WARNINGS
1. When this product is administered, the patients should be put under careful observation of their conditions by implementing frequent laboratory tests (tests such as blood tests, hepatic function tests, and renal function tests), and if any abnormality is observed, appropriate measures should be taken; in addition, it should be carefully studied whether the administration could be further continued or not. [This product is known to strongly depress bone marrow and renal functions, and early deaths possibly related to this product have been noted in clinical studies. In the clinical studies, serious thrombocytopenia was noted in 28.5% of the patients treated with this product and serious leucopenia in 21.1%. Such adverse reactions may result in fatal bleeding, infection and others.]
2. This product should be administered by physicians having adequate experiences in the chemotherapy for cancers at medical institutions where cases of emergency can be handled adequately. Furthermore, this product should be administered only to patients who have been carefully chosen, and are considered suitable for administration of this product. [See “CONTRAINDICATIONS” section]
3. Read the package insert of this product carefully before use.

CONTRAINDICATIONS (AQUPLA® is contraindicated in the following patients.)
1. Patients with serious bone marrow depression [Bone marrow depression is exacerbated.]
2. Patients with serious renal impairment [Renal impairment is exacerbated.]
3. Patients with a history of serious hypersensitivity to this product or other platinum-containing drugs
4. Pregnant women or women suspected of being pregnant [See “Use during Pregnancy, Delivery or Lactation” section]

DESCRIPTION
1. Composition

<table>
<thead>
<tr>
<th>Brand name</th>
<th>AQUPLA® 10 mg for IV inj.</th>
<th>AQUPLA® 50 mg for IV inj.</th>
<th>AQUPLA® 100 mg for IV inj.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient/content (Content per vial)</td>
<td>Neadaplatin 10 mg</td>
<td>Neadaplatin 50 mg</td>
<td>Neadaplatin 100 mg</td>
</tr>
<tr>
<td>Additive</td>
<td>Dextran 70 10 mg</td>
<td>Dextran 70 50 mg</td>
<td>Dextran 70 100 mg</td>
</tr>
</tbody>
</table>

2. Product description

<table>
<thead>
<tr>
<th>Brand name</th>
<th>AQUPLA® 10 mg for IV inj.</th>
<th>AQUPLA® 50 mg for IV inj.</th>
<th>AQUPLA® 100 mg for IV inj.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>White to pale yellowish white, light mass (Injection)</td>
<td>White to pale yellowish white, light mass (Injection)</td>
<td>White to pale yellowish white, light mass (Injection)</td>
</tr>
<tr>
<td>pH</td>
<td>6.5-7.5</td>
<td>6.5-7.5</td>
<td>6.5-7.5</td>
</tr>
<tr>
<td>Osmotic pressure ratio (Ratio against isotonic sodium chloride solution)</td>
<td>Approx. 0.1 0.02 g / mL aqueous solution</td>
<td>Approx. 0.1 0.02 g / mL aqueous solution</td>
<td>Approx. 0.1 0.02 g / mL aqueous solution</td>
</tr>
</tbody>
</table>
INDICATIONS

DOSAGE AND ADMINISTRATION
1. The usual adult dosage is 80 to 100 mg/m² (body surface area) once a day, which should be followed by a drug-free period of at least 4 weeks. This constitutes one course of therapy, which is to be repeated. The dosage should be adjusted according to the patient’s age, disease and symptoms.
2. Prior to administration, this product is dissolved in 300 mL or more of physiological saline or 5% xylitol for injection, and intravenously infused over a period of more than 60 minutes.
3. Administration of this product should be followed by intravenous infusion of more than 1000 mL of fluids.

PRECAUTIONS
1. Careful Administration (AQPLA® should be administered with care in the following patients.)
   (1) Patients with bone marrow depression [Bone marrow depression may be exacerbated. (See “WARNINGS” section)]
   (2) Patients with renal impairment [Renal impairment may be exacerbated. (See “WARNINGS” section)]
   (3) Patients with hepatic impairment [Hepatic impairment may be exacerbated.]
   (4) Patients with auditory disorder [Auditory disorder may be exacerbated.]
   (5) Patients complicated with infection [Bone marrow depression due to this product may aggravate the infection.]
   (6) Patients with chickenpox [Fatal systemic disorder may develop.]
   (7) Elderly patients [Bone marrow depression may be exacerbated. (See “Use in the Elderly” section)]
2. Important Precautions
   (1) Since serious adverse reactions such as bone marrow depression and abnormal renal function may occur, the patients should be put under careful observation of their conditions by implementing frequent laboratory tests (tests such as blood tests, hepatic function tests, and renal function tests). If any abnormality is observed, appropriate measures such as dose reduction or temporal discontinuation of therapy should be taken. In addition, bone marrow depression and renal impairment may be more pronounced in patients with already depressed bone marrow or renal function as a result of the previous treatment, especially with cisplatin. In such patients, the initial dose should be properly reduced, and full attention should be paid to their laboratory values on blood and renal function. A long-term use should be done with caution, since it may be associated with pronounced development of adverse reactions, which may last long.
   (2) Full attention should be paid to possible development or exacerbation of infection or bleeding tendency.
   (3) Renal impairment occurs more severely when the urine volume is reduced (reduction of the urine volume may increase the drug concentration in the urine and prolong the time of contact with the drug, leading to an intensified toxicity to the renal tubules). Therefore, when this product is administered, attention should be paid to maintenance of the urine volume, and appropriate fluids or diuretics such as D-mannitol and furosemide should be administered as required. In addition, in case of forced diuresis with furosemide, the patient should be supplied enough water by infusion etc., because exacerbation of renal impairment and auditory disorder have been reported with administration of analogous drugs. Particular attention should be paid to patients who have difficulties in taking water orally or those who have nausea/vomiting, anorexia, diarrhea, etc.
   (4) Since gastrointestinal symptoms such as nausea/vomiting, anorexia, etc. may occur, the patient’s condition should be carefully observed and appropriate measures should be taken, if necessary.
   (5) If this product should be administered to children or patients with reproductivity, due consideration should be taken of its possible effects on their sexual glands.
   (6) In the clinical studies of this product (632 cases in total), sudden death (2 cases) and death after Adams-Stokes attack (1 case) have been reported. One case of sudden death occurred in a patient who had been suffering from heart failure due to underlying hypertension; the other occurred in a patient who had coronary infarction resulting from past myocardial infarction or hemorrhage from the cerebral metastatic lesion; and in one case of Adams-Stokes attack, since patient’s ECG indicated a depressed ST before the administration, it was supposed that anorexia and anemia due to administration of this product were the cause of the attack. However, the causal relationship with this product still remains unknown since no autopsy data were available in any of those cases.

3. Drug Interactions
   Precautions for coadministration (AQPLA® 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 antitumor agents (agents such as alkylating agents, metabolic antagonists, antibiotics, and alkaloids) radiation exposure</td>
<td>Bone marrow depression may be exacerbated. If any abnormality is observed, appropriate measures such as dose reduction or temporal discontinuation of therapy should be taken.</td>
<td>Mechanism is unknown. Both drugs can cause bone marrow depression.</td>
</tr>
</tbody>
</table>
4. Adverse Reactions

Adverse reactions to this drug including abnormal laboratory findings were observed in 569 (95.3%) of 597 patients evaluated for safety at the time of approval.

Adverse reactions to this drug including abnormal laboratory findings were observed in 2339 (75.67%) of 3091 patients evaluated for safety at completion of reexamination. Major adverse reactions were gastrointestinal symptoms, including nausea in 224 patients (7.25%), vomiting in 138 patients (4.46%), anorexia in 105 patients (3.40%), and alopecia in 73 patients (2.36%). Of these, serious cases included nausea in 8 patients (0.26%), vomiting in 7 patients (0.23%), and alopecia in 12 patients (0.39%).

Major abnormal laboratory findings were bone marrow depression, including leukopenia in 1521 patients (49.21%), decreased hemoglobin in 729 patients (23.58%), and thrombocytopenia in 1329 patients (43.00%). Of these, serious cases were leukopenia in 379 patients (12.26%) and thrombocytopenia in 340 patients (11.00%), which were considered as dose limiting-factors for this product.

Abnormal laboratory findings indicating renal impairment included increased BUN in 201 patients (6.50%) and increased serum creatinine in 95 patients (3.07%). Of these, serious cases included increased BUN in 201 patients (6.50%) and in-creased serum creatinine in 95 patients (3.07%). Of these, serious cases included increased BUN in 18 patients (0.58%). Abnormal laboratory findings indicating hepatic impairment included increased AST (GOT) in 221 patients (7.15%) and increased ALT (GPT) in 259 patients (8.38%).

(Incidence of adverse reactions is based on the results at the time of approval and at completion of reexamination.)

(1) Clinically significant adverse reactions

1) Shock, anaphylactoid reaction (5% ≥1%): Since shock or anaphylactoid reaction (hot flushes, dyspnea, chill, decreased blood pressure), etc. may occur, patients should be carefully observed. If any abnormality is observed, the therapy should be discontinued, and appropriate measures should be taken.

2) Bone marrow depression: Pancytopenia (5% ≥1%), anemia, leucopenia, neutropenia, thrombocyto-penia and bleeding tendency (1% ≥0.1%) may occur. Peripheral blood, therefore, should be carefully observed and if any abnormality is observed, appropriate measures such as prolongation of the dosing interval, dose reduction or temporal discon-tinuation of therapy should be taken.

3) Renal failure (1% ≥0.1%): Since serious renal impairment such as renal failure may occur, patients should be carefully observed. If any abnormality is observed, it should be carefully studied whether the administration could be further continued or not.

4) Adams-Stokes attack: One case of Adams-Stokes attack resulting in death has been reported. [See “Important Precautions” section]

5) Deafness, lowered hearing ability (5% ≥1%), tinnitus (1% ≥0.1%): Since deafness, lowered hearing ability for the high frequencies or tinnitus may occur, patients should be carefully observed on their conditions by auditory tests as required. If any abnormality is observed, appropriate measures such as temporal discontinuation of therapy should be taken. Special caution should be taken for patients who received other platinum products in their previous treatment, patients with already lowered hearing ability and patients with decreased renal function even before the start of the treatment.

6) Interstitial pneumonia (<0.1%): Interstitial pneumonia, accompanied with fever, cough, dyspnea, abnormal chest X-ray findings, etc. may occur. Patients should be closely observed. If any abnormality is observed, the therapy should be discontinued and appropriate treatment such as corticosteroid therapy should be taken.

7) Syndrome of Inapp ADH Secretion (Incidence unknown): Syndrome of Inapp ADH Secretion, accompanied with hyponatraemia, blood hyposmosis, increased urinary sodium excretion, hypersthenuria, disturbed consciousness, etc. may occur. If such symptoms occur, the therapy should be discontinued and appropriate measures such as restriction of water intake should be taken.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>Incidence</th>
<th>≥5%</th>
<th>≥5% ≥0.1%</th>
<th>&lt;0.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body system</td>
<td>Psychoneurologic</td>
<td>Renal</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>Headache, dizziness, peripheral neurological disorders such as numbness of limbs, dysguesia</td>
<td>Decreased creatinine clearance, increased β₂-microglobulin, hematocrit, proteinuria, oliguria, increased uric acid</td>
<td>Diarrhea, ileus, abdominal pain, constipation, stomatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mechanism is unknown. Both drugs can cause renal impairment and auditory disorder.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside antibiotics</td>
<td>Renal impairment and auditory disorder may be exacerbated. If any abnormality is observed, appropriate measures such as temporal discontinuation of therapy should be taken.</td>
</tr>
<tr>
<td>Vancomycin hydrochloride</td>
<td>Renal impairment and auditory disorder may be exacerbated. If any abnormality is observed, appropriate measures such as temporal discontinuation of therapy should be taken.</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>Renal failure (1% ≥0.1%): Since serious renal impairment such as renal failure may occur, patients should be carefully observed. If any abnormality is observed, it should be carefully studied whether the administration could be further continued or not.</td>
</tr>
<tr>
<td></td>
<td>Adams-Stokes attack: One case of Adams-Stokes attack resulting in death has been reported. [See “Important Precautions” section]</td>
</tr>
<tr>
<td></td>
<td>Deafness, lowered hearing ability (5% ≥1%), tinnitus (1% ≥0.1%): Since deafness, lowered hearing ability for the high frequencies or tinnitus may occur, patients should be carefully observed on their conditions by auditory tests as required. If any abnormality is observed, appropriate measures such as temporal discontinuation of therapy should be taken. Special caution should be taken for patients who received other platinum products in their previous treatment, patients with already lowered hearing ability and patients with decreased renal function even before the start of the treatment.</td>
</tr>
<tr>
<td></td>
<td>Syndrome of Inapp ADH Secretion (Incidence unknown): Syndrome of Inapp ADH Secretion, accompanied with hyponatraemia, blood hyposmosis, increased urinary sodium excretion, hypersthenuria, disturbed consciousness, etc. may occur. If such symptoms occur, the therapy should be discontinued and appropriate measures such as restriction of water intake should be taken.</td>
</tr>
<tr>
<td></td>
<td>Other adverse reactions</td>
</tr>
<tr>
<td></td>
<td>Mechanism is unknown. Both drugs can cause renal impairment and auditory disorder.</td>
</tr>
</tbody>
</table>
5. Use in the Elderly

(1) This product is excreted mainly from the kidney. Since the elderly generally have a decreased renal functions due to which the excretion is delayed, attention should be paid to possible bone marrow depression. If any abnormality is observed, attention should be paid to the interval of administration for instance, resuming the treatment only after a full recovery is confirmed.

(2) It is desirable for the elderly that the administration should be started at a dose of 80 mg/m² (body surface area) once a day.

(3) Adverse reactions observed in 194 elderly patients aged 65 years or older at the time of approval were leukopenia in 153 patients (78.9%), thrombocytopenia in 117 patients (60.3%), and decreased hemoglobin in 130 patients (67.0%).

Adverse reactions observed in 1113 elderly patients aged 65 years or older at completion of reexamination were leukopenia in 560 patients (50.31%), thrombocytopenia in 525 patients (47.17%), and decreased hemoglobin in 257 patients (23.09%).

6. Use during Pregnancy, Delivery or Lactation

(1) This product should not be used in women who are or may become pregnant. [Animal studies have shown that this product had teratogenic effects and caused fetal death in rats, and that it caused fetal death in rabbits.]

(2) Nursing mothers should discontinue breast feeding during treatment. [Cisplatin, an analogous drug has been reported to be excreted in breast milk.]

7. Pediatric Use

The safety of this product in children has not been established. [no clinical experience. (See “Important Precautions” section)]

8. Precautions concerning Use

(1) Method of preparation: Use promptly after reconstitution.

(2) Cautions in preparation

1) Since this product is a complex compound, do not inject it mixed with other antitumor agents.

2) Intravenous infusion of this product in combination with amino acid fluids or acidic fluids at pH 5 or less (electrolytes fluid, fluid for intravenous hyperalimentation, 5% fructose injection, etc.) should be avoided, as it causes degradation.

3) Do not use with medical devices containing aluminum, since this product reacts with aluminum to form precipitates, which may decrease the activity.

4) Do not expose this product to direct sunlight or high temperature, since it is degraded by light and heat.

3) Caution in administration: If the drug solution leaks out of the blood vessel at the time of intravenous administration, it may cause induration or necrosis at the injection site. Therefore, drug solution should be carefully injected not to leak out of the blood vessel.

9. Other Precautions

(1) Positive results have been reported in both reverse mutation tests with bacteria, and chromosomal aberration tests with cultured human lymphocytes and mouse bone marrow cells.

(2) In repeated dose toxicity studies in rats (intermittent intravenous administration once a week for 6 months), development of mammary glandular tumor has been reported among females.

PHARMACOKINETICS

1. Plasma concentrations

(1) Nedaplatin for injection was administered to 7 patients with malignant tumors by intravenous infusion at 80 mg/m² and 100 mg/m² over about 60 minutes and the total platinum concentrations in the plasma were measured by atomic absorption spectrometry. The concentrations, though variable from patient to patient to some extent, reached a peak at completion of intravenous infusion, decreasing biphasically thereafter, with the AUC being almost proportional to the doses. The elimination half-life for α phase (T 1/2α) was about 0.1 to 1 hour while the elimination half-life for the β phase (T 1/2β) was about 2 to 13 hours. 

<table>
<thead>
<tr>
<th>Case</th>
<th>Dose (mg/m²)</th>
<th>Age</th>
<th>Gender</th>
<th>Cmax (µg/mL)</th>
<th>AUC0-24 (µg hr/mL)</th>
<th>T 1/2α (hr)</th>
<th>T 1/2β (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>Male</td>
<td>8.45</td>
<td>15.47</td>
<td>0.10</td>
<td>1.88</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Female</td>
<td>4.95</td>
<td>15.05</td>
<td>0.75</td>
<td>13.13</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Female</td>
<td>5.27</td>
<td>28.01</td>
<td>0.26</td>
<td>1.89</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Male</td>
<td>6.51</td>
<td>17.94</td>
<td>0.99</td>
<td>7.53</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Female</td>
<td>5.31</td>
<td>20.79</td>
<td>4.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>Male</td>
<td>5.96</td>
<td>31.92</td>
<td>0.99</td>
<td>5.78</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>Female</td>
<td>6.72</td>
<td>28.08</td>
<td>0.79</td>
<td>4.82</td>
<td></td>
</tr>
</tbody>
</table>

(2) Free (unbound) platinum concentrations in plasma of a patient with malignant tumor (Case No.7 in the above table) were measured by ultrafiltration, and the result indicated that the platinum exists almost completely in a free form.
Figure 1: Total platinum and free platinum concentrations in plasma

Table 2: Pharmacokinetic parameters

<table>
<thead>
<tr>
<th></th>
<th>Cmax (μg/mL)</th>
<th>AUC 0-24 (μg·hr/mL)</th>
<th>T1/2 α (hr)</th>
<th>T1/2 β (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total platinum concen-</td>
<td>6.72</td>
<td>28.08</td>
<td>0.79</td>
<td>4.82</td>
</tr>
<tr>
<td>tration in plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free platinum concen-</td>
<td>6.50</td>
<td>22.77</td>
<td>0.90</td>
<td>2.71</td>
</tr>
<tr>
<td>tration in plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Distribution (For reference)
In rats, 10 minutes after a single intravenous dose of 3 mg/kg of nedaplatin, platinum concentrations in kidney and bladder, which are on route of excretion, were higher than in plasma, but platinum concentrations in other tissues were lower. Elimination of the platinum from each tissue was slower than from plasma, and platinum was still detected in the liver, kidney and femur (femora) of male rats, and in kidney of female rats 24 hours after administration.

3. Metabolism (For reference)
Nedaplatin was hardly metabolized in rats and dogs, and behaved in its unchanged form in plasma.

4. Excretion
Nedaplatin for injection was administered to patients with malignant tumors by intravenous infusion at 80 mg/m² and 100 mg/m² over about 60 minutes, and the 24-hour urinary recovery of platinum as determined by atomic absorption spectrometry was in the range of 40 to 69%.1)

CLINICAL STUDIES
In phase II clinical trials2-9) performed before NDA approval, the number of cases evaluated for efficacy was 418 cases and the clinical efficacy rate were as follows.

Table 3: Clinical studies

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cases of CR + PR /Cases evaluated for efficacy</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck cancer</td>
<td>(11+27) / 90</td>
<td>42.2</td>
</tr>
</tbody>
</table>

Table 4: Activity against transplantable animal tumor cell lines

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Tumor (Site of transplantation)</th>
<th>Method/route of administration</th>
<th>Maximum ILS% (note 1)</th>
<th>Chemotherapeutic coefficient (note 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>Lewis lung cancer (subcutaneous)</td>
<td>5 consecutive days, intraperitoneal</td>
<td>&gt; 53</td>
<td>2.2 (78/35)</td>
</tr>
</tbody>
</table>

Note 1) ILS% (increased life span %) = [(Mean of survival days in treated group – Mean of survival days in control group)] / Mean of survival days in control group) × 100
Note 2) Chemotherapeutic coefficient = Total dose at max ILS% / Total dose at ILS 30%

(3) When lung cancer cell lines (6 cell lines), head and neck cancer cell lines (3 cell lines), esophageal cancer cell lines (1 cell line) and cervical cancer cell lines (2 cell lines) in human, each transplanted into nude mice (BALB/c- nu/ nu), were treated with single intravenous doses of nedaplatin in 1/2 of LD50 (29.6 mg/kg), nedaplatin showed a definite tumor-growth inhibition against the lung cancer cells (4 cell lines), esophageal cancer cells (1 cell line) and cervical cancer cells (1 cell line). (in vivo)

2. Mechanism of action
After nedaplatin enters cells, the bond between alcoholic oxygen of the glycolate ligand and platinum is cleaved and water coordinates to platinum, resulting in formation of ion species (active species or a quocomplex). Then, the disconnected glycolate ligand becomes unstable and released, yielding various ion species, which bind with DNA. In short, this product is considered to bind with DNA by the same way as cisplatin, and to inhibit DNA duplication, consequently possibly exerting antitumor activity. In ad-
dition, it has been confirmed that this product and cisplatin bind with exactly the same bases in their reactions with DNA.\(^{10}\)

**PHYSICOCHEMISTRY**

Nonproprietary name: Nedaplatin (JAN)
Chemical name: *cis-Diammineglcolatoplatinum*
Molecular formula: C\(_2\)H\(_8\)N\(_2\)O\(_3\)Pt
Molecular weight: 303.17

**Structural formula:**

\[
\begin{array}{c}
\text{H}_2\text{N}
\end{array}\quad \begin{array}{c}
\text{Pt}
\end{array}
\begin{array}{c}
\text{O}
\end{array}\quad \begin{array}{c}
\text{O}
\end{array}
\begin{array}{c}
\text{H}_2\text{N}
\end{array}
\]

**Description:**

Nedaplatin is white to light yellow crystalline powder. It is sparingly soluble in water, and practically insoluble in ethanol (95) and in diethyl ether.

**Melting point:**

As the temperature is raised, decomposition occurs with changes such as discoloration and foaming, and no definite melting point may be discernible.

**Partition coefficient:**

0.006 (pH 7, chloroform/buffer solution system)

**PACKAGING**

AQUPLA® for Intravenous Injection 10 mg: 1 vial
AQUPLA® for Intravenous Injection 50 mg: 1 vial
AQUPLA® for Intravenous Injection 100 mg: 1 vial

**REFERENCES**

[Reference request No.]

1) Oguma T. et al.: Internal document (Platinum disposition in cancer patients following intravenous infusion, 1992) [199201728]
10) Ohara O. et al.: Internal document (Study on reaction specificity of platinum compound and nucleic acid, 1993) [199302374]

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

Drug Information Center
SHIONOGI & CO., LTD.
1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541-0045, Japan
TEL: 0120-956-734
FAX: 06-6202-1541
http://www.shionogi.co.jp/med/

**Manufactured and Distributed by:**

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