1. Name of the medicinal product

Salbutamol and Theophylline Tablets (Jopamol-F Tablets)

2. Qualitative and quantitative composition

Each Uncoated tablet contains:
Theophylline (Anhydrous) BP……………100 mg
Salbutamol Sulphate BP
Equivalent to Salbutamol ………..2 mg
Excipients………………….qs.
Approved colour used

3. Pharmaceutical form

Solid Dosage Form

4. Clinical particulars

4.1 Therapeutic indications

Salbutamol and Theophylline 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

For oral use.

4.3 Contraindications

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 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 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.

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 bronchodilators in particular short-acting inhaled $beta_2$-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, 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.

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

Salbutamol and Theophylline Tablets contain carmoisine (E122) which may cause allergic reactions.

This medicine contains less than 1 mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction
Salbutamol and Theophylline Tablets are 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.

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
None 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.

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..

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

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
Pharmacotherapeutic group: Selective beta-2-adrenoreceptor agonists, ATC code: R03CC02

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
The tablets also contain: maize starch, lactose monohydrate, dispersed pink (erythrosine (E127), carmoisine (E122), titanium dioxide (E171)), sodium starch glycollate, talc, magnesium stearate.

6.2 Incompatibilities
None known.

6.3 Shelf life
4 years

6.4 Special precautions for storage
Store below 25°C in a dry place.

6.5 Nature and contents of container

Polypropylene tubes with low density polyethylene caps. Packing material: high density polyethylene film.

28s, 30s, 56s, 60s, 84s, 100s, 250s, 500s, 1000s

Polyethylene container with a polypropylene lid.

28s

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.