- Sustained-release theophylline preparation -

**THEOLONG** Tablets 50mg
**THEOLONG** Tablets 100mg
**THEOLONG** Tablets 200mg
**THEOLONG** Granules 50%

**Powerful drug:** THEOLONG Tablets 200mg and Granules 50%

**Prescription drug**

<table>
<thead>
<tr>
<th>Tablets 50 mg</th>
<th>Tablets 100 mg</th>
<th>Tablets 200 mg</th>
<th>Granules 50 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval No.</td>
<td>16100AMZ04455000</td>
<td>16100AMZ04456000</td>
<td>16100AMZ04457000</td>
</tr>
<tr>
<td>Date of latest approval of indications</td>
<td>Jan 1989</td>
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</tr>
</tbody>
</table>

**Storage**

THEOLONG should be stored at room temperature.

THEOLONG bottled tablets should be protected from moisture after opening package. (Hardness of tablets may be decreased by moisture.

THEOLONG granules should be protected from moisture after opening package. (Granules may absorb moisture.)

**Expiration date**

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

**Caution:** Use only as directed by a physician.

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

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

**DESCRIPTION**

1. Composition

**Tablets 50 mg:**

Each white, speckled sustained-release tablet contains 50 mg of theophylline.

It also contains ethylcellulose, croscarmellose sodium, light anhydrous silicic acid, microcrystalline cellulose, hydrogenated oil, calcium stearate, talc, corn starch, lactose hydrate, hydroxypropylcellulose and hydrated silicon dioxide as inactive ingredients.

**Tablets 100 mg:**

Each white, speckled sustained-release tablet contains 100 mg of theophylline.

It also contains ethylcellulose, croscarmellose sodium, light anhydrous silicic acid, microcrystalline cellulose, hydrogenated oil, calcium stearate, talc, corn starch, lactose hydrate, hydroxypropylcellulose and hydrated silicon dioxide as inactive ingredients.

**Tablets 200 mg:**

Each white, speckled sustained-release tablet contains 200 mg of theophylline.

It also contains ethylcellulose, croscarmellose sodium, light anhydrous silicic acid, microcrystalline cellulose, hydrogenated oil, calcium stearate, talc, corn starch, lactose hydrate, hydroxypropylcellulose and hydrated silicon dioxide as inactive ingredients.

**Granules 50%:**

Each 1 g of white, sustained-release granules contains 500 mg of theophylline.

It also contains light anhydrous silicic acid, hydrogenated oil, talc, povidone and hydrated silicon dioxide as inactive ingredients.

**Granules 50%:**

Each 1 g of white, sustained-release granules contains 500 mg of theophylline.

It also contains light anhydrous silicic acid, hydrogenated oil, talc, povidone and hydrated silicon dioxide as inactive ingredients.

2. **Product description**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Dosage form and identification code</th>
<th>Appearance</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>THEOLONG Tablets 50mg</td>
<td>Sustained-release tablets</td>
<td>White, speckled pattern due to sustained-release granules</td>
<td></td>
</tr>
<tr>
<td>TE50</td>
<td>Diameter (mm) 7.1, Weight (mg) 50, Thickness (mm) 3.3</td>
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</tr>
<tr>
<td>THEOLONG Tablets 100mg</td>
<td>Sustained-release tablets</td>
<td>White, speckled pattern due to sustained-release granules</td>
<td></td>
</tr>
<tr>
<td>TE100</td>
<td>Diameter (mm) 8.1, Weight (mg) 100, Thickness (mm) 4.2</td>
<td></td>
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</tr>
<tr>
<td>THEOLONG Tablets 200mg</td>
<td>Sustained-release tablets</td>
<td>White, speckled pattern due to sustained-release granules</td>
<td></td>
</tr>
<tr>
<td>TE200</td>
<td>Diameter (mm) 10.1, Weight (mg) 200, Thickness (mm) 5.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THEOLONG Granules 50%</td>
<td>Granules</td>
<td>White, sustained-release</td>
<td></td>
</tr>
</tbody>
</table>
INDICATIONS
Bronchial asthma, asthmatic (asthmoid) bronchitis, chronic bronchitis and pulmonary emphysema

<Precautions>
THEOLONG Tablets 50mg, Tablets 100mg and Granules 50% (Tablets 200mg are not approved for use in children.)
Asthmatic (asthmoid) bronchitis:
It should be considered to prioritize other drug therapy since this indication is often accompanied by fever. [Many cases of convulsions during the administration of theophylline is much infants with fever.]

DOSAGE AND ADMINISTRATION
The usual adult dosage for oral use is 200 mg of theophylline twice daily, in the morning and at bed time. The usual children’s dosage for oral use is 100 - 200 mg of theophylline twice daily, in the morning and at bed time. The dosage may be adjusted depending on patient’s age and symptoms.

Tablets 50 mg:
The usual adult dosage for oral use is 4 tablets twice daily in the morning and at bed time. The usual children’s dosage for oral use is 2 to 4 tablets twice daily, in the morning and at bed time. The dosage may be adjusted depending on patient’s age and symptoms.

Tablets 100 mg:
The usual adult dosage for oral use is 2 tablets twice daily, in the morning and at bed time. The usual children’s dosage for oral use is 1 to 2 tablets twice daily, in the morning and at bed time. The dosage may be adjusted depending on patient’s age and symptoms.

Tablets 200 mg:
The usual adult dosage for oral use is 1 tablet twice daily, in the morning and at bed time. The dosage may be adjusted depending on patient’s age and symptoms.

Granules 50%:
The usual adult dosage for oral use is 0.4 g of theophylline twice daily, in the morning and at bed time. The usual children’s dosage for oral use is 0.2 - 0.4 g of theophylline twice daily, in the morning and at bed time. The dosage may be adjusted depending on patient’s age and symptoms.

<Precautions>
THEOLONG Tablets 50mg, Tablets 100mg and Granules 50% (Tablets 200mg are not approved for use in children.)

This drug should be administered with caution carefully observing clinical symptoms and monitoring while its blood level. Please refer to the Guideline* and other relevant updates for recommended dosage and regimen for pediatric use of this drug in bronchial asthma.

*Japanese Pediatric Guideline for the Treatment and Management of Asthma 2012

1. Recommended dose of theophylline (usually administered 2 times daily)

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 6 months</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>6 months - under 1 year old</td>
<td>4-5 mg/kg</td>
</tr>
<tr>
<td>1 year - under 2 years old</td>
<td>4-5 mg/kg</td>
</tr>
<tr>
<td>2 years - 15 years old</td>
<td>4-5 mg/kg</td>
</tr>
</tbody>
</table>

2. Cases requiring special attention for administration:
Excepting the case of patients of 2 years of age and older with chronic severe symptoms, when other drugs have lacked effectiveness, THEOLONG should be administered after full consideration of indication it is being used for based on careful observation of the patient’s condition (symptoms such as pyrexia, convulsions, etc…). In principle, it is not recommended for patients under 2 years of age with convulsive disorders such as febrile convulsions and epilepsy.

PRECAUTIONS
1. Careful Administration (THEOLONG 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 THEOLONG enhances kidney load, urinary protein may increase.]
   (4) Patients with congestive heart failure
   [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) 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.]
   (6) Elderly patients
   [See “Use in the Elderly” section.]
   (7) Pregnant women, women suspected of being pregnant, parturient women or nursing mothers
   [See “Use during Pregnancy, Delivery or Lactation” section.]
   (8) 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, THEOLONG should be administered with care to them, monitoring the blood theophylline concentration. Particular care is required with the following.
2. Important Precautions
(1) 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.

(2) If adverse reactions occur, THEOLONG should be reduced in dosage or discontinued, and it is advisable to determine the blood theophylline concentration.

(3) 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.

(4) 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
THEOLONG is metabolized mainly by CYP1A2. [See “PHARMACOKINETICS” section.]
Precautions for coadministration (THEOLONG 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></td>
<td>When concomitantly administered with these drugs, CNS stimulation may be potentiated.</td>
</tr>
<tr>
<td>Aminophylline hydrate</td>
<td></td>
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<tr>
<td>Choline theophylline</td>
<td></td>
<td></td>
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<tr>
<td>Diprophylline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caffeine hydrate, etc.</td>
<td></td>
<td></td>
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<tr>
<td>CNS stimulants</td>
<td></td>
<td></td>
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<tr>
<td>Ephedrine hydrochloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ephedra herb, etc.</td>
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<td></td>
</tr>
<tr>
<td>THEOLONG may cause excessive CNS stimulation. [See “Overdosage” section.]</td>
<td></td>
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<tr>
<td>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>
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<td></td>
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<tr>
<td>Ketamine hydrochloride</td>
<td>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.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Considered to be due to lowering of the convulsant threshold.</td>
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<tr>
<td>Cimetidine</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>
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<tr>
<td></td>
<td></td>
<td>It is considered that the blood theophylline concentration increases due to decreasing theophylline clearance caused by the inhibition of hepatic drug metabolizing enzymes.</td>
</tr>
<tr>
<td>Moxifloxacin</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. Also THEOLONG may decrease the blood concentration of zafirlukast.</td>
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<tr>
<td></td>
<td></td>
<td>It is considered that the blood theophylline concentration increases due to decreasing theophylline clearance caused by the inhibition of hepatic drug metabolizing enzymes. The mechanism by which THEOLONG decreases the blood concentration of zafirlukast is unknown.</td>
</tr>
<tr>
<td>Caffeine hydrate, etc.</td>
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<tr>
<td>Diprophylline</td>
<td></td>
<td></td>
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<tr>
<td>Aminophylline hydrate</td>
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<tr>
<td>Procaterol hydrochloride hydrate, etc.</td>
<td></td>
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<tr>
<td>Theophylline</td>
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<tr>
<td>Halothane</td>
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<tr>
<td></td>
<td></td>
<td>It is considered that theophylline and halothane have synergistic and additive effects with respect to the heart.</td>
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Eisai Co., Ltd. 3
4. Adverse Reactions

Adverse reactions were reported in 139 of 842 patients (16.51%). (At the approval)

(1) Clinically significant adverse reactions (incidence unknown)

1) 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.

2) 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.

3) 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.

4) 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.

5) 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.

6) Anaphylactic shock
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.

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) Tachyphena and hyperglycemia
Tachyphena or hyperglycemia may occur.

<table>
<thead>
<tr>
<th>2%</th>
<th>5%</th>
<th>Incidence</th>
<th>unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Rash and pruritus</td>
<td>Urticaria, erythema (erythema exsudativum multiforme, etc.) and fixed eruption</td>
<td></td>
</tr>
<tr>
<td>Psychoneurologic</td>
<td>Headache, insom-</td>
<td>Nervousness (excite-</td>
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<tr>
<td></td>
<td>nia, dizziness,</td>
<td>ment, monosones and</td>
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<tr>
<td></td>
<td>tinnitus, tremor</td>
<td>iritated feeling),</td>
<td></td>
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<td></td>
<td>and numbness</td>
<td>anxiety, involuntary</td>
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<tr>
<td></td>
<td></td>
<td>movement and hyper-</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Palpitations and</td>
<td>Hot facial flushes,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>facial pallor</td>
<td>tachycardia and</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>arrhythmia (ventricular</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>extrasystole, etc.)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, vomi-</td>
<td>Diarrhea, abdomi-</td>
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<td></td>
<td>ting and ano-</td>
<td>nal pain, feeling of</td>
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<td></td>
<td>rexia</td>
<td>enlarged abdomen and</td>
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<td></td>
<td></td>
<td>dyspnea (heart burn, etc.)</td>
<td></td>
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<tr>
<td>Urinary</td>
<td>Albuminuria and pol-</td>
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<td></td>
<td>lakiuria</td>
<td></td>
<td></td>
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<tr>
<td>Metabolic</td>
<td>Elevation of blood</td>
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<tr>
<td></td>
<td>uric acid and CK (CPK), etc.</td>
<td></td>
<td></td>
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<tr>
<td>Hepatic</td>
<td>Elevation of AST (GOT), ALT (GPT), AI-P, LDH and γ-GTP, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia and eosino-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>philia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>malaise</td>
<td>Edema, arthralgia,</td>
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<tr>
<td></td>
<td></td>
<td>melosalgia, sweating,</td>
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<td></td>
<td></td>
<td>chest pain, hypo-</td>
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<td></td>
<td></td>
<td>calaemia, epistaxis</td>
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<tr>
<td></td>
<td></td>
<td>and numbness (mouth</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>and periglottic area)</td>
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</tr>
</tbody>
</table>
5. Use in the Elderly
THEOLONG should be administered with care to elderly patients watching for the occurrence of 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) THEOLONG 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. [THEOLONG has been reported to have reproductive toxicity, such as teratogenic effects on the fetus, etc. in animals (mice, rats and rabbits). Also, THEOLONG 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. [THEOLONG is excreted into human milk, giving rise to nervousness in nursing infants.]

7. Pediatric Use
THEOLONG 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 rhabdomyolisis, 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 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 anesthesia 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
(1) Preparation
When THEOLONG granules are dispensed, it is desirable that combination with other drugs be avoided since temporary adjustment of the THEOLONG dosage or its discontinuation will be required in the case that pyrexia is observed.
(2) Caution in handing over drug
1) THEOLONG should be taken without chewing since it is a sustained release preparation.
2) THEOLONG should be taken orally with water.
3) For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the package prior to use. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, causing perforation and resulting in serious complications such as mediastinitis.]
(3) White granules derived from THEOLONG may rarely be present in feces.
PHARMACOKINETICS
1. Blood concentration

(1) Change in the blood concentration
THEOLONG Tablets were administered to seven patients with asthma at a dose of 200 mg of theophylline twice daily for three days to achieve a steady state in the theophylline blood concentration.

The blood theophylline concentration was determined 12 hr after the final administration. The mean blood concentration \( C_{\text{max}} \) was 10.16 μg/mL. The area under plasma concentration-time curve (AUC), the mean residence time (MRT), the peak plasma concentration \( C_{\text{max}} \) and the time to reach \( C_{\text{max}} \) (Tmax) are shown in the table below. The change in the blood theophylline concentration was compared for the fasting and postprandial states. It was demonstrated that both \( C_{\text{max}} \) and the trough plasma concentration \( C_{\text{min}} \) were inside the effective range. 1)

(2) Therapeutic Drug Monitoring (TDM)
Range of effective blood concentration: 8-20μg/mL in adults
Main cytochrome P450 subfamily involved in metabolism: CYP1A2

2. Effect of meal
THEOLONG Tablets were administered to three patients with asthma at 200 mg of theophylline twice daily for consecutive dosage. The blood theophylline concentration at the steady state was compared for the fasting and postprandial states. The change in the blood theophylline concentration and pharmacokinetic parameters are shown in following table. 1)

3. Absorption, metabolism and excretion
According to the results of studies done outside Japan, orally administered theophylline is little affected by the first-pass effect but is metabolized in the liver and is almost completely excreted in the urine (theophylline 12.5%, 1-methyl uric acid 20.2%, 1-methylxanthine 13.1%, 1-methylxanthine 1.0% and 1,3-dimethyl uric acid 53.2%). 2, 3)

CLINICAL STUDIES
1. Open labeled clinical trials for dose-finding 4-8

<table>
<thead>
<tr>
<th>Subjects (Number of patients)</th>
<th>Utility rating (%)</th>
<th>Moderately to remarkably useful</th>
<th>Fairly to remarkably useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchial asthma Children (284 patients)</td>
<td>73.6 %</td>
<td>91.2 %</td>
<td></td>
</tr>
<tr>
<td>Chronic Bronchitis (22 patients)</td>
<td>59.0 %</td>
<td>83.9 %</td>
<td></td>
</tr>
</tbody>
</table>

2. Double-blind clinical trial
The clinical usefulness of THEOLONG has been demonstrated in a multicenter double-blind clinical trial on adult patients with bronchial asthma. 9)

PHARMACOLOGY
1. Bronchodilative action
In experiments with isolated bronchial muscle of guinea pigs and humans, theophylline dilated the muscle. Also, clinically, it has been demonstrated that theophylline reduced the respiration resistance of patients with bronchial asthma. 10-13)

2. Mechanism of action
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. ², ¹³)

PHYSICOCHEMISTRY
Nonproprietary name: Theophylline (JAN)
Chemical name: 3,7-Dihydro-1,3-dimethyl-1H-purine-2,6-dione
Molecular formula: C₇H₈N₄O₂
Molecular weight: 180.16
Structural formula:

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{H} \\
\text{N} & \quad \text{C} & \quad \text{H}_3 \\
\text{O} & \quad \text{N} & \quad \text{CH}_3
\end{align*}
\]

Description:
Theophylline occurs as white crystals or crystalline powder. It is odorless. It is soluble in N,N-dimethylformamide, slightly soluble in water, in ethanol(95) and in chloroform, and practically insoluble in diethylether. It dissolves in potassium hydroxide TS and in ammonia TS.

Melting point: 271-275°C

PACKAGING
THEOLONG Tablets 50 mg:
Boxes of 100 and 500 in press-through packages
THEOLONG Tablets 100 mg:
Boxes of 100, 140 (14 Tabs. x 10), 500 and 1,400 (14 Tabs. x 100) in press-through packages, and bottles of 500
THEOLONG Tablets 200 mg:
Boxes of 100, 140 (14 Tabs. x 10) and 1,000 in press-through packages, and bottles of 500
THEOLONG Granules 50%:
Cans of 100 g

REFERENCES