**1. NAME OF THE MEDICINAL PRODUCT**
**THEOPHYLLINE & SALBUTAMOL SULPHATE TABLETS**

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION:**
Each Uncoated Tablet Contains:
Theophylline (Anhydrous) BP 100 mg
Salbutamol Sulphate BP eq. to Salbutamol 2 mg
Excipients.....QS
Approved Colour Used.

Excipients with known effect: Methyl hydroxybenzoate and Propyl hydroxybenzoate

**3. PHARMACEUTICAL FORM:** Uncoated tablet
**Description:** White circular shaped flat uncoated tablet having embossing "TA" on one side & breakline on other side of each tablet.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications:**
**THEOPHYLLINE & SALBUTAMOL SULPHATE TABLETS** are indicated for Emphysema, Chronic bronchitis, Asthma.

**4.2 Posology and method of administration**
Posology
**Adult:** Per tab contains Salbutamol 2 mg and Theophylline 100 mg: 1 or 2 tab 3-4 times daily.
**Child:** Child (under 6 years) Salbutamol (0.5-1mg) + Theophylline (25-50mg) t.i.d/q.i.d. SR (S 4mg + T 300mg) 1 tab b.i.d.

Method of administration
For oral use.
The tablets should be taken during or after a meal. They should be swallowed whole, with a sufficient amount of liquid.

**4.3 Contraindications**
**THEOPHYLLINE & SALBUTAMOL SULPHATE TABLETS** are contraindicated in:
Patients with a history of hypersensitivity to theophylline or other components in the product.

**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 Theophylline & Salbutamol Sulphate Tablets becomes less effective. The dosage or frequency of administration should only be increased on medical advice.
- Use with caution in patients with severe hypertension, or chronic alcoholism.
- Cardiovascular effects may be seen with sympathomimetic drugs. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) 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.

**4.5 Interaction with other medicinal products and other forms of interaction**
- Increased theophylline toxicity with propranolol, cimetidine, erythromycin (7-5 days), quinolone antibiotics. Reduced efficacy with rifampicin, phenobarbitone, phenytoin, carbamazepine, sulfinpyrazone and smoking. Increased risk of hypokalaemia with diuretics.

Potentially fatal: With anaesthetics, pancuronium bromide and sympathomimetics (increased risk of arrythmias).
- The effects of salbutamol may be altered by tricyclic antidepressants (e.g. clomipramine) and monoamine oxidase inhibitors (e.g. rasagiline, selegiline, isocarboxazid, phenelzine, tranylcypromine).

**4.6 Pregnancy and Lactation**
**Pregnancy**
Salbutamol should only be used during pregnancy if it is considered essential by the physician. There are no adequate data from well controlled studies of the use of theophylline in pregnant women. Theophylline has been reported to give rise to teratogenic effects in mice, rats and rabbits. The potential risk for humans is unknown. Theophylline should not be administered during pregnancy unless clearly necessary.

**Lactation**
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.
Theophylline is secreted in breast milk, and may be associated with irritability in the infant, therefore it should only be given to breast feeding women when the anticipated benefits outweigh the risk to the child.

**Fertility**
There have been no studies indicating the effects on fertility.

**4.7 Effects on the ability to drive and use machines**
None Known

**4.8 Undesirable effects**
The common side effects are:
- Upset stomach
- Diarrhoea
- Insomnia
- Seizures
- Skin rash
- Headache, Dizzness
- Tremor
- Palpitations
- Tachycardia
- Arrhythmia
- Nausea, Vomiting
- Heartburn
- Diaphoresis
- Hypokalaemia (high dose).

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

**5. PHARMACOLOGICAL PROPERTIES**
**5.1 Pharmacodynamic properties**
**Salbutamol:**
Pharmacotherapeutic Group: Bronchodilators ATC Code: R03CC02

Salbutamol is a selective Beta-2-adrenergic agonist administered for the symptomatic relief of bronchospasm associated with chronic or acute asthma, bronchitis or other obstructive pulmonary diseases. Because of its relative specificity for $\beta_2$receptors, salbutamol relaxes smooth muscle of the bronchi, uterus and vascular supply to the skeletal muscle, but generally has much less stimulant action on the heart than does isoproterenol which has powerful action on all beta receptors.

**Theophylline:**

Pharmacotherapeutic Group: Bronchodilators ATC Code: M01AB05

Theophylline is a bronchodilator. In addition it affects the function of a number of cells involved in the inflammatory processes associated with asthma and chronic obstructive airways disease. Of most importance may be enhanced suppressor T-lymphocyte activity and reduction of eosinophil and neutrophil function. These actions may contribute to an anti-inflammatory prophylactic activity in asthma and chronic obstructive airways disease.

Theophylline stimulates the myocardium and produces a diminution of venous pressure in congestive heart failure leading to marked increase in cardiac output.

**5.2 Pharmacokinetic properties**

**Salbutamol**

**Absorption:** Salbutamol is readily absorbed from the gastrointestinal tract. Its effects occur within 15 minutes and last for about 14 hours.

**Distribution:** Salbutamol does not cross the blood brain barrier to a significant extent, but it crosses the placental barrier.

**Metabolism:** The peak plasma concentration of salbutamol and its metabolites is 5.1-11.7µg% at 2.5-3 hours after an oral dose of 4mg.

**Elimination:** The drug is excreted in urine in about 24 hours, 50% of the drug being excreted within 4 hours.

**Theophylline**

**Absorption:** Following oral administration, theophylline is efficiently absorbed and is associated with an absolute bioavailability approximating 100%.

**Distribution and protein binding:** Theophylline is distributed through all body compartments; approximately 60% is bound to plasma proteins.

**Metabolism:** Theophylline is metabolised in the liver to 1, 3-dimethyl uric acid and 3-methylxanthine.

**Elimination:** Theophylline and its metabolites are excreted mainly in the urine. Approximately 10% is excreted unchanged. The mean elimination half life associated with **THEOPHYLLINE & SALBUTAMOL SULPHATE TABLETS** is approximately 7 hours.

**Special Population**

**Geriatric:** The clearance of theophylline is decreased by an average of 30% in healthy elderly adults (> 60 yrs) compared to healthy young adults. Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in elderly patients

**Pediatrics:** The clearance of theophylline is very low in neonates. Theophylline clearance reaches maximal values by one year of age, remains relatively constant until about 9 years of age and then slowly decreases by approximately 50% to adult values at about age 16.

**Gender:** Gender differences in theophylline clearance are relatively small and unlikely to be of clinical significance. Significant reduction in theophylline clearance, however, has been reported in women on the 20th day of the menstrual cycle and during the third trimester of pregnancy.

**Race:** Pharmacokinetic differences in theophylline clearance due to race have not been studied.

**Renal Insufficiency:** Only a small fraction, e.g., about 10%, of the administered theophylline dose is excreted unchanged in the urine of children greater than three months of age and adults.

**Hepatic Insufficiency:** Theophylline clearance is decreased by 50% or more in patients with hepatic insufficiency (e.g., cirrhosis, acute hepatitis, cholestasis). Careful attention to dose reduction and frequent monitoring of serum theophylline concentrations are required in patients with reduced hepatic function.

### 5.3 Preclinical safety Data:

**Salbutamol:** 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.

**Theophylline:** Despite the extensive use of Theophylline preparations in medicine there have been no wellcontrolled outcome trials. Most published studies are of asses the bronchodilator response.

## 6. Pharmaceutical particulars

### 6.1 List of excipients

Calcium Hydrogen Phosphate, Maize starch, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Gelatin, Purified Talc, Magnesium Stearate, Sodium Starch Glycolate, Colloidal Anhydrous Silica.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store below 30°C in a dry & dark place.
Keep all medicines out of reach of children.

### 6.5 Nature and contents of container

**Packaging:**
**Primary packing:** 50 Tablets in a HDPE Bottle.
**Secondary packing:** 1 HDPE Bottle is packed in a carton along with leaflet.

### 6.6 Special precautions for disposal and other handling

No special requirements.

## 7. Applicant / Manufacturer

**Applicant**

| | |
|---|---|
| **Name and address** | **Nasajones Industries Limited**<br>No. 31/32 Office Complex, Middle Road by Ado Bayero Square S/G, Kano. |
| **Tel** | -- |
| **Fax** | -- |
| **Email** | -- |

**Manufacturer**

| | |
|---|---|
| **Name and address** | **M/s. IMPULSE PHARMA PVT. LTD.**<br>J-201, J-202/1, MIDC Tarapur, Boisar,<br>Dist. Palghar - 401506, Maharashtra State, India |
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