# Package Insert of Iohexol Injection

Please read this package insert carefully and use it under the guidance of physician

**[Name of Medical Product]**

Generic name: Iohexol Injection

Trade name: Shuangbei

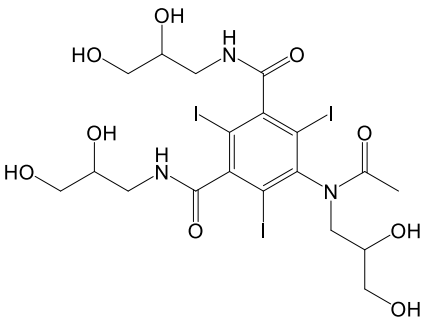
English name: Iohexol Injection

Chinese Pinyin: Dianhaichun Zhusheye

**[Ingredients]** Iohexol

Chemical name: 5-[acetyl(2,3-dihydroxypropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodbenzol-1,3-dicarboxamid

Chemical structural formula:




Molecular formula: $C_{19}H_{26}I_3N_3O_9$

Molecular weight: 821.14

**[Excipient]**

Tromethamine, calcium disodium edetate, hydrochloric acid (adjust pH) and water for injection.

**[Description]**

A clear colorless to pale yellow liquid.

**[Indications]**

This product is an X-ray contrast agent. It can be used for angiocardiography, arteriography, urography, enhanced CT examination; cervical, thoracic and lumbar myelography, CT cisternography following intrathecal injection (i.e., an injection into the subarachnoid space); arthrography, endoscopic retrograde cholangiopancreatography (ERCP), herniography or fistulography, hysterosalpingography, sialography, percutaneous transhepatic cholangiography (PTC), sinography, gastroenterography, T-tube angiography, etc.

**[Strength]** 35 g iodine (I) per 100 mL

## [Dosage and Administration]

Dosages used depends on the type of examination, patient age, weight, cardiac output, general condition, and the technique used. In general, the commonly used iodine concentrations and volumes of this drug are similar to those of other iodinated contrast agents currently used. As other contrast agents, patients must be appropriately hydrated before and after administration. The following doses may be used as clinical guidance.

1. Intravenous injection

| Scope of application | Concentration | Amount | Description |
|---|---|---|---|
| Urography<br>Adults<br><br>Children < 7 kg<br>> 7kg | <br>300mgI/ml<br>or 350 mg I/mL<br>300mgI/ml<br>300mgI/ml | <br>40-80ml<br>40-80ml<br>3 mL/kg (weight)<br>2 mL/kg (weight) (up to 40 mL) | <br>> 80 mL for high-dose urography | |
| Lower extremity venography | 300mgI/ml | 20-100 mL per leg | |
| Digital subtraction angiography (DSA) | 300mgI/ml<br>or 350 mg I/mL | 20-60 mL/injection<br>20-60 mL/injection | |
| Enhanced CT<br>Adults<br><br>Children | <br>300mgI/ml<br>or 350 mg I/mL<br>300mgI/ml | <br>100-200ml<br>100-150ml<br>1.5-2 mL/kg (weight) | <br>The total iodine is usually<br>30-60g |

2. Intra-arterial injection

| Scope of application | Concentration | Amount | Description |
|---|---|---|---|
| Arteriography<br>Aortic angiography<br>Selective cerebral arteriography<br>Lower extremity arteriography<br>Other arteriographies | <br>300mgI/ml<br>300mgI/ml<br>350mgI/ml<br>300mgI/ml<br>or 350 mg I/mL<br>300mgI/ml | <br>30-40 mL/injection<br>5-10 mL/injection<br>40-60 mL/injection<br>30-50 mL/injection<br><br>Depending on the type of examination | <br>Select the amount of each injection according to the injection site. |
| Angiocardiography<br>Adults<br>Injection on left ventricular and aortic root<br>Selective coronary angiography<br>Children | <br><br>350mgI/ml<br><br>350mgI/ml<br><br>300mgI/ml<br>or 350 mg I/mL | <br><br>30-60 mL/injection<br><br>4-8 mL/injection<br><br>Depending on age, weight, and condition (up to 8 mL/kg weight) | |
| Digital subtraction angiography (DSA) | 300mgI/ml | 1-15 mL/injection | Depending on the injection site.<br>The maximum dosage (uncommon) may be up to 30 mL. |

3. Myelography

| Scope of application | Concentration | Amount | Description |
|---|---|---|---|
| Myelography | 300mgI/ml | 7-10ml | To reduce possible adverse effects, the total iodine should not exceed 3 g. |

4. Intracavitary use

| Scope of application | Concentration | Amount | Description |
|---|---|---|---|
| Arthrography | 300mgI/ml<br>or 350 mg I/mL | 5-15ml<br>5-10ml | |
| Hysterosalpingography | 300mgI/ml | 15-25ml | |
| Sialography | 300mgI/ml | 0.5-2ml | |
| Gastroenterography<br>Oral administration<br>Adults<br>Children | | <br><br>Depending on individuals<br>Depending on individuals | <br><br>Dilutable<br>Maximum dose is 50 mL |
| <u>Enhanced CT</u><br>Oral administration<br>Adults<br><br>Children<br><br>Rectum<br>Children | <br><br>Diluting with water to about 6mgI/ml<br>Diluting with water to about 6mgI/ml<br><br>Diluting with water to about 6mgI/ml | <br><br>Adding 800-2000 mL diluent once<br>Adding 15-20 ml/kg (weight) once<br><br>Depending on individuals | <br>Examples:<br>Diluting 300 or 350 mg I/mL with water 350mgI/ml<br>The ratio is 1: 50. |

**[Adverse Reactions]**

<u>Common adverse reactions (for all iodinated contrast agents)</u>

*Adverse reactions related to radiography are listed below, including adverse reactions in different examinations with nonionic-monomer contrast agent, as detailed in the corresponding sections.*

Adverse reactions related to iodinated contrast agents are generally slight to moderate in nature and transient. Adverse effects related to nonionic contrast agents are less compared with ionic contrast agents. Severe and lethal adverse reactions are rare.

**Slight paresthesias** such as hot sensation or transient metallic taste is common. Abdominal discomfort or pain and gastrointestinal reactions such as nausea, vomiting, and diarrhea may occur. **Allergic reactions** are less common and usually manifest as slight respiratory and skin reactions, such as dyspnea, rash, erythema, urticaria, pruritus, and angioedema, which may occur immediately after injection or after a few days. Serious reactions such as laryngeal edema, bronchospasm, pulmonary edema, and anaphylactic shock are rare. Serious and even toxic skin reactions have been reported. **Anaphylactoid reactions** may not be related to dose and route of administration. The initial symptoms of serious reactions may be only minimal allergic symptoms. The contrast agent must be discontinued immediately, and if necessary, appropriate treatment should be given intravascularly. Patients taking β-**blockers** may have atypical symptoms of allergic reactions, and may be incorrectly considered vagal reactions. **Vagal reactions** may cause hypotension and bradycardia, and are rare in adverse reactions related to the contrast agents. **Headache or fever** may occur. **Hypertension** may also occur. Fever with chills is uncommon.

**Iodism or "iodide mumps"** is a rare complication related to iodinated contrast agents, and is characterized by swelling and tenderness of the parotid glands, which may persist for up to 10 days after examination.

Intravascular injection (intra-arterial and intravenous injection)

*Please read the section "Common Adverse Reactions" first. Only the adverse reactions that are likely to occur after intravascular injection of nonionic-monomer contrast agent are described as follows.*
The nature of adverse reactions induced by intra-arterial injection of contrast agent is related to the site and dose of injection. Selective arteriography or other appropriate technical procedures may place the target organs in the high concentration of contrast agent, which may lead to complications in the organs. Peripheral angiography often causes distal **pain and hot sensation** (incidence > 1:10). Transient elevation in serum creatinine is also common after injection of iodinated contrast agents, but is usually clinically insignificant. Renal failure is rare. However, it may occur in high-risk patients, and fatal cases have been reported in these patients. Coronary, intracerebral, or renal artery injections may cause arterial spasm and **ischemia**. **Nervous system reactions**, such as seizures or transient dyskinesia or sensory disturbances, are very rare. Contrast agent uptake by cerebral cortex through blood-brain barrier is uncommon after follow-up CT scans, sometimes with transient confusion or cortical blindness. Serious **cardiac complications** such as asystolia, arrhythmia, cardiac function decreased, or myocardial ischemia are rare.

Thrombophlebitis and venous thrombosis are rare after venography. Very few cases of **arthralgia** have been reported.

Serious respiratory symptoms and signs (including dyspnoea, bronchospasm, laryngospasm, non-cardiogenic pulmonary edema) and cough may occur.

Hyperthyroidism may occur. Redness may occur. Injection site reactions may occur. Dizziness, chest discomfort, palpitations, and flushing may occur.

Intraspinal use

*Please read the section "Common Adverse Reactions" first. Only the adverse reactions that are likely to occur after intraspinal injection of nonionic-monomer contrast agent are described as follows.*
Adverse reactions may be delayed hours or even days after examination through intrathecal injection. The incidence was similar to that of lumbar puncture alone. Headache, nausea, vomiting, and dizziness are common. It is mainly related to the decrease of subarachnoid pressure caused by leakage of cerebrospinal fluid at the puncture point. Some patients have serious headaches that last several days. Do not withdraw too much cerebrospinal fluid to avoid excessive pressure drop. Slight localized pain, peripheral paresthesia, and radicular pain are uncommon at injection sites (1:100 < incidence < 1:10). Pain of lower extremities and cramps are uncommon. Photophobia and pseudomeningitis due to meningeal irritation are uncommon. Chemical meningitis with significant signs is very rare, and may be related to infectious meningitis. Rare reactions include transient brain dysfunction (including seizures, transient loss of consciousness, dyskinesia and sensory disturbances). Few patients have EEG changes. Temporary blindness may occur. Cervical pain may occur. Injection site reactions may occur.

Intracavitary application

*Please read the section "Common Adverse Reactions" first. Only the adverse reactions that are likely to occur after intracavitary injection of nonionic-monomer contrast agent are described as follows.*

**Systemic allergic reactions** are uncommon.

ERCP: Slight increase in amylase level is common. Contrast agent is uncommonly found in kidneys after ERCP, suggesting a significant increase in the risk of post-ERCP **pancreatitis**. Cases of necrotizing pancreatitis have also been reported.

**Oral** contrast agents may cause gastrointestinal discomfort.

**Hysterosalpingography**: Transient slight pain in the lower abdomen is common.

**Arthrography**: Pains are common after angiography. Arthritis with significant signs is rare, and may be related to infectious arthritis.

**Herniography**: Slight postoperative pain is common.

**[Contraindications]**

It is contraindicated in patients with serious manifestations of thyrotoxicosis. It is contraindicated in patients with a history of serious allergy to this product.

**[Precautions]**

General precautions for the use of nonionic-monomer contrast agent:

1. Special attention should be paid to patients with allergies, asthma and adverse reactions to iodinated contrast agents. Prophylactic medications such as steroids and H1/H2 histamine receptor antagonists may be considered for these patients.

2. The risk of serious reactions related to this product is low. However, iodinated contrast agents can provoke anaphylactoid reactions or other allergic reactions. Therefore, first aid measures should be trained in advance, and necessary rescue drugs and devices should be prepared for possible serious reactions.

3. In view of the low accuracy of pre-test in predicting allergic reactions caused by nonionic contrast agents and the possibility that the pre-test itself may lead to serious allergic reactions, it is not recommended to use pretest to predict iodine allergic reactions.

4. Venous access should be kept smooth throughout the X-ray examination.

5. In the *in-vitro* tests, the effect of nonionic contrast agents on the coagulation system is lighter than that of ionic contrast agents. During angiography, great care should be taken in the intravascular technical procedures, and the catheter should be irrigated with heparinized saline from time to time to reduce the thrombosis and embolism related to the technical procedures.

6. Patients, especially patients with multiple myeloma, diabetes, renal insufficiency, infants and young children, and the elderly, must be appropriately hydrated before and after the use of contrast agent. Electrolyte disturbance and hemodynamic disorders are common in infants (< 1 year old), particularly neonates. Special attention should be paid to patients with serious heart diseases and pulmonary arterial hypertension because they are prone to developing hemodynamic disorders and cardiac rhythm disturbances.

7. Patients with acute encephalopathy, brain tumor or history of epilepsy should be prevented from seizures, and special attention should be paid to them. The risks of seizures and neurologic

reactions are significantly increased in patients with alcohol or drug abuse. Transient hearing loss or deafness occurs in a few patients after myelography, which is possibly caused by a decrease in CSF pressure after lumbar puncture.

8. In view of high risks of acute renal failure after the use of contrast agent, special attention should be paid to patients with pre-existing renal impairment and diabetes and patients with atypical globulinemia (multiple myelomatosis and Waldenstrom macroglobulinemia).

9. Preventive actions include:

- Identify patients with high-risk factors.
- Ensure patients are appropriately hydrated and, if necessary, the infusion may be maintained intravenously prior to examination until the contrast agent is cleared from kidneys.
- Avoid any nephrotoxic agent, oral gallbladder contrast agent, surgery for arterial occlusion, renal angioplasty or other major surgeries that increase the renal burden until the contrast agent is cleared.
- Repeat radiographic testing is delayed until renal function returned to the pre-examination level.

To prevent lactic acidosis, the level of serum creatinine must be determined before intravascular injection of iodinated contrast agent into diabetic patients taking metformin. For patients with abnormal serum creatinine/renal function, metformin must be discontinued and the examinations with contrast agent must be postponed until after 48 hours of discontinuation. Metformin should be reused only after renal function and serum creatinine level are constant. In some emergency cases of patients with abnormal or unknown renal function, the physician must assess both advantages and disadvantages of using contrast agent and take precautions, such as discontinuation of metformin, adequate hydration of patients, testing of renal functions, and careful observation of symptoms of lactic acidosis.

There is a potential risk of transient hepatic dysfunction. Special attention should be paid to patients with serious hepatic and renal insufficiency due to significantly longer time to clear contrast agent. Hemodialysis patients may receive the examinations with contrast agents. Immediate hemodialysis is not necessary after the injection of contrast agent because there is no evidence showing that hemodialysis can protect patients with renal impairment from contrast-induced nephropathy.

Iodinated contrast agents may exacerbate symptoms of myasthenia gravis. Patients with pheochromocytoma should be treated with α-blockers to prevent hypertensive crisis in interventional procedures. Special attention should also be paid to patients with hyperthyroidism. Patients with multinodular goiter may develop hyperthyroidism after using iodinated contrast agents. The possibility of transient hypothyroidism in preterm infants after using contrast agents should be clearly recognized.

Contrast media extravasation (CME) occasionally causes localized pain or edema, which gradually subsides without sequelae. However, inflammation and even tissue necrosis may occasionally occur. Routine treatment is to elevate affected limb and cold-compress at local sites. Surgical decompression is required in case of compartment syndrome.

10. <u>Observation time:</u>

Patients should be observed for at least 30 minutes after the use of contrast agent because most serious adverse reactions occur during this period. However, there is still the possibility of a delayed response.

11. Intraspinal injection:

After myelography, patients should rest for 1 h with 20 °-raised head and chest. Patients can carefully get out of bed and walk without bending over. If patients are still in bed, keep their head and chest raised for 6 hours. Patients with low seizure thresholds should be closely monitored during this period, and outpatients should not be stay alone for the first 24 hours.

12. Effects on the ability to drive vehicles and operate machines:

Do not drive a vehicle or operate a machine within 24 hours after intraspinal injection.

13. As all non-gastrointestinal drugs, this product should be visually inspected before use to check for particulate matter, discoloration and container damage.

This product should be drawn into the barrel before use. Each vial is for single use only, and the unused portion should be discarded.

**[Pregnancy and Lactation]**

The safety of this product during human pregnancy has not been established. The results of experimental animal studies do not directly or indirectly indicate a damage in human reproduction, embryonic or fetal development. Because radiation exposure should be avoided at any time of pregnancy, caution must be exercised when considering the implementation of contrast examination for pregnant women. This product should not be used in pregnant women unless the clinician believes that the advantages far outweigh the disadvantages.

Contrast agent is excreted very little in human milk and is absorbed very little through gastrointestinal tract. Therefore, there is little possibility of damage to breastfed infants.

**[Pediatric Use]**

See [Dosage and Administration].

**[Geriatric Use]**

The elderly must be appropriately hydrated before and after the use of contrast agent.

**[Drug Interaction]**

1. The use of iodinated contrast agent may lead to transient renal insufficiency, which may cause lactic acidosis in diabetic patients taking metformin (see [Precautions] for details).

Patients treated with interleukin-2 within 2 weeks are at increased risk of delayed reactions (cold-like symptoms and skin reactions).

3. All iodinated contrast agents affect the determination of thyroid function, and the decrease in iodine binding capacity of thyroid may persist for several weeks.

4. High concentrations of contrast agent in serum and urine can affect laboratory measurements of bilirubin, proteins, or inorganic substances such as iron, copper, calcium, and phosphorus. These measurements should not be performed on the day of use of contrast agent.

5. Although there is no clear incompatibility, this product should not be directly mixed with other drugs. A separate syringe should be used.

**[Overdose]**

Preclinical study data suggests that this product has a high safety margin, and a fixed upper dose level has not been established for daily intravascular use. Systemic overdose is unlikely in patients with normal renal function unless the patient receives a dose of more than 2000 mgI/kg body weight over a fixed period of time. The duration of the examination was important because kidneys have limited capacity to tolerate high concentrations of contrast agent (t 1⁄2 to 2 hours). Accidental overuse is most likely to occur in children undergoing complex vascular examinations, particularly after repeated injections of high concentrations of contrast agent.

Once excess occurs, the imbalance between water and electrolytes must be corrected immediately. Renal function should be monitored continuously for 3 days and, if necessary, hemodialysis should be done to clear excess contrast agent. There are no specific antagonists of contrast agent.

**[Pharmacological and Toxicological Properties]**

The results of animal study show that the product has an enhancement effect on liver, abdominal aorta, CT scan imaging in dogs. It has also been reported in the literature that the toxicity of this product is lower than that of nonionic contrast agents such as Metrizomide. For venography in rats, rabbits, and dogs, the product is excreted predominantly in urine and a small fraction (5% in rats and 1% in dogs) in feces. No organ resorption has been identified and no metabolites have been detected in animals. The protein binding rate of this product is less than 2%; proteinuria occurs during renal arteriography in dogs.

**[Pharmacokinetics]**

It has been reported that nearly 100% of iohexol could be excreted in urine in unchanged form within 24 hours after intravenous injection, with the highest urinary iohexol concentrations occurring within one hour after injection and no metabolite produced.

**[Storage]**

Keep in a tight, light-resistant container.

**[Packaging]** In glass bottle with halogenated butyl rubber stopper. 1 vial/box; 10 vials/box; 30 vials/box.

[**Shelf Life**] 36 months

**[Criteria]** Volume II, Chinese Pharmacopoeia (2015)

**[Approval No.]** GYZZ H20053800

**[Marketing Authorization Holder]**

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