- ULCERATIVE COLITIS/CROHN’S DISEASE REMEDY -

PENTASA® Tablets 250 mg
PENTASA® Tablets 500 mg

< The Japanese Pharmacopoeia Mesalazine Extended-release Tablets >

Prescription drug

Storage
This product should be stored in a light-proof, sealed container at room temperature.

Expiration date
This product should be used before the expiration date indicated on the outer cases.

CONTRAINDICATIONS (This product is contraindicated in the following patients.)
(1) Patients with serious renal dysfunction [Renal dysfunction may be further aggravated.]
(2) Patients with serious hepatic dysfunction [Hepatic dysfunction may be further aggravated.]
(3) Patients with a history of hypersensitivity to ingredients contained in this product [Refer to the section of “Important Precautions.”]
(4) Patients with a history of hypersensitivity to salicylic acid esters or salicylates [Cross allergy may develop.]

DESCRIPTION

<table>
<thead>
<tr>
<th>Brand name</th>
<th>PENTASA Tablets 250 mg</th>
<th>PENTASA Tablets 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive ingredients</td>
<td>Crystalline cellulose, ethylcellulose, povidone, t alc, magnesium stearate, hydrous silicon dioxide</td>
<td></td>
</tr>
<tr>
<td>Color/formulation</td>
<td>White to pale-yellow, plain-scored tablets with grayish-white to pale-grayish-yellow maculae</td>
<td></td>
</tr>
</tbody>
</table>

Appearance

- KP-007 -
  Diameter: 9.5 mm
  Thickness: 4.6 mm
  Weight: About 375 mg

- KP-011 -
  Long diameter: 17.0 mm
  Short diameter: 7.2 mm
  Thickness: 5.1 mm
  Weight: About 750 mg

INDICATIONS

Ulcerative colitis (excluding severe cases), and Crohn’s disease

DOSAGE AND ADMINISTRATION

Ulcerative colitis: The usual oral dosage of this product in adults is 1500 mg of mesalazine daily in three divided doses after meals, in the remission stage, however, this product may be administered once daily, as required. The dosage may be adjusted according to patients’ ages and symptoms, with the upper limit of 2250 mg daily.

In the active stage, however, this product may be administered in a daily dose of 4000 mg in two divided portions, as required.

The usual oral dosage of this product in children is 30 to 60 mg/kg of mesalazine daily in three divided doses after meals. The dosage may be adjusted according to patients’ ages and symptoms, with the upper limit of 2250 mg daily.

Crohn’s disease: The usual oral dosage of this product in adults is 1500 to 3000 mg of mesalazine daily in three divided doses after meals. The dosage may be reduced according to patients’ ages and symptoms.

The usual oral dosage of this product in children is 40 to 60 mg/kg of mesalazine daily in three divided doses after meals. The dosage may be adjusted according to patients’ ages and symptoms.

<Precautions concerning Dosage and Administration>
1. Increase in the dosage to 4000 mg daily should be only applied to the patients with moderate relapse-remitting type of ulcerative colitis (excluding proctitis) (see the section of “CLINICAL STUDIES”).
2. Because the efficacy of mesalazine have not been established after administration at a daily dose of 4000 mg for more than eight weeks, special attention should be paid to the conditions of patients with adequate monitoring when mesalazine is administered at a daily dose of 4000 mg.

PRECAUTIONS

1. Careful Administration (This product should be carefully administered to the following patients.)

(1) Patients with reduced renal function
[Excretion may be delayed to cause adverse reactions.]
(2) Patients with reduced hepatic function
[Metabolism may be delayed to cause adverse reactions.]
(3) Patients with hypersensitivity to salazosulfapyridine
(Refer to the clause (2) of the section of “Important Precautions.”)

2. Important Precautions

(1) Mesalazine may induce hypersensitivity symptoms (fever, abdominal pain, diarrhea, cosinophilia, etc.), and aggravate ulcerative colitis/Crohn’s disease. If any of the abnormal findings is observed, appropriate therapeutic measures such as a reduction in the dose or discontinuation of administration should be taken.

(2) Administration of this product to patients with allergic symptoms to salazosulfapyridine caused a similar allergic symptom in three (7.7%) out of 39 cases in the domestic clinical studies, and two (4.7%) out of 43 cases in the foreign clinical study. Therefore, this product should be carefully administered to patients with allergic symptoms to salazosulfapyridine.

(3) Since interstitial nephritis has been reported, patients should be carefully monitored for renal function including creatinine during the period of treatment. If any of abnormal findings is observed, appropriate therapeutic measures such as a reduction in the dose or discontinuation of administration should be taken.

(4) Since hepatitis, hepatic dysfunction and jaundice have been reported, patients should be carefully monitored for laboratory variables for hepatic function such as AST (GOT) and ALT (GPT) during the period of treatment. If any of abnormal findings is observed, appropriate measures such as a reduction in the dose or discontinuation of administration should be taken.

(5) When this product is co-administered with mesalazine enema, attention should be especially paid to the patients with reduced hepatic or renal function and elderly patients, taking an increase in the total dose of mesalazine into consideration. If any of abnormal findings is observed, appropriate measures such as a reduction in the dose or discontinuation of administration should be taken.

3. Drug Interactions

Precautions for co-administration
Since drug interactions have been reported in the literature, this product should be carefully administered in combination with the following drugs:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Sign or Symptom and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>Changes in laboratory values (urine volume, and urinary excretions of sodium, potassium</td>
<td>A high dose (300 mg/kg) of</td>
</tr>
<tr>
<td>Steroids</td>
<td>and chloride ions) should be monitored.</td>
<td>mesalazine increases urine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>volume and urinary excretions</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Myelosuppression may occur.</td>
<td>of sodium, potassium</td>
</tr>
<tr>
<td>Mecaptepurine</td>
<td></td>
<td>and chloride ions in an</td>
</tr>
<tr>
<td></td>
<td></td>
<td>animal study (rats).</td>
</tr>
</tbody>
</table>

4. Adverse Reactions

The number of cases of adverse reactions including laboratory test abnormalities was 292 (11.54%) out of 2531 objective cases of safety analysis in clinical studies at approvals of supplementing dosage regimen and post-marketing surveillances. The major adverse reactions included diarrhea in 66 (2.61%), melena/hematochezia in 28 (1.11%), digestive symptoms including abdominal pain in 25 (0.99%), rash in 17 (0.67%), fever in 15 (0.59%), and hepatic dysfunction in 14 (0.55%). The major laboratory test abnormalities included increased CRP in 24 (0.95%), increased ALT (GPT) in 21 (0.83%), and increased WBC in 18 (0.71%).

The following incidents of adverse reactions were calculated based on both the results of clinical studies at approvals of supplementing dosage regimen and those of post-marketing surveillances. The adverse reactions with incidence unknown were found in spontaneous reporting:

(1) Clinically significant adverse reactions

1) Intestinal ulcer disease (0.01% ≤ <0.1%)<sup>Note</sup>
Intestinal ulcer disease (eosinophilic pneumonia, alveolitis, pneumonitis, interstitial pneumonia, and others) has been reported. If any of symptoms such as fever, coughing, dyspnea, and abnormal findings in chest radiograms is observed, appropriate measures such as discontinuation of administration should be taken.

2) Myocarditis (0.01% ≤ <0.1%) and pericarditis (0.01% ≤ <0.1%)<sup>Note</sup>, and pleurisy (incidence unknown)
Myocarditis, pericarditis and pleurisy may occur. If any of symptoms such as pleural effusion, chest pain, and abnormal findings in electrocardiograms is observed, appropriate measures such as discontinuation of administration should be taken.

3) Interstitial nephritis, nephrotic syndrome, and reduced renal function (<0.01%)<sup>Note</sup>, and acute renal failure (incidence unknown)
Since interstitial nephritis, nephrotic syndrome, reduced renal function and acute renal failure may occur, patients should be carefully monitored for renal
function variables during the period of treatment. If any of abnormal findings is observed, appropriate measures such as discontinuation of administration should be taken.

4) **Aplastic anemia,** pancytopenia, agranulocytosis (<0.01%) and *thrombocytopenia* (0.01%≤<0.1%) Since aplastic anemia, pancytopenia, agranulocytosis, and thrombocytopenia may occur, patients should be carefully monitored for hematological variables during the period of treatment. If any of abnormal findings is observed, appropriate measures such as discontinuation of administration should be taken.

5) **Hepatitis** (0.01%≤<0.1%), *hepatic dysfunction* (incidence unknown) and jaundice (0.01%≤<0.1%)

Since hepatitis, hepatic dysfunction with increased AST (GOT), ALT (GPT) and/or γ-GTP and jaundice may occur, patients should be carefully monitored for hepatic function variables during the period of treatment. If any of abnormal findings is observed, appropriate measures such as discontinuation of administration should be taken.

6) **Pancreatitis** (0.01%≤<0.1%)

Since pancreatitis may occur, patients should be carefully monitored for serum amylase levels during the period of treatment. If any of abnormal findings is observed, appropriate measures such as discontinuation of administration should be taken.

**Note** The incidences of adverse reactions are based on the results of post-marketing surveillances in foreign countries.

**2) Other Adverse Reactions**

If any of the following adverse reactions is observed, appropriate measures such as discontinuation of administration should be taken.

<table>
<thead>
<tr>
<th>Incidence of adverse reactions</th>
<th>1%≤</th>
<th>0.1～&lt;1%</th>
<th>&lt;0.1%</th>
<th>Unknown (Note1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermato-logic</td>
<td>Rash, itching, papule</td>
<td>Erythema, urticaria, depilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>Diarrhea</td>
<td>Abdominal pain, melena, hematochezia, increased amylase, nausea, feeling of enlarged abdomen, anorexia, constipation, stomatitis</td>
<td>Mucous stool, vomiting</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>Hepatic function abnormal such as increases in AST (GOT), ALT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Renal**

Renal dysfunctions such as increases in creatinine, urinary NAG and urinary microglobulin, and urinary protein

**Chromaturia**

**Hematologic**

Decreased WBC, eosinophilia, anemia

**Others**

Fever, headache, arthralgia, general malaise Edema, myalgia, increased CK, lupus-like syndrome Swelling, peripheral neuropathy, dizziness, chest pain, neck pain

Note 1) Based on spontaneous reporting, etc.

Note 2) Based on the results of post-marketing surveillances in foreign countries.

5. **Use in the Elderly**

Because elderly patients have generally reduced physiological functions (renal and hepatic functions, etc.), this product should be administered with a special care, such as a low starting dosage (e.g., 750 mg/day).

6. **Use during Pregnancy, Delivery or Lactation**

(1) This product should be administered to pregnant or possibly pregnant women only if the expected therapeutic benefits outweigh the potential risks associated with treatment.

[Hematological disorders (leukopenia, thrombopenia, and anemia) have been reported abroad to develop in newborns, thus the safety of this product has not been established in pregnant women. However, no teratogenicity has been found in the animal study of mesalazine.]

(2) Use of this product is not recommended in lactating women. If the use is judged to be essential, breast feeding must be discontinued during treatment.

[Mesalazine has been reported to be excreted in the breast milk in humans. Diarrhea has been reported to develop in infants in Japan and abroad.]

7. **Pediatric Use**

Since the clinical experiences of this product is limited in children, this product should be administered in children under the supervision of a medical specialist, taking account of the expected benefits and possible risks associated with treatment.

8. **Precautions concerning Use**

**Precautions for oral administration**: Although this product can be orally administered by dividing a tablet into two pieces, patients should be instructed not to bite the tablet in administration because of controlled release...
formulation. Porphyrization of the tablets with a mortar should be avoided.

**Precautions for dispensing:** Patients should be instructed to remove the tablet from the PTP sheet prior to use. (It has been reported that if a PTP sheet is swallowed in error, its sharp corners may penetrate the esophageal mucosa, leading to serious complications such as mediastinitis.)

**9. Other Precautions**

1. Although this product may become slightly colored during storage, its pharmacological efficacy remains unchanged.
2. Since the coating material of this product, ethylcellulose, is insoluble in water, white materials may be observed in stool.

**PHARMACOKINETICS**

1. **Blood Concentrations**

   (1) Single Oral Administration of PENTASA Tablets and Mesalazine

   When a single dose of this product at 1000 mg (four 250-mg tablets) of mesalazine or of the bulk at 1000 mg of mesalazine was orally administered to healthy adults in a fasted state, a time-course profile and pharmacokinetic parameters of the unchanged form in plasma are shown in the following figure and table, respectively:

   - **Figure 1** A time-course profile of the plasma concentrations of the unchanged form after a single dose of PENTASA Tablets or mesalazine is orally administered to healthy adults in a fasted state

   - **Table 1** Pharmacokinetic Parameters of the Unchanged Form after Single Oral Administration of PENTASA Tablets or Mesalazine to Healthy Adults in a Fasted State

<table>
<thead>
<tr>
<th>Time points</th>
<th>Unchanged form</th>
<th>Acetylated form</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 (n=5)</td>
<td>Day 6 (n=5)</td>
</tr>
<tr>
<td></td>
<td>Day 1 (n=6)</td>
<td>Day 6 (n=6)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>7189.5 ± 5093.1</td>
<td>7242.0 ± 3334.5</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>2.8 ± 0.8</td>
<td>3.0 ± 0.9</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>6.0 ± 3.8</td>
<td>5.3 ± 1.4</td>
</tr>
<tr>
<td>AUC (ng·hr/mL)</td>
<td>23065.7 ± 12961.4</td>
<td>44063.7 ± 10722.4</td>
</tr>
</tbody>
</table>

   (2) Repeated Oral Administration of PENTASA Tablets (1000 mg as Mesalazine) Three Times Daily for 7 Days

   When this product was repeatedly administered at an oral dose of 1000 mg (four 250-mg tablets) of mesalazine three times a day for seven days, the plasma concentrations of both the unchanged and acetylated forms of mesalazine reached their steady states within 4 days after the start of administration, without a tendency to accumulate in the body.

   (3) Repeated Oral Administration of PENTASA Tablets (2000 mg as Mesalazine) Twice Daily for 6 Days

   When this product was repeatedly administered at an oral dose of 2000 mg (eight 250-mg tablets) of mesalazine twice daily for six days to healthy adults, the pharmacokinetic parameters are shown in Table 2. The plasma concentrations of both the unchanged and acetylated forms of mesalazine reached their steady states within 4 days after the start of administration, without a tendency to accumulate in the body.

<table>
<thead>
<tr>
<th>Time points</th>
<th>Unchanged form</th>
<th>Acetylated form</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 (n=6)</td>
<td>Day 6 (n=6)</td>
</tr>
<tr>
<td></td>
<td>Day 1 (n=6)</td>
<td>Day 6 (n=6)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>7676.0 ± 4671.4</td>
<td>7385.3 ± 3142.5</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>3.0 ± 0.9</td>
<td>2.8 ± 0.8</td>
</tr>
<tr>
<td>T1/2 (hr)</td>
<td>7.9 ± 2.7</td>
<td>5.8 ± 1.4</td>
</tr>
<tr>
<td>AUC (ng·hr/mL)</td>
<td>44063.7 ± 10722.4</td>
<td>56552.5 ± 18400.0</td>
</tr>
</tbody>
</table>

   Mean ± S.D., #1: AUC0-24, #2: AUC0-72

2. **Metabolism and Excretion**

   When this product was orally administered at a single dose of 1000 mg (four 250-mg tablets) of mesalazine to healthy adults after a meal, the urinary excretion rate at 96 hours after administration was 28.4% (27.7% as the acetyl form) of the dose, and the fecal excretion rate 50.0% (23.5% as the acetyl form).

   When this product was orally administered at a repeated dose of 2000 mg (eight 250-mg tablets) of mesalazine twice a day for 6 days to healthy adults, the urinary excretion reached a steady state within 4 days after administration, and the cumulative rate was 34.7% (25.6% as the acetyl form) of the dose, without a tendency to accumulate in the body.

   The protein binding rates of mesalazine and its metabolite, the acetyl form, were appropriately 70 and 88%, respectively.

   When this product was orally administered at a single dose of 1000 mg (four 250-mg tablets) of mesalazine after a meal, the plasma concentrations of mesalazine and its acetyl form tended to decrease as compared with those administered in a fasted state; however, no significant differences were found in the urinary and fecal excretion rates up to 96 hrs after administration between fasted and fed states.
CLINICAL STUDIES

1. Clinical Efficacy\(^{(1)(6)}\)

In the clinical studies including a double-blind comparative study performed at domestic medical institutions, the results of efficacy of this product in 189 cases analyzed are summarized in Table 3.

Table 3 The Results of Clinical Studies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Stage</th>
<th>Dosage* (mg/day)</th>
<th>Administration period</th>
<th>Improvement or efficacy rate of moderate or better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerative colitis</td>
<td>Active phase</td>
<td>750 to 2250</td>
<td>4 weeks</td>
<td>Improvement rate: 70.3% (78/111)</td>
</tr>
<tr>
<td></td>
<td>Remission phase</td>
<td>750 to 2250</td>
<td>12 months</td>
<td>Efficacy rate: 91.9% (34/37)</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Active phase</td>
<td>1500 to 3000</td>
<td>4 to 12 weeks</td>
<td>Improvement rate: 54.8% (17/31)</td>
</tr>
<tr>
<td></td>
<td>Remission phase</td>
<td>1500 to 3000</td>
<td>12 months</td>
<td>Efficacy rate: 90.0% (9/10)</td>
</tr>
</tbody>
</table>

#: Three times daily dosing

The usefulness of this product for treatment of ulcerative colitis was demonstrated in the double-blind comparative study.

2. Dose Comparative Study (Comparison between Daily Doses of 4000 and 2250 mg)

A domestic 8-week repeated dose comparative study was conducted in patients with a moderate relapse-remitting type of ulcerative colitis (excluding proctitis). As a result, there was a significant difference in improvement in UC-DAI score\(^{5}\) between the dose groups, as shown in Table 4.

#: UC-DAI scores are obtained by totalizing four-grade scores (from 0 to 3) of defecation frequency, melena, mucosal findings by endoscopy, and overall evaluation by investigators (the score range: 0 to 12).

Table 4 Improvement in UC-DAI scores in Dose Comparative Study

<table>
<thead>
<tr>
<th>Dose group (mg)</th>
<th>At the start of dosing(^{(4)})</th>
<th>Eight weeks after dosing or at withdrawal(^{(5)})</th>
<th>Change between pre- and post-dosing(^{(4)})</th>
<th>Difference in change between dose groups(^{(6)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>2250(^{(3)})</td>
<td>7.0 ± 0.8</td>
<td>6.1 ± 3.6</td>
<td>-0.8</td>
<td>-2.2*</td>
</tr>
<tr>
<td>(n=59)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4000(^{(3)})</td>
<td>7.0 ± 0.8</td>
<td>4.0 ± 2.9</td>
<td>-3.0</td>
<td>-3.4 to -1.0</td>
</tr>
</tbody>
</table>

#1: Three times daily dosing, #2: Twice daily dosing
#3: Mean ± S.D., #4: Mean [95% confidence interval] *: t-test, t=3.705, P<0.001

3. Dosage Regimen Comparative Study (Comparison between once daily dosing and three times daily dosing)

A domestic 52-week repeated comparative study was conducted in patients with quiescent ulcerative colitis to verify noninferiority of once daily dosing (1500 mg or 2250 mg at a time) to three times daily dosing (500 mg or 750 mg at a time) in remission rate. As a result, it was verified that once daily dosing was noninferior to three times daily dosing in remission rate evaluated as UC-DAI score (Table 5).

Table 5 Remission rate

<table>
<thead>
<tr>
<th>Dosing group</th>
<th>Number of investigational patients</th>
<th>Patients in maintenance of remission(^{(1)})</th>
<th>Remission rate (%)(^{(2)})</th>
<th>Difference between dosing groups(^{(3)}) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once daily</td>
<td>141</td>
<td>112</td>
<td>79.4</td>
<td>7.8 [-2.2 to 17.8]</td>
</tr>
<tr>
<td>Three times daily</td>
<td>141</td>
<td>101</td>
<td>71.6</td>
<td></td>
</tr>
</tbody>
</table>

#1: Number of patients who had not experienced relapse after 52 weeks or at discontinuation
#2: Remission rate (%) = (Patients in maintenance of remission / number of investigational patients) x 100
#3: Remission rate of once daily group minus that of three times daily group [95% confidence interval], Margine of noninferiority: -10%

PHARMACOLOGY

1. Suppressive Action on Lesion in Experimental Animal Models

(1) Ulcerative colitis-like model\(^{(56,57)}\)

Oral administration of mesalazine granules significantly suppressed lesions in the rat acetate acid-induced model at doses of 50 and 100 mg/kg, and in the rabbit λ-decomposed carrageeinin-induced model at a dose of 150 mg/kg.

(2) Crohn’s disease-like model\(^{(59)}\)

Oral administration of mesalazine granules significantly suppressed lesions in the rat TNB-induced model at a dose of 50 mg/kg.

2. Mechanism of Action\(^{(58)}\)

An in vitro study showed that mesalazine had a free-radical (DPPH)-reducing action, hydrogen peroxide-eliminating action, hypochlorous ion-eliminating action, and lipid peroxide-suppressing action (also in vivo). In addition, mesalazine suppressed the biosynthesis of leukotriene B\(_4\) (LTB\(_4\)) in rat neutrophils (in vitro).

These results indicate that the major mechanisms of mesalazine would include elimination of active oxygen species released from inflammatory cells, suppression of the progress of inflammation and impairment of the tissues, and suppression of biosynthesis of LTB\(_4\) resulting in supression of infiltration of inflammatory cells into the tissues. Separately, mesalazine may also participate in suppressions of histamine release from the mast cells, biosynthesis of platelet activating factor (PAF), and production of interleukin-1β (IL-1β) (in vivo).
PHYSICOCHEMISTRY

Nonproprietary name: Mesalazine (JAN)

Chemical name: 5-Amino-2-hydroxybenzoic acid

Molecular formula: C7H7NO3

Molecular weight: 153.14

Structural formula:

\[
\text{H}_2\text{N} \quad \text{COH} \\
\text{OH}
\]

Description:
Mesalazine occurs as white, light grey, or reddish white crystals or crystalline powder.
It is very slightly soluble in water, and practically insoluble in ethanol (99.5).
It dissolves in dilute hydrochloric acid.

Melting point:
270 to 275°C (Decomposition)

Partition coefficient:
0.03 (pH 3 to 9, water-octanol system)

PACKAGING

PENTASA Tablets 250 mg

PTP: 100 tablets (10 tablets x 10)
500 tablets (10 tablets x 50)

PENTASA Tablets 500 mg

PTP: 100 tablets (10 tablets x 10)
500 tablets (10 tablets x 50)

REFERENCES

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17) Stoschus B. et al., J. Hepatology, 26, 425 (1997)
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31) Kristensen K.S. et al., Lancet, 335, 605 (1990)
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51) Ohta T. et al., Pharmacometrics, 47(6), 513 (1994)
53) Jens H. et al., Am. J. Gastroenterol., 85, 331 (1990)

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TEL: 0120-409-341 (Toll-free)
9:00 to 17:30 (Monday through Friday exclusive of national holidays)

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