1. NAME OF THE MEDICINAL PRODUCT

THEO-VENTOKRIS TABLETS (SALBUTAMOL & THEOPHYLLINE TABLETS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Salbutamol Sulphate BP eq. to Salbutamol 2mg. Theophylline (Anhydrous) BP 120mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White, circular, flat, uncoated tablet plain on one side and break-line on other side of each tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Theoventokris is particularly indicated for patients who experience side effects with maximal therapeutic doses of either Theophylline or Salbutamol alone and patients with severe asthma who require more than one drug from any class of bronchodilators.

4.2 Posology and method of administration

Posology

Optimum dosage must be individualised due to variability of Theophylline pharmacokinetics with age, diet, smoking, cardiac failure and liver disease.
The usual starting dose is one tablet of Theoventokris thrice daily. In select patients, if further bronchodilation is required, dosage may be increased to one tablet of Theoventokris thrice daily.

Method of administration

For Oral use.

The tablets should be swallowed and not chewed.

4.3 Contraindications

Theoventokris is contraindicated for Hypersensitivity to xanthine derivatives.

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 Theoventokris tablets becomes less effective. The dosage or frequency of administration should only be increased on medical advice.

Patients taking Theoventokris 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 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 Theoventokris 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 is chaemia 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.

4.5 Interaction with other medicinal products and other forms of interaction

Sympathomimetic agents: Concomitant use is not recommended since such use may lead to deleterious cardiovascular effects.
Monoamine oxidase inhibitors: Salbutamol should be used with caution in patients being treated with these drugs, since the action of salbutamol on the vascular system may be potentiated.
Beta-blockers and salbutamol inhibit the effect of each other. Propranolol increases serum theophylline levels.
Cimetidine, erythromycin, oral contraceptive steroids, and ciprofloxacin increase serum theophylline levels.
Carbamazepine, phenobarbital and rifampin decrease levels of theophylline.

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.

Breastfeeding
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 tablets on human fertility.

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		Pulmonary oedema			

disorders					
Gastroin testinal disorders	Nausea				Vomiting
Musculo skeletal and connecti ve tissue disorder s	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

Symptoms

Manifestations of overdosage include anginal pain, hypertension, hypokalemia, and exaggeration of the pharmacological effects.

The oral Ld 50 in rats and mice was greater than 2,000 mg/kg.

There is insufficient evidence to determine if dialysis is beneficial for overdosage of tablets.

Management

Administration of activated charcoal may be of value. Monitor for adverse reactions, with symptomatic treatment and hospitalisation if necessary.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Beta-adrenoceptor agonist, ATC code:
Salbutamol: R03AC02 Theophylline: R03DA04

Mechanism of action

Salbutamol

Stimulates 2 adrenergic receptors to produce sympathomimetic actions in smooth muscles.

Theophylline

Directly relaxes bronchial smooth muscles and pulmonary blood vessels. Causes increase in intracellular cAMP through inhibition of phosphodiesterase. Prostaglandin antagonism, stimulation of endogenous catecholamines and cGMP inhibition.

5.2 Pharmacokinetic properties

Salbutamol

Salbutamol is rapidly and well absorbed following oral administration. In studies involving normal volunteers, the mean steady-state peak and trough plasma levels of Salbutamol were 6.7 and 3.8 ng/mL, respectively, following dosing with a 2 mg Salbutamol Tablet every 6 hours and 14.8 and 8.6 ng/mL, respectively, following dosing with a 4 mg Salbutamol Tablet every 6 hours. Maximum

Salbutamol plasma levels are usually obtained between 2 and 3 hours after dosing and the elimination half-life is 5 to 6 hours. These data indicate that Salbutamol, administered orally, is dose proportional and exhibits dose independent pharmacokinetics.

Salbutamol Tablets have been formulated to provide a duration of action of up to 12 hours. In studies conducted in normal adult volunteers, the mean steady-state peak and trough plasma levels of Salbutamol were 6.5 and 3.0 ng/mL, respectively, following dosing with a 4 mg Salbutamol Tablet every 12 hours. In addition, it has been shown that administration of a 4 mg Salbutamol Tablet every 12 hours, and a 2 mg Salbutamol Tablet every 6 hours for 5 days gave comparable peak Salbutamol levels and similar extent of absorption at steady state.

In other studies, the analysis of urine samples of subjects given tritiated Salbutamol (4 to 10 mg) orally showed that 65% to 90% of the dose was excreted over 3 days, with the majority of the dose being excreted within the first 24 hours. Sixty percent of this radioactivity was shown to be the metabolite of Salbutamol. Feces collected over this period contained 4% of the administered dose.

Theophylline

Theophylline and choline theophyllinate are well absorbed from the gastrointestinal tract. Peak levels occur 1 – 2 h following administration of oral liquid preparation. The time to peak increase with increased dose. Food decreases the rate but not the completeness of absorption. Theophylline does not undergo first – pass hepatic metabolism. The dissolution rate appears to be rate limiting step for absorption. The systemic bioavailability of good formulations is 90 – 100 %.

Because of the relatively short plasma half-life of Theophylline many sustained release formulations have been developed, which have bioavailability in the range 80 – 100 %. Food reduced the rate but not extent of absorption from most sustained release preparation.

Theophylline is rapidly distributed after intravenous administrat6ion. Following intravenous administration, the plasma Theophylline concentration – over time curve fits a 2 compartment open pharmacokinetic model. The early - distribution phase is rapid and completed within 30 to 45 minutes. Theophylline readily distributes into all body compartments; it crosses the placenta and into breast milk. Theophylline is approximately 60 % (50 – 70) bound to plasma proteins in normal volunteers and otherwise normal asthmatic and COPD patients. The volume of distribution is 0.3 – 0.7 $l.kg^{-1}$ with mean value of 0.5 $l.kg^{-1}$.

The plasma protein binding is decreased in premature newborns (63, patients with hepatic cirrhosis (32 %), academia and the elderly. This results in a corresponding increase in the volume of distribution for Theophylline in these patients. The volume of distribution is decreased (0.3 $l.kg^{-1}$) in obese patients. The cerebral spinal fluid concentrations are approximately 90% of serum concentrations are approximately 60% of the corresponding plasma concentration in children and adults and 93% in premature newborns. Salivary concentrations correlate with but are not identical to free concentrations Theophylline in the plasma. Due to the inter and intrapatients variability in the saliva/plasma concentration ratio, salivary concentrations should not be used for monitoring Theophylline therapy. In children and adults, Theophylline is primarily eliminated by hepatic biotransformation with approximately 10% eliminated unchanged by the kidney. In premature infants the urinary excretion of unchanged Theophylline ranges from 90 % to 50 % depending on the age of the infant and then decreases as the patient grows older. The metabolic pathways are capacity – limited. However, following single doses in humans the renal excretion is initially increased due to diuresis giving an apparent linear elimination curve. Nonlinear pharmacokinetics have been reported in children and adults with steady – state theophylline concentrations within the usual therapeutic concentrations within the usual therapeutic range. Increases in plasma concentration can be up to twice that expected from the dose ratio. Dose – dependent elimination has not been found consistently in all studies due to the considerable inter individual variability in metabolic capacity.

Theophylline elimination kinetics have been extensively studied. The mean elimination half life and ranges have been reported for the following age groups. Premature neonates 30 h (12 – 57) 1 – 6 months 12 h (6.7 – 29) , 6 months – 1 year 5.3 h (2.2 – 10), 1 – 4 years 3.4 h (1.9 – 5.5), 6 – 17 years 3.7 h (1.4 – 7.9) and healthy adults 8.2 h (3.6 – 12.8). There is a wide inter individual variability in plasma theophylline clearance at all ages necessitating the routine monitoring of plasma theophylline concentrations to achieve optimal benefit and prevent toxicity. Upon et al demonstrated that individuals may commonly show fluctuations as large as 30% in theophylline clearance over a few weeks time.

A number if factors are known to affect the hepatic metabolism and thus the clearance of theophylline. A decreased theophylline clearance is associated with liver cirrhosis but not with acute hepatitis or cholestasis. Severe congestive heart failure and corpulmonale may produce a 40 – 70 % reduction in theophylline clearance. Viral infections particularly influenza B virus have been associated with increased steady – state theophylline plasma levels with toxicity. Acute hypoxia may decrease theophylline clearance of theophylline. Renal failure has no discernible effect on theophylline clearance. Theophylline clearance is increased in cigarette and marijuana smokers and by rifampin, sulfinpyrazone, Phenobarbital at full anticonvulsant doses, carbamazepine and phenytoin. Clearance is reduced by cimetidine, propranolol, erythromycin, troleandomycin disuliram, verapamil, diltiazem, enoxacin, ciprofloxacin, pefloxacin, norfloxacin and pipemidic acid.

Oral absorption	90 – 100 %
Presystemic metabolism	Nil
Plasma half – life	
Range	1.4 – 12.8 h
Mean : Adult	8.2 h
Children	3.7 h
Volume of distribution	0.5 $l.kg^{-1}$
Plasma protein binding	60 %

5.3 Preclinical safety data Salbutamol Sulphate:

In controlled clinical trials in patients with asthma, the onset of improvement in pulmonary function, as measured by maximal mid-expiratory flow rate, MMEF, was noted within 30 minutes after a dose of Salbutamol Tablets with peak improvement occurring between 2 and 3 hours. In controlled clinical trials, in which measurements were conducted for 6 hours, significant clinical improvement in pulmonary function (defined as maintaining a 15% or more increase in FEV_1 and a 20% or more increase in MMEF over baseline values) was observed in 60% of patients at 4 hours and in 40% at 6 hours. In other single-dose, controlled clinical trials, clinically significant improvement was observed in at least 40% of the patients at 8 hours with the 4 mg Salbutamol Tablet. No decrease in the effectiveness of Salbutamol Tablets has been reported in patients who received long-term treatment with the drug in uncontrolled studies for periods up to 6 months.

In another controlled clinical study in adult asthmatic patients, it has been demonstrated that the initiation of therapy with either the 4 mg Salbutamol Tablet dosed every 12 hours, or the 2 mg Salbutamol Tablet dosed every 6 hours, achieve therapeutically equivalent effects.

Theophylline

Despite the extensive use of Theophylline preparations in medicine there have been no well-controlled outcome trials. Most published studies are of asses the bronchodilator response.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize Starch, Dibasic Calcium Phosphate, Sodium Starch Glycolate, Methyl Paraben sodium, Propyl Paraben sodium, Magnesium Stearate, PVPK-90, Purified Talc, Colloidal Silicon Dioxide (Aerosil) & Cross Carmelose Sodium.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C, protect from light & moisture.

Keep all medicines out of reach of children.

6.5 Nature and contents of container

The tablets are packed in Alu/PVC blister and inserted in a mono carton. Pack sizes: 10x10 Tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. MANUFACTURER NAME

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