

PRODUCT MONOGRAPH

PrAA-THEO LA

Theophylline Anhydrous
Sustained-Release Tablets
House Standard

100, 200 and 300 mg

Bronchodilator

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THERAPEUTIC CLASSIFICATION

Bronchodilator

ACTIONS AND CLINICAL PHARMACOLOGY

Theophylline relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels to relieve bronchospasm and increase flow rates and vital capacity. It also produces other actions typical of the xanthine derivatives: coronary vasodilation, diuresis, increase in gastric secretion, and cardiac, cerebral, and skeletal muscle stimulation. The actions of theophylline may be mediated through inhibition of phosphodiesterase and a resultant increase in intracellular cyclic adenosine monophosphate, but the exact mechanism(s) has not been determined. Theophylline is usually readily absorbed and distributed into all body compartments. Protein binding accounts for some 55-65%. The liver is the primary site of metabolism.

The therapeutic serum concentration of theophylline is accepted as 10 to 20 mcg/mL (55-110 mcmmol/L); levels above 20 mcg/mL are associated with toxic reactions. The pharmacokinetics of theophylline are influenced by a number of variables such as: age, disease state, smoking, concomitant medication. Therefore the optimum therapeutic maintenance dose should be determined by individual titration.

AA-THEO LA Tablets are sustained-release tablets which produce peak blood levels between 5-8 hours after dosing in adults. Once the steady state level has been reached (3 days), the therapeutic blood levels persist for 12 hours in most adult patients. The mean elimination half-life of theophylline in nonsmoking adults is about 8 hours. The degree of fluctuation between peak trough theophylline levels can be defined as follows:

% Theophylline Fluctuation

	<u>Nonsmoking Adults</u>
Theophylline sustained- release tablets 200, 300 mg	27%
Theophylline sustained- release tablets 100 mg	34%

INDICATIONS AND CLINICAL USE

AA-THEO LA (theophylline) Tablets are indicated for the symptomatic treatment of reversible bronchospasm associated with asthma, chronic bronchitis, emphysema and related bronchospastic disorders.

CONTRAINDICATIONS

AA-THEO LA (theophylline) is contraindicated in patients with:

- hypersensitivity to theophylline or xanthine derivatives;
- peptic ulcer;
- coronary artery disease (when, in the physicians judgement, myocardial stimulation might prove harmful).

WARNINGS

In clinical situations where immediate bronchodilatation is required, such as status asthmaticus, AA-THEO LA (theophylline) is not suitable.

Since theophylline has a narrow therapeutic index, the margin of safety above therapeutic doses is small. In patients showing intolerance to theophylline, the therapy should be reassessed.

Theophylline clearance can be changed by various disease states, as well as by the age of

the patient, concomitant use of other medications and lifestyle habits (see PRECAUTIONS).

The use of AA-THEO LA in children under the age of twelve years is not recommended.

PRECAUTIONS

AA-THEO LA (theophylline) tablets should be swallowed whole. Do not break, chew or crush.

Marked differences in serum levels may be seen in patients receiving the same theophylline dose. This may be explained by differences between patients in the rate of metabolism. Smokers and children are usually high metabolizers. Dosage regimens should therefore be individualized.

Theophylline half-life is shorter in smokers than in nonsmokers. Smokers may require larger or more frequent doses of theophylline.

Ideally, serum theophylline levels should be monitored in all patients and a theophylline half-life calculated which would enable doses and dosing regimens to be tailored to each patient to maintain a therapeutic level, to ensure optimal clinical response and to avoid toxicity.

The incidence of toxicity increases at serum theophylline levels greater than 15 mcg/mL (82.5 mcmol/L) and levels above 20 mcg/mL (110 mcmol/L) are usually quite toxic in most adult patients. High serum levels may be seen in some patients receiving doses considered to be conventional. The possibility of overdose should therefore not be considered with large doses only. Overdosage of theophylline may cause peripheral vascular collapse.

Reduced theophylline clearance has been documented in the following readily identifiable groups:

- 1) patients with impaired renal or hepatic function;
- 2) patients over 55 years of age, particularly males and those with chronic lung disease;
- 3) those with cardiac failure from any cause;

4) patients taking certain drugs (i.e., macrolide antibiotics and cimetidine).

Decreased clearance may be associated with either influenza immunization or active infection with influenza.

Laboratory monitoring of serum theophylline is especially appropriate in the above individuals to maintain an appropriate theophylline dosage.

Serious side effects such as tachycardia, arrhythmia, seizures, vascular collapse and even death may occur without warning and may not be preceded by less severe symptoms such as nausea and restlessness.

Use with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, hyperthyroidism, acute myocardial injury, cor pulmonale, congestive heart failure, liver disease, in the elderly (especially males).

Patients with congestive heart failure frequently have markedly prolonged serum levels with theophylline persisting in serum for long periods following discontinuation of the drug.

Theophylline may occasionally act as a local irritant to the gastrointestinal tract although gastrointestinal symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 mcg/mL (110 μmol/L).

Theophylline increases gastric secretion, and caution should be exercised in patients with a history of peptic ulcer.

Although AA-THEO LA has pharmacokinetic properties similar to other controlled-release theophylline products, it is not possible to ensure interchangeability between different products. Careful clinical monitoring is required when changing from one drug product to another.

The concurrent administration of other theophylline derivatives along with AA-THEO LA is not recommended.

Laboratory Test Interactions

In the interpretation of biochemistry tests, it should be remembered that theophylline may cause an elevation of urine catecholamines and plasma free fatty acids.

When plasma levels of theophylline are measured by spectrophotometric methods, coffee, tea, cola beverages, chocolate and acetaminophen contribute to falsely high values.

When a high pressure liquid chromatography (HPLC) method is used, plasma theophylline concentration may be falsely increased by caffeine, some cephalosporin and sulfa medications.

Food Interaction

Theophylline clearance is increased when diet includes a low carbohydrate, high protein intake, or a high carbohydrate, low protein intake and there is a chronic ingestion of charcoal broiled meats. However, the administration of AA-THEO LA with meals appears not to significantly effect the amount of theophylline released from AA-THEO LA tablets.

Usage in Pregnancy and Lactation

Theophylline crosses the placental barrier and also passes freely into breast milk, where concentrations are similar to plasma levels. Safe use in pregnancy has not been established relative to possible adverse effects on fetal development, but neither have adverse effects on fetal development been established. Therefore, use of theophylline for uncontrolled asthma in pregnant women and nursing mothers should be balanced against the risk of potential effects on the fetus or on the nursing newborn.

DRUG INTERACTIONS

- A. Theophylline pharmacokinetics are altered by the concurrent use of various drugs as listed below:

DRUG	THEOPHYLLINE
(a) cimetidine, propranolol, allopurinol, macrolide antibiotics (erythromycin), oral contraceptives	↑ $t_{1/2}$, ↓ clearance

(b) Alkalinizing agents	↑ $t_{1/2}$, ↓ clearance
(c) Influenza vaccine	↑ $t_{1/2}$, clearance reported to be decreased or no change.
(d) Phenytoin, barbiturates, carbamazepine, isoproterenol, rifampin	↓ $t_{1/2}$, ↑ clearance
(e) Smoking (tobacco)	↓ $t_{1/2}$, ↑ clearance
(f) Acidifying agents	↓ $t_{1/2}$, ↑ clearance

B. Concurrent use of theophylline influences effects of certain drugs:

DRUG	EFFECTS
(a) Digitalis glycosides	↑ Cardiac effect
(b) Thiazides	↑ diuresis
(c) Nephrotoxic drugs	↑ nephrotoxicity
(d) Lithium	↑ Ratio of lithium/ creatinine clearance, thus decrease serum lithium
(e) Sympathomimetic amines	↑ toxicity, ↑ CNS stimulation
(f) Coumarin anticoagulants	↓ anticoagulant activity, increase prothrombin and fibrinogen blood concentrations, shorten prothrombin time
(g) Allopurinol	↓ antihyperuremic action
(h) Probenecid and pyrazolon derivatives	↓ uricosuric action
(i) Ketamine	↓ threshold value for inducing convulsions

ADVERSE REACTIONS

The most common adverse reactions are nausea, vomiting, epigastric pain, headache and tremor. These are usually early signs of toxicity; however, with high doses cardiac arrhythmias or seizures may be the first signs to appear. Adverse reactions reported with theophylline preparations include:

Gastrointestinal: nausea, vomiting, epigastric pain, hematemesis, diarrhea, anorexia, reactivation of peptic ulcer, intestinal bleeding.

Central Nervous System: headaches, irritability, restlessness, insomnia, hyperactivity,

reflex hyperexcitability, muscle twitching, clonic and tonic generalized convulsions.

Cardiovascular: palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, life-threatening ventricular arrhythmias.

Respiratory: tachypnea.

Renal: albuminuria, diuresis and hematuria.

Others: hyperglycemia and inappropriate ADH syndrome.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Insomnia, restlessness, mild excitement or irritability, and rapid pulse, are early symptoms which may progress to mild delirium. Sensory disturbances such as tinnitus or flashes of light are common. Anorexia, nausea and vomiting are frequently early observations of theophylline overdose.

Fever, diuresis, dehydration and extreme thirst may be seen. Severe poisoning results in bloody, syrup-like 'coffee-ground' vomitus, tremors, tonic extensor spasm interrupted by clonic convulsions, extrasystoles, quickened respiration, stupor and finally coma.

Cardiovascular disorders and respiratory collapse, leading to shock, cyanosis and death follow gross overdoses.

Treatment

A. Monitoring serum theophylline levels

Following intake of theophylline sustained-release tablets, the blood theophylline peak levels may not show until 5-8 hours post-ingestion in adults. Patients ingesting overdoses of sustained-release theophylline formulations may have, after the initial rise in blood theophylline, also a secondary increase in theophylline levels. One report on fatal self-poisoning has attributed this to compacted tablet masses in the gastrointestinal tract. Careful clinical and laboratory monitoring of stabilized patients

is advisable.

- B. If potential oral overdose is established and seizure has not occurred:
- 1) induce vomiting;
 - 2) administer a cathartic (this is particularly important when a sustained-release preparation has been taken);
 - 3) administer activated charcoal.
- C. If the patient is having a seizure:
- 1) establish an airway;
 - 2) administer oxygen;
 - 3) treat the seizure with intravenous diazepam, 0.1 to 0.3 mg/kg up to a total dose of 10 mg;
 - 4) monitor vital signs, maintain blood pressure and provide adequate hydration.
- D. Post-seizure coma:
- 1) maintain airway and oxygenation;
 - 2) if a result of oral medication, follow above recommendations to prevent absorption of drug, but intubation and lavage will have to be performed instead of inducing vomiting, and the cathartic and charcoal will need to be introduced via a large bore gastric lavage tube;
 - 3) continue to provide full supportive care and adequate hydration while waiting for drug to be metabolized. In general, the drug is metabolized sufficiently rapidly so as not to warrant consideration of dialysis. However, if serum levels exceed 50 mcg/mL (257 mcmol/L), charcoal hemoperfusion may be indicated.

DOSAGE AND ADMINISTRATION

Therapeutic serum levels are generally considered to be between 10 and 20 mcg/mL (55 mcmol/L and 110 mcmol/L). Due to variable rates of elimination, there is patient-to-patient variation in dosage needed to achieve a therapeutic serum level. Because of the variation from patient to patient, the variation within the same patient, and the relatively narrow therapeutic range, dosage should be individualized. Monitoring of serum

theophylline concentrations is also extremely important, especially in the initial stages of therapy (see PRECAUTIONS).

It is preferable to monitor peak concentrations rather than trough concentrations. Therefore, blood samples should be drawn 4-8 hours after AA-THEO LA dosing. It should be ascertained that all doses have been taken for 60 hours prior to blood sampling (steady state is usually achieved within 3 days). Depending on the sensitivity of the assay method used, dietary xanthines may interfere with assay results. If a dosage increase is not tolerated, dosage should be reduced to the previously tolerated level. Do not attempt to maintain dosage which is not tolerated or which produces serum concentrations above the therapeutic range.

AA-THEO LA tablets should be swallowed whole. Do not break, chew or crush.

Adults:

The usual initial adult dose is 200-300 mg every 12 hours. This dose may be increased by 50-100 mg every 12 hours at 3 day intervals until a satisfactory response is obtained or toxic effects appear.

Dosage adjustments should be based upon serum theophylline concentration and/or upon the patient's clinical response. However, doses of 450 mg every 12 hours or higher (900mg/day) should not be given unless serum theophylline concentration can be monitored. It should not be necessary to exceed a daily dose of 16 mg/kg in adult patients. Even with serum level monitoring, this dose may lead to side effects because of day-to-day variations in blood levels within individual patients.

Children:

The use of AA-THEO LA in children under the age of twelve years is not recommended.

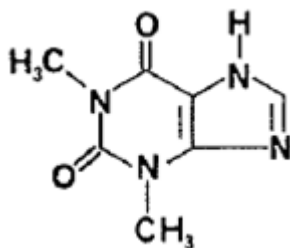
PHARMACEUTICAL INFORMATION

Drug Substance

Proper/Common Name: Theophylline anhydrous

Chemical Name: 1,3-dimethyl-xanthine

Structural Formula:



Molecular Formula: C₇H₈N₄O₂

Molecular Weight: 180.2 g/mol

Description: Theophylline is a white, odourless, crystalline powder which has a bitter taste. It is slightly soluble in water, but more soluble in hot water; freely soluble in solutions of alkali hydroxides and in ammonia; sparingly soluble in alcohol, chloroform and ether.

Composition

In addition to theophylline, AA-THEO LA also contains the non-medicinal ingredients hydroxypropyl methylcellulose, lactose, colloidal silicon dioxide and magnesium stearate.

Stability and Storage Recommendations

Store at controlled room temperature 15-30°C (59-86°F).

AVAILABILITY OF DOSAGE FORMS

AA-THEO LA formulated as sustained-release tablets contains anhydrous theophylline with no colour additives. AA-THEO LA is available in three strengths: 100 mg, 200 mg and 300 mg.

AA-THEO LA 100 mg: White, round, biconvex tablets; scored and engraved "THE" over 100" on one side, and "APO" on the other.

AA-THEO LA 200 mg: White, oval, biconvex, tablets; scored and engraved "THE

200” on one side and "APO” on the other.

AA-THEO LA 300 mg: White, capsule-shaped, biconvex, tablets; scored and engraved
“THE 300” on one side, and "APO" on the other.

AA-THEO LA is available in bottles of 100.

PATIENT INFORMATION

AA-THEO LA

Theophylline Sustained-Release Tablets

AA-THEO LA is our brand name for a drug called 'theophylline' (thee-OFF-i-lin). It is used to treat breathing conditions such as asthma, bronchitis, and emphysema. AA-THEO LA works to open up air passages in the lungs and helps prevent wheezing and shortness of breath.

AA-THEO LA is a 'sustained-release' form of theophylline. This means its effects last longer than some other forms of this drug. Other brands of 'sustained-release' theophylline are available. In general, these work in a similar way to AA-THEO LA and have the same side effects.

Read this leaflet carefully. It has been prepared by the manufacturer to help you become more informed about AA-THEO LA. It contains general information about this drug and is intended to add to more specific advice provided by your doctor or pharmacist.

This leaflet should not take the place of information given by your doctor or pharmacist. Because of your specific health condition, these professionals may have given you different or additional information. If so, be sure to follow their advice. If you have any questions or concerns after reading this leaflet, or if any of the information seems different, talk to your doctor or pharmacist as soon as you can. Do not stop taking your AA-THEO LA without the advice of your doctor.

BEFORE YOU START AA-THEO LA

Before you start AA-THEO LA be sure you have told your doctor:

- about all other health problems you have now, or have had in the past;
- about all other medicines you take, including ones you can buy without a prescription;
- about any allergies or bad reactions you have or have had in the past, to foods or drugs;
- if you are pregnant or plan to become pregnant;
- if you are breast-feeding;
- if you are on any kind of diet;
- if you smoke, or have smoked regularly within the past two years.

HOW TO TAKE AA-THEO LA

- Take AA-THEO LA exactly as prescribed by your doctor. Do not miss doses and do not take extra tablets without your doctor's advice. If you are not clear about

the directions, ask your doctor or pharmacist.

- It is important to take all doses of AA-THEO LA, even when you feel well. This keeps a constant amount of AA-THEO LA in your body so it can help prevent breathing problems.
- Take AA-THEO LA at evenly spaced times through the day. For example, if you are to take 2 tablets a day, take each one about 12 hours apart. You should also get into the habit of taking each dose around the same time(s) every day.
- It is a good idea to ask your doctor or pharmacist ahead of time what to do about missed doses. In general, if you remember a missed dose within several hours, take it as soon as possible; then go back to your regular schedule. However, if it is almost time for your next dose, do not take the missed dose. Just take your next dose on schedule. Never take a double dose of AA-THEO LA to make up for missed tablets.
- AA-THEO LA tablets must not be crushed, chewed or broken into small pieces.
- AA-THEO LA should not be used to relieve sudden breathing attacks because it would take too long to start working.

SPECIAL PRECAUTIONS

- AA-THEO LA has been prescribed for your current condition only. Do not use it for any other problem unless your doctor tells you. Do not give it to other people to use. only.
- Do not change brands or dosage forms of AA-THEO LA without your doctor's advice. Check the bottle label for the name AA-THEO LA and if a refill of your medicine looks different, check with your pharmacist.
- Do not take any other medicine(s) without the advice of a doctor or pharmacist. Some medicines may affect the way AA-THEO LA works for you. This includes vaccines (e.g., for flu), and medicines you can buy without a prescription.
- Your dose of AA-THEO LA may need to be changed under certain conditions. Check with your doctor at once if:
 - you develop diarrhea, chest infection, fever, or flu (influenza);
 - you plan to become pregnant;
 - you start or stop smoking;
 - you eat large amounts of charcoal broiled foods;
 - you wish to go on a high protein, low carbohydrate diet or low protein, high carbohydrate diet.
- Keep AA-THEO LA out of the reach of children. As heat and moisture may cause the medicine to break down, do not keep your bottle in the bathroom medicine cabinet or other such places.

POSSIBLE SIDE EFFECTS

AA-THEO LA is very effective for breathing problems. But like all medicines, it may cause side effects in some people. These can occur with any theophylline medicine.

Theophylline affects different people in different ways. Just because other people have reported these effects, does not mean you will get them.

The following may be early warning signs of too much theophylline for your body. Tell your doctor right away if you notice any of these symptoms.

AA-THEO LA may not have caused these problems in your case, but only a doctor can assess this.

Remember, if any of this information concerns you, do not stop taking AA-THEO LA on your own. Instead, discuss your concerns with your doctor as soon as you can.

- unexplained digestive or stomach problems, such as: nausea, vomiting, heartburn, loss of appetite, stomach pains, diarrhea, black stools (bowel movements) or blood in your stools.
- unexplained changes in general well-being, such as: mood change (restlessness, nervousness, irritability, difficulty sleeping), confusion, memory problems, dizziness, unusual tiredness or weakness, trembling or muscle twitching, convulsions (seizures).
- any of the following unless easily explained by something else: hearing changes (e.g., ringing or buzzing in the ears), vision changes (e.g., seeing flashes of light), unusually fast breathing, unusually fast, pounding or irregular heartbeat, headache, fever, flushing, extreme flushing, extreme thirst, or an unusual increase or decrease in urination ('passing water').

Other side effects which cannot be predicted may occur in some people. If you notice any bothersome or unusual effects while taking AA-THEO LA, check with a doctor (or pharmacist) right away.

GENERAL INFORMATION

- Remember, this leaflet is not a substitute for talking with your doctor. All drugs can have both helpful and harmful effects. Both depend on the individual person and his or her particular health condition. Your doctor has decided that the benefits outweigh the risks in your case. This leaflet alerts you to many of the times you should call your doctor, but other situations which cannot be predicted may arise. Nothing about this leaflet should prevent you from talking with your doctor about any questions or concerns you have regarding AA-THEO LA.
- More detailed information about AA-THEO LA has been written for health professionals. This information may be obtained through your doctor or pharmacist.

PHARMACOLOGY

Theophylline is chemically named 1,3-dimethyl-xanthine. The pharmacologic actions of theophylline include stimulation of respiration, augmentation of cardiac inotropy and chronotropy, relaxation of smooth muscles, including those in the bronchi and blood vessels (other than cerebral vessels) and diuresis. The main use of theophylline has been in the treatment of reversible airway obstruction.

Pharmacokinetics

Theophylline is usually readily absorbed following oral administration.

The drug is 55-65% bound to plasma proteins at the therapeutic plasma concentration range of 10 to 20 mcg/ml (55-110 μ mol/L). It is not likely to be subject to pronounced displacement effect. In the case of sustained-release products, steady-state plasma concentrations are achieved within 3 days in most patients.

Theophylline is distributed into all body compartments and crosses the placental barrier producing high fetal concentrations. It is also excreted in human breast milk. Volume of distribution (V_d) ranges from 0.3 to 0.7 L per kg (30-70% ideal body weight) and averages 0.45 L per kg among both children and adults. However, the mean V_d for premature neonates, adults with hepatic cirrhosis or uncorrected acidemia, and the elderly is slightly larger since protein binding is reduced in these patients.

Theophylline is metabolized by the liver to 3-methylxanthine, 1-methyluric acid and 1,3-dimethyluric acid. About 10% of a dose is excreted unchanged in the urine.

The enzymes responsible for theophylline metabolism are unknown but do not include xanthine oxidase. Serum uric acid concentrations do not increase; therefore, the drug is not contraindicated in the presence of either gout or allopurinol administration.

The half-life of theophylline is influenced by a number of known variables. It is prolonged in patients suffering from chronic alcoholism, impaired hepatic or renal function, congestive heart failure, and in patients receiving macrolide antibiotics and cimetidine. Older adults (over age 55) and patients with chronic obstructive pulmonary disease, with or without cor pulmonale, may also have much slower clearance rates. For such patients, the theophylline half-life may exceed 24 hours.

Administration of influenza vaccine and infection with influenza have been associated with the impaired rate of theophylline elimination and consequent increases in serum theophylline levels, sometimes with toxic symptoms.

The half-life of theophylline in smokers (one to two packs/day) averages four to five hours, much shorter than the half-life in non-smokers which averages seven to nine hours. The increase in theophylline clearance caused by smoking is probably the result of induction of drug metabolizing enzymes that do not readily normalize after cessation of smoking. It appears that between three months and two years may be necessary for normalization of the effect of smoking on theophylline pharmacokinetics.

Comparative Bioavailability

A multi-dose, two-way, randomized crossover study was performed on healthy human volunteers. The rate and extent of absorption of theophylline was measured and compared following oral administration of one 300 mg tablet (AA-THEO LA or THEO-DUR) every 12 hours for 9 doses. Results for AUC and C_{max} are reported for the 96 - 108 hour steady-state interval and are summarized as follows:

	<u>Geometric means (CV)</u>		
	<u>THEO DUR</u>	<u>AA-THEO LA</u>	Percentage of THEO-DUR
AUC _T (mcg.hr/mL)	102.72 (26)	95.89 (24)	93.4
C _{max} (mcg/mL)	9.57 (23)	8.89 (24)	92.9

An additional single-dose bioavailability study was performed to determine the effect of food on the bioavailability of theophylline tablets. The rate and extent of absorption of theophylline after a single 1000 mg oral dose of AA-THEO LA (5x 200 mg tablets) administered under fasting and fed conditions were measured and compared. The results are summarized as follows:

	<u>Arithmetic mean (SD)</u>	
	AA-THEO LA without food	AA-THEO LA with food
AUC _T (mcg.hr/mL)	353.2 (101.3)	347.4 (97.3)
C _{max} (mcg/mL)	17.79 (2.68)	20.29 (2.85)

TOXICOLOGY

Theophylline has a narrow therapeutic range which, in connection with an inter- and intra-individual pharmacokinetic variation makes it difficult to estimate a toxic dose. Usually, a dose of 600mg theophylline given to an adult will not cause any toxic effects. Rather, the risk of toxic effects is related to the plasma level of theophylline, and plasma concentrations above 20 mcg/ml (110 μ mol/L) may produce toxic effects.

The risk of severe toxic effects is markedly increased with plasma concentrations in excess of 25 mcg/ml (140 μ mol/L).

Tolerance to many of the toxic effects of theophylline is widely recognized. The tolerance of an oral overdose of theophylline is individual, and doses of 50 mg/kg and higher have been reported as lethal. Rectal administration of 9 mg/kg theophylline as aminophylline (ethylenediamine, salt of theophylline) has produced adverse drug experiences in children.

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