SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

DR. MEYER'S ASMANOL TABLET

1. Name of the medicinal product

Dr. Meyer's Asmanol Tablet

2. Qualitative and quantitative composition

Each tablet contains:

Salbutamol Base BP	2.00mg
Theophylline BP	60.00mg
Chlorpheniramine Maleate BP	2.00mg

Excipients:

Nipagin (Methyl Paraben)	0.12mg
Nipasol (Propyl Paraben)	0.06mg
Dicalcium Phosphate	100.00mg
Corn Starch (Paste)	8.00mg
Corn Starch (Bulk)	90.00mg
Corn Starch (Lubricant)	10.00mg
Talcum	2.00mg
Magnesium Stearate	2.00mg
Purified Water	q.s.

3. Pharmaceutical form

Tablet

White circular shaped tablet with 'ASMANOL' inscribed on one side and breakline on the other side presented in white HDPE plastic securi container with red press on cap containing 50 tablets with insert

4. Clinical particulars

4.1 Therapeutic indications

Dr. Meyer's Asmanol tablet is indicated for both suppressive and therapeutic use. It is used as a bronchodilator for bronchial asthma and for reversible bronchospasm that may occur in association with bronchitis and emphysema (chronic obstructive pulmonary disease).

4.2 Posology and method of administration

Posology:

Adults:

The average adult dosage of Dr. Meyer's Asmanol is one tablet to be taken 3 times daily, or taken when an asthmatic attack threatens. In severe cases, two tablets to be taken 3 times daily.

One or two tablets taken at the beginning of an asthmatic attack will often abort it.

One tablet taken on retiring helps prevent night attacks.

Children:

6 - 12 years: ½ or 1 tablet to be taken two to three times daily.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to any of the ingredients; porphyria. It is also contra-indicated in patients with hypertension, myocardial insufficiency, and hyperthyroidism.

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 Dr. Meyer's Asmanol tablets becomes less effective.

The dosage or frequency of administration should only be increased on medical advice. Patients taking Dr. Meyer's Asmanol 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 Dr. Meyer's Asmanol 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

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.

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 tablets on human fertility.

4.7 Effects on ability to drive and use machines

The anticholinergic properties of chlorphenamine may cause drowsiness, dizziness, blurred vision and psychomotor impairment in some patients which may seriously affect ability to drive and use machinery.

4.8 Undesirable effects

Side-effects of Dr. Meyer's Asmanol have generally been mild and self-limited, requiring no treatment. The most common have been minor epigastric distress, palpitation, tremulousness, insomnia, difficulty in micturition, and CNS stimulation.

Dr. Meyer's Asmanol may cause fine tremor of skeletal muscle (particularly the hands), Palpitations, tachycardia, nervous tension, headache peripheral vasolidation, and rarely muscle cramps.

Potentially serious hypokalaemia has been reported after large doses, hypertensivity reactions have occurred including paradoxical bronchospasm angioedema, urticarial, hypotension and collapse.

It may exhibit the adverse effects, most of which mimic the results of excessive stimulations of the sympathetic nervous system. Side-effects such as anxiety, dyspnea, hyperglycaemia, restlessness, sweating, hypersalivation, weakness, dizziness and coldness of extremities may occur even with low doses. Overdosage may cause cardiac arrhythmias and a sharp rise in blood pressure (sometimes leading to cerebral heamorrhage and pulmonary oedema); these effects may occur at normal dosage in susceptible subjects. It does not readily cross the blood-brain barrier, its centra effects, which encompass anxiety, fear, restlessness, insomnia, confusion, irritability, and nausea and vomiting, may occur similarly.

Other side-effects may include difficulty in micturition with urinary retention, intense vasoconstriction resulting in tissue necrosis and sloughing

4.9 Overdose

Symptoms and Signs

The most common signs and symptoms of overdose are 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

5.1 Pharmacodynamic properties

A Pharmacotherapeutic group: Beta-adrenoreceptor agonists, Antihistamine

ATC code: Salbutamol - R03AC02, Theophylline - R03DA04, Chlorpheniramine Maleate - R06AB02

Salbutamol:

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.

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.

Chlorpheniramine Maleate:

Chlorphenamine is a potent antihistamine (H1-antagonist). Antihistamines diminish or abolish the actions of histamine in the body by competitive reversible blockade of histamine-H1-receptor sites on tissues. Chlorphenamine also has anticholinergic activity

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 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 α - 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 has 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 of 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 has 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 %

Chlorpheniramine Maleate:

Chlorphenamine is well absorbed from the gastrointestinal tract and following oral administration the effects develop within 30 minutes, and are maximal within 1 to 2 hours and last about 4 to 6 hours. The plasma half-life has been estimated to be 12 to 15 hours.

The drug is widely distributed throughout the body including the CNS.
The main site of metabolic transformation is in the liver. Chlorphenamine is metabolised to the monodesmethyl and didesmethyl derivatives. About 22% of an oral dose is excreted unchanged in the urine.

Little if any is excreted unchanged in the urine; most appears there as degradation products that are almost completely excreted within 24 hours. The drug is eliminated more rapidly by children than by adults.

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.

Chlorpheniramine Maleate:

No data of relevance which is additional to that already included in other sections of the SPC

6. Pharmaceutical particulars

6.1 List of excipients

Nipagin (Methyl Paraben)	0.12mg
Nipasol (Propyl Paraben)	0.06mg
Dicalcium Phosphate	100.00mg
Corn Starch (Paste)	8.00mg
Corn Starch (Bulk)	90.00mg
Corn Starch (Lubricant)	10.00mg
Talcum	2.00mg
Magnesium Stearate	2.00mg
Purified Water	q.s.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

Do not use after the expiry date given on the pack.

6.4 Special precautions for storage

Store below 30°C, protect from light.

6.5 Nature and contents of container

White HDPE plastic secure container with red press on caps

Pack sizes of 50 tablets

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.

7. Applicant / Manufacturer:

Vitabiotics Nigeria Limited

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Ikeja, Lagos,

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