PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE

ALCOPHYLLEX (16, 667 / 1,667 / 6,667 mg / 120 mg / 50 mg, mixture)

2. QUALITATIVE AND QUANTITATIVE 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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Mixture (Oral liquid).

A dark brown liquid with an odour of raspberry.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

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.

Method of administration: Oral administration only.

Shake the bottle before use.

Doses must be taken orally with an adequate amount of fluid (half to one glass)

4.3 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 2 years. (see section 4.2 Posology and method of administration)

- Concurrent use of ALCOPHYLLEX in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see section 4.4)
- Recent myocardial infarction. Acute tachyarrhythmia.
- Concomitant use with ephedrine in children.

4.4 Special warnings and precautions for use

A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tend to recur or is accompanied by high fever, rash or persistent headache, the patient should be advised to consult a doctor.

ALCOPHYLLEX should not be taken for persistent or chronic cough such as occurring with smoking, asthma, emphysema or where cough is accompanied by excessive phlegm (mucous).

Theophylline:

Theophylline should be given with caution to patients with peptic ulceration, hyperthyroidism, hypertension, cardiac arrhythmias, or other cardiovascular diseases, 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.

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 hypertrophy.

The use of high doses of diphenhydramine-containing medicines, such as ALCOPHYLLEX, may lead to serious heart problems, seizures, coma and death.

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.

Excipient warnings

- Contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose- galactose mal-absorption or sucrose-isomaltase insufficiency should not take ALCOPHYLLEX.
- This medicine contains 0,021 mg of alcohol (ethanol) in each 5 mL which is equivalent to 0,5 % v/v. The small amount of alcohol in this medicine will not have any noticeable effects.
- This medicine contains 50 mg sodium per 5 mL of syrup equivalent to 10 mg/mL of syrup. This is equivalent to 0,5 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Elderly:

Elderly patients are more susceptible to the central nervous system depressant and hypotensive effects. The elderly are particularly prone to dizziness, sedation, confusion, hypotension and anticholinergic effects.

There is some evidence that theophylline exhibits dose-dependent kinetics, at least in sick and elderly patients. Care should be exercised by titration of dosage requirements in small increments and by monitoring serum theophylline levels.

Paediatrics:

May cause excitability especially in children.

ALCOPHYLLEX is unsuitable for children suffering from diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

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, propranolol, erythromycin* and some other *macrolides, disulfiram, fluvoxamine, interferon alfa, tetracycline, quinolones*, *oral contraceptives, caffeine, verapamil, zileuton, tacrine, thiabendazole, 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 depressants including *alcohol*, *barbiturates, hypnotics, narcotic analgesics, sedatives*, and *tranquilisers* 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.

Interactions with Laboratory tests

None known

Taking ALCOPHYLLEX with food, drink and alcohol

ALCOPHYLLEX should be taken with food to minimise possible side effects.

Xanthine containing beverages (e.g.: tea, coffee, cocoa) may interfere with some serum theophylline assays.

4.6 Fertility, pregnancy and lactation

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

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

4.7 Effects on 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.

4.8 Undesirable effects

Theophylline:

System Organ Class	***Frequency***	***Undesirable effect***
Metabolism and nutrition disorders	Unknown	Hyperglycaemia, hypokalaemia, hypomagnesaemia.
Psychiatric disorders	Frequent	Insomnia, anxiety, irritability, agitation, restlessness
Nervous system disorders	Frequent	Headache, CNS stimulation reflex hyperexcitability, tremor, convulsions, insomnia.
Ear and labyrinth disorders	Unknown	Vertigo
Cardiac disorders	Frequent	Palpitations, tachycardia, dysrhythmia.
	Less Frequent	More serious signs of high serum levels (usually above 30 microgram/mL, such as cardiac dysrhythmias may appear without prior warning).
	Unknown	Extrasystoles
Vascular disorders	Unknown	Flushing, hypotension.

Respiratory, thoracic, and mediastinal disorders	Unknown	Tachypnoea
Gastrointestinal disorders	Frequent	Gastric irritation, nausea, vomiting, abdominal pain, reactivation of peptic ulcer, gastro-oesophageal reflux, gastrointestinal bleeding
	Unknown	Diarrhoea
Skin and subcutaneous tissue disorders	Unknown	Rash and alopecia.
Renal and urinary disorders	Unknown	Potentiation of diuresis, albuminuria, haematuria, inappropriate ADH secretion (high dose).

Side effects are related to theophylline plasma levels: nausea and vomiting, excitation, nervousness and insomnia occur at plasma concentrations of 20 to 30 mg/L, hysteria at 30 mg/L, cardiac dysrhythmias and coma at concentrations greater than 40 mg/L. These toxic phenomena are enhanced by hypoxia and acidosis. The treatment of toxic effects is symptomatic: (whether or not temporary) discontinuance of the administration of theophylline, correction of the acidosis and hypoxia, and careful supervision of any therapeutic intervention that may aggravate underlying heart or lung diseases, such as overloading with water and salt, oxygen, sedatives, anti-emetics and beta blockers.

Diphenhydramine hydrochloride:

System Organ Class	*Frequency*	*Undesirable effect*
Blood and the lymphatic system disorders	Less Frequent	Haemolytic anaemia, leucopoenia, thrombocytopaenia
Immune system disorders	Less Frequent	Allergic reactions
Metabolism and nutrition disorders	Less Frequent	Anorexia or increased appetite, hyper-chloraemic acidosis, hypokalaemia.
Psychiatric disorders	Frequent	Elation or depression, irritability, nightmares, euphoria, extra-pyramidal effects, mental confusion.
	Unknown	Insomnia, nervousness.
Nervous system disorders	Frequent	Headache, drowsiness or progressive drowsiness, inability to concentrate, lassitude, dizziness, insomnia, nervousness, tremors, tingling, epileptiform seizures, convulsions
	Unknown	Muscular weakness, tinnitus, incoordination.
Eye disorders	Less Frequent	Blurred vision
Ear and labyrinth disorders	Less Frequent	Tinnitus
Cardiac disorders	Unknown	Dizziness, tightness of the chest, tachycardia and sedation varying from slight drowsiness to deep sleep.
	Less Frequent	Hyperventilation
Vascular disorders	Unknown	Hypotension

Gastrointestinal disorders	Frequent	Gastrointestinal disturbances, nausea, vomiting, diarrhoea or constipation, epigastric pain, dryness of the mouth and thirst.
Renal and urinary disorders	Unknown	Difficulty in micturition, dysuria.
Skin and subcutaneous tissue disorders	Less Frequent	Photosensitisation of the skin.
Investigations	Unknown	Cross-sensitivity to related drugs.

Ammonium chloride:

System Organ Class	***Frequency***	***Undesirable effect***
Metabolism and nutrition disorders	Unknown	Acidosis and hypokalaemia.
Gastrointestinal disorders	Unknown	Nausea and vomiting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit /risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. Adverse Drug Reactions may also report to Adcock Ingram Limited using the following email:

Adcock.AEReports@adcock.com.

4.9 Overdose

Theophylline:

Common clinical manifestations of theophylline toxicity after overdose include nausea, vomiting, diarrhoea, agitation, tremor, hypertonicity, hyperventilation, supraventricular and ventricular dysrhythmias, 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: See section 4.8

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.

5. PHARMACOLOGICAL PROPERTIES

A 10.1 Antitussives and expectorants

ATC code: R03DA

5.1 Pharmacodynamic properties

Bronchodilator, antihistaminic and expectorant.

Theophylline is a methylated xanthine and is therefore related to caffeine and theobromine. The pharmacological action of theophylline results in the relaxation of smooth muscle. It also exhibits activities typical of xanthines such as CNS stimulation including the respiratory centre, cardiac stimulation, coronary vasodilatation, diuresis and increased gastric secretion. The mechanism of action of theophylline in vivo has not been fully elucidated. One mechanism of smooth muscle relaxation may be inhibition of phosphodiesterase that reduces intracellular hydrolysis of cyclic AMP. Increased intracellular concentrations of cyclic AMP have been associated with relaxation of bronchial smooth muscle. There is no evidence that tolerance develops with continued use of theophylline.

Diphenhydramine hydrochloride is an antihistamine and, by its atropine-like action, relieves cough.

Ammonium chloride reduces the secretion viscosity and facilitate elimination of mucus through reflex stimulation of bronchial secretion by its irritant and/or other chemical properties.

5.2 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 t½ 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.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Ethanol
- Caramel colorant [E150]
- Citric acid monohydrate [E330]
- Methylparaben [E218]
- Propylparaben [E216]
- Purified water

- Raspberry flavour
- Sucrose

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 ^{o}C.

6.5 Nature and contents of container

100 mL & 200 mL:

Amber PVC bottle with LLDPE pilfer proof closure.

Amber glass bottle with white polypropylene closure cap.

Amber PET medical round bottle with white polypropylene and HDPE child-proof screw-on cap.

2,5 L:

Amber HDPE container with white polypropylene screw on closure with EXPE liner.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Return all unused or expired medicine to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand, 1685

Customer Care: 0860 ADCOCK /232625.

8. REGISTRATION NUMBERS

G 720 (Act 101/1965).

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1974.

10. DATE OF REVISION OF THE TEXT

21 July 2025.

Botswana: BOT2404383 S3

Namibia: NS1 14/10.1/0380