- Nonionic contrast medium -

**Iomeron® 300 Injection Syringe 50mL**

**Iomeron® 300 Injection Syringe 75mL**

**Iomeron® 300 Injection Syringe 100mL**

**Iomeron® 350 Injection Syringe 50mL**

**Iomeron® 350 Injection Syringe 75mL**

**Iomeron® 350 Injection Syringe 100mL**

**Iomeron® 350 Injection Syringe 135mL**

<i>lomeprol injections</i>

Prescription drug

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**Warnings**

1. Serious adverse reactions such as shock may occur.
2. Never use IOMERON for cisternography or myelography, because its injection into the brain and spinal canal may cause serious adverse reactions.

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**Contraindications**

(IOMERON is contraindicated in the following patients.)

1. Patients with a history of hypersensitivity to iodine or iodinated contrast media
2. Patients with serious thyropathy
   - [Symptoms may be aggravated due to changes in thyroid gland function because the iodine concentration may increase in the thyroid gland.]

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**Relative Contraindications**

(As a general rule, IOMERON is contraindicated in the following patients. If the use of IOMERON is considered essential, it should be administered with care.)

1. Patients with an extremely poor general condition
2. Patients with bronchial asthma
   - [It has been reported that patients with bronchial asthma have a higher risk of adverse reactions than those without bronchial asthma.]
3. Patients with serious cardiac function disorders
   - [Cardiac function may be impaired due to deterioration in hemodynamics.]
4. Patients with serious hepatic function disorders
   - [Symptoms may be aggravated.]
5. Patients with serious renal function disorders

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**Description**

**IOMERON 300 Injection Syringe:**

Each mL of Syringe contains 612.4 mg (equivalent to 300 mg of iodine) of iomeprol.

**IOMERON 350 Injection Syringe:**

Each mL of Syringe contains 715.6 mg (equivalent to 350 mg of iodine) of iomeprol.
INDICATIONS

IOMERON 300 Injection Syringe:
Visualization in computed tomography, intravenous urography, cerebral angiography, thoracic angiography, abdominal angiography, peripheral angiography, intravenous digital subtraction angiography and intraarterial digital subtraction angiography

IOMERON 350 Injection Syringe:
Visualization in computed tomography, intravenous urography, angiocardiology, thoracic angiography, abdominal angiography, peripheral angiography, intravenous digital subtraction angiography and intraarterial digital subtraction angiography

DOSAGE AND ADMINISTRATION

The usual adult doses are as indicated below. The dosage may be adjusted depending on the patient’s age, body weight, symptoms and purpose of use. In the case of multiple-dose administration, a total dosage of 250 mL should not be exceeded.

<table>
<thead>
<tr>
<th>Radiological examination</th>
<th>IOMERON 300 Injection Syringe</th>
<th>IOMERON 350 Injection Syringe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>40 - 100 mL</td>
<td></td>
</tr>
<tr>
<td>Visualization in computed tomography</td>
<td>40 - 100 mL</td>
<td>40 - 100 mL</td>
</tr>
<tr>
<td>Intraarterial digital subtraction angiography</td>
<td>10 - 50 mL</td>
<td>10 - 50 mL</td>
</tr>
<tr>
<td>Intraarterial digital subtraction angiography</td>
<td>3 - 40 mL</td>
<td>3 - 40 mL</td>
</tr>
</tbody>
</table>

The dosage according to body weight of IOMERON 350 Injection Syringe is referred to “<precaution>.”

PRECAUTIONS

1. Careful Administration (IOMERON should be administered with care in the following patients.)

1. Patients with a personal or familial predisposition to allergic reactions, such as bronchial asthma, rash or urticaria, etc.
2. Patients with a history of drug hypersensitivity
3. Patients with symptoms of dehydration
4. Patients with hypertension
5. Patients with arteriosclerosis
6. Patients with diabetes mellitus
7. Patients with myasthenia gravis
8. Patients with thyropathy
9. Patients with central nervous system disorders
10. Patients with acute pancreatitis
11. Patients with myasthenia gravis
12. Patients with a history of drug hypersensitivity
13. Patients with diabetes mellitus
14. Patients with myasthenia gravis

2. Important Precautions

1. Patients should be carefully interviewed to prepare for shock or any other emergency.
2. Hypersensitive reactions may occur after administering IOMERON, regardless of dose or route of administration. Shock or other serious adverse reactions resulting from its use are not always due to hypersensitive reac-
3. Drug Interactions
Precautions for coadministration (IOMERON 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>Biguanide antidiabetic agents Metformin hydrochloride Bufometin hydrochloride, etc.</td>
<td>Lactic acidosis has been reported after iodine contrast media coadministration with biguanide antidiabetic agents. When using IOMERON, appropriate measures, such as temporary discontinuation of biguanide antidiabetic agents, should be taken.</td>
<td>Blood concentration of biguanide antidiabetic agents may increase due to a decrease in their renal excretion.</td>
</tr>
</tbody>
</table>

4. Adverse Reactions
Adverse reactions were reported in 398 of 7,820 patients (5.09%). (At the end of reexamination period and at the time of additional approval of dosage and administration on visualization in dynamic computed tomography of hepatic region)

(1) Clinically significant adverse reactions
1) Shock
Syncope, unconsciousness, dyspnea, respiratory arrest, cardiac arrest or other symptoms due to shock (including delayed reactions) (<0.1%) may occur. Patients should be carefully observed, since even mild hypersensitivity symptoms may develop into serious symptoms. In the event of such symptoms, appropriate measures should be taken immediately.

2) Anaphylaxis
Anaphylaxis (including delayed reactions) (<0.1%) such as dyspnea or pharyngolaryngeal edema may occur. Patients should be carefully observed. In the event of such symptoms, appropriate measures should be taken immediately.

3) Pulmonary edema
Pulmonary edema (<0.1%) may occur. In the event of such symptoms, appropriate measures should be taken immediately.

4) Acute respiratory distress syndrome
Acute respiratory distress syndrome (incidence unknown) may occur. In the event of such symptoms, appropriate measures should be taken immediately.

5) Ventricular fibrillation and coronary artery spasm
Ventricular fibrillation (incidence unknown) or coronary artery spasm (incidence unknown) may occur. In the event of such symptoms, appropriate measures should be taken immediately.

6) Hepatic function disorders and jaundice
Hepatic function disorders (<0.1%) such as elevation of AST (GOT), ALT (GPT) or γ-GTP, or jaundice (incidence unknown) may occur. In the event of such abnormal findings, appropriate measures should be taken immediately.

7) Cerebrovascular disorders
Ischemic or permanent cerebral circulatory failure (cerebral ischemia) (incidence unknown) may occur. In the event of such abnormal findings, appropriate measures should be taken immediately.

8) Convulsive seizure
Convulsive seizure (<0.1%) may occur. In the event of such symptoms, appropriate measures should be taken immediately.

9) Disturbed consciousness and syncope
Disturbed consciousness (incidence unknown) and syncope (incidence unknown) without shock may occur. Patients should be carefully observed, and if symptoms such as decreased consciousness occur, appropriate measures should be taken immediately.

10) Paralysis
Paralysis (incidence unknown) during cerebral angiography has been reported. Patients should be carefully observed. In the event of such symptoms, appropriate measures should be taken immediately.

11) Renal failure
Acute kidney injury (<0.1%) may occur. Patients should be carefully observed. In the event of such symptoms, appropriate measures should be taken immediately.

12) Thrombocytopenia
Thrombocytopenia (incidence unknown) may occur. Patients should be carefully observed. In the event of such symptoms, appropriate measures should be taken immediately.

13) Dermatologic disorders
Oculo-muco-cutaneous syndrome (Stevens-Johnson syndrome) (incidence unknown) or acute generalized exanthematous pustulosis (incidence unknown) may occur. Patients
should be carefully observed, and if symptoms such as fever, erythema, small pustules, itching, eye hyperemia, stomatitis, etc. occur, appropriate measures should be taken immediately.

(2) Other adverse reactions

<table>
<thead>
<tr>
<th>5%&gt;</th>
<th>≥0.1%</th>
<th>&lt;0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Rash, redness, itching, urticaria and wheals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoneurologic</td>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychoneurologic</td>
<td>Photophobia, sensation of warmth, sneezing, difficulty in breathing, and tinnitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Decrease in blood pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Sneeze</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Fever, malaise and feeling of warmth</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note) In the event of such symptoms, treatment should be discontinued and appropriate measures taken.

5. Use in the Elderly

IOMERON is excreted mainly through the kidneys. As renal functions are often lower in the elderly, there is a tendency for the blood concentration to remain high. IOMERON should be administered carefully to the elderly, observing their condition.

6. Use during Pregnancy, Delivery or Lactation

(1) IOMERON should only be used in pregnant women or women suspected of being pregnant provided that the expected diagnostic benefits are evaluated to outweigh the possible risk of treatment.

(2) Nursing mothers should discontinue breast feeding temporarily during treatment.

7. Pediatric Use

The safety in low birth weight infants, neonates, nursing infants, infants and children has not been established (insufficient clinical experience).

8. Effects on Laboratory Tests

When it is necessary to carry out a diagnostic procedure using radioactive iodine such as thyroid gland function testing, it should be done before administering IOMERON. In addition, no testing with radioactive iodine should be done within one month of using IOMERON. (It may influence the test results.)

9. Precautions concerning Use

(1) Route of administration

Never use IOMERON for cisternography or myelography.

(2) Rate of administration

In IOMERON 350 Injection Syringe, rate of administration is up to 5.0mL/second in the case of visualization in dynamic computed tomography of hepatic region. The safety in rate of administration more than 5.0mL/second has not been established.

(3) Preparatory measures

1) Heat IOMERON to body temperature before use.
2) Do not restrict patients’ water intake before use.
3) In urography, gas should be eliminated from the intestines beforehand and the patients should be fasted until the radiographic procedure has been completed.

(4) Administration

1) Vascular pain may occur after intravenous administration of IOMERON.
2) In an in vitro study, nonionic contrast media have a weaker blood coagulation inhibiting effect than ionic contrast media. Therefore, prior to angiography, thoroughly flush out the catheter. When injecting IOMERON, avoid leaving it in contact with blood in a syringe or a catheter for long periods of time.
3) If IOMERON is mixed with antihistamines or adrenocortical hormone preparations, this may cause changes of compatibility. Therefore, they should be administered separately when used concomitantly.
4) Since redness, swelling, blister, vascular pain or other symptoms may occur when contrast media leak out of a vascular vessel, they should be administered carefully.

5) Precaution during administration

If IOMERON should be used in power injector, infusion pressure is not over 13kg/cm² (185PSI).

(5) Post-administration

Post-administration, let patients take enough water to aid the excretion of the contrast medium.

(6) Opening package

IOMERON should be used promptly after opening package.

PHARMACOKINETICS

(Reference)

1. Blood concentration and urinary excretion

In 10 healthy adult male volunteers who were administered at intravenously at a single dose of 40 or 80 mL (note) of iomopro 400mg/mL at a rate of 10 mL/min, changes in the plasma iodine concentration were practically in proportion to the dose and, after administration, the plasma iodine
Eisai Co., Ltd.

concentration declined in a biphasic manner. The elimination half-life in plasma was 22.3 min for \( t_{1/2a} \) (distribution phase) and 1.95 hr for \( t_{1/2b} \) (excretion phase). The volume of central compartment (Vc) was 0.11 L/kg and total plasma clearance was 99.0 mL/min.

Further, the urinary excretion rate of the unchanged drug was 80.0 % of dosage up to 4 hr and 97.5 % up to 24 hr after administration. 1)

**Note** A single dose of 80mL of iomeprol 400mgI/mL is unapproved.

### Pharmacokinetic parameters after single intravenous administration at a single dose of iomeprol 400 mgI/mL

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Normal (n=6)</th>
<th>Mild (n=6)</th>
<th>Moderate (n=6)</th>
<th>Severe (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{1/2a} ) (hr)</td>
<td>22.3±6.79</td>
<td>3.67±0.46</td>
<td>6.9±1.6</td>
<td>15.1±4.3</td>
</tr>
<tr>
<td>AUC0→∞ (hr)</td>
<td>7.7±2.6</td>
<td>10.3±1.2</td>
<td>22.1±4.5</td>
<td>46.4±3.1</td>
</tr>
<tr>
<td>CL (mL/min)</td>
<td>8.3±1.7</td>
<td>8.7±0.9</td>
<td>8.2±2.5</td>
<td>10.7±3.3</td>
</tr>
<tr>
<td>CLR (mL/min)</td>
<td>31.8±6.5</td>
<td>31.8±6.5</td>
<td>31.8±6.5</td>
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</tr>
<tr>
<td>GFR(^{\text{CrCl}}) (mL/min)</td>
<td>120±30</td>
<td>72±9.8</td>
<td>38±16.8</td>
<td>20±3.16</td>
</tr>
<tr>
<td>FE (%)</td>
<td>93.5±5.5</td>
<td>90.4±4.6</td>
<td>85.1±9.0</td>
<td>68.5±10.6</td>
</tr>
</tbody>
</table>

*Note 1) n=5  Note 2) Inulin clearance measurement method.

### Cumulative urinary excretion rate after administration at a single dose of 40mL and 80mL\(^{\text{Note}}\) of iomeprol 400mgI/mL.

2. Blood concentration at the time of renal function disorder and urinary excretion

(Data from outside Japan)

Iomeprol 400 mgI/mL was administrated intravenously at a single dose of 50 mL to six healthy volunteers with normal renal function (GFR\(^{\text{Note}}\) > 100 mL/min/1.73m²), six patients with mild renal failure (GFR\(^{\text{Note}}\) 51-75 mL/min/1.73m²), six patients with moderate renal failure (GFR\(^{\text{Note}}\) 26-50 mL/min/1.73m²), and four patients with severe renal failure (GFR\(^{\text{Note}}\) < 25 mL/min/1.73m²), iomeprol concentration in plasma and urine were determined.

### Time course in mean plasma iodine concentrations after administration at a single doses of 40mL and 80mL\(^{\text{Note}}\) of iomeprol 400mgI/mL

### Pharmacokinetic parameters of iomeprol in healthy volunteers and renal function disorders

<table>
<thead>
<tr>
<th>Severity of renal function disorder</th>
<th>Normal (n=6)</th>
<th>Mild (n=6)</th>
<th>Moderate (n=6)</th>
<th>Severe (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{1/2a} ) (hr)</td>
<td>2.3±0.44</td>
<td>3.67±0.46</td>
<td>6.9±1.6</td>
<td>15.1±4.3</td>
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*Note 1) n=5  Note 2) Inulin clearance measurement method.

### CLINICAL STUDIES

1. Effectiveness

(1) Computed tomography and urography

The radiographic efficacy in 226 patients (those included in radiographic efficacy evaluation) reported in open labeled clinical trials was 100%. 3, 4)
(2) Visualization in dynamic computed tomography of hepatic region (IOMERON 350 Injection and IOMERON 350 Injection Syringe)

In phase II / phase III clinical trial in 173 patients with hepatic tumors, were evaluated by independent 3 assessors on radiographic efficacy of tumor mass in fixed contrast dose of 100 mL, 1.5 mL and 1.8 mL per kg bodyweight. Rate of subjects who judged “excellent” or “good” was 98.3 % ~ 100 % except for 1 patient of fixed contrast dose of 100 mL. Rate of subjects who judged “excellent” was 63.8 % in fixed contrast dose of 100 mL, 57.9 % in 1.5 mL per kg bodyweight and 84.5 % in 1.8 mL per kg bodyweight. In radiographic efficacy of tumor mass, when IOMERON was compared fixed contrast dose of 100 mL with 1.8 mL per kg bodyweight, 1.8 mL per kg bodyweight was significantly superior to fixed contrast dose of 100 mL. When IOMERON was compared 1.5 mL per kg bodyweight with 1.8 mL per kg bodyweight, 1.8 mL per kg bodyweight was significantly superior to 1.5 mL per kg bodyweight. 5)

2. Overall usefulness
In 228 patients (those included in overall usefulness evaluation) in open labeled clinical trials, the overall usefulness evaluated in consideration of ease of handling and sanitary advantages was 89.9% (205 patients). This evaluation included “easier to handle compared to conventional vial preparations” or better ratings. 3, 4) In 228 patients (those included in overall usefulness evaluation) in open labeled clinical trials, the overall usefulness evaluated in consideration of ease of handling and sanitary advantages was 89.9% (205 patients). This evaluation included “easier to handle compared to conventional vial preparations” or better ratings. 3, 4)

3. Delayed adverse reactions
(1) A breakdown by time of occurrence of delayed adverse reactions which occurred 1 hr after the injection of IOMERON 300 Injection, 350 Injection, 400 Injection (vial) and IOMERON 300 Injection Syringe, 350 Injection Syringe or thereafter in clinical trial at approval is shown in the table below. 3, 4, 6)

![Table 1: Delayed adverse reactions](image)

* Except for abnormal in laboratory test values Tables in parentheses indicate % of total (%): %

(2) A breakdown by time of occurrence of delayed adverse reactions which occurred 1 hr after the injection of IOMERON 350 Injection (vial) and IOMERON 350 Injection Syringe or thereafter in clinical trial at approval of dosage and administration on visualization in dynamic computed tomography of hepatic region is shown in the table below.

![Table 2: Delayed adverse reactions](image)

* Except for abnormal in laboratory test values Tables in parentheses indicate % of total (%): %

Adverse reactions which occurred 1 hr after the injection of IOMERON were itching in 1 patient, rash in 1 patient, malaise in 1 patient, feeling of discomfort in 1 patient, increase in blood pressure in 1 patient, bronchitis in 1 patient and epistaxis in 1 patient.

In clinical trial, laboratory test values were determined within 3 days. Abnormal in laboratory test values which occurred 1 day after the injection of IOMERON were 5 patients (leucopenia in 2 patients, leukocytosis in blood bilirubin increase 1 patient, in 1 patient, elevation of ALT (GPT) in 1 patient. 5)

**PHYSICOCHEMISTRY**

**Nonproprietary name:** Iomeprol (JAN, INN)

**Chemical name:** diastereomeric mixture of N, N’-bis (2,3-dihydroxypropyl)-5-[hydroxyacetyl] methylamino]-2,4,6-triiodo-1,3-benzenedicarboxamide

**Molecular formula:** C_{17}H_{22}I_{3}N_{3}O_{8}

**Molecular weight:** 777.09

**Structural formula:**

![Structural formula](image)

**Description:** Iomeprol occurs as a white crystalline powder. It is odorless. It is very soluble in water, soluble in methanol, slightly soluble in ethanol (99.5), and practically insoluble in chloroform and in diethyl ether. An aqueous solution (1 in 10) shows no optical rotation.

**Partition coefficient:** 2.972×10^{-3} (water : 1-octanol)

**PACKAGING**

- **IOMERON 300 Injection Syringe 50 mL:** Boxes of 5 syringes
- **IOMERON 300 Injection Syringe 75 mL:** Boxes of 5 syringes
- **IOMERON 300 Injection Syringe 100 mL:** Boxes of 1 or 5 syringes
- **IOMERON 350 Injection Syringe 50 mL:** Boxes of 5 syringes
- **IOMERON 350 Injection Syringe 75 mL:** Boxes of 5 syringes
- **IOMERON 350 Injection Syringe 100 mL:** Boxes of 1 or 5 syringes
- **IOMERON 350 Injection Syringe 135 mL:** Boxes of 5 syringes

**REFERENCES**

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

Manufactured and marketed by:
Bracco-Eisai Co., Ltd.
11-6, Otsuka 3-chome, Bunkyo-ku, Tokyo, 112-0012

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

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