persistent asthma unresponsive to salbutamol, treatment with inhaled corticosteroids is recommended to achieve and maintain control. Failing to respond to treatment with salbutamol may signal a need for urgent medical advice or treatment.

Increasing use of short-acting inhaled beta-2 agonists to control 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.

The use of Ventolin parenteral preparations in the treatment of severe bronchospasm or status asthmaticus does not obviate the requirement for glucocorticoid steroid therapy as appropriate.

When practicable, administration of oxygen concurrently with parenteral Ventolin is recommended particularly when it is given by intravenous infusion to hypoxic patients.

In common with other beta-adrenoceptor agonists, Ventolin can induce reversible metabolic changes such as reversible hypokalaemia and increased blood glucose levels. The diabetic patient may be unable to compensate for this and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

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.

Diabetic patients and those concurrently receiving corticosteroids should be monitored frequently during intravenous infusion of Ventolin so that remedial steps (e.g. an increase in insulin dosage) can be taken to counter any metabolic change occurring. For these patients Ventolin Solution for Intravenous Infusion should be diluted with Sodium Chloride Injection BP, rather than Sodium Chloride and Dextrose Injection BP.

Lactic acidosis has been reported very rarely in association with high therapeutic doses of intravenous and nebulised short-acting beta-agonist therapy, mainly in patients being treated for an acute asthma exacerbation (see section 4.8). Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting beta-agonist treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

Salbutamol causes peripheral vasodilation which may result in reflex tachycardia and increased cardiac output. Caution should be used in patients with angina , severe tachycardia or thyrotoxicosis.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of myocardial ischaemia associated with salbutamol.

Tocolysis

Any decision to initiate therapy with Ventolin Injection should be undertaken after careful consideration of the risks and benefits of treatment. In the treatment of premature labour, before salbutamol parenteral preparations are given to any patient with known or suspected heart disease, an adequate assessment of the patient's cardiovascular status should be made by a physician experienced in cardiology.

Treatment should only be carried out in facilities adequately equipped to perform continuous monitoring of maternal and foetal health status. Tocolysis with salbutamol parenteral preparations is not recommended when membranes have ruptured or the cervix dilation is beyond 4 cm.

Ventolin Injection should be used with caution in *tocolysis* and supervision of cardiorespiratory function and ECG monitoring, should be performed throughout treatment.

The following monitoring measures must be constantly applied to the mother and, when feasible/appropriate, to the foetus:

- blood pressure and heart rate
- ECG
- electrolyte and fluid balance – to monitor for pulmonary oedema
- glucose and lactate levels – with particular regard to diabetic patients
- potassium levels– beta-agonists are associated with a decrease in serum potassium which increases the risk of arrhythmias (see section 4.5) Treatment should be discontinued if signs of myocardial ischaemia (such as chest pain or ECG changes) develop. Ventolin Injection should not be used as a tocolytic agent in patients with significant risk factors for, or a suspicion of any kind of pre-existing heart disease (e.g. tachyarrhythmias, heart failure, or valvular heart disease; see section 4.3). *Pulmonary oedema*As maternal pulmonary oedema and

myocardial ischaemia have been reported during or following treatment of premature labour with beta-2 agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG, should be monitored. Patients with predisposing factors including multiple pregnancies, fluid overload, maternal infection and pre-eclampsia may have an increased risk of developing pulmonary oedema. Administration with a syringe pump as opposed to i.v. infusion will limit risk of fluid overload. If signs of pulmonary oedema or myocardial ischaemia develop, discontinuation of treatment should be considered (see section 4.2 and 4.8). *Blood pressure and heart rate*In the treatment of premature labour by i.v. infusion of salbutamol increases in maternal heart rate of the order 20 to 50 beats per minute usually accompany the infusion. The maternal pulse rate should be monitored and the need to control such increases by dose reduction or drug withdrawal should be evaluated on a case by case basis. Generally maternal pulse rate should not be allowed to exceed a steady rate of 120 beats per minute. The effect of infusion on foetal heart rate is less marked, but increases of up to 20 beats per minute may occur. Maternal blood pressure may fall slightly during the infusion; the effect being greater on diastolic than on systolic pressure. Falls in diastolic pressure are usually within the range of 10 to 20mmHg. In order to minimise the risk of hypotension associated with tocolytic therapy, special care should be taken to avoid caval compression by keeping the patient in the left or right lateral positions throughout the infusion. *Diabetes*Administration of beta agonists is associated with a rise of blood glucose. Therefore blood glucose and lactate levels should be monitored in mothers with diabetes and diabetic treatment adjusted accordingly to meet the needs of the diabetic mother during tocolysis (see section 4.5). *Hyperthyroidism*Ventolin Injection should only be administered cautiously to patients suffering from thyrotoxicosis after careful evaluation of the benefits and risks of treatment. *Respiratory indications*Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol for respiratory disease, 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. This medicine contains less than 1 mmol sodium (23 mg) per 5ml ampoule, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

Salbutamol is not contra-indicated in patients under treatment with monoamine oxidase inhibitors (MAOIs), however the effects of salbutamol may be altered by guanethidine, reserpine, methyldopa and tricyclic antidepressants.

The use of the drug will inhibit the effects of oxytocic drugs.

Salbutamol will inhibit the effects of non-selective beta-adrenoceptor blockers.

Halogenated anaesthetics
Owing to the additional antihypertensive effect, there is increased uterine inertia with risk of haemorrhage; in addition, serious ventricular rhythm disorders due to increased cardiac reactivity, have been reported on interaction with halogenated anaesthetics. Treatment should be discontinued, whenever possible, at least 6 hours before any scheduled anaesthesia with halogenated anaesthetics.

Corticosteroids
Systemic corticosteroids are frequently given during premature labour to enhance foetal lung development. There have been reports of pulmonary oedema in women concomitantly administered with beta-agonists and corticosteroids. Corticosteroids are known to increase blood glucose and can deplete serum potassium, therefore concomitant administration should be undertaken with caution with continuous patient monitoring owing to the increased risk of hyperglycaemia and hypokalaemia (see section 4.4).

Anti-diabetics
The administration of beta-agonists is associated with a rise of blood glucose, which can be interpreted as an attenuation of anti-diabetic therapy; therefore individual anti-diabetic therapy may need to be adjusted (see section 4.4).

Potassium depleting agents
Owing to the hypokalaemic effect of beta-agonists, concurrent administration of serum potassium depleting agents known to exacerbate the risk of hypokalaemia, such as diuretics, digoxin, methyl xanthines and corticosteroids, should be administered cautiously after careful evaluation of the benefits and risks with special regard to the increased risk of cardiac arrhythmias arising as a result of hypokalaemia (see section 4.4).

4.6 Fertility, 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.

Salbutamol has been in widespread use for many years in human beings without apparent ill consequence; this indicates its well established use in the management of premature labour. However, 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.

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. Because no consistent pattern of defects can be discerned, and baseline rate for congenital anomalies is 2-3%, a relationship with salbutamol use cannot be established.

Breast-feeding
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.

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 reactions 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 reactions were generally determined from clinical trial data. Rare and very rare reactions were generally determined from spontaneous data.

The most common undesirable effects of Ventolin Injectionare correlated with the betamimetic pharmacological activity and may be limited or avoided by a close monitoring of hemodynamic parameters, such as blood pressure and heart rate, and an appropriate adjustment of the dose. They normally recede upon therapy discontinuation.

Unless otherwise indicated the following undesirable effects have been reported for Ventolin Injection in the management of severe bronchospasm associated with asthma or bronchitis and for the treatment of status asthmaticus.

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

Metabolism and nutrition disorders
Common **Hypokalaemia.
Potentially serious hypokalaemia may result from beta-2 agonist therapy.
Rare: *Hyperglycaemia.
Very rare Lactic acidosis
Lactic acidosis has been reported very rarely in patients receiving intravenous and nebulised salbutamol therapy for the treatment of acute asthma exacerbation.

Nervous system disorders
Very common: Tremor.
Common: Headache.
Very rare: Hyperactivity.

Cardiac disorders

Very common: **Tachycardia, **palpitations.
Common *Decrease in diastolic pressure.
Uncommon ***Myocardial ischaemia (see section 4.4)
Rare: **Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles

Vascular disorders:

Common: *Hypotension (see section 4.4)
Rare: **Peripheral vasodilatation.

Respiratory, thoracic and mediastinal disorders:

Uncommon: *Pulmonary oedema.
In the management of pre-term labour, salbutamol injection/solution for infusion have uncommonly been associated with pulmonary oedema. Patients with predisposing factors including multiple pregnancies, fluid overload, maternal infection and pre-eclampsia may have an increased risk of developing pulmonary oedema.

Gastrointestinal disorders

Very rare: Nausea, vomiting.
In the management of premature labour, intravenous infusion of salbutamol has very rarely been associated with nausea and vomiting.

Musculoskeletal and connective tissue disorders

Common: Muscle cramps.

Injury, poisoning and procedural complications

Very rare: Slight pain or stinging on i.m. use of undiluted injection.

* These reactions have been reported in association with the use of short acting beta-agonists in obstetric indications and are considered class effects (see section 4.4)

**** These reactions have been reported for Ventolin Injection in the management of severe bronchospasm associated with asthma or bronchitis and for the treatment of status asthmaticus, and for short acting beta-agonists used in obstetric indications.

*** Myocardial ischaemia has been reported uncommonly with salbutamol injection/solution for infusion in the management of pre-term labour, rarely in association with the use of short acting beta-agonists in obstetric indications, and 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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient beta agonist pharmacologically mediated events (see Special Warnings and Precautions for Use and Undesirable Effects).

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.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective beta-2adrenoceptor agonist
ATC code: R03A C02

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 hour) 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%.

5.3 Preclinical 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 2.5mg/kg, 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 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 50mg/kg/day, 78 times the maximum human oral dose.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of salbutamol up to 50 mg/kg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Dilute Sulphuric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Unopened: 48 months
Once opened: Use immediately. Discard any unused contents.

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C.

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C.
Keep the ampoules in the outer carton to protect from light.

6.5 Nature and contents of container

Ventolin Injection is presented in a 1 ml, clear, neutral Type I, glass ampoule and is available in boxes of 5 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The following infusion fluids are compatible with Ventolin Solution for Injection 0.5mg/ml:

5% w/v Dextrose Injection BP
0.9% w/v Sodium Chloride Injection BP
0.18% Sodium Chloride and
4% w/v Dextrose Intravenous Infusion BP

Chemical and physical in-use stability has been demonstrated for 24 hours at 20-25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

For single use only. Discard any unused contents.

To open the ampoule:
- Flick down any liquid in the ampoule neck.
- Hold ampoule upright.
- Break off the top tag in one quick turn.
- Attach syringe direct to ampoule or insert syringe.
- Withdraw contents using firm consistent pressure.

7 MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1077/049/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 10 November 1975

Date of last renewal: 5 August 2008

10 DATE OF REVISION OF THE TEXT

March 2024