

Revised: December 2007 (11th version)

Standard Commodity Classification No. of Japan
872115

- Cardiotonic and antiasthmatic agent -

**Neophyllin<sup>®</sup> Tablets 100 mg**

&lt;Aminophylline hydrate preparation&gt;

Prescription drug

Storage
NEOPHYLLIN should be stored at room temperature. NEOPHYLLIN should be protected from light and moisture after opening package (contents may change color).

Approval No.	21900AMX00667000
Date of listing in the NHI reimbursement price	Jun 2007
Date of initial marketing in Japan	Oct 1950
Date of latest reevaluation	Mar 1998

Expiration date
NEOPHYLLIN should be used before the expiration date indicated on the package or label.

Caution
See "PRECAUTIONS FOR HANDLING" section.

Caution : Use only as directed by a physician.

**CONTRAINDICATIONS (NEOPHYLLIN is contraindicated in the following patients.)**




Patients with a history of serious adverse reactions to NEOPHYLLIN or other xanthine derivatives

**DESCRIPTION****1. Composition**

Each white plain tablet contains 100 mg of aminophylline hydrate.

It also contains carmellose calcium, calcium stearate, cornstarch, hydroxypropylcellulose and povidone as inactive ingredients.

**2. Product description**

Brand name	Dosage form and identification code	Appearance			Description
		Face	Reverse	Lateral	
NEOPHYLLINE Tablets 100mg	Plain tablets				White scored
	EISAI NE100	Diameter (mm) 8.1	Weight (mg) 200	Thickness (mm) 3.0	

**INDICATIONS**

Bronchial asthma, asthmatic (asthmatoïd) bronchitis, dyspnea caused by obstructive pulmonary diseases (pulmonary emphysema and chronic bronchitis, etc.), cor pulmonale, congestive heart failure and cardiac asthma (prevention of attack)

**DOSAGE AND ADMINISTRATION**

The usual adult dosage for oral use is 3 to 4 tablets (300 to 400 mg of aminophylline hydrate) daily in three to four divided doses.

The children's dosage for oral use is 2-4 mg/kg of aminophylline hydrate three to four times daily.

The dosage may be adjusted depending on the patient's age and symptoms.

**PRECAUTIONS****1. Careful Administration (NEOPHYLLIN should be administered with care in the following patients.)**

- (1) Patients with epilepsy  
[Seizures may be caused by central nervous system (CNS) stimulation.]
- (2) Patients with hyperthyroidism  
[Hypermetabolism accompanying hyperthyroidism and the action of catecholamines may be potentiated.]
- (3) Patients with acute nephritis  
[Since NEOPHYLLIN enhances kidney load, urinary protein may increase.]
- (4) Patients with hepatic function disorders  
[Since the theophylline clearance may diminish causing an increase in the blood theophylline concentration, the dosage should be reduced on the basis of the determined blood theophylline concentration, etc.]
- (5) Elderly patients  
[See "Use in the Elderly" section.]
- (6) Pregnant women, women suspected of being pregnant, parturient women or nursing mothers  
[See "Use during Pregnancy, Delivery or Lactation" section.]
- (7) Children
  - 1) Since convulsions are likely to occur in children (especially nursing infants) more frequently than in adults, and also, because theophylline clearance may be variable, NEOPHYLLIN should be administered with care to them, monitoring the blood theophylline concentration. Particular care is required with the following.
    - a) Children with a history of epilepsy or convulsions  
[Convulsions may occur.]

## b) Children with fever

[The blood theophylline concentration may increase and convulsions or other symptoms may occur.]

## c) Nursing infants (&lt;6 months)

[The theophylline clearance is unsteady in nursing infants. There may be an decrease in the theophylline clearance and an increase in the blood theophylline concentration in nursing infants (<6 months).]

- 2) The safety in low birth weight infants and neonates has not been established (no clinical experience).

## 2. Important Precautions

- (1) If NEOPHYLLIN is administered to patients with congestive heart failure, the blood theophylline concentration may increase. Caution should be taken for such patients.
- (2) The occurrence of adverse reactions due to theophylline may cause an increase in the blood theophylline concentration. It is advisable to regularly monitor the blood theophylline concentration and based on this, set up an individual dosage plan for each patient.
- (3) If adverse reactions occur, NEOPHYLLIN should be reduced in dosage or discontinued, and it is advisable to determine the blood theophylline concentration.
- (4) When the drug is administered to children, especially infants, it is advisable that the parents be instructed in advance to take actions such as temporarily decreasing the dosage or discontinuing the drug in the case that pyrexia is observed.
- (5) When the drug is used for children, due to their general inability to complain of subjective symptoms, parents should be advised to observe their condition carefully, and if any abnormality is observed, report this immediately to the physician, or take other appropriate measures.

## 3. Drug Interactions

NEOPHYLLIN is metabolized mainly by CYP1A2. [See “PHARMACOKINETICS” section.]

Precautions for coadministration (NEOPHYLLIN should be administered with care when coadministered with the following drugs.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Other xanthine derivatives Theophylline Choline theophylline Diprophylline Caffeine, etc. CNS stimulants Ephedrine hydrochloride Ephedra herb, etc.	NEOPHYLLIN may cause excessive CNS stimulation. [See “Overdosage” section.] Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken.	When concomitantly administered with these drugs, CNS stimulation may be potentiated.

Sympathetic nervous system stimulants ( $\beta$ -stimulants) Isoprenaline hydrochloride Clenbuterol hydrochloride Tulobuterol hydrochloride Terbutaline sulphate Procaterbol hydrochloride, etc.	Adverse reactions due to $\beta$ -stimulants such as hypokalemia or cardiovascular symptoms (tachycardia, arrhythmia, etc.) may be potentiated. Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken.	It is considered that the action of $\beta$ -stimulants may be potentiated due to their cardiostimulant action. The mechanism of hypokalemia enhancement is unknown.
Halothane	Adverse reactions such as arrhythmia, etc. may be potentiated. Also, continuous coadministration with halothane may cause an increase in the blood theophylline concentration. Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken.	It is considered that theophylline and halothane have synergistic and additive effects with respect to the heart.
Ketamine hydrochloride	Convulsions may occur. Caution should be exercised with respect to convulsions. In the event of abnormal findings, appropriate measures such as the administration of an anticonvulsant, should be taken.	Considered to be due to lowering of the convulsant threshold.
Cimetidine Mexiletine hydrochloride Propafenone hydrochloride Amiodarone hydrochloride Enoxacin Pipemidic acid trihydrate Ciprofloxacin hydrochloride Norfloxacin Tosufloxacin tosylate Pazufloxacin mesilate Prulifloxacin Erythromycin Clarithromycin Roxithromycin Tiabendazole Ticlopidine hydrochloride Verapamil hydrochloride Diltiazem hydrochloride Fluvoxamine maleate Fluconazole Disulfiram	Symptoms of theophylline toxicity may occur. [See “Overdosage” section.] Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken.	It is considered that the blood theophylline concentration increases due to decreasing theophylline clearance by the inhibition of hepatic drug metabolizing enzymes.
Aciclovir Valaciclovir hydrochloride Interferon Ipriflavone Ciclosporin Allopurinol		Considered to be due to increase in the blood theophylline concentration.

Zafirlukast	Symptoms of theophylline toxicity may occur. [See "Overdosage" section.] Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken. Also NEOPHYLLIN may decrease the blood concentration of zafirlukast.	It is considered that the blood theophylline concentration increases due to decreasing theophylline clearance by the inhibition of hepatic drug metabolizing enzymes. The mechanism by which NEOPHYLLIN decreases the blood concentration of zafirlukast is unknown.
Rifampicin Phenobarbital Lansoprazole Ritonavir	Effect of theophylline may be diminished. As the blood theophylline concentration may decrease, appropriate measures should be taken.	It is considered that the blood theophylline concentration decreases due to increasing theophylline clearance through the induction of hepatic drug metabolizing enzymes.
Phenytoin Carbamazepine	The effects of theophylline and the co-administered drug may be diminished. As the blood theophylline concentration may decrease, appropriate measures should be taken. Also, caution should be exercised with respect to decreasing effect and blood concentration of coadministered drug.	It is considered that the blood theophylline concentration decreases due to increasing theophylline clearance through the induction of hepatic drug metabolizing enzymes.
Dipyridamole	NEOPHYLLIN may diminish the effect of dipyridamole.	Due to adenosine antagonism.
Ramatroban	NEOPHYLLIN may elevate the blood concentration of ramatroban.	The mechanism of elevation of the blood concentration of ramatroban is unknown.
Riluzole	NEOPHYLLIN may increase the action of riluzole (induction of adverse reactions).	An <i>in vitro</i> study has suggested that NEOPHYLLIN inhibits the metabolism of riluzole.
Cigarette smoking	Symptoms of theophylline toxicity may occur when someone stops smoking (including during use of nicotine preparations as a supporting agent to stop smoking). [See "Overdosage" section.] Caution should be exercised with respect to adverse reactions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken.	It is considered that the blood theophylline concentration decreases due to the increasing theophylline clearance, through the induction of hepatic drug metabolizing enzymes by smoking. Also, it is considered that blood theophylline concentration is increased by stopping smoking.
<i>Hypericum perforatum</i> (foods including St. John's Wort)	Foods including <i>Hypericum perforatum</i> may potentiate the metabolism of NEOPHYLLIN and decrease the blood theophylline concentration. These foods should be avoided when taking NEOPHYLLIN.	It is considered that hepatic drug metabolizing enzymes induced by <i>Hypericum perforatum</i> potentiate the metabolism of NEOPHYLLIN and increase theophylline clearance.

#### 4. Adverse Reactions (incidence unknown)

##### (1) Clinically significant adverse reactions

###### 1) Shock and anaphylactic shock

Shock or anaphylactic shock (urticaria, pallor, diaphoresis, decrease in blood pressure or dyspnea, etc.) may occur. In the event of such symptoms, treatment should be discontinued and appropriate measures taken.

###### 2) Convulsions and disturbed consciousness

Convulsions or disturbed consciousness such as delirium or coma, may occur. Appropriate measures, such as the administration of an anticonvulsant, should be taken.

###### 3) Acute encephalopathy

Acute encephalopathy may occur in continuation to convulsions and disturbed consciousness. In the event of such symptoms, treatment should be discontinued and appropriate measures, such as administration of anticonvulsants, taken.

###### 4) Rhabdomyolysis

Since rhabdomyolysis may occur, caution should be exercised with respect to weakness, myalgia or elevation of CK (CPK), etc. In the event of such symptoms, treatment should be discontinued and appropriate measures taken. Caution should be exercised with respect to acute renal failure due to rhabdomyolysis.

###### 5) Gastrointestinal hemorrhage

Gastrointestinal hemorrhage (hematemesis of melena) caused by ulcers may occur. In the event of such symptoms, appropriate measures, such as discontinuation of the medication, should be taken.

###### 6) Pure red cell aplasia

Pure red cell aplasia may occur. In the event of anemia, appropriate measures, such as discontinuation of the medication, should be taken.

###### 7) Hepatic function disorders and jaundice

Hepatic function disorders (elevation of AST (GOT) or ALT (GPT), etc.) and jaundice may occur. Patients should be carefully observed. In the event of abnormal findings, treatment should be discontinued and appropriate measures taken.

###### 8) Tachypnea and hypoglycemia

Tachypnea or hypoglycemia may occur.

##### (2) Other adverse reactions

	Incidence unknown
Hypersensitivity	Rash, pruritus, urticaria, erythema (erythema exsudativum multiforme, etc.) and fixed eruption
Psychoneurologic	Headache, insomnia, nervousness (excitement, moroseness or irritated feeling), anxiety, dizziness, tinnitus, tremors, numbness, involuntary movement and hypertonia
Cardiovascular	Hot facial flush, palpitations, tachycardia, facial pallor and arrhythmia (ventricular extrasystole, etc.)
Gastrointestinal	Nausea, vomiting, anorexia, abdominal pain, diarrhea, feeling of enlarged abdomen, dyspepsia (heart burn etc.) and hiccups
Urinary	Proteinuria and pollakiuria
Metabolic	Elevation of serum level of uric acid and CK (CPK), etc.
Hepatic	Elevation of AST (GOT), ALT (GPT), Al-P, LDH and $\gamma$ -GTP, etc.
Hematologic	Anemia and eosinophilia
Others	Edema, malaise, arthralgia, melosalgia, sweating, chest pain, hypokalaemia, epistaxis and numbness (mouth and periglottic area)

## 5. Use in the Elderly

NEOPHYLLIN should be administered with care to elderly patients watching for the occurrence of the adverse reactions.

[When elderly subjects were compared with young subjects, it was reported that the peak blood theophylline concentration and AUC were higher in the elderly than in the young.]

## 6. Use during Pregnancy, Delivery or Lactation

(1) NEOPHYLLIN should only be used for pregnant women or women suspected of being pregnant, if the expected therapeutic benefits are evaluated to outweigh the possible risk of treatment.

[NEOPHYLLIN has been reported to have reproductive toxicity, such as teratogenic effects on the fetus, etc. in animals (mice, rats and rabbits). Also, NEOPHYLLIN may be transported across the placenta to the fetus and cause vomiting and nervousness, etc. in neonates.]

(2) Nursing mothers should discontinue breast feeding during treatment.

[NEOPHYLLIN is excreted into human milk, giving rise to nervousness in nursing infants.]

## 7. Pediatric Use

NEOPHYLLIN should be administered with care to children.

[See "Careful Administration" section.]

## 8. Overdosage

### (1) Symptoms

When the blood theophylline concentration is high, toxic symptoms, such as gastrointestinal symptoms (notably nausea or vomiting), psychoneurologic symptoms (headache, insomnia, anxiety, excitement, convulsions, delirium, disturbed consciousness or coma, etc.), cardiovascular symptoms (tachycardia, ventricular tachycardia, atrial fibrillation or decrease in blood pressure, etc.), hypokalemia or other electrolyte abnormalities, stimulated respiration or rhabdomyolysis, etc. are likely to occur. Serious symptoms may appear immediately, without developing gradually from mild symptoms.

### (2) Treatments

In the case of overdosage, theophylline should be withdrawn and symptomatic therapy for toxic symptoms conducted. Procedures for the removal of residual theophylline in the gastrointestinal tract are emesis, gastric lavage, administration of purgatives and oral administration of activated charcoal, etc. Procedures for removal of theophylline in the blood are accelerated elimination using an infusion solution, oral administration of activated charcoal, hemoperfusion or hemodialysis using charcoal as adsorbent, etc. Although the blood theophylline concentration may have decreased, it may rise again due to the transfer of theophylline from the tissues.

1) If the patient has no convulsions or arrhythmias

a) If the patient is seen within a few hours of overdosage, induction of emesis may be of value. This is particularly effective if it is within 1 hr.

b) Administer purgatives. But, caution should be exercised with respect to body fluid and electrolyte abnormalities.

c) Administer repeated doses of activated charcoal and monitor the blood theophylline concentration.

d) If convulsions are anticipated, the administration of phenobarbital, etc., should be considered. Since phenobarbital may cause respiratory depression, caution should be exercised in administration.

2) If the patient has convulsions

a) Establish an airway.

b) Supply oxygen.

c) Treat the convulsions with intravenous diazepam, etc. If they cannot be controlled, the use of a general anesthetic should be considered.

d) Monitor vital signs, maintain blood pressure and provide adequate hydration.

3) If the patient is in a post-convulsion coma

a) Maintain an airway and supply oxygen.

b) Purgatives and activated charcoal will need to be administered via a large bore gastric lavage tube.

c) Keep the patient in the ICU with adequate hydration until the blood theophylline concentration falls. If the repeated oral administration of activated charcoal does not decrease the blood concentration, hemoperfusion or hemodialysis using activated charcoal should be considered.

4) If the patient has arrhythmia

a) Take adequate measures such as pacing, direct current defibrillation or the use of antiarrhythmic drugs, etc.

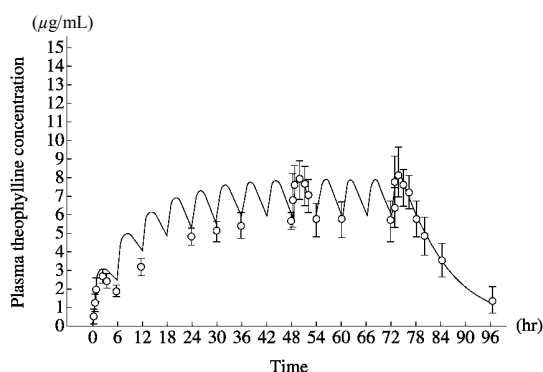
b) Monitor vital signs, maintain blood pressure and provide adequate hydration. Also, if electrolyte abnormalities are present, they should be corrected.

## PHARMACOKINETICS

### 1. Blood concentration

#### (1) Time course of the blood concentration

When NEOPHYLLIN Tablets 100 mg was administered orally to 7 healthy adult male volunteers at 100 mg of aminophylline four times a day every 6 hr (400 mg/day) for 13 consecutive times, the plasma theophylline concentration increased gradually for 2 days and reached an almost steady-state on the third day after administration (after 48 hr). The peak plasma theophylline concentration ( $C_{max}$ ), time to reach  $C_{max}$  ( $t_{max}$ ), half-life ( $t_{1/2}$ ) and area under the plasma concentration-time curve (AUC) at the steady-state (the 13th time) are shown in the following table.



Time course of plasma theophylline concentration for oral consecutive administration of NEOPHYLLIN Tablets 100 mg (Mean±S.D., n=7)

Pharmacokinetic parameters at steady-state of NEOPHYLLIN Tablets 100 mg (n=7)

	$C_{max}$	$t_{max}$	$t_{1/2}$	AUC
Mean	8.62 µg/mL	1.43hr	9.61hr	42.70 µg · hr/mL
S.D.	1.26	0.53	1.65	5.79

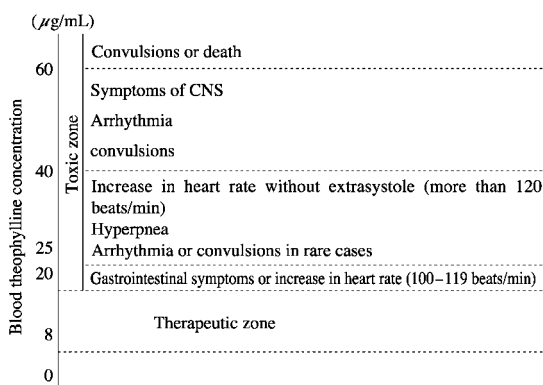
(2) Therapeutic Drug Monitoring (TDM)

Range of effective blood concentration: 8-20µg/mL in adults

Main cytochrome P450 subfamily involved in metabolism: CYP1A2

2. Correlation between blood concentration and therapeutic effect-adverse reactions

It is essential to determine the dosage of aminophylline and other theophylline preparations by monitoring the blood theophylline concentration. In most cases, the therapeutic blood theophylline concentration is considered to be 8-20 µg/mL. However, accompanying an increase in the blood concentration, since theophylline tends to cause adverse reactions such as gastrointestinal symptoms, the administration should be started with a standard dose and increased or decreased depending on the patient's symptoms.<sup>1-3)</sup>



Correlation between the blood theophylline concentration and therapeutic effects-adverse reactions

PHARMACOLOGY

1. Myocardial stimulation

Experiments on isolated myocardia from animals have demonstrated that aminophylline directly stimulates the myocardium and increases the cardiac output. Since aminophylline increases the cardiac output of patients with heart disease through myocardial stimulation accompanied by a reduction in venous pressure, it is effective for congestive heart failure.<sup>4-6)</sup>

2. Diuretic action

Aminophylline hydrate increases the urine volume and the excretion of both  $Na^+$  and  $Cl$  in dogs. The mechanism of the diuretic action involves an increase in renal blood flow and glomerular filtration rate due to cardiovascular effects, or inhibition of tubular reabsorption of  $Na^+$  and  $Cl$ , etc.<sup>4,7-9)</sup>

3. Bronchodilation

Aminophylline hydrate dilates isolated guinea pig bronchi and this bronchodilative effect has also been confirmed clinically in asthmatic patients. Aminophylline hydrate has also been demonstrated to remedy decreased pulmonary artery pressure and impaired respiratory function in patients with obstructive pulmonary diseases.<sup>10-12)</sup>

4. Mechanism of action

Active ingredient of NEOPHYLLIN, Aminophylline hydrate is the salt which consists of 2 molecules of theophylline and 1 molecules of ethylenediamine, and exists as theophylline in body.

Several hypotheses have been proposed to elucidate the mechanism of action of theophylline: they include increasing the cellular concentration of c-AMP through inhibition of phosphodiesterase activity; antagonism to adenosine receptors; regulation of intracellular  $Ca^{2+}$  distribution, etc.<sup>4,13,14)</sup>

PHYSICOCHEMISTRY

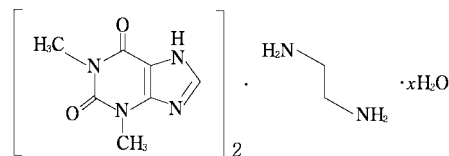
Nonproprietary name: Aminophylline Hydrate

Chemical name:

1,3-Dimethyl-1*H*-purine-2,6 (3*H*,7*H*)-dione hemi (ethylenediamine) hydrate

Molecular formula:  $C_{14}H_{16}N_8O_4 \cdot C_2H_8N_2 \cdot xH_2O$

Structural formula:



Description:

Aminophylline hydrate occurs as white to pale yellow granules or powder. It is odorless or slightly ammonia-like odor, and has a bitter taste.

It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol (95) and in diethylether. To 1 g of aminophylline add 5 mL of water, and shake: it dissolves almost completely. Separation of crystals begins in 2 to 3 minutes, and these crystals dissolve on the addition of a small amount of ethylenediamine.

It is gradually affected by light, and gradually loses ethylenediamine in air.

### **PRECAUTIONS FOR HANDLING**

When NEOPHYLLIN is dispensed with other drugs, there may frequently be incompatibility. It is advisable not to dispense NEOPHYLLIN with other drugs.

### **PACKAGING**

#### **NEOPHYLLIN Tablets 100 mg:**

Bottles of 100 and 500

### **REFERENCES**

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### **REQUEST FOR LITERATURE SHOULD BE MADE TO:**

Safety Management Department

Fax: 03-3811-2710

Eisai Co., Ltd.

### **REQUEST FOR DRUG INFORMATION SHOULD BE MADE TO:**

Customer Information Services Section

Phone: 0120-419-497

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