PATIENT INFORMATION LEAFLET

SCHEDULING STATUS:

S2

1 NAME OF THE MEDICINE

ADCO-DIATUSSIN SYRUP

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL contains:	
Theophylline	56,31 mg
Diphenhydramine hydrochloride	28,15 mg
Sodium citrate	113,83 mg
Menthol	2,28 mg
Ammonium chloride	273,86 mg

Preservatives:

Methyl hydroxybenzoate 0,10 % $^{m}/_{v}$

Propyl hydroxybenzoate 0,02 % $^{m}/_{v}$

Contains sugar (sucrose) 5,78 g

Contains Alcohol 0,001 mL (0,01 % $^{v/v}$)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Syrup.

Clear amber syrup with a raspberry-cherry odour.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Alleviation of cough.

4.2 Posology and method of administration

Posology

Adults: 10 mL (two medicine measures) every four hours.

Children 6 to 12 years: 2,5 mL to 5 mL (half to one medicine measure) every four hours.

Should not be given to children under 6 years.

Method of administration

For oral use only

Shake well before use.

4.3 CONTRAINDICATIONS

- Hypersensitivity to theophylline, diphenhydramine hydrochloride, sodium citrate, menthol, ammonium chloride or any of the other
- Excipients of ADCO-DIATUSSIN SYRUP listed in section 6.1.
- Patients with impaired hepatic or renal function
- During an asthma attack.
- Patients with peptic ulcer, gout and severe hypotension.
- Safety during pregnancy and lactation has not been established.
- Patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria.
- Epilepsy
- Porphyria
- Children under the age of 6 years. (see section 4.2)
- Patients taking monoamine oxidase inhibitors (MAOIs) (see section 4.5)
- Recent myocardial infarction.
- Acute tachyarrhythmia.
- Concomitant use with ephedrine in children.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

- ADCO-DIATUSSIN SYRUP may lead to toxic levels of theophylline and patients should be cautioned accordingly.
- Not to be used by diabetic patients.
- Large doses of diphenhydramine hydrochloride may precipitate convulsions in epileptics.
- It should be used with care in conditions which can be exacerbated or otherwise adversely affected by atropine, such as glaucoma and prostatic hypertrophy.
- Diphenhydramine hydrochloride may suppress the positive results of skin allergy tests.
- Use with caution in alcoholics, patients with cor pulmonale, patients with acute febrile conditions, hypoxia, acute pulmonary oedema or any other lung disease.

- Serum concentration monitoring is advised, especially when transferring a patient from another formulation.
- Theophylline should be given with caution to patients with peptic ulceration, hyperthyroidism or cardiovascular disease and cardiac arrhythmias as these conditions may be exacerbated.
- ADCO-DIATUSSIN SYRUP should be used with caution in patients with cardiac failure, hypertension, peripheral and pulmonary oedema and in toxaemia of pregnancy.
- 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
- 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 ADCO- DIATUSSIN SYRUP, may lead to serious heart problems, seizures, coma and death.
- 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.
- Menthol may give rise to hypersensitivity reactions.

Children

- ADCO-DIATUSSIN SYRUP may cause central nervous system stimulation, especially in children.
- Theophylline should also be given with caution to neonates as clearance may be decreased in these patients.

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.

- Clearance of theophylline may be decreased in these patients.

Excipient Warnings

- ADCO-DIATUSSIN SYRUP contains 0,00025 ml of alcohol (ethanol) in each 2,5 mL, or 0,079 mg of alcohol (ethanol) per mL, which is equivalent to 0,01 % v/v. The amount in 2,5 mL of this medicine is equivalent to less than 0,005 mL of beer or 0,002 mL of wine. The small amount of alcohol in this medicine will not have any noticeable effects.
- ADCO-DIATUSSIN SYRUP contains 0,3 ml propylene glycol in each 2,5 ml which is equivalent to 12 % v/v.
    - While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.
    - Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce adverse effects in children less than 5 years old.
    - While propylene glycol has not been shown to cause reproductive or developmental toxicity in animals or humans, it may reach the foetus and was found in milk. As a consequence, administration of propylene glycol to pregnant or lactating patients should be considered on a case by case basis.
    - Medical monitoring is required in patients with impaired renal or hepatic functions because various adverse events attributed to propylene glycol have been reported such as renal dysfunction (acute tubular necrosis), acute renal failure and liver dysfunction.
- ADCO-DIATUSSIN SYRUP contains 1,45 g of sucrose per 2,5 mL. This should be taken into account in patients with diabetes mellitus.
- Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
- ADCO-DIATUSSIN SYRUP contains parabens which may cause allergic

reactions (possibly delayed).

- ADCO-DIATUSSIN SYRUP contains 6,67 mg of sodium per 2,5 mL of syrup or 2,7 mg of sodium per mL of syrup, equivalent to 0,14% of the WHO recommended maximum daily intake for sodium.

4.5 Interaction with other medicines and other forms of interaction

- Diphenhydramine hydrochloride may enhance the sedative effects of central nervous system depressants including alcohol, barbiturates, hypnotics, narcotic, analgesics sedatives and tranquillisers
- The effects of anticholinergic drugs such as atropine and tricyclic antidepressants may be enhanced by concomitant administration.
- Monoamine oxidase inhibitors may enhance the anticholinergic effects of antihistamines like diphenhydramine hydrochloride in ADCO-DIATUSSIN SYRUP
  They also have an additive anti-muscarinic action with other antimuscarinics such as atropine and tricyclic antidepressants
- The bronchodilator and toxic effects of theophylline and sympathomimetics or other xanthines are additive.
- Interaction with allopurinol, cimetidine, influenza vaccine, propranolol and erythromycin, some other macrolides, disulfiram, fluvoxamine, interferon alfa, tetracycline, quinolones, oral contraceptives, caffeine, verapamil, zileuton, tacrine, thiabendazole, viloxazine and BCG vaccination may result in decreased hepatic theophylline clearance and increased serum half-life, necessitating dosage reduction.
- Phenytoin and some other anticonvulsants, ritonavir, sulfinpyrazone, rifampicin and cigarette smoking may increase theophylline clearance necessitating an increase in dose or dosing frequency.
- ADCO-DIATUSSIN SYRUP can potentiate hypokalaemia associated with the use of beta-2-agonists, corticosteroids, and diuretics.
- There is a risk of synergistic toxicity if ADCO-DIATUSSIN SYRUP is given with halothane or ketamine

- ADCO-DIATUSSIN SYRUP may antagonise the effects of adenosine and of competitive neuromuscular blockers.
- ADCO-DIATUSSIN SYRUP may enhance the elimination of lithium.
- Isoniazid impairs the elimination of ADCO-DIATUSSIN SYRUP
- Diphenhydramine in ADCO-DIATUSSIN SYRUP may mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibacterials.
- ADCO-DIATUSSIN SYRUP can enhance the absorption of aluminium from the gastrointestinal tract.

Taking ADCO-DIATUSSIN SYRUP with food, drink and alcohol

ADCO-DIATUSSIN SYRUP 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 during pregnancy and lactation has not been established. See section 4.3.

No fertility data available.

4.7 Effects on ability to drive and use machines

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. It is unsafe to drive a vehicle or be in charge of machinery while using the medicine, as impaired decisions could lead to accidents.

4.8 Undesirable side effects

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	Frequent	Thirst
	Less Frequent	Anorexia or increased appetite, hyper-chloraemic acidosis, acidosis, hypokalaemia, hypernatremia
	Unknown	Hyperglycaemia, hypomagnesaemia.
Psychiatric disorders	Frequent	Elation or depression, irritability, nightmares, euphoria, mental confusion, sedation varying from slight drowsiness to deep sleep, anxiety, restlessness, agitation
Nervous system disorders	Frequent	Headache, drowsiness or progressive drowsiness, inability to concentrate, lassitude, dizziness, extra-pyramidal effects, insomnia, nervousness, tremors, tingling, epileptiform seizures, convulsions, CNS stimulation reflex hyperexcitability
	Unknown	Muscular weakness, incoordination, muscle twitching, weakness, heaviness of the hands
Eye disorders	Less Frequent	Blurred vision
Ear and labyrinth disorders	Less Frequent	Tinnitus,
	Unkown	Vertigo
Cardiac disorders	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, tachycardia, dysrhythmia, palpitations
Vascular disorders	Unknown	Hypotension

Respiratory, thoracic, and mediastinal disorders	Less Frequent	Hyperventilation
	Unknown	Tachypnoea, tightness of the chest.
Gastrointestinal disorders	Frequent	nausea, vomiting, diarrhoea or constipation, epigastric pain, dryness of the mouth, abdominal pain, gastric irritation, reactivation of peptic ulcer, gastro-oesophageal reflux, gastrointestinal bleeding
Renal and urinary disorders	Unknown	Difficulty in micturition, dysuria.
Skin and subcutaneous tissue disorders	Less Frequent	Photosensitisation
	Unknown	Rash and alopecia.
Renal and urinary disorders	Unknown	Potentiation of diuresis, albuminuria, haematuria, inappropriate ADH secretion (high dose).
Investigations	Unknown	Cross-sensitivity to related drugs.

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.

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. Health care

providers are requested to report any suspected adverse reactions to SAHPRA

via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform

(who- umc.org) found on SAHPRA website.

You 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 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

Diphenhydramine hydrochloride overdosage may be fatal, especially in children. The main symptoms are central nervous system stimulation and antimuscarinic effects including ataxia, excitement, hallucinations, muscle tremor, convulsions, dilated pupils, dry mouth, flushed face, hyperpyrexia. Deepening coma and respiratory collapse and finally death from respiratory failure. Hypotension may occur.

Sodium Citrate

Retention of sodium leads to the accumulation of fluid with cerebral, peripheral and pulmonary oedema. Symptoms of hypernatraemia may include restlessness, weakness, thirst, reduced salivation and lacrimation, swollen tongue, flushing of skin, pyrexia, dizziness, headache, oliguria, hypotension, tachycardia, delirium, hyperpnoea and respiratory arrest. Other symptoms of overdosage are gastrointestinal upset, drowsiness, hypochloraemic acidosis and hypokalaemia. Severe overdosage of

theophylline or idiosyncrasy may lead to maniacal behaviour, diuresis and repeated vomiting with extreme thirst, tremor, delirium, hyperthermia, tachycardia, tachypnoea, electrolyte disturbances, convulsions and death.

Treatment is symptomatic and supportive.

Ammonium Chloride

Large doses of ammonium chloride may cause nausea, vomiting, headache, thirst, hyperventilation and progressive drowsiness, mental confusion and lead to profound hyperchloraemic acidosis and hypokalaemia.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 10.1 Antitussives and expectorants

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 96,5 %
- Flavour wild Cherry
- Caramel
- Raspberry essence
- Propylene glycol (E1520)
- Sucrose
- Methylhydroxybenzoate
- Propylhydroxybenzoate
- Purified water

6.2 Incompatibilities

None.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store in a cool, dry place at or below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Clear amber syrup with a raspberry-cherry odour.

100 ml PVC amber medical round bottle with LDPE white snap-on cap.

150 ml Amber Glass Bottle with 28 mm Medropp Generic.

2,5 litre Amber HDPE container with HDPE white screw cap.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF THE CERTIFICATE OF

REGISTRATION:

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