CTD MODULE 1 ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION	
Product Name :	**ASTHAREN TABLETS (Salbutamol sulphate 4mg)**

1.5 Product Information: ASTHAREN TEBLETS

1.5.1 Prescribing information (Summary of products characteristics):

1.6 1. Name of the Medicinal Product: ASTHAREN TEBLETS

Strength: Each tablet contains Salbutamol sulphate BP 4.0 mg
Pharmaceutical form: Oral Tablets

2. Qualitative and Quantitative composition:

Qualitative composition and Quantitative composition:

Component and quality standard (and grade, if applicable)	**Function**	**Strength (label claim)**			
		Each tablet contains Salbutamol sulphate BP 4.0 mg			
		Quantity in mg per tablet	**%**	**Quantity in Kg per 1,000,000 tablets**	**%**
Contents of **ASTHAREN TABLETS**					
Salbutamol sulphate	Active	4.820	2.61	4.820	2.61
Maize starch (mixing)	Diluent	80.805	43.68	80.805	43.68
Lactose anhydrous	Diluent	90.000	48.65	90.000	48.65
Maize starch (paste)	Bindar	8.000	4.32	8.000	4.32
Ponceau 4R supra colour	Colouring agent	0.200	0.11	0.200	0.11
Sodium methyl paraben	Preservative	0.250	0.13	0.250	0.13
Sodium propyl paraben	Preservative	0.125	0.07	0.125	0.07
Magnesium stearate	Lubricant	0.800	0.43	0.800	0.43
Total	NA	185.00	100.00	185.00	100.00

3. Pharmaceutical form: Oral Tablets

4. Clinical particular's:

4.1 Therapeutic indication:

Salbutamol Tablets are indicated in adults, adolescents and children aged 2 to 12 years.
1. For the relief of bronchospasm in bronchial asthmas of all types.
2. Chronic bronchitis.
3. Emphysema.

4.2 Posology and method of administration:

Posology
Adults:
The usual effective dose is 4mg three or four times per day. If adequate bronchodilation is not obtained each single dose may be gradually increased to as much as 8mg. However, it has been established that some patients obtain adequate relief with 2mg three or four times daily. In elderly patients or in those known to be unusually sensitive to beta-adrenergic stimulant drugs, it is advisable to initiate treatment with 2mg three or four times per day.
Children:
The following doses should be administered three or four times daily.
2-6 years: 1-2mg
6-12 years: 2mg
Over 12 years: 2-4mg
The product is not recommended for children under 2 years of age. The drug is well tolerated by children so that, if necessary, these doses may be cautiously increased.

Method of Administration: Oral route.

4.3 Contraindication:

Hypersensitivity to the active substance or any of the excipients.
Non-i.v. formulations of salbutamol must not be used to arrest uncomplicated premature labour or threatened abortion.

4.4 Special warning and precaution 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 salbutamol tablets becomes less effective. The dosage or frequency of administration should only be increased on medical advice.

Patients taking salbutamol 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 (e.g. 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 salbutamol tablets 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 nebulized administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives and steroids. 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.

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

Salbutamol tablets contain carmoisine (E122) which may cause allergic reactions.

4.5 Interactions with other medicinal products and other forms of interactions:

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

The effects of salbutamol may be altered by tricyclic antidepressants (e.g. clomipramine) and monoamine oxidase inhibitors (e.g. rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine).

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 (e.g. bendroflumethiazide, indapamide, bumetanide, furosemide), digoxin, methyl xanthines (e.g. aminophylline, theophylline) and corticosteroids (e.g. betamethasone, prednisolone, triamcinolone), 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.

There is an increased risk of hypokalaemia if high doses of theophylline or high doses of corticosteroids are given with higher doses of salbutamol.

Additional information on special populations:

Not Applicable

Pediatric population:

Not Applicable

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.

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.

4.7 Effects on ability to drive and use machines:

Not known.

4.8 Undesirable effects:

The frequencies of adverse reactions are ranked according to the following MedDRA convention: Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000); Not known (cannot be estimated from the available data).

System organ class	Common	Uncommon	Rare	Very rare	Not known
Immune system disorders				Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse	
Metabolism and nutrition disorders	Hypokalaemia (with high doses)	Hyperglycaemia			Lactic acidosis Metabolic change
Nervous system disorders	Tremor Headache Dizziness			Hyperactivity	
Cardiac disorders	Cardiac arrhythmias* Tachycardia Palpitations	Myocardial ischemia		Peripheral vasodilation	
Respiratory, thoracic and mediastinal disorders		Pulmonary oedema			
Gastrointestinal disorders	Nausea				Vomiting
Musculoskeletal and connective tissue disorders	Muscle cramps			Akathisia	Feeling of muscle tension

* including atrial fibrillation, supraventricular tachycardia and extrasystoles.

4.9 Overdose and Treatment:

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.

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.

5. Pharmacological Properties:

5.1 Pharmacodynamic properties:

Salbutamol is a selective beta-2-adrenergic 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:

Absorption

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%.

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-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-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 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 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.
Reproductive studies in the rabbit at doses of 50mg/kg/day orally (i.e. much higher than the normal human dose) have shown foetuses 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.

6. Pharmaceutical Particulars:

6.1 List of excipients

Astharen tablets contains the following excipients:
Maize starch, Lactose anhydrous, Ponceau 4R supra colour, Sodium methyl paraben, Sodium propyl paraben, Magnesium stearate.

6.2 Incompatibilities

None known

6.3 Shelf life

24 Months

6.4 Special precaution for storage

Store under normal storage conditions (15°C - 30°C). Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

Aluminium/ transparent PVC blister of 10 tablet and 10 of such blister is packed in a unit box with pack insert.

6.6 Special precautions for disposal

No special precaution

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES:

Marketing Authorization Holder:
Rene Industries Ltd
Address: PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

Manufactured by:
Rene Industries Ltd
Address: PO Box 6034, Plot No.680, Kamuli, Kireka, Kampala, Uganda.

8. MARKETING AUTHORISATION NUMBER:

Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION:

Not Applicable

10. DATE OF REVISION OF THE TEXT:

Not Applicable

11. DOSIMETRY (IF APPLICABLE):

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

Not Applicable