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The latest Japanese text is available on PMDA website.

Revised: July 2022 (2nd version of new form)

Storage: Room temperature
Shelf Life: 3 years
Therapeutic Category: Non-ionic contrast medium
Regulatory Classification: Prescription-only drug

Note) Use only as directed by a physician.

Iomeprol solution for injection

Iomeron® 300 injection 20mL
Iomeron® 300 injection 50mL
Iomeron® 300 injection 100mL
Iomeron® 350 injection 20mL
Iomeron® 350 injection 50mL
Iomeron® 350 injection 100mL
Iomeron® 400 injection 50mL
Iomeron® 400 injection 100mL

1. WARNINGS
1.1 Serious adverse reactions such as shock may occur. [see 8.1-8.5, 9.1.8, 9.1.9, 11.1.1-11.1.3]
1.2 Do not use this drug for cisternography or myelography because its intracerebral and intrathecal administration may cause serious adverse reactions. [see 14.2.1]

2. CONTRAINDICATIONS (This drug is contraindicated to the following patients.)
2.1 Patients with a history of hypersensitivity to iodine or iodinated contrast media [see 8.1]
2.2 Patients with serious thyroid disease [Administration of this drug can cause higher blood concentration of iodine in the thyroid gland, affecting thyroid gland function, which can lead to aggravation of symptoms.] [see 9.1.14]

3. COMPOSITION AND PRODUCT DESCRIPTION
3.1 Composition
Each syringe contains the following ingredients:

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Iomeron 300 injection</th>
<th>Iomeron 350 injection</th>
<th>Iomeron 400 injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300</td>
<td>350</td>
<td>400</td>
</tr>
<tr>
<td>Iodine concentration (mg/mL)</td>
<td>20.0</td>
<td>50.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Content (mL)</td>
<td>20</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Active ingredient</td>
<td>Iomeprol (g) (iodine (g))</td>
<td>12.25</td>
<td>30.62</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(15)</td>
<td>(30)</td>
</tr>
</tbody>
</table>
### 3.2 Product Description

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Iomeron 300 injection</th>
<th>Iomeron 350 injection</th>
<th>Iomeron 400 injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trometamol (mg)</td>
<td>20  50  100</td>
<td>20  50  100</td>
<td>50  100</td>
</tr>
<tr>
<td>Hydrochloric acid</td>
<td>Adequate dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 4. INDICATIONS

**<Iomeron 300 injection>**
Cerebral angiography, Thoracic angiography, Abdominal angiography, Peripheral angiography, Intravenous digital subtraction angiography, Intraarterial digital subtraction angiography, Computed tomography (CT) enhancement, Intravenous urography.

**<Iomeron 350 injection>**

**<Iomeron 400 injection>**
Angiocardiography, Thoracic angiography, Abdominal angiography, Intravenous urography.

#### 6. DOSAGE AND ADMINISTRATION

The usual adult dosage is indicated below. The dosage may be determined by the patient’s age, body weight, symptoms and indication. In the case of multiple administration, a total dosage of 250 mL should not be exceeded.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Iomeron 300 injection</th>
<th>Iomeron 350 injection</th>
<th>Iomeron 350 injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral angiography</td>
<td>5 - 15mL</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Angiocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging of heart chambers</td>
<td>—</td>
<td>20 - 50mL</td>
<td>20 - 40mL</td>
</tr>
<tr>
<td>Imaging of coronary arteries</td>
<td>—</td>
<td>3 - 10mL</td>
<td>3 - 8mL</td>
</tr>
<tr>
<td>Thoracic angiography</td>
<td>5 - 50mL</td>
<td>5 - 50mL</td>
<td>5 - 50mL</td>
</tr>
<tr>
<td>Abdominal angiography</td>
<td>5 - 60mL</td>
<td>5 - 60mL</td>
<td>5 - 60mL</td>
</tr>
<tr>
<td>Peripheral angiography</td>
<td>10 - 80mL</td>
<td>10 - 80mL</td>
<td>—</td>
</tr>
<tr>
<td>Intravenous digital subtraction angiography</td>
<td>10 - 50mL</td>
<td>10 - 50mL</td>
<td>—</td>
</tr>
<tr>
<td>Intraarterial digital subtraction angiography</td>
<td>3 - 40mL</td>
<td>3 - 40mL</td>
<td>—</td>
</tr>
<tr>
<td>CT enhancement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When administering, intravenous drip infusion, etc. should be used as appropriate.</td>
<td>40 - 100mL</td>
<td>40 - 100mL</td>
<td></td>
</tr>
<tr>
<td>When administering, intravenous drip infusion, etc. should be used as appropriate. For dynamic CT enhancement in the hepatic region, 1.8</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>
mL/kg can be intravenously administered by body weight (up to 135 mL)

<table>
<thead>
<tr>
<th>Intravenous urography</th>
<th>40 - 100mL</th>
<th>30 - 100mL</th>
<th>50mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>When administering, intravenous drip infusion, etc. should be used as appropriate.</td>
<td></td>
<td></td>
<td>When administering, intravenous injection should be used as appropriate.</td>
</tr>
</tbody>
</table>

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

For dynamic CT enhancement in the hepatic region with Iomeron 350, refer to this table for the dosage by body weight.

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Dosage (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;56</td>
<td>40 - 100</td>
</tr>
<tr>
<td>Not to exceed 1.8 mL/kg for 56 - 75 kg</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>108 (1.8 mL/kg body weight)</td>
</tr>
<tr>
<td>65</td>
<td>117 (1.8 mL/kg body weight)</td>
</tr>
<tr>
<td>70</td>
<td>126 (1.8 mL/kg body weight)</td>
</tr>
<tr>
<td>75</td>
<td>135 (1.8 mL/kg body weight)</td>
</tr>
<tr>
<td>75&lt;</td>
<td>135</td>
</tr>
</tbody>
</table>

8. IMPORTANT PRECAUTIONS

8.1 Patients should be carefully interviewed to take measures against shock, etc. [see 1.1, 2.1, 9.1.8, 9.1.9, 11.1.1-11.1.3]

8.2 Hypersensitivity reaction to this drug may occur independently of the dosage or the route of administration. Serious adverse reactions due to this drug such as shock are not necessarily hypersensitivity to iodine, and those reactions are not predictable. For administering this drug, make sure that appropriate emergency measures should be immediately available. [see 1.1, 11.1.1-11.1.3]

8.3 This drug should be administered carefully, monitoring the patient’s condition from the start of administration, with special attention for the occurrence of hypersensitivity reaction. In case of any abnormality observed, administration should be discontinued immediately, and appropriate measures should be taken. [see 1.1, 11.1.1-11.1.3]

8.4 During and after the administration of this drug, the patient’s condition should be monitored carefully since serious delayed adverse reactions, etc. (including shock) may occur. [see 1.1, 11.1.1-11.1.3].

8.5 When administering this drug to outpatients, it is necessary to explain delayed adverse reactions may occur from one hour to several days after the administration, and to instruct to contact the attending physician immediately if any symptoms such as queasiness, chest pain, back pain, pyrexia, skin eruptions and itching, occur. [see 1.1, 11.1.1-11.1.3]

8.6 Ensure adequate hydration since iodinated contrast media may impair renal functions. [see 9.1.5, 9.1.13, 9.1.15, 9.2.1, 9.2.2, 9.8, 11.1.11, 14.1.2 and 14.3]

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BackgroundS

9.1 Patients with Complication or History of Diseases, etc.

9.1.1 Patients with an extremely poor general condition
Do not administer this drug unless it is deemed unavoidable for diagnosis.

9.1.2 Patients with bronchial asthma
Do not administer this drug unless it is deemed unavoidable for diagnosis. Higher incidence of adverse reactions has been reported in patients with bronchial asthma.

9.1.3 Patients with serious cardiac disorders
Do not administer this drug unless it is deemed unavoidable for diagnosis. This drug can cause deterioration of hemodynamics, which can lead to impairment of cardiac function.

— 3 —
9.1.4 Patients with macroglobulinemia
Do not administer this drug unless it is deemed unavoidable for diagnosis. There have been reports of other iodinated contrast media in which gel formation of the blood occurred and patients deceased.

9.1.5 Patients with multiple myeloma
Do not administer this drug unless it is deemed unavoidable for diagnosis. There have been reports of other iodinated contrast media in which renal tubule obstruction occurred due to binding to urinary protein. [see 8.6 and 11.1.11]

9.1.6 Patients with tetany
Do not administer this drug unless it is deemed unavoidable for diagnosis. Blood calcium decreased may occur, leading to aggravation of the symptom.

9.1.7 Patients known or suspected of having pheochromocytoma
Do not administer this drug unless it is deemed unavoidable for diagnosis. If examination is necessary for unavoidable reason, this drug should be administered cautiously with the intravenous access secured. Appropriate measures should be readily available to treat attacks of blood pressure increased, tachycardia, arrhythmia or other symptoms. An example of such measures is to prepare a sufficient amount of alpha-blocker such as phentolamine mesilate or beta-blocker such as propranolol hydrochloride.

9.1.8 Patients whose a personal, parents or siblings have allergic predisposition, such as bronchial asthma, rash or urticaria, etc.
[See 1.1, 8.1, 11.1.1-11.1.3]

9.1.9 Patients with a history of drug hypersensitivity
[See 1.1, 8.1, 11.1.1-11.1.3]

9.1.10 Patients with dehydration
Dehydration may be aggravated.

9.1.11 Patients with hypertension
Hemodynamics may be aggravated.

9.1.12 Patients with arteriosclerosis
Hemodynamics may be aggravated.

9.1.13 Patients with diabetes mellitus
Renal functions may be impaired. [see 8.6 and 11.1.11]

9.1.14 Patients with thyroid disease (except patients with serious thyroid disease)
Administration of this drug can cause higher blood concentration of iodine in the thyroid gland, affecting thyroid gland function, which can lead to aggravation of symptoms. [see 2.2]

9.1.15 Patients with acute pancreatitis
Provide sufficient intravenous fluids before and after the administration of this drug in accordance with guidelines, etc. Symptoms may be aggravated. [see 8.6, 14.1.2 and 14.3]

9.1.16 Patients with myasthenia gravis
Occurrence of cardiopulmonary arrest, etc. has been reported. Symptoms may be aggravated.

9.1.17 Patients with central nervous system disorders
Cerebrovascular disorder or convulsions, etc. may occur.

9.2 Patients with Renal Impairment
9.2.1 Patients with serious renal impairment
Do not administer this drug unless it is deemed unavoidable for diagnosis. Since contrast media are excreted mainly through the kidneys, the excretion may be delayed and renal function may be aggravated. [see 8.6, 9.8, 11.1.11 and 16.6.1]

9.2.2 Patients with impaired renal function
Renal function may be aggravated. [see 8.6, 9.8, 11.1.11 and 16.6.1]

9.3 Patients with Hepatic Impairment
9.3.1 Patients with serious hepatic impairment
Do not administer this drug unless it is deemed unavoidable for diagnosis. Symptoms may be aggravated. [see 11.1.7]
9.3.2 Patients with impaired hepatic function
Hepatic functions may be aggravated. [see 11.1.7]

9.5 Pregnant Women
Administration of this drug to women who are or may be pregnant should be limited to the case in which the diagnostic benefit is considered to surpass the risk. Administration of this drug is followed by X-ray radiation.

9.6 Breast-feeding Women
Diagnostic benefit using this drug and the benefit of breast milk nutrients should be weighed for consideration of continuing or discontinuing breastfeeding. Excretion of this drug into breast milk has been reported in animal studies (rats, intravenous administration).

9.7 Pediatric Use
No clinical study has been conducted in pediatric patents.

9.8 Geriatric Use
This drug should be administered to the elderly patients with careful monitoring. This drug is excreted mainly through the kidneys. Since renal function of the elderly tends to be decreased, this drug blood concentration may remain high. [see 8.6, 9.2.1 and 9.2.2]

10. INTERACTIONS
10.2 Precautions for Co-administration (This drug should be administered with caution when co-administered with the following.)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Clinical symptoms / Measures</th>
<th>Mechanism / Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide class antidiabetic agents</td>
<td>Lactic acidosis has been reported due to coadministration with iodinated contrast media and biguanide class antidiabetic agents. When administering this drug, appropriate measures such as temporarily discontinuing biguanide class antidiabetic agents should be taken.</td>
<td>The decrease in renal excretion of biguanide class antidiabetic agents is considered to lead to the increase of its blood concentration.</td>
</tr>
<tr>
<td>Metformin hydrochloride</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buformin hydrochloride, etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. ADVERSE REACTIONS
Following adverse reactions may occur. Monitor patients’ condition carefully and take appropriate measures such as discontinuing the administration upon onset of any abnormality.

11.1 Clinically Significant Adverse Reactions
<General>
11.1.1 Shock
Syncope, loss of consciousness, dyspnoea, respiratory arrest, cardiac arrest, etc. may occur, as symptoms of shock (including delayed reaction) (frequency unknown). Patients should be monitored carefully since even mild hypersensitivity symptom can lead to serious symptoms. [see 1.1, 8.1-8.5, 9.1.8 and 9.1.9]

11.1.2 Anaphylaxis
Anaphylaxis (including delayed reaction) (frequency unknown) such as dyspnoea or pharyngeal/laryngeal edema may occur. [see 1.1, 8.1-8.5, 9.1.8, 9.1.9 and 11.1.3]

11.1.3 Acute coronary syndrome accompanying allergic reaction (frequency unknown) [see 1.1, 8.1-8.5, 9.1.8, 9.1.9, 11.1.2 and 11.1.6]

11.1.4 Pulmonary edema (frequency unknown)

11.1.5 Acute respiratory distress syndrome (frequency unknown)

11.1.6 Ventricular fibrillation and coronary arteriospasm (frequency unknown for both) [see 11.1.3]

11.1.7 Hepatic impairment and jaundice (frequency unknown for both)
Hepatic impairment such as increased AST, ALT and γ-GTP or jaundice may occur. [see 9.3.1 and 9.3.2]

11.1.8 Cerebrovascular disorders
Transient or permanent cerebral circulatory failure (cerebral ischemia) (frequency unknown) may occur.

11.1.9 Seizure (frequency unknown)

11.1.10 Consciousness disturbed and syncope
Since consciousness disturbed (frequency unknown) or syncope (frequency unknown) without shock may occur, patients should be monitored carefully for the level of consciousness, etc. even after completion of the examination.

11.1.11 Renal failure
Acute kidney injury (0.04%) may occur. [see 8.6, 9.1.5, 9.1.13, 9.2.1 and 9.2.2]

11.1.12 Platelets decreased (frequency unknown)

11.1.13 Skin disorder
Oculomucocutaneous syndrome (Stevens-Johnson syndrome) (frequency unknown), and acute generalized exanthematous pustulosis (frequency unknown) may occur. Patients should be carefully monitored and appropriate measures should be taken immediately if pyrexia, erythema, small pustules, itchy sensation, ocular hyperaemia, stomatitis, or other symptoms are observed.

11.2 Other Adverse Reactions

<table>
<thead>
<tr>
<th>Hypersensitivity</th>
<th>≥ 0.1%</th>
<th>&lt; 1.5%</th>
<th>&lt; 0.1%</th>
<th>Frequency unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash, Itching, Urticaria</td>
<td></td>
<td></td>
<td>Redness, Wheals</td>
<td></td>
</tr>
<tr>
<td>Psychoneurotic disorders</td>
<td></td>
<td></td>
<td></td>
<td>Light headedness, Sleepiness</td>
</tr>
<tr>
<td>Headache, Dizziness</td>
<td></td>
<td>Tremor, Photophobia,</td>
<td>Aphasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Light headedness, Sleepiness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Somnolence), Anxiety (Unrest), Weakness,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amnesia, Language disorder, Visual</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>impairment such as transient blindness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td>Thirst, Diarrhea</td>
<td>Abdominal pain, Anorexia, Saliva</td>
<td></td>
</tr>
<tr>
<td>Nausea, Vomiting</td>
<td></td>
<td></td>
<td>increased, Oral discomfort, Stomatitis</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td></td>
<td>ST depressed,</td>
<td>Tachycardia, Arrhythmia, Cardiac failure,</td>
<td></td>
</tr>
<tr>
<td>Blood pressure decreased, Blood</td>
<td></td>
<td>Bradycardia,</td>
<td>Facial pallor, Cyanosis</td>
<td></td>
</tr>
<tr>
<td>pressure increased</td>
<td></td>
<td>Extrasystoles,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palpitations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory disorders</td>
<td></td>
<td>Dyspnoea, Rhinitis,</td>
<td>Wheezing, Hoarseness, Pharyngolaryngeal</td>
<td></td>
</tr>
<tr>
<td>Sneezing</td>
<td></td>
<td>Cough</td>
<td>discomfort</td>
<td></td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td></td>
<td></td>
<td>Hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>Back pain, Pyrexia,</td>
<td>BUN increased, Serum creatinine increased,</td>
<td></td>
</tr>
<tr>
<td>Facial hot flushes, Blood</td>
<td></td>
<td>Feeling hot, Heavy</td>
<td>Anuria, Edema, Numbness, Vascular pain,</td>
<td></td>
</tr>
<tr>
<td>potassium increased, Chest pain,</td>
<td></td>
<td>sweating</td>
<td>Hiccups, Conjunctivitis, Lacrimation, Eye</td>
<td></td>
</tr>
<tr>
<td>Malaise, Chills, Taste</td>
<td></td>
<td></td>
<td>abnormalities</td>
<td></td>
</tr>
<tr>
<td>abnormality/Dysosmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12. INFLUENCE ON LABORATORY TESTS
In case a diagnosis using radioactive iodine tests such as thyroid function tests are required, they should be conducted prior to the administration of this drug. Radioactive iodine test should not be performed for at least one month after the administration of this drug.
14. PRECAUTIONS CONCERNING USE
14.1 Precautions Prior to Administration of the Drug
<General>
14.1.1 Warm this drug to body temperature before administration.
14.1.2 Do not restrict fluid intake prior to administration of this drug. [see 8.6 and 9.1.15]

<Intravenous urography>
14.1.3 Intestinal gas should be eliminated prior to the examination, and the patients should be fasted until the examination completes.

14.2 Precautions Concerning Administration of the Drug
14.2.1 Do not use this drug for cisternography or myelography. [see 1.2]
14.2.2 Rate of administration of Iomeeron 350 is up to 5.0 mL/second for the dynamic CT enhancement in the hepatic region.
14.2.3 Vascular pain may occur after intravenous administration of this drug.
14.2.4 Since non-ionic contrast media have less anti-coagulant activity in vitro than ionic media, intravascular catheters should be flushed frequently in the angiography with this drug. This drug should not be allowed to remain in contact with blood for long time in a syringe or catheter in administration.
14.2.5 Since mixing this drug with antihistamines or corticosteroids can cause incompatibility, they should be administered separately if used in combination.
14.2.6 In case extravasation of contrast media occur, patient may develop redness, swelling, blister, or vascular pain, etc. Extreme caution during administration is necessary to avoid extravasation.

14.3 Precautions Concerning Post-Administration of the Drug
After the administration of this drug, ensure adequate hydration to allow prompt excretion of the contrast medium. [see 8.6 and 9.1.15]

16. PHARMACOKINETICS
16.1 Blood Level
A single dose of 40 mL or 80 mL\(^{\text{Note}}\) of Iomeprol 400 mgI/mL was administered intravenously to 10 healthy male volunteer at a rate of 10 mL/min, plasma iodine level changed almost in proportion to the dosage, and showed a biphasic elimination after completion of administration. The elimination half-lives in plasma, t1/2α (distribution phase) and t1/2β (excretion phase) were 22.3 minutes and 1.95 hours, respectively. The volume of distribution (Vc) was 0.11 L/kg, and the total clearance was 99.0 mL/min. \(^{1}\)

\(^{\text{Note}}\) The maximum single dose of Iomeprol 400 mgI/mL approved is 60 mL.
Mean plasma iodine level – time curve after administration of 40 mL and 80 mL\(^{Note}\) of Iomeprol 400 mg/mL

Pharmacokinetic parameters after single intravenous administration of Iomeprol 400 mg/mL.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (Mean ± S.D., n=10 Healthy male volunteer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2α (min)</td>
<td>22.33±6.79</td>
</tr>
<tr>
<td>t1/2β (hr)</td>
<td>1.95±0.15</td>
</tr>
<tr>
<td>Vc (L/kg)</td>
<td>0.11±0.02</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.24±0.05</td>
</tr>
<tr>
<td>CL (mL/min)</td>
<td>99.03±21.22</td>
</tr>
</tbody>
</table>

16.5 Excretion

A single dose of 40 mL or 80 mL\(^{Note}\) of Iomeprol 400 mg/mL was administered intravenously to 10 healthy male volunteers at a rate of 10 mL/min, 80.9% of the dosage was excreted as unchanged Iomeprol in urine in 4 hours, and 97.5% in 24 hours of administration.\(^{1}\)

Note) The maximum single dose of Iomeprol 400 mg/mL approved is 60 mL.

Cumulative urinary excretion rate after administration of 40 mL and 80 mL\(^{Note}\) of Iomeprol 400 mg/mL.

16.6 Patients with Specific Backgrounds

16.6.1 Patients with renal impairment

A single dose of 50 mL of Iomeprol 400 mg/mL was administered intravenously to 6 healthy volunteers with normal renal function (GFR\(^{Note}\) >100 mL/min/1.73m\(^2\)), 6 patients with mild renal impairment (GFR\(^{Note}\) 51-75 mL/min/1.73m\(^2\)), 6 patients with moderate renal impairment (GFR\(^{Note}\) 26-50 mL/min/1.73m\(^2\)), and 4 patients with severe renal impairment (GFR\(^{Note}\) ≤25 mL/min/1.73m\(^2\)), and plasma and urinary Iomeprol levels were determined. Plasma Iomeprol level and pharmacokinetic parameters after the administration of Iomeprol are as follows. In patients with renal impairment, the elimination half-life (t1/2β) is prolonged and the renal clearance and glomerular filtration rate decreased in proportion to severity of renal impairment, compared with healthy volunteers. The urinary excretion rate up to 120 hours of Iomeprol administration decreases in proportion to severity of renal impairment in the same manner; decrease to 68.3% in patients with severe renal impairment, compared with 93.5% in healthy volunteers. The urinary excretion rate of patients with mild renal impairment and those with moderate impairment is 90.4% and 85.1% respectively, and the decrease was not as significant as the one for patients with severe renal impairment.\(^{2}\) (data of non-Japanese). [see 9.2.1 and 9.2.2]

Note) Insulin clearance measurement
Plasma Iomeprol level-time curve after single dose of intravenous administration of 50 mL of Iomeprol 400 mg/mL (data of non-Japanese)

Pharmacokinetic parameters of Iomeprol in healthy volunteer and patients with renal impairment (data of non-Japanese)

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Healthy volunteer (n=6)</th>
<th>Severity of renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mild (n=6)</td>
</tr>
<tr>
<td>t1/2β (hr)</td>
<td>2.34±0.44</td>
<td>3.67±0.46</td>
</tr>
<tr>
<td>AUC0-∞ (hr)</td>
<td>7.7±2.6</td>
<td>10.3±1.2</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>8.3±1.7</td>
<td>8.7±0.9</td>
</tr>
<tr>
<td>CL_T (mL/min)</td>
<td>95±25</td>
<td>66.8±8.2</td>
</tr>
<tr>
<td>CL_R (mL/min)</td>
<td>88.3±30*</td>
<td>60.5±8.1</td>
</tr>
<tr>
<td>GFRnote(2) (mL/min)</td>
<td>120±30</td>
<td>72±9.8</td>
</tr>
<tr>
<td>Urinary excretion rate 0.12hr (%)</td>
<td>93.5±5.5*</td>
<td>90.4±4.6</td>
</tr>
</tbody>
</table>

Note1) n= 5  Note2) Inulin clearance measurement

17. CLINICAL STUDIES
17.1 Clinical Studies for Efficacy and Safety
< Urography/ angiography and CT >
17.1.1 Domestic phase III clinical study

In comparative study and general clinical studies conducted using the vial formulation, the effective rate of the contrast effect in the 1,925 patients for whom contrast effect was assessed was 98.2% (1,891 patients).

Out of 2,147 subjects of comparative study and general clinical studies (combined iomeron 300/350/400 injections [vial products] and iomeron 300/350 syringes), adverse reactions were reported regarding 120 patients (5.59%) and the major adverse reactions were nausea in 31 patients (1.44%) and rash in 24 patients (1.12%).

Among adverse reactions occurred, delayed adverse reactions occurred after one hour or later of administration were as follows3,4,5.

<table>
<thead>
<tr>
<th>Number of patients assessed</th>
<th>Within 1 hour after administration</th>
<th>Within 3 hours after administration</th>
<th>Within 6 hours after administration</th>
<th>Within 12 hours after administration</th>
<th>Within 24 hours after administration</th>
<th>From 24 hours after administration</th>
<th>Total number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,147</td>
<td>114 (70.4)</td>
<td>20 (12.3)</td>
<td>8 (4.9)</td>
<td>4 (2.5)</td>
<td>7 (4.3)</td>
<td>9 (5.6)</td>
<td>162 (100.0)</td>
</tr>
</tbody>
</table>

* Abnormality in laboratory test values was excluded since onset time of them were not investigated.
<Dynamic CT enhancement in the hepatic region>

17.1.2 Domestic phase II/III comparative study (Iomeron 350 injections and Iomeron 350 syringes) 6)

In 173 patients with hepatic mass lesion, the contrast enhanced efficacy on mass lesions of dose groups of 100 mL, 1.5 mL/kg and 1.8 mL/kg body weight were evaluated to be "Excellent " or "Good" (hereafter, "Good" or better), except for one patient in the 100 mL dose group, and the rate of "Good" or better was high, ranging from 98.3% to 100.0%. The rate of patients evaluated "Excellent" was 63.8% in the 100 mL dose group, 57.9% in the 1.5 mL/kg group, and 84.5% in the 1.8 mL/kg group.

As a result of comparing the contrast enhanced efficacy of mass lesions in 100mL dose group and the 1.8mL/kg group, 1.8mL/kg group was demonstrated significantly higher efficacy than the 100mL group. In a paired comparative of 1.5 mL/kg group and 1.8 mL/kg group, 1.8 mL/kg group was significantly better than the 1.5 mL/kg group.

Among adverse reactions occurred, delayed adverse reactions occurred in one hour of administration or later were as follows.

<table>
<thead>
<tr>
<th>Number of patients assessed</th>
<th>Within 1 hour after administration</th>
<th>Within 3 hours after administration</th>
<th>Within 6 hours after administration</th>
<th>Within 12 hours after administration</th>
<th>Within 24 hours after administration</th>
<th>From 24 hours after administration</th>
<th>Total number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>173</td>
<td>6 (33.3)</td>
<td>0</td>
<td>1 (5.6)</td>
<td>0</td>
<td>11 (61.1)</td>
<td>18 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Excluding feeling hot and vascular pain

Adverse reactions which occurred after one hour or later of administration were pruritus (1), rash (1), malaise (1), discomfort (1), blood pressure increased (1), bronchitis (1), epistaxis (1), white blood cell decreased (2), white blood cell increased (1), blood bilirubin increased (1) and ALT increased (1). None of them were serious.

18. PHARMACOLOGY

18.1 Mechanism of contrast enhancement

Three Iodine atoms (atomic number 53, atomic weight 127) coordinated to the benzene ring, which is the basic framework of contrast media, have high absorption of X-rays. With contrast media containing iodine atoms, X-ray photography shows contrast difference between the blood vessels containing contrast media and other organs, and can create images of intended blood vessels or urinary tract, etc.

19. PHYSICOCHEMICAL PROPERTIES

Nonproprietary name : Iomeprol
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 of Iomeprol]

Physicochemical description:

Iomeprol is a white crystalline powder, and it is odorless. It is highly water-soluble, soluble in methanol, slightly soluble in ethanol (99.5), and practically insoluble in chloroform and in diethyl ether.

A solution of Iomeprol (1 in 10) shows no optical rotation.

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

20. PRECAUTIONS FOR HANDLING
22. PACKAGING

- <Iomeron 300 injection 20 mL>
  Boxes of 5 vials
- <Iomeron 300 injection 50 mL>
  Boxes of 5 vials
- <Iomeron 300 injection 100 mL>
  Boxes of 5 vials
- <Iomeron 350 injection 20 mL>
  Boxes of 5 vials
- <Iomeron 350 injection 50 mL>
  Boxes of 5 vials
- <Iomeron 350 injection 100 mL>
  Boxes of 5 vials
- <Iomeron 400 injection 50 mL>
  Boxes of 5 vials
- <Iomeron 400 injection 100 mL>
  Boxes of 5 vials

23. REFERENCES


24. REFERENCE REQUEST AND CONTACT INFORMATION

Eisai Co., Ltd., Customer Joy
4-6-10, Koishikawa, Bunkyo-ku, Tokyo, 112-8088, Japan
Toll-free number : 0120-419-497

26. MARKETING AUTHORIZATION HOLDER, etc.

26.1 Marketing Authorization Holder
Bracco-Eisai Co., Ltd.
3-11-6, Otsuka, Bunkyo-ku, Tokyo, Japan

26.2 Marketed by :
Eisai Co., Ltd.
4-6-10, Koishikawa, Bunkyo-ku, Tokyo, Japan

26.3 Licensed by :
Bracco Suisse S.A.