PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAA-THEO LA

Theophylline Anhydrous

Sustained-Release Tablets, 100, 200, 300 mg and Oral

House Standard

Bronchodilator

ATC Code: R03DA04

AA PHARMA INC.

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Vaughan, Ontario

L4K 4N7

Date of Initial Authorization:
DEC 31, 1993

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RECENT MAJOR LABEL CHANGES

1 Indications	12/2021
3 Serious Warnings and Precautions Box	12/2021
7 Warnings and Precautions	12/2021

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AA-THEO LA (theophylline) Tablets are indicated for:

Symptomatic treatment of reversible bronchospasm associated with asthma, chronic bronchitis, emphysema and related bronchospastic disorders in patients 12 years and older.

1.1 Pediatrics

Pediatrics (<12 years of age): The use of AA-THEO LA in children under the age of twelve years is not recommended.

1.2 Geriatrics

Geriatrics (>65 years of age): Dose Reduction may be required in elderly patients (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

AA-THEO LA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging. AA-THEO LA (theophylline sustained release tablets) should not be administered in patients with:

- hypersensitivity to theophylline, xanthines derivative, or the excipients used in these drug products, or component of the container.
- coronary artery disease (where cardiac stimulation might prove harmful)
- peptic ulcers
- concomitant use with ephedrine in children

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

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. Serum theophylline levels should be monitored in patients (see 7 WARNINGS AND PRECAUTIONS and 9 DRUG INTERACTIONS).

Serious side effects associated with overdosage include 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).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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 7 WARNINGS AND 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.

Elderly patients are at a greater risk of experiencing serious toxic effects from theophylline than younger patients. Careful attention to dose reduction and monitoring of serum theophylline concentrations are required in elderly patients due to pharmacokinetic and pharmacodynamic changes associated with aging, including the potential for decreased theophylline clearance.

4.2 Recommended Dose and Dosage Adjustment

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.

4.4 Administration

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

5 OVERDOSAGE

Overdoses of theophylline may cause serious side effects such as tachycardia, arrhythmias, seizures, vascular collapse and even death. These may occur without warning and may not be preceded by less severe side effects such as nausea or restlessness.

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 overdosage.

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 overdosages.

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) Administration of oral activated charcoal has been found to reduce high theophylline serum concentrations. Multiple doses of activated charcoal should be also considered. Seizure prophylaxis may be indicated for certain patients.

2) Administer a cathartic (this is particularly important when a sustained-release preparation has been taken). Repeated doses of cathartic are not recommended due to possible adverse effects.

3) In severe poisoning or cases where gastric decontamination is not feasible, extracorporeal removal (i.e., hemodialysis, charcoal-column hemoperfusion) can be employed.

C. If the patient is having a seizure:

1) Establish an airway.

2) Administer oxygen.

3) Intravenous benzodiazepines are generally considered as first line therapy although some benzodiazepines may have reduced efficacy in theophylline overdose due to suspected pharmacodynamics interactions. Second line agents should be used if resistant, although phenytoin should be avoided.

4) Monitor vital signs, maintain blood pressure and provide adequate

hydration.

D. Post-seizure coma:

1) Maintain airway and oxygenation.

2) Consider the recommendations (B above, steps 1 to 3) to prevent absorption of the drug. Note that an unprotected airway is a contraindication to activated charcoal administration due to concerns of aspiration.

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.

The human oral lethal dose is estimated to be from 50 to 500 mg/kg. Children are more susceptible to the toxic effects of theophylline than adults.

The incidence of adverse reactions increases at serum concentrations over 15 mg/L (82.5 µmol/L). Levels in excess of (20 mg/L) 110 µmol/L are usually quite toxic in most patients, although a few patients can tolerate higher levels without significant side-effects. Tolerance to some of the toxic effects of theophylline is known to occur.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 100 mg, 200 mg and 300 mg	colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, and magnesium stearate.

AA-THEO LA is available in bottles of 100.

Description

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 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.

7 WARNINGS AND PRECAUTIONS

General

In clinical situations where immediate bronchodilation is required, such as status asthmaticus, AA-THEO LA is not appropriate.

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.

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.

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.

Monitoring and Laboratory Tests

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.
5) patients on a high carbohydrate, low protein diet

6) patients with hypothyroidism (and when starting acute treatment for hypothyroidism)
7) patients with a sustained high fever

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

Cardiovascular

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

Many patients who require theophylline may exhibit tachycardia due to their underlying disease process so that the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated.

Use with caution in patients with severe cardiac disease, severe hypoxemia, hypertension, acute myocardial injury, cor pulmonale, congestive heart failure.

Endocrine and Metabolism

Due to potential increased theophylline clearance, dose increase and monitoring of serum theophylline concentrations may be required in patients with hyperthyroidism (and when starting acute hyperthyroidism treatment) and cystic fibrosis.

Gastrointestinal

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 mcmol/L).

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

Hepatic

Use with caution in patients with liver disease or porphyria.

Neurologic

Theophylline may exacerbate frequency and duration of seizures and therefore caution should be exercised in patients with history of seizures.

Renal

Use with caution in elderly males with pre-existing partial urinary tract obstruction, such as prostatic enlargement, due to risk of urinary retention.

Respiratory

Particular care is advised in patients suffering from severe asthma who require acute theophylline administration. It is recommended that serum theophylline concentrations are

monitored in such situations.

7.1 Special Populations

7.1.1 Pregnant Women

Theophylline crosses the placental barrier, where concentrations are similar to plasma levels. Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. AA-THEO LA should not be administered during pregnancy unless considered essential by the physician. Theophylline should be given to pregnant women only when the anticipated benefits outweigh the risk to the child.

7.1.2 Breast-feeding

Theophylline passes freely into breast milk, where concentrations are similar to plasma levels. Therefore, use of theophylline for uncontrolled asthma in nursing mothers should be balanced against the risk of potential effects on the nursing newborn.

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Dose reduction may be required in elderly patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions are gastric irritation, 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 classified by body system include:

Gastrointestinal: Abdominal pain, 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 and tremors, clonic and tonic generalized convulsions.

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

Skin and Subcutaneous: Prurtius and rash.

Immune: Anaphlactic reaction, anaphylactoid reaction and hypersensitivity.

Respiratory: tachypnea.

Psychiatric: Agitation, anxiety, insomnia and sleep disorder.

Renal: albuminuria, diuresis, hematuria and urinary retention.

Others: hyperuricemia, hyperglycemia and inappropriate ADH syndrome.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Concurrent use of theophylline and a number of drugs (e.g. cimetidine, macrolides, phenytoin, quinolones) has been shown to be associated with an increased risk of hospitalization. As theophylline is metabolized by CYP1A2, concomitant use of drugs that inhibit this enzyme is expected to decrease theophylline clearance.

9.4 Drug-Drug Interactions

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

DRUG	THEOPHYLLINE
Acyclovir, allopurinol, carbimazole, cimetidine, diltiazem, disulfiram, fluconazole, interferon, quinolone antibiotics (ciprofloxacin), macrolide antibiotics (erythromycin), methotrexate, mexiletine, oral contraceptives, propranolol, pentoxifylline, selective serotonin re-uptake inhibitors (e.g. fluvoxamine), terbinafine, thiabendazole, verapamil	↑ $t_{½}$, ↓ clearance
Alkalinizing agents	↑ $t_{½}$, ↓ clearance
Treatments associated with hypothyroidism	↑ $t_{½}$, ↓ clearance
Treatments associated with hyperthyroidism	↓ $t_{½}$, ↑ clearance
Influenza vaccine	↑ $t_{½}$, clearance reported to be decreased or no change.
Aminoglutethimide, barbiturates, carbamazepine, isoproterenol, phenytoin, rifampin, ritonavir, sulfinpyrazone	↓ $t_{½}$, ↑ clearance
Alcohol, smoking (tobacco)	↓ $t_{½}$, ↑ clearance
Acidifying agents	↓ $t_{½}$, ↑ clearance

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

DRUG	EFFECTS
Adenosine receptor agonists	Inhibits the effect of adenosine receptor agonists
Benzodiazepines	Opposes the sedatory effects
Digitalis glycosides	↑ Cardiac effect

Halothane	Occurrence of arrhythmias
Thiazides	↑ diuresis
Nephrotoxic drugs	↑ nephrotoxicity
Lithium	↑ Ratio of lithium/creatinine clearance, thus decrease serum lithium
Lomustine	Results in thrombocytopenia
Sympathomimetic amines	↑ toxicity, ↑ CNS stimulation
Coumarin anticoagulants	↓ anticoagulant activity, increase prothrombin and fibrinogen blood concentrations, shorten prothrombin time
Allopurinol	↓ antihyperuremic action
Probenecid and pyrazolon derivatives	↓ uricosuric action
Ketamine	↓ threshold value for inducing convulsions
Terbinafine	↑ exposure by 25% (AUC and Cmax)

For COPD patients, the concomitant use of theophylline and roflumilast should usually be avoided.

Care should be taken with concomitant use of β-adrenergic agonists, glucagon and other xanthine drugs, as these will potentiate the effects of theophylline. The incidence of toxic effects may be enhanced by the concomitant use of ephedrine.

Hypokalemia resulting from β_2 agonist therapy, steroids, diuretics and hypoxia may be potentiated by xanthines. Particular care is advised in patients suffering from severe asthma who require hospitalization. It is recommended that serum potassium concentrations are monitored in such situations. Theophylline may decrease steady-state phenytoin levels.

9.5 Drug-Food Interactions

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

9.6 Drug-Herb Interactions

Theophylline clearance is increased with concurrent use of Hypericum perforatum (St. John's Wort).

9.7 Drug-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.

Theophylline may cause elevation of urine catecholamines, plasma uric acid and free fatty acids.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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 mcmol/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.

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.

10.2 Pharmacodynamics

Theophylline is chemically named 1,3-dimethyl-xanthine. Thepharmacologic 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.

10.3 Pharmacokinetics

Absorption

Theophylline is usually readily absorbed following oral administration.

Distribution:

The drug is 55-65% bound to plasma proteins at the therapeutic plasma concentration range of 10 to 20 mcg/ml (55-110 mcmol/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 (Vd) 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 Vd for premature neonates, adults with hepatic cirrhosis or uncorrected acidemia, and the elderly is slightly larger since protein binding is reduced in these patients.

Metabolism:

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 metabolism of theophylline at therapeutic concentrations is primarily dependant on the CYP1A2 enzyme.

Serum uric acid concentrations do not increase; therefore, the drug is not contraindicated in the presence of either gout or allopurinol administration.

Elimination

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

	Nonsmoking Adults
Theophylline sustained- release tablets 200, 300 mg	27%
Theophylline sustained- release tablets 100 mg	34%

Special Populations and Conditions

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.

11 STORAGE, STABILITY AND DISPOSAL

Store at controlled room temperature 15°C - 30°C.

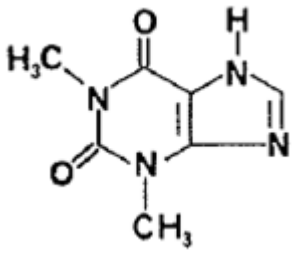
12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Theophylline anhydrous
Chemical name:	1,3-dimethyl-xanthine
Molecular formula and molecular mass:	$C_7H_8N_4O_2$ and 180.2 g/mol
Structural formula:	
Physicochemical properties:	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.

14 CLINICAL TRIALS

14.2 Comparative Bioavailability Studies

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:

	Geometric means (CV)		
	THEO DUR	AA-THEO LA	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:

	Arithmetic mean (SD)	
	AA-THEO LA without food	AA-THEO LA with food
AUC_T (mcg.hr/mL)	353.2 (101.3)	347.4 (97.3)
Cmax (mcg/mL)	17.79 (2.68)	20.29 (2.85)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Carcinogenicity:

No evidence of carcinogenicity was observed in 2-year oral gavage studies carried out in mice (oral doses of 7.5 - 150 mg/kg) and rats (oral doses of 7.5 - 75 mg/kg). Therefore, it is unlikely

that theophylline poses a carcinogenic risk in humans.

Genotoxicity:

Theophylline has been studied using the bacterial Ames test and with in vivo and in vitro cytogenetic tests. Theophylline showed limited evidence of mutagenicity in these tests.

Mammalian cells in vitro and in vivo showed increased sister chromatid exchanges, but negative results were observed in all other assays.

Reproductive and Developmental Toxicology:

In 13-week oral gavage studies conducted with 37.5, 75, and 150 mg/kg/day theophylline administered to mice and rats, significant effects on body and testicular weights were observed. Male mouse terminal body and testicular weights were reduced, and male rats had reduced testicular weights. Parallel studies in mice and rats with 0.1, 0.2 and 0.4% theophylline administered in the feed produced reduced body weights in male and female mice, but not rats. In rats, the average cauda epididymis weight was reduced at the high dose compared to a control group, and there was an increase in abnormal sperm.

In 14-week continuous breeding assays in mice using 125, 265, and 530 mg/kg/day (0.075, 0.15, and 0.30%) theophylline administered in the feed, negative effects on reproduction were observed. These included a dose-dependent decrease in the number of live pups produced per litter, a decrease in the number of litters produced per pair and a decrease in the live pup weight (high dose), a decrease in the percentage of pups born alive (mid and high doses), and an increase in the number of days needed to produce each litter (high dose).

The observed changes in fertility indicated the likelihood of embryotoxicity. Other studies have indicated that high dose theophylline can also have teratogenic effects. In mice, theophylline administered intraperitoneally during gestation produced cleft palate, aberrant digit formation, micrognathia, and micromelia in the offspring. Therefore theophylline should be considered to have the potential for developmental toxicity in humans.

17 SUPPORTING PRODUCT MONOGRAPHS

Product Monograph PrUNIPHYL® (Theophylline Sustained Release Tablets, 400 mg and 600 mg), Elvium Life Sciences, Date of Revision: (SEP 30, 2020), Submission control (241455).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAA-THEO LA

Theophylline Sustained-Release Tablets

Read this carefully before you start taking **AA-THEO LA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AA-THEO LA**.

Serious Warnings and Precautions

Your healthcare professional will monitor your theophylline levels, any medicines you take, and your lifestyle habits.

AA-THEO LA can cause serious side effects associated with an overdose such as:

- **abnormally fast heartbeat**
- **abnormal heart rhythm**
- **seizures**
- **vascular collapse**
- **death**

These may occur without warning. Less serious side effects such as nausea or restlessness may not happen before.

Tell your healthcare professional if you:

- **have severe heart disease**
- **have severe hypoxemia (low levels of oxygen in your blood)**
- **have high blood pressure**
- **have thyroid problems**
- **have had a heart attack**
- **have cor pulmonale (right sided heart enlargement and heart failure)**
- **have heart failure**
- **have liver disease**
- **are 65 years of age or older, especially male**

What is AA-THEO LA used for?

AA-THEO LA is used in adults and children 12 years of age and older for the treatment of breathing problems such as asthma, chronic bronchitis, emphysema, and other problems that cause spasms in the airway.

How does AA-THEO LA work?

AA-THEO LA contains the medicine theophylline. Theophylline opens the airways in the lungs which helps prevent wheezing and shortness of breath.

What are the ingredients in AA-THEO LA?

Medicinal ingredients: theophylline anhydrous

Non-medicinal ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, and magnesium stearate.

AA-THEO LA comes in the following dosage forms:

Sustained-release tablets: 100 mg, 200 mg and 300mg.

Do not use AA-THEO LA if:

- You are allergic to theophylline, xanthine derivatives, or the other ingredients of AA-THEO LA
- You have ulcers in your stomach or small intestine (peptic ulcers)
- You have damage or disease in the heart's major blood vessels
- You are giving this medicine to your child and they are also taking ephedrine

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AA-THEO LA. Talk about any health conditions or problems you may have, including if you:

- have liver or kidney problems;
- are over 55 years of age, particularly male, and have lung disease;
- have heart problems;
- have history of ulcers in your stomach or small intestine (peptic ulcers);
- are taking other theophylline derivatives or are switching from a different brand of theophylline;
- are pregnant or plan to become pregnant;
- are breast-feeding or are planning to breastfeed;
- start or stop smoking;
- have a history of seizures;
- have cystic fibrosis;
- have the flu (influenza) or another virus or have recently had the flu shot;
- have a continuous high fever;
- have a high carbohydrate and low protein diet;
- have a condition called porphyria that affects your blood cells;

- have prostate problems or trouble passing urine;
- have severe asthma.

Other warnings you should know about:

Laboratory Tests and Monitoring: Your healthcare professional may perform tests while you are receiving AA-THEO LA. This is to make sure that you are receiving the correct dose.

Emergency use: APO-THEO LA is **not** to be used in an emergency where rapid relief of breathing problems (bronchospasm) is required.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AA-THEO LA:

- cimetidine, a medicine used to treat stomach ulcers,
- medicines used to treat high blood pressure such as propranolol, verapamil, and diltiazem,
- medicines used to treat fungal, bacterial and viral infections such as fluconazole, terbinafine, ciprofloxacin, erythromycin, rifampin, ritonavir, and acyclovir,
- oral birth control,
- alkalinizing agents used to manage disorders associated with low pH,
- the flu shot (influenza vaccine),
- medicines used to treat seizures such as phenytoin and carbamazepine,
- barbiturates, medicines used to help you sleep,
- isoproterenol, a medicine used to treat breathing problems and slow heart rate,
- smoking (tobacco),
- acidifying agents,
- medicines used to treat heart problems such as digitalis glycosides and mexiletine,
- thiazides used as diuretic agents,
- medicines that damage the kidneys (nephrotoxic drugs),
- lithium, a medicine used to treat mental health problems,
- sympathomimetic amines, a medicine used to treat cardiac arrest and low blood pressure, or even delay premature labor,
- medicine used to prevent blood clots called coumarin,
- medicines used to treat gout such as sulfinpyrazone, allopurinol and probenecid,
- ketamine, a medicine used as an anesthetic,
- medicines used to treat cancer such as interferons, lomustine and methotrexate,
- medicines used to treat breathing problems such as adenosine receptor antagonists, xanthines, B-adrenergic agonists, and roflumilast,
- glucagon, a medicine used to treat low blood sugar,
- carbimazole, a medicine used to treat thyroid problems,
- disulfiram, a medicine used to support the treatment of alcohol use disorder
- benzodiazepines, medicines used to treat anxiety, seizures, panic disorders and insomnia
- pentoxifylline, a medicine used to treat muscle pain in people with peripheral artery disease
- aminoglutethimide, a medicine used to treat conditions where the body makes too much of a certain hormone, for example in Cushing's Syndrome,

- selective serotonin re-uptake inhibitors (SSRIs) such as fluvoxamine, medicines used to treat depression
- thiabendazole, a medicine used to kill parasites
- halothane, a medicine used for general anaesthesia
- St. John's Wort (*Hypericum perforatum*), a herbal medicine used to treat depression
- alcohol
- low carbohydrate and high protein diets
- high carbohydrate and low protein diets
- long-term ingestion of charcoal broiled meats.

Certain beverages and food may results in false values during laboratory tests of theophylline levels. This includes coffee, tea, cola beverages, chocolate, acetaminophen, and some cephalosporin and sulfa medicines.

How to take AA-THEO LA:

- Take AA-THEO LA exactly as your healthcare professionals tells you. Do NOT change your dose without talking to your healthcare professional. Talk to your healthcare professional if you are unsure.
- Swallow AA-THEO LA tablets whole.
- Do NOT break, crush or chew the tablets.

Usual dose:

Adults: The usual starting dose is 200-300 mg every 12 hours. Your healthcare professional will decide on the dose that is best for you. Based on how you respond and how you tolerate your medicine, your healthcare professional may change your dose.

Children (12 years of age and older): The use of AA-THEO LA in children under the age of 12 years is not recommended. For children 12 years of age and older, your dose will be decided by your healthcare professional.

Overdose:

Early symptoms of an overdose include difficulty sleeping, restlessness, mild excitement or irritability, rapid pulse, ringing in the ears, seeing flashes of light, loss of appetite, nausea, and vomiting. Other symptoms of an overdose include fever, increased amount of urine, dehydration and extreme thirst.

If you think you, or a person you are caring for, have taken too much AA-THEO LA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you missed a dose of this medication, take it as soon as you remember. But if it is almost time for your next dose, skip the missed dose and continue with your next scheduled dose. Go back to the regular

dosing schedule. Do not take two doses at the same time.

What are possible side effects from using AA-THEO LA?

These are not all the possible side effects you may have when taking AA-THEO LA. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- flushing
- difficulty emptying your bladder
- diarrhea
- muscle twitching
- rash and itching
- being unusually or abnormally active
- feeling restless or irritable
- difficulty sleeping (insomnia)
- loss of appetite (anorexia)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Epigastric pain: pain in the upper abdomen	✓		
Headache	✓		
Nausea	✓		
Tremor: involuntary rhythmic shaking in one or more parts of your body		✓	
Vomiting		✓	
UNKNOWN			
Albuminuria (presence of protein in urine): swelling of the hands, feet, face		✓	
Allergic Reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat			✓
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat			✓
Diuresis (increased urine production)		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Gastrointestinal (GI) bleeding: blood in vomit, black tarry stool, bright red blood in your stool or coming from rectum, rapid pulse, low blood pressure, low urine flow, confusion, weakness, dizziness			✓
Hematemesis: vomiting blood, black tarry stool			✓
Hematuria (blood in the urine): pink, red or very dark urine		✓	
Hyperglycemia: (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision and fatigue		✓	
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up)		✓	
Palpitation (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly		✓	
Reactivation of peptic ulcer: vomiting, abdominal pain, dark stools, weight loss			✓
Seizures (fits): uncontrollable shaking with or without loss of consciousness			✓
Syndrome of inappropriate antidiuretic hormone secretion (SIADH): concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits (seizures) which may be due to inappropriate secretion of ADH (antidiuretic hormone).			✓
Tachycardia (abnormally fast heartbeat): dizziness, light headedness, shortness of breath, racing heart		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Tachypnea (abnormally rapid breathing): feeling short of breath, blue tint to the fingers and lips		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Keep out of reach and sight of children.

If you want more information about AA-THEO LA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (https://www.aapharma.ca/en/), or by calling 1-877-998-9097.

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