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 gram of white to pale yellow granules or powder contains 1 g of aminophylline hydrate, JP.

2. Product description
NEOPHYLLIN is white to pale yellow granules or powder.

INDICATIONS
Bronchial asthma, asthmatic (asthmoid) 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 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 (<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.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other xanthine derivatives</td>
<td>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.</td>
<td>When concomitantly administered with these drugs, CNS stimulation may be potentiated.</td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Choline theophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diphenoxylate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeine hydrodate, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS stimulants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedrine hydrochloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedra herb, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathetic nervous system stimulants (β-stimulants)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoprenaline hydrochloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clenbuterol hydrochloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terbutaline sulphate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaterol hydrochloride hydrate, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse reactions due to β-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.</td>
<td></td>
<td>It is considered that the action of β-stimulants may be potentiated due to their cardiotonic action. The mechanism of hypokalemia enhancement is unknown.</td>
</tr>
<tr>
<td>Halothane</td>
<td>Adverse reactions such as arrhythmia, etc. may be potentiated. Also, continuous co-administration 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.</td>
<td>It is considered that theophylline and halothane have synergistic and additive effects with respect to the heart.</td>
</tr>
<tr>
<td>Ketamine hydrochloride</td>
<td>Convolusions may occur. Caution should be exercised with respect to convulsions. In the event of abnormal findings, appropriate measures such as discontinuation of the medication or reduction in dosage, should be taken.</td>
<td>Considered to be due to lowering of the convulant threshold.</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>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.</td>
<td>It is considered that the blood theophylline concentration increases due to decreasing theophylline clearance by the inhibition of hepatic drug metabolizing enzymes.</td>
</tr>
<tr>
<td>Aciclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valaciclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipriflavone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclesonide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larinapirin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lansoprazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of theophylline may be diminished. As the blood theophylline concentration may decrease, appropriate measures should be taken.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>It is considered that the blood theophylline concentration decreases due to increasing theophylline clearance through the induction of hepatic drug metabolizing enzymes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 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) Tachyphoea and hypoglycemia
Tachyphoea or hypoglycemia may occur.

(2) Other adverse reactions

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

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, NEO-
PHYLLIN 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 activated 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 overdose, 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.

9. Precautions concerning Use
Preparation
When NEOPHYLLIN Powder is dispensed, it is desirable that combination with other drugs be avoided since temporary adjustment of the NEOPHYLLIN dosage or its discontinuation will be required in the case that pyrexia is observed.

PHARMACOKINETICS

1. Blood concentration
(1) Time course of the blood concentration
When NEOPHYLLIN Powder was administered orally to 8 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 ($C_{\text{max}}$), time to reach $C_{\text{max}}$ ($t_{\text{max}}$), 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 Powder

(Mean±S.D., n=8)

Pharmacokinetic parameters at steady-state of NEOPHYLLIN Powder (n=8)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax μg/mL</td>
<td>9.05</td>
<td>1.06</td>
</tr>
<tr>
<td>tmax hr</td>
<td>1.38</td>
<td>0.52</td>
</tr>
<tr>
<td>t1/2 hr</td>
<td>9.25</td>
<td>1.67</td>
</tr>
<tr>
<td>AUC μg⋅hr/mL</td>
<td>44.68</td>
<td>5.97</td>
</tr>
</tbody>
</table>

(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 mg/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.1-4)

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.5-7)

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.5,8-10)

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.11-13)

4. Mechanism of action
Active ingredient of NEOPHYLLIN, Aminophylline hydrate is the salt which consists of 2 molecules of theophylline and 1 molecule 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 Ca²⁺ distribution, etc.5,14,15)

PHYSICOCHEMISTRY
Nonproprietary name: Aminophylline Hydrate
Chemical name: 1,3-Dimethyl-1H-purine-2,6(3H,7H)-dione hemi (ethylenediamine) hydrate
Molecular formula: \((\text{C}_7\text{H}_8\text{N}_4\text{O}_2)\cdot\text{C}_2\text{H}_8\text{N}_2\cdot x\text{H}_2\text{O}\)
Structural formula:

- Convulsions or death
- Symptoms of CNS
- Arrhythmia
- Convulsions
- Increase in heart rate without extrasystole (more than 120 beats/min)
- Hyperpnea
- Arrhythmia or convulsions in rare cases
- Gastrointestinal symptoms or increase in heart rate (100–119 beats/min)

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

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 diethyl ether. 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
1) When NEOPHYLLIN is dispensed with other drugs, there may frequently be incompatibility. It is advisable not to dispense NEOPHYLLIN with other drugs.
2) When NEOPHYLLIN is exposed directly to sunlight for long periods, it gradually diminishes ethylenediamine and becomes colored. NEOPHYLLIN should not be exposed directly to sunlight.

PACKAGING
Aminophylline Hydrate, JP
NEOPHYLLIN Powder: Cans of 100 g

REFERENCES

REQUESTS FOR LITERATURE AND PRODUCT INFORMATION SHOULD BE MADE TO:
Customer information Service
FreeDial: 0120-419-497
Eisai Co., Ltd.

Manufactured and marketed by:
Eisai Co., Ltd.
6-10, Koishikawa 4-chome, Bunkyo-ku, Tokyo, 112-8088