CONTRAINDICATIONS (SELECTOL is contraindi-
cated in the following patients.)
(1) Patients with a history of hypersensitivity to any of the
ingredients of the product
(2) Patients with diabetic ketoacidosis or metabolic acidosis
[The suppression of cardiac contractility in the presence
of acidosis may be enhanced.]
(3) Patients with severe bradycardia (marked sinus brady-
cardia), 2nd or 3rd degree atrioventricular block, sinoatrial
block, or sick sinus syndrome [Symptoms of these
disorders may be aggravated.]
(4) Patients with cardiogenic shock [The cardiogenic
shock may be aggravated due to suppression of cardiac
function.]
(5) Patients with congestive heart failure or right heart fail-
ure secondary to pulmonary hypertension [Symptoms
of these disorders may be aggravated due to a reduction
of cardiac output.]
(6) Women of confirmed or potential pregnancy [See Use
during Pregnancy, Delivery or Lactation.]

DESCRIPTION
1. Composition
SELECTOL® Tablets 100 mg:
Each tablet contains 100 mg of celiprolol hydrochloride.
SELECTOL® Tablets 200 mg:
Each tablet contains 200 mg of celiprolol hydrochloride.

2. Product description
SELECTOL® Tablets 100 mg are supplied as whitish
round film-coated tablets.
SELECTOL® Tablets 200 mg are supplied as whitish
round film-coated tablets scored on the reverse side.

INDICATIONS
Mild to moderate essential hypertension and renal parenchymal
hypertension
Angina pectoris

DOSAGE AND ADMINISTRATION
Mild to moderate essential hypertension and renal paren-
chymal hypertension
The usual adult dosage for oral use is 100-200 mg of celiprolol
hydrochloride administered once daily after a meal. The dos-
age may be adjusted according to the patient’s age and condition
but the daily dose may not exceed 400 mg.

Angina pectoris
The usual adult dosage for oral use is 200 mg of celiprolol hy-
drochloride administered once daily after a meal. The dosage
may be adjusted according to the patient’s age and condition
but the daily dose may not exceed 400 mg.
<Precautions>
In patients with pheochromocytoma, monotherapy with SELECTOL may cause a rapid increase of blood pressure. Use of SELECTOL should always follow initial treatment with an \( \alpha \)-blocker and should not be instituted without combination of an \( \alpha \)-blocker.

PRECAUTIONS
1. Careful Administration (SELECTOL should be administered with care in the following patients.)
   (1) Patients with bronchial asthma or at risk of developing bronchospasm
       [Asthma exacerbations or bronchospasm may be induced.]
   (2) Patients at risk of developing congestive heart failure
       [SELECTOL may aggravate symptoms by suppressing the cardiac function. Patients should be observed carefully and precautions such as coadministering digitalis should be taken.]
   (3) Patients with hypoglycemia, those with poorly controlled diabetes mellitus, or those fasted for a long time
       [Blood glucose level should be monitored because SELECTOL is likely to mask sympathetic symptoms such as tachycardia that occur as the initial signs of hypoglycemia.]
   (4) Patients with thyrotoxicosis
       [SELECTOL may mask symptoms of thyrotoxicosis such as tachycardia.]
       (See Important Precautions.)
   (5) Patients with severe hepatic disease
   (6) Patients with severe renal disease
       [Precautions such as reducing the dose should be taken in patients with a serum creatinine level \( \geq 4.0 \text{ mg/dL} \).]
       [The blood elimination half-life of SELECTOL may be prolonged.]
   (7) Patients with peripheral circulation disturbance (e.g., Raynaud’s syndrome, intermittent claudication)
       [Symptoms of these conditions may be aggravated.]
   (8) Patients with first degree atrioventricular block
       [SELECTOL may aggravate symptoms by impairing the impulse conducting system.]
   (9) Patients with atypical angina
       [Symptoms may be aggravated.]
   (10) Elderly patients
       [See Use in the Elderly.]
   (11) Pediatric patients
       [See Pediatric Use.]

2. Important Precautions
   (1) During chronic use of SELECTOL, cardiac function tests (e.g., measurement of vital signs, electrocardiography, and X-ray study) should be performed periodically. If any sign of bradycardia or hypotension is observed, the dose should be reduced or administration should be discontinued. If necessary, the patient should be treated with atropine sulfate or any other appropriate drug. The hepatic and renal functions and the hematological profile should also be monitored.
   (2) Symptomatic aggravation and/or myocardial infarction have been reported in patients with angina pectoris following abrupt withdrawal of a drug in the same therapeutic category (propranolol hydrochloride). When SELECTOL is to be temporarily discontinued, the therapy should be gradually tapered while closely monitoring the patient’s condition. The patient should be instructed not to discontinue using SELECTOL at his/her discretion without receiving a definitive direction of the prescribing physician. Similar precautions should be taken in patients, especially elderly patients, treated with SELECTOL for any indication other than angina pectoris.
   (3) When withdrawal of SELECTOL is necessary in patients with thyrotoxicosis, the therapy should be gradually tapered while closely monitoring the patient’s condition because abrupt withdrawal of the product may aggravate symptoms.
   (4) It is advisable that SELECTOL should not be used within 48 hours before surgery.
   (5) Since SELECTOL may induce dizziness or light-headedness, patients should be cautioned against engaging in potentially hazardous activities requiring alertness, such as operating machinery or driving a car, especially during the early phase of treatment.
3. Drug Interactions

Precautions for coadministration (SELECTOL 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>Calcium-channel blockers, including verapamil hydrochloride and diltiazem hydrochloride</td>
<td>Signs of impaired impulse conduction (e.g., bradycardia, atrioventricular block) and congestive heart failure may occur. Care should be taken for dosage when coadministering SELECTOL with these drugs.</td>
<td>SELECTOL and any of these drugs administered in combination exert additive negative inotropic effect, impulse conduction suppressing effect, and antihypertensive effect.</td>
</tr>
<tr>
<td>Other sympatholytic agents, including reserpine</td>
<td>Since excessive suppression of sympathetic activity may occur, precautions should be taken such as reducing the dose.</td>
<td>SELECTOL and any of these drugs administered in combination exert an additive sympatholytic effect.</td>
</tr>
<tr>
<td>Hypoglycemic agents, including insulin, tolbutamide, and acetohexamide</td>
<td>Concomitant use of SELECTOL may enhance the effect of hypoglycemic agents or mask hypoglycemic symptoms such as tachycardia and sweating. Blood glucose level should be monitored during coadministration of these drugs.</td>
<td>SELECTOL suppresses glycogen degradation in the liver by blocking β-receptors and masks hypoglycemic signs induced by epinephrine secreted during hypoglycemia.</td>
</tr>
<tr>
<td>Clonidine hydrochloride and guanabenz acetate</td>
<td>SELECTOL may enhance the rebound phenomenon following withdrawal of clonidine hydrochloride or guanabenz acetate. When clonidine hydrochloride or guanabenz acetate together with SELECTOL are to be withdrawn, SELECTOL should be withdrawn first and then clonidine hydrochloride or guanabenz acetate should be gradually tapered.</td>
<td>After withdrawal of clonidine hydrochloride, the blood norepinephrine level increases. When any β-blocker is coadministered, the α-adrenergic effect of norepinephrine becomes predominant, causing a rapid increase of blood pressure. Based on the mechanism of its action, similar responses are expected after withdrawal of guanabenz acetate coadministered with any β-blocker.</td>
</tr>
<tr>
<td>Class I antiarrhythmic agents, including disopyramide phosphate, procainamide hydrochloride, and ajmaline, and amiodarone hydrochloride</td>
<td>Since excessive suppression of cardiac function may occur, precautions should be taken such as reducing the dose.</td>
<td>SELECTOL and any of these drugs administered in combination exert an additive suppressive effect on cardiac function.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
<th>β-blockers</th>
<th>Antihypertensive agents, including indomethacin</th>
<th>Digitalis preparations, including digoxin and methyldigoxin</th>
<th>Anesthetics, including ether</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium-channel blockers, including verapamil hydrochloride and diltiazem hydrochloride</td>
<td>Blood pressure may increase.</td>
<td>The antihypertensive effect of SELECTOL may be diminished by concomitant use of any of these drugs.</td>
<td>The vasodilatory effect of SELECTOL is inhibited by concomitant use of any other β-blocker.</td>
<td>The sympathetic effect of SELECTOL and any anesthetic drug administered in combination exert an additive sympatholytic effect.</td>
</tr>
<tr>
<td>Other sympatholytic agents, including reserpine</td>
<td>Since excessive suppression of sympathetic activity may occur, precautions should be taken such as reducing the dose.</td>
<td>Non-steroidal anti-inflammatory drugs, including indomethacin</td>
<td>Since signs of impulse conduction disturbance (e.g., bradycardia, atrioventricular block) may appear, cardiac function should be carefully monitored.</td>
<td>Non-steroidal anti-inflammatory drugs inhibit the synthesis/release of vasodilatory prostaglandins.</td>
</tr>
<tr>
<td>Hypoglycemic agents, including insulin, tolbutamide, and acetohexamide</td>
<td>Concomitant use of SELECTOL may enhance the effect of hypoglycemic agents or mask hypoglycemic symptoms such as tachycardia and sweating. Blood glucose level should be monitored during coadministration of these drugs.</td>
<td>SELECTOL and any of these drugs administered in combination exert an additive sympatholytic effect.</td>
<td>Since the antihypertensive effect may be enhanced, care should be taken for dosage when coadministering SELECTOL with these drugs.</td>
<td>SELECTOL and any of these preparations administered in combination exert an additive suppressive effect on impulse conduction.</td>
</tr>
<tr>
<td>Clonidine hydrochloride and guanabenz acetate</td>
<td>SELECTOL may enhance the rebound phenomenon following withdrawal of clonidine hydrochloride or guanabenz acetate. When clonidine hydrochloride or guanabenz acetate together with SELECTOL are to be withdrawn, SELECTOL should be withdrawn first and then clonidine hydrochloride or guanabenz acetate should be gradually tapered.</td>
<td>After withdrawal of clonidine hydrochloride, the blood norepinephrine level increases. When any β-blocker is coadministered, the α-adrenergic effect of norepinephrine becomes predominant, causing a rapid increase of blood pressure. Based on the mechanism of its action, similar responses are expected after withdrawal of guanabenz acetate coadministered with any β-blocker.</td>
<td>Since excessive suppression of sympathetic activity may occur, precautions should be taken such as reducing the dose.</td>
<td>Since the antihypertensive effect may be enhanced, care should be taken for dosage when coadministering SELECTOL with these drugs.</td>
</tr>
</tbody>
</table>
4. Adverse Reactions

Adverse reactions to SELECTOL were reported in 259 of 10,381 patients (2.49%) treated with the drug. They included dizziness, headache, throbbing heart, malaise, increased AST (GOT) • ALT (GPT), hyperuricemia, and increased CK (based on data collected from the time of approval up to the end of January 1998).

The incidence of adverse reactions reported only spontaneously is deemed “unknown”.

(1) Clinically significant adverse reactions

Cardiac failure, atrioventricular block, and sinoatrial block
Cardiac failure (<0.1%), atrioventricular block (incidence unknown), and sinoatrial block (incidence unknown) may occur. Cardiac function tests should be performed periodically and if any sign of these conditions is noted, administration should be discontinued.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence Anatomical category</th>
<th>&gt;0.1%, &lt;5%</th>
<th>&lt;0.1%</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic*</td>
<td>Rash, itching, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Throbbing heart</td>
<td>Chest pain, bradycardia, hypotension, facial hot flushes, increased cardiothoracic ratio, etc.</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Coughing, asthma, shortness of breath, nasal discharge, nasal obstruction, stridor, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoneurologic</td>
<td>Dizziness and headache</td>
<td>Numbness, tremor, insomnia, sleepiness, depressed state, etc.</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea, thirst, abdominal pain, diarrhea, dyspepsia, etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmic*</td>
<td>Decreased lacrimation, etc.</td>
<td>Blurred vision (reported with other β-blockers)</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>Abnormal hepatic function [e.g., increased AST (GOT), increased ALT (GPT), increased ALP, and increased LDH]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Abnormal renal function [e.g., increased creatinine, proteinuria, and increased BUN]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Miscellaneous: Malaise, increased triglycerides, increased total cholesterol, increased uric acid, and increased CK
Edema, arthralgia, leukopenia, aggravation of hyperglycemia, calf cramps*, myalgia*, weakness, etc.

* Administration should be discontinued in the event of the symptom(s).

5. Use in the Elderly

When administering SELECTOL to elderly patients, the points listed below should be taken into consideration.

Therapy with SELECTOL should be instituted with special care, starting at a low dose (100 mg/day, for example) with careful monitoring of the patient’s condition.

1) An excessive reduction of blood pressure is generally undesirable in elderly patients. [Cerebral infarction and other vascular events may occur.]

2) If discontinuation of SELECTOL is necessary, the therapy should be gradually tapered. (See Important Precautions.)

6. Use during Pregnancy, Delivery or Lactation

(1) SELECTOL should not be used in women with confirmed or potential pregnancy. [The safety of this product in pregnant women has not been established.]

(2) When administering SELECTOL to a nursing mother, breast feeding must be discontinued during treatment with the product. [Animal studies in rats have shown that celiprolol is excreted in breast milk.]

7. Pediatric Use

The safety of SELECTOL in children has not been established.

8. Overdosage

Signs and symptoms: Foreseeable signs and symptoms of overdosage of β-blockers include bradycardia, complete atrioventricular block, cardiac failure, hypotension, and bronchospasm.

Treatments: Administration of SELECTOL should be discontinued and, if necessary, appropriate measures for facilitating drug elimination such as gastric lavage should be taken. Appropriate treatments such as those listed below should be provided.

(1) Bradycardia or complete atrioventricular block: Administer atropine sulfate, isoproterenol, etc., or institute artificial cardiac pacing.

(2) Cardiac failure or hypotension: Administer a cardiotonic or pressor agent, intravenous fluids, etc., or institute assisted circulation.

(3) Bronchospasm: Administer intravenously a β2-agonist or aminophylline, etc., or institute assisted ventilation. During these treatments, the patient should be kept under strict supervision.
9. **Precautions Concerning Use**

At time of dispensing: For drugs supplied in blister packs, instruct the patient to remove the drug from the package prior to use.

[It has been reported that, if a blister pack is swallowed, the sharp corners of the pack may penetrate the esophageal mucosa, resulting in severe complications such as mediastinitis.]

10. **Other Precautions**

   (1) After oral administration in a fasted state, the peak plasma concentration of celiprolol was reported to be about twice higher than that observed after postprandial administration.

   (2) Patients currently treated with any \( \beta \)-blocker may be liable to develop more severe anaphylactic shock to other drugs and may become unresponsive to a standard dose of epinephrine.

### PHARMACOKINETICS\(^{1-6}\)

1. **Plasma concentration**

   After single oral doses of 50-400 mg of celiprolol hydrochloride, the plasma concentration of the parent compound reached a peak at 2-5 hours and subsequently declined with a half-life of 1.5-6 hours in 5 healthy adult volunteers.

   

<table>
<thead>
<tr>
<th>Dose (mg/body)</th>
<th>Tmax (hr)</th>
<th>Cmax (ng/mL)</th>
<th>AUC0-24hr (ng・hr/mL)</th>
<th>( T_{1/2} ) (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>2.2±0.8</td>
<td>13.1±2.5</td>
<td>47.6±12.4</td>
<td>3.94±1.68</td>
</tr>
<tr>
<td>100</td>
<td>3.0±0.0</td>
<td>116±9</td>
<td>304±75</td>
<td>1.45±0.35*</td>
</tr>
<tr>
<td>200</td>
<td>4.4±2.1</td>
<td>295±105</td>
<td>1830±403</td>
<td>4.81±2.27</td>
</tr>
<tr>
<td>400</td>
<td>5.4±1.9</td>
<td>855±479</td>
<td>6810±3560</td>
<td>5.89±0.85</td>
</tr>
</tbody>
</table>

   Each value represents the mean ± standard deviation of 5 subjects.

   *The shorter \( T_{1/2} \) for the 100 mg dose compared with other dose levels may be incidental and attributable to measurement problems; the plasma concentration of the parent compound was unmeasurable at 8 hours postdose in 4 of the 5 subjects in this dose group.

3. **Plasma protein binding**

   The *in vitro* protein binding rate in human plasma was measured to be 20-27% at concentrations ranging from 0.1 to 10 \( \mu \)g/mL.

4. **Urinary excretion**

   After single oral doses (50, 100, 200, and 400 mg) of celiprolol hydrochloride administered to 5 healthy adult volunteers, the parent compound was the major compound excreted in the urine. There were only small amounts of celiprolol glucuronide, mono-deethylated compound, and its glucuronide in the urine. By 24 hours after administration, 3.5%, 3.3%, 6.7%, and 15.1% of the respective doses were recovered in the urine as the parent compound or any of these metabolites were mostly present as glucuronides in the urine.

5. **Absorption and excretion during repeated administration**

   Celiprolol hydrochloride was administered to 5 healthy adult volunteers at 400 mg once daily for 5 consecutive days. The plasma concentration of the parent compound over time and the urinary excretion profile were similar to those observed after single oral doses, indicating little possibility of accumulation of the drug during repeated administration.

6. **Plasma concentration in patient populations**

   The plasma concentration of celiprolol hydrochloride was monitored after single oral doses of the drug in patients with essential hypertension, hypertensive patients with impaired renal function, and patients with angina pectoris. The plasma concentration of the drug tended to be higher in hypertensive patients with impaired renal function than in healthy adult volunteers, while the plasma concentration-time profile observed in patients with essential hypertension or angina pectoris was similar to that observed in healthy adults.
CLINICAL STUDIES\textsuperscript{51-10)\textsuperscript{5}}

The efficacy data obtained in a total of 715 evaluable patients treated with celiprolol hydrochloride in clinical studies conducted in Japan, including double-blind controlled studies, are summarized below.

<table>
<thead>
<tr>
<th>Target disease</th>
<th>Response rate\textsuperscript{*} (No. of patients with a rating of “effective” or better/No. of evaluable patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension \textsuperscript{Note 1)}</td>
<td>66.8%(348/521)</td>
</tr>
<tr>
<td>Renal parenchymal hypertension</td>
<td>76.3%(29/38)</td>
</tr>
<tr>
<td>Angina pectoris \textsuperscript{Note 2)}</td>
<td>71.2%(111/156)</td>
</tr>
</tbody>
</table>

Note 1): In a study evaluating the effect of celiprolol hydrochloride administered once daily on the circadian rhythm of blood pressure, the drug exerted an antihypertensive effect lasting for 24 hours. Forty-nine elderly (age \( \geq 70 \) years) patients were treated with the drug and 28 of 38 evaluable patients (73.7\%) were responders (having a rating of “decreased” or better).

Note 2): A treadmill exercise study has shown that celiprolol hydrochloride administered once daily improves exercise tolerance and that this effect lasts for 24 hours after each dose.

\*: In patients with hypertension or renal parenchymal hypertension, the response rate is calculated as the number of patients with a rating of “decreased” or better relative to the number of evaluable patients.

PHARMACOLOGY

1. \( \beta \textsubscript{1}-\text{selective} \beta -\text{blocking activity (in vitro)}\textsuperscript{11)}\)
   The potency of celiprolol hydrochloride in antagonizing various effects of isoproterenol hydrochloride (pA\textsubscript{2}) is 8.03 for the chronotropic effect on guinea pig heart, 7.98 for the inotropic effect on guinea pig heart, and 6.43 for the relaxant effect on guinea pig tracheal muscle. These data indicate \( \beta \textsubscript{1} \) selectivity of the \( \beta \) -receptor blocking activity of celiprolol hydrochloride.

2. Intrinsic sympathomimetic activity\textsuperscript{11,14)\textsuperscript{12)}
   Celiprolol hydrochloride has been shown to have intrinsic sympathomimetic activity as potent as that of pindolol in the myocardium and tracheal muscle from normal and reserpine-treated guinea pigs (in vitro). In dogs, celiprolol hydrochloride induced bronchodilation as evidenced by a reduction of airway resistance and a decrease of dead space. Celiprolol hydrochloride had no significant effect on the respiratory function of hypertensive patients with asthma.

3. Postsynaptic \( \alpha \textsubscript{2} \)-receptor blocking activity (in vitro)\textsuperscript{15)}
   Experiments using rats with spinal cord ablation and using rat vas deferens have shown that celiprolol hydrochloride blocks postsynaptic \( \alpha \textsubscript{2} \)-adrenergic receptors.

4. Vasodilatory activity (in vitro)\textsuperscript{11,12,13)\textsuperscript{14)}
   Celiprolol hydrochloride has been shown to cause vasodilation by stimulating \( \beta \textsubscript{2} \)-adrenergic receptors through its intrinsic sympathomimetic activity.

5. Antihypertensive action\textsuperscript{51,11,16)}
   Celiprolol hydrochloride exerts a sustained antihypertensive effect in rat hypertension models (spontaneously hypertensive rats, rats with DOCA/Salt-induced hypertension, rats with renal hypertension). In hypertensive patients, the drug has been shown to exert a sustained antihypertensive effect when administered once daily.

6. Anti-angina effect\textsuperscript{13,17,18)}
   In angina models (rats and dogs with angina induced by isoproterenol hydrochloride), celiprolol hydrochloride, like propranolol hydrochloride, has exhibited an anti-angina effect by reducing myocardial oxygen consumption. In patients with angina pectoris, once-daily administration of celiprolol hydrochloride has been shown to be effective in controlling angina.

7. Effect on renal function\textsuperscript{19,20)}
   In dogs and hypertensive patients, celiprolol hydrochloride has been shown to have no significant effect on renal function.

8. Metabolic effect\textsuperscript{21,22,23)}
   Celiprolol hydrochloride has been reported to have no effect on serum lipid profile or glucose tolerance in rats loaded with glucose or cholesterol, or hypertensive patients.

PHYSICOCHEMISTRY

Nonproprietary name: Celiprolol hydrochloride (JAN)
Chemical name: \((\pm)-3\-[3\text{-acetyl}-4\-[3\text{-}(\text{tert-butylamino})-2\text{-hydroxypropoxy}]}\text{-phenyl}\) -1,1-diethylurea hydrochloride
Molecular formula: \(C\textsubscript{20}H\textsubscript{33}N\textsubscript{3}O\textsubscript{4} \cdot \text{HCl}\)
Molecular weight: 415.96
Structural formula:

\[
\text{NHCON} \quad \text{C}_\text{4H}_\text{15} \quad \text{C}_\text{4H}_\text{6}
\]

\[
\text{COCH}_3 \quad \text{CH}_3 \\
\text{OCH}_3\text{CHCH}_2\text{NH} \quad \text{CH}_3 \cdot \text{HCl} \\
\text{OH} \quad \text{CH}_3
\]

Melting point: 193-202\(^\circ\)C (decomposition)
Description:
Celiprolol hydrochloride occurs as white crystals or a crystalline powder with no odor and a slightly bitter taste. It is freely soluble in water, methanol and glacial acetic acid, sparingly soluble in dehydrated ethanol, and practically insoluble in acetic anhydride and ether.
Partition coefficient: 0.06 (n-octanol: Fluid I)
0.16 (n-octanol: Fluid II)
PACKAGING

SELECTOL® Tablets 100 mg:
Boxes of 100, 500, 700, and 1,000 tablets in press-through packages, and bottles of 500 tablets.

SELECTOL® Tablets 200 mg:
Boxes of 100, 280, and 500 tablets in press-through packages, and bottles of 500 tablets.

REFERENCES
8) Abe Y. et al.: Data on file, Nippon Shinyaku Co., Ltd.

REQUEST FOR LITERATURE SHOULD BE MADE TO:
Pharmaceutical Information Center
Nippon Shinyaku Co., Ltd.
14, Monguchi-cho, Nishinosho, Kisshoin, Minami-ku, Kyoto,
601-8550, Japan
Fax: 075-313-7990

INFORMATION ON LONG-TERM ADMINISTRATION
This product may be prescribed for a single period of up to 30 days in accordance with Notification No. 73, issued on March 17, 2000 by the Ministry of Health and Welfare of Japan.