SCHEDULING STATUS: **S2**

PROPRIETARY NAME AND DOSAGE FORM:

ALCOPHYLLEX (MIXTURE)

COMPOSITION:

Each 5 ml contains:

Theophylline	16,667 mg
Hydroxyethyl theophylline (Etofylline)	1,667 mg
Diphenhydramine hydrochloride	6,667 mg
Ammonium chloride	120 mg
Sodium citrate	50 mg
Preservatives:	
Methylparaben	0,1 % m/v
Propylparaben	0,015 % m/v
Alcohol	0,5 % v/v
Contains sugar: Sucrose	3,266 g

Other inactive ingredients: caramel colourant, citric acid monohydrate, purified water, raspberry flavor.

PHARMACOLOGICAL CLASSIFICATION:

A 10.1 Antitussives and expectorants

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Bronchodilator, antihistaminic and expectorant.

Pharmacokinetic properties

Theophylline: Theophylline is rapidly and completely absorbed following oral administration. The rate,

but not the extent, of absorption is decreased by food, and food may also affect theophylline clearance. Peak serum-theophylline concentrations occur 1 to 2 hours after ingestion. Theophylline is about 40 to 60 % bound to plasma proteins. Theophylline is metabolised in the liver, mainly by CYP1A2, and a number of factors are known to influence hepatic metabolism such as age, smoking, disease, diet and drug interactions.

Diphenhydramine: Diphenhydramine is well absorbed from the gastrointestinal tract and reaches peak plasma concentrations in ~ 2 hours. Diphenhydramine is distributed widely throughout the body, including the CNS. Diphenhydramine is highly bound to plasma proteins and metabolism is extensive. Little, if any, is excreted unchanged in the urine; most appears there as metabolites. The plasma elimination $t_{½}$ ranges between 4-8 hours.

Ammonium chloride: Ammonium chloride is absorbed from the gastrointestinal tract. The ammonium ion is converted into urea in the liver; the anion thus liberated into the blood and extracellular fluid causes a metabolic acidosis and decreases the pH of the urine; this is followed by transient diuresis.

Sodium citrate: Sodium citrate is metabolised, after absorption, to bicarbonate.

INDICATIONS:

Bronchospasm associated with bronchial congestion e.g. bronchial asthma, paroxysmal dyspnoea, colds, bronchitis, tracheitis, etc.

CONTRAINDICATIONS:

- If you are hypersensitive to theophylline, hydroxyethyl theophylline (etofylline), diphenhydramine hydrochloride, ammonium chloride, sodium citrate or any of the other ingredients of ALCOPHYLLEX.
- Premature infants or neonates.
- During acute attacks of asthma.
- Patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria.
- Impaired hepatic or renal function.

- Epilepsy.
- Porphyria
- Children under the age of two years.

WARNINGS and SPECIAL PRECAUTIONS:

- ALCOPHYLLEX should be given with caution to patients with peptic ulceration, hyperthyroidism, hypertention, cardiac arrhythmias or other cardiovascular disease as these conditions may be exacerbated (see **"**SPECIAL PRECAUTIONS**"**).
- ALCOPHYLLEX should also be given with caution to patients with heart failure, acute febrile illness and the elderly, since in all of these circumstances theophylline clearance may be decreased (see **"**SPECIAL PRECAUTIONS").

Special Precautions

Theophylline:

Theophylline should be given with caution to patients with peptic ulceration, hyperthyroidism, hypertension, cardiac arrhythmias or other cardiovascular disease, as these conditions may be exacerbated. It should also be given with caution to patients with congestive heart failure, hepatic dysfunction or chronic alcoholism, acute febrile illness, severe hypoxia, cor pulmonale, acute pulmonary oedema, or other chronic lung disease, and to neonates and the elderly (see **"**WARNINGS**"**).

Diphenhydramine hydrochloride:

Diphenhydramine hydrochloride may produce epileptiform seizures in patients with focal lesions of the cerebral cortex. Because of its antimuscarinic properties diphenhydramine hydrochloride should be used with care in conditions such as narrow angle glaucoma, urinary retention and prostatic hyperthrophy.

Sodium citrate:

Sodium citrate should be administered with caution to patients with congestive heart failure, renal impairment, cirrhosis of the liver, or hypertension, and to patients receiving corticosteroids.

Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrose-isomaltase insufficieny should not take ALCOPHYLLEX**.** Sucrose may have an effect on the glycaemic control of patients with diabetes mellitus.

Effects on the ability to drive and use machines

The use of this medicine may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or other central nervous system depressants. Patients should be warned not to drive a motor vehicle, operate dangerous machinery or climb dangerous heights, as impaired decision making could lead to accidents.

INTERACTIONS:

Theophylline:

- The bronchodilator and toxic effects of *theophylline* and *sympathomimetics* or other *xanthines* are additive. Concomitant use with other xanthine medications should be avoided.
- Interaction with *allopurinol, cimetidine, propranalol, erythromycin* and some other *macrolides*, *disulfiram, fluvoxamine, interferon alfa, tetracycline, quinolones, oral contraceptives, caffeine, verapamil, zileuton, tacrine, tiabendazole, viloxazine, BCG vaccination* and *influenza vaccination* may result in decreased hepatic theophylline clearance and increased serum half-life.
- *Phenytoin* and some other *anticonvulsants*, *ritonavir, rifampicin, sulfinpyrazone* and *cigarette smoking* may increase theophylline clearance.
- ALCOPHYLLEX can potentiate hypokalaemia associated with the use of *beta$_2$ agonists, corticosteroids,* and *diuretics*.
- There is a risk of synergistic toxicity if ALCOPHYLLEX is given with *halothane* or *ketamine*.
- ALCOPHYLLEX may antagonise the effects of *adenosine* and of *competitive neuromuscular blockers.*
- ALCOPHYLLEX may enhance the elimination of *lithium*.
- *Isoniazid* impairs the elimination of ALCOPHYLLEX.

Diphenhydramine:

- *Monoamine oxidase inhibitors* may enhance the antimuscarinic effects of antihistamines and antihistamines have an additive anti-muscarinic action with other antimuscarinic drugs such as *atropine* and *tricyclic antidepressants.*
- The sedative effects of *central nervous system depressan*ts including *alcohol*, *barbiturates*, *hypnotics, narcotic analgesics, sedatives* and *tranquillisers* may be enhanced.
- ALCOPHYLLEX could mask the warning signs of damage caused by *ototoxic* drugs such as *aminoglycoside antibacterials.*
- Antihistamines may suppress positive skin test results and should be stopped several days before the tests.

Sodium citrate:

- ALCOPHYLLEX can enhance the absorption of *aluminium* from the gastrointestinal tract.

HUMAN REPRODUCTION:

Safety and/or efficacy during pregnancy and lactation has not been established.

Theophylline and diphenhydramine crosses the placenta and are distributed into breast milk.

DOSAGE AND DIRECTIONS FOR USE:

Adults: 2 to 3 medicine measures (10 to 15 ml) every four hours

Children 2 to 6 years: ½ to 1 medicine measure (2,5 to 5 ml) every four hours

7 to 12 years: 1 to 2 medicine measures (5 to 10 ml) every four hours.

Not for use in children under 2 years of age.

SIDE EFFECTS:

Theophylline:

Psychiatric disorders

The following side effects have been reported but the frequencies are unknown:

Insomnia, anxiety and restlessness.

Nervous system disorders

The following side effect has been reported but the frequency is unknown:

Headache.

Ear and labyrinth disorders

The following side effect has been reported but the frequency is unknown:

Vertigo.

Cardiac disorders

The following side effect has been reported but the frequency is unknown:

Palpitations.

Gastrointestinal disorders

The following side effects have been reported but the frequencies are unknown:

Nausea, vomiting, abdominal pain and gastrointestinal bleeding.

Diphenhydramine hydrochloride:

Blood and the lymphatic system disorders

The following side effect has been reported but the frequency is unknown:

Thrombocytopenia.

Immune system disorders

The following side effect has been reported but the frequency is unknown:

Allergic reactions.

Metabolism and nutrition disorders

The following side effects have been reported but the frequencies are unknown:

Anorexia or increased appetite.

Psychiatric disorders

The following side effects have been reported but the frequencies are unknown:

Euphoria, insomnia and nervousness.

Nervous system disorders

The following side effects have been reported but the frequencies are unknown:

Muscular weakness, tinnitus, headache, tremors, incoordination and convulsions.

Eye disorders

The following side effect has been reported but the frequency is unknown:

Blurred vision.

Cardiac disorders

The following side effects have been reported but the frequencies are unknown:

Dizziness, tightness of the chest, tachycardia and sedation varying from slight drowsiness to deep sleep.

Vascular disorders

The following side effect has been reported but the frequency is unknown:

Hypotension,

Gastrointestinal disorders

The following side effects have been reported but the frequencies are unknown:

Nausea, vomiting, diarrhoea or constipation, epigastric pain, dryness of the mouth.

Renal and urinary disorders

The following side effects have been reported but the frequencies are unknown:

Difficulty in micturition and dysuria.

General disorders and administrative site conditions

The following side effect has been reported but the frequency is unknown:

Lassitude.

Investigations

The following side effect has been reported but the frequency is unknown:

Cross-sensitivity to related drugs

Ammonium chloride:

Metabolism and nutrition disorders

The following side effects have been reported but the frequencies are unknown:

Acidosis and hypokalaemia.

Gastrointestinal disorders

The following side effects have been reported but the frequencies are unknown:

Nausea and vomiting.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULAR OF ITS TREATMENT:

Theophylline:

Common clinical manifestations of theophylline toxicity after overdose include nausea, vomiting, diarrhoea, agitation, tremor, hypertonicity, hyperventilation, supraventricular and ventricular arrhythmias, hypotension, and seizures. Metabolic disturbances such as hypokalaemia, hyperglycaemia, hypophosphataemia, hypercalcaemia, metabolic acidosis, and respiratory alkalosis often occur. Other toxic effects reported include dementia, toxic psychosis, symptoms of acute pancreatitis, rhabdomyolysis with associated renal failure, and acute compartment syndrome. Serious toxic symptoms may not be preceded by minor symptoms. After theophylline overdosage, elimination may be enhanced by repeated oral doses of activated charcoal. An osmotic laxative may also be considered. Treatment is symptomatic and supportive.

Diphenhydramine hydrochloride:

Overdose may be fatal especially in infants and children in whom the main symptoms are CNS stimulation and antimuscarinic effects, including ataxia, excitement, hallucinations, muscle tremor, convulsions, dilated pupils, dry mouth, flushed face and hyperpyrexia. Deepening coma, cardiorespiratory collapse and death may occur. In adults, the usual symptoms are CNS depression with drowsiness, coma and convulsions. Hypertension may occur. Elderly patients are more susceptible to the CNS depressant and hypotensive effects even at therapeutic levels.

Ammonium chloride: As under ‘SIDE EFFECTS’.

Sodium citrate:

Excessive doses may lead to metabolic alkalosis, especially in patients with impaired renal function. Symptoms may include shortness of breath, muscle weakness, and mental disturbances such as restlessness, convulsions and coma.

Treatment is symptomatic and supportive.

IDENTIFICATION:

Dark brown liquid with an odour of raspberry.

PRESENTATION:

100 ml, 200 ml and 2,5 L containers.

STORAGE INSTRUCTIONS:

Store at or below 30 °C in airtight containers. Protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

REFERENCE NUMBER:

G 720 (Act 101/1965)

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Adcock Ingram Limited

1 New Road

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Midrand, 1685

Customer Care: 0860 ADCOCK/232625

DATE OF PUBLICATION OF THE PACKAGE INSERT:

1974

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