# HOVID IOHEXOL SOLUTION FOR INJECTION U.S.P.

VIIOH01-var5 (MY)

## DESCRIPTION

**Hovid Iohexol Solution for Injection U.S.P. 300mg I/mL**
Clear, colorless to pale yellow solution practically free from visible particles filled in 50mL/32mm Clear molded type-I glass vial stoppered with 31 mm Grey Chlorobutyl RTU Rubber Stopper and sealed with 33 mm Purple aluminium flip off seal. Appearance of product shall remain the same after dilution (if diluted before use).

**Hovid Iohexol Solution for Injection U.S.P. 350mg I/mL**
Clear, colorless to pale yellow solution practically free from visible particles filled in 50mL/32mm Clear molded type-I glass vial stoppered with 31 mm Grey Chlorobutyl RTU Rubber Stopper and sealed with 33 mm Magenta aluminium flip off seal. Appearance of product shall remain the same after dilution (if diluted before use).

## COMPOSITION

**Hovid Iohexol Solution for Injection U.S.P. 300mg I/mL**
Each ml contains 647mg of Iohexol, equivalent to 300 mg of Iodine.

**Hovid Iohexol Solution for Injection U.S.P. 350mg I/mL**
Each ml contains 755mg of Iohexol, equivalent to 350 mg of Iodine.

## PHARMACODYNAMICS

For most of the haemodynamic, clinical-chemical and coagulation parameters examined following intravenous injection of iohexol in healthy patients, no significant deviation from preinjection values has been found. The few changes observed in the laboratory parameters were minor and considered to be of no clinical importance.

## PHARMACOKINETICS

Close to 100 per cent of the intravenously injected iohexol is excreted unchanged through the kidneys within 24 hours in patients with normal renal function. The maximum urinary concentration of iohexol appears within approximately 1 hour after injection. The elimination half-life is approximately 2 hours in patients with normal renal function. No metabolites have been detected. The protein binding of iohexol is so low (less than 2%), that it has no clinical relevance and can therefore be neglected.

## INDICATIONS

X-ray contrast medium for use in adults and children for cardioangiography, arteriography, urography, phlebography and CT-enhancement. Lumbar, thoracic, cervical myelography and computed tomography of the basal cisterns, following subarachnoid injection. Arthrography, endoscopic retrograde pancreatography, (ERP), endoscopic retrograde cholangiopancreatography (ERCP), herniography, hysterosalpingography, sialography and studies of the gastrointestinal tract.

## CONTRAINDICATIONS

Iohexol is contraindicated in patients with:
- known hypersensitivity to iohexol
- thyrotoxicosis manifestation

## WARNING AND PRECAUTIONS

*Special precautions for use of non-ionic monomeric contrast media in general*
A positive history of allergy, asthma, or untoward reactions to iodinated contrast media would require special caution. Premedication with corticosteroids or histamine H1 and H2 antagonists might be considered in these cases.

The risk of serious reactions in connection with use of Iohexol is regarded as minor. However, iodinated contrast media may provoke anaphylactic reactions or other manifestations of hypersensitivity. If serious reaction occurs, a course of action with necessary drugs and equipment available for immediate treatment should be planned. It is advisable to always use an indwelling cannula or catheter for quick intravenous access throughout the entire X-ray procedure.

When performing vascular catheterization procedures, healthcare professionals should pay meticulous attention to the angiographic technique and flush the catheter frequently (e.g.: with heparinized saline) so as to minimize the risk of procedure-related thrombosis and embolism.

Adequate hydration should be assured before and after contrast media administration. This applies especially to patients with multiple myeloma, diabetes mellitus, renal dysfunction, as well as to infants, small children and elderly patients. Young infants (age < 1 year) and especially neonates are susceptible to electrolyte disturbance and haemodynamic alterations.

Care should also be taken in patients with serious cardiac disease and pulmonary hypertension as they may develop haemodynamic changes or arrhythmias. Patients with acute cerebral pathology, tumours or a history of epilepsy are predisposed for seizures and merit particular care. Besides, alcoholics and drug addicts have an increased risk for seizures and neurological reactions.

To prevent acute renal failure following contrast media administration, special care should be exercised in patients with pre-existing renal impairment and diabetes mellitus as they are at risk. Patients with paraproteinemias (myelomatosis and Waldenström's macroglobulinemia) are also at risk.

*Preventive measures include:*
- Identification of high risk patients.
- Ensuring adequate hydration. If necessary by maintaining an i.v. infusion from before the procedure until the contrast medium has been cleared by the kidneys.
- Avoiding additional strain on the kidneys in the form of nephrotoxic drugs, oral cholecystographic agents, arterial clamping, renal arterial angioplasty, or major surgery, until the contrast medium has been cleared.
- Postponing a repeat contrast medium examination until renal function returns to pre-examination levels.

To prevent lactic acidosis, serum creatinine level should be measured in diabetic patients treated with metformin prior to intravascular administration of iodinated contrast medium.

*Normal serum creatinine/renal function:*
Administration of metformin should be stopped at the time of administration of contrast medium and not resumed for 48 hours or until renal function/serum creatinine is normal.

*Abnormal serum creatinine/renal function:*
Metformin should be stopped and the contrast medium examination delayed for 48 hours. Metformin should only be restarted if renal function/serum creatinine is unchanged.

*In emergency cases where renal function is abnormal or unknown, the physician should evaluate the risk/benefit of the contrast medium examination, and precautions should be implemented:*
Metformin should be stopped, patient hydrated, renal function monitored and patient observed for symptoms of lactic acidosis.

A potential risk of transient hepatic dysfunction may exist.

Particular care is required in patients with severe disturbance of both renal and hepatic function as they may have significantly delayed contrast medium clearance. Patients on haemodialysis may receive contrast media for radiological procedures provided dialysis is performed immediately afterwards.

The administration of iodinated contrast media may aggravate the symptoms of myasthenia gravis. In patients with phaeochromocytoma undergoing interventional procedures, alpha blockers should be given as prophylaxis to avoid a hypertensive crisis. Special care should be exercised in patients with hyperthyroidism. Patients with multinodular goiter may be at risk of developing hyperthyroidism following injection of iodinated contrast media. One should also be aware of the possibility of inducing transient hypothyroidism in premature infants receiving contrast media.

Extravasation of contrast media may on rare occasions give rise to local pain, and oedema, which usually recedes without sequela. However, inflammation and even tissue necrosis have been seen. Elevating and cooling the affected site is recommended as routine measures. Surgical decompression may be necessary in cases of compartment syndrome.

*Observation-time*
After contrast medium administration the patient should be observed for at least 30 minutes, since the majority of serious side effects occurs within this time. However, delayed reactions may occur.

*Intrathecal use*
Following myelography the patient should rest with the head and thorax elevated by 20° for one hour. Thereafter he/she may ambulate carefully but bending down must be avoided. The head and thorax should be kept elevated for the first 6 hours if remaining in bed. Patients suspected of having a low seizure threshold should be observed during this period. Outpatients should not be completely alone for the first 24 hours.

*Effects on Ability to Drive and Use Machines*
It is not advisable to drive a car or use machines during the first 24 hours following intrathecal examination.

## PREGNANCY AND LACTATION

The safety of Iohexol use in human pregnancy has not been established. An evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to reproduction, development of the embryo or fetus, the course of gestation and peri- and postnatal development. Since whenever possible, radiation exposure should be avoided during pregnancy, the benefits of an X-ray examination, with or without contrast media, should be carefully weighed against the possible risk. Iohexol should not be used in pregnancy unless the benefit outweighs risk and it is considered essential by the physician. Contrast media are poorly excreted in human breast milk and minimal amounts are absorbed by the intestine. Harm to the nursing infant is therefore unlikely.

## MAIN SIDE/ ADVERSE EFFECTS

*General*
Undesirable effects associated with the use of iodinated contrast media are usually mild to moderate and transient in nature, and less frequent with non-ionic than with ionic contrast media. Serious reactions as well as fatalities are only seen on very rare occasions.

The most frequent adverse event is a mild, general sensation such as a feeling of warmth or a transient metallic taste. Abdominal discomfort/pain is very rare and gastrointestinal reactions like nausea or vomiting are rare.

Hypersensitivity reactions are rare and usually present as mild respiratory or cutaneous symptoms like dyspnoea, rash, erythema, urticaria, pruritus and angioedema. They may appear either immediately after the injection or up to a few days later. Severe manifestations such as laryngeal oedema, bronchospasm or pulmonary oedema are very rare.

Severe cutaneous adverse reactions may occur with the use of iodinated contrast media. Anaphylactoid reactions may occur irrespectively of the dose and mode of administration and mild symptoms of hyper-sensitivity may represent the first signs of a serious reaction. Administration of the contrast medium must be discontinued immediately and, if necessary, specific therapy instituted via the vascular access.

Patients using beta blockers may present with atypical symptoms of anaphylaxis which may be misinterpreted as a vagal reaction. Vagal reactions giving hypotension and bradycardia usually occurs on very rare occasions.

*Intravascular Administration (Intraarterial and Intravenous use)*
The nature of the undesirable effects specifically seen during intraarterial use depend on the site of injection and dose given. Selective arteriographies and other procedures in which the contrast medium reaches a particular organ in high concentrations may be accompanied by complications in that particular organ.

It is common to experience distal pain or heat sensation in peripheral angiography. Renal failure is very rare but it may occur in high risk patients.
Arterial spasm may follow injection into coronary, cerebral or renal arteries and result in transient ischaemia.

Neurological reactions are very rare. They may include seizures or transient motor or sensory disturbances. On very rare occasions, the contrast medium may cross the blood-brain barrier resulting in uptake of contrast medium in the cerebral cortex being visible on CT-scanning until the day following examination, sometimes associated with transient confusion or cortical blindness.

Serious cardiac complications, including cardiac arrest, arrhythmia, depression or signs of ischaemia, are very rare. Post phlebographic thrombophlebitis or thrombosis is very rare.

*Intrathecal Administration*
Undesirable effects following intrathecal use may be delayed and present some hours or even days after the procedure. Headache, nausea, vomiting or dizziness are common and may largely be attributed to pressure loss in the subarachnoid space resulting from leakage at the puncture site. Some of these patients may experience a severe headache that lasts for several days. Excessive removal of cerebrospinal fluid should be avoided in order to minimize pressure loss.

Mild local pain, paraesthesia and radicular pain would occasionally occur at the site of injection. Cramping and pain in the lower limbs are seen on very rare occasions. Meningeal irritation giving photophobia and meningism may happen occasionally. Frank chemical meningitis appear on very rare occasions. There might also be a possibility of an infective meningitis which should be considered.

On very rare occasions, manifestations of transient cerebral dysfunction are seen. These include seizures, transient confusion or transient motor or sensory dysfunction. Changes in the EEG may be noted in a few of these patients.

*Body Cavity Administration*
Systemic hypersensitivity reactions are rare.

*Endoscopic Retrograde Choleangio Pancreatography (ERCP):* Some elevation of amylase levels is common. Post ERCP renal opacification is seen on rare occasions and is associated with an increased risk of post ERCP pancreatitis. Rare cases of necrotizing pancreatitis have also been observed.

*Oral use:* Gastrointestinal upset occasionally occur.

*Hysterosalpingography (HSG):* Transient pain in the lower abdomen is common. Arthrography: Post procedural pain is common. Frank arthritis is rare. The possibility of infective arthritis should be considered in such cases.

*Herniography:* Mild post-procedural pain is common.

Skin and Subcutaneous Tissue Disorders
Severe cutaneous adverse reactions {e.g. Stevens-Johnsons syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP)} have been reported in post-marketing experience of iodinated contrast media.

## DRUG INTERACTIONS
Use of iodinated contrast media may result in a transient impairment of renal function and this may precipitate lactic acidosis in diabetics who are taking metformin.

Patients treated with interleukin-2 less than two weeks previously have been associated with an increased risk for delayed reactions (flu-like symptoms or skin reactions). All iodinated contrast media may interfere with tests on thyroid function, thus the iodine binding capacity of the thyroid may be reduced for up to several weeks.

High concentrations of contrast media in serum and urine can interfere with laboratory tests for bilirubin, proteins or inorganic substances (e.g. iron, copper, calcium and phosphate). These substances should therefore not be assayed on the day of examination.

## OVERDOSE AND TREATMENT
Accidental overdosing is most likely following complex angiographic procedures in children, particularly when multiple injections of contrast medium with high-concentration are given.

There is no specific antidote in cases of overdose. Any resulting water or electrolyte imbalance must be corrected and the renal function shall be monitored. If needed, haemodialysis may be used for clearance of excessive contrast medium.

## DOSAGE AND ADMINISTRATION
Route of Administration: For intravenous, intra-arterial and intrathecal use, and use in body cavities.

For single use only.
Any remaining solution should be discarded.
The dosage varies depending on the type of examination, age, weight, cardiac output and general condition of the patient and the technique used. Usually the same iodine concentration and volume is used as with other iodinated X-ray contrast media in current use. Adequate hydration should be assured before and after administration as for other contrast media. The following dosages may serve as a guide:

**GUIDE FOR INTRAVENOUS USE**

| INDICATION | | CONCENTRATION | VOLUME | COMMENTS |
|---|---|---|---|---|
| **Urography** | Adults | 300 mg I/ml | 40 - 80 ml | 80 ml may be exceeded in selected cases |
| | | or 350 mg I/ml | 40 - 80 ml | |
| | Children < 7kg | 240 mg I/ml | 4 ml/kg | |
| | | or 300 mg I/ml | 3 ml/kg | |
| | Children > 7kg | 240 mg I/ml | 3 ml/kg | |
| | | or 300 mg I/ml | 2 ml/kg (max 40ml) | |
| **Phlebography (leg)** | | 200 mg I/ml | 20 - 100 ml/leg | |
| | | or 240 mg I/ml | | |
| | | or 300 mg I/ml | | |
| **Digital subtraction angiography** | | 300 mg I/ml | 20 - 60 ml/inj | |
| | | or 350 mg I/ml | 20 - 60 ml/inj | |
| **CT-enhancement** | Adults | 140 mg I/ml | 100 - 400 ml | Total amount of iodine usually 30 – 60 g |
| | | or 200 mg I/ml | 100 - 300 ml | |
| | | or 240 mg I/ml | 100 - 250 ml | |
| | | or 300 mg I/ml | 100 - 200 ml | |
| | | or 350 mg I/ml | 100 - 150 ml | |
| | Children | 240 mg I/ml | 2 - 3 ml/kg bw up to 40 ml | In a few cases up to 100 ml may be given |
| | | or 300 mg I/ml | 1 - 3 ml/kg bw up to 40 ml | |

**GUIDE FOR INTRA-ARTERIAL USE**

| INDICATION | | CONCENTRATION | VOLUME | COMMENTS |
|---|---|---|---|---|
| **Arterio-graphies** | arch aortography | 300 mg I/ml | 30 - 40 ml/inj | Volume pr. Injection depends on the site of injection |
| | selective cerebral | 300 mg I/ml | 5 - 10 ml/inj | |
| | aortography | 350 mg I/ml | 40 - 60 ml/inj | |
| | femoral | 300 mg I/ml | 30 - 50 ml/inj | |
| | | or 350 mg I/ml | | |
| | various | 300 mg I/ml | Depending on type of examination | |
| **Cardioan-giography** | Adults | left ventricle and aortic root inj.: 350 mg I/ml | 30 - 60 ml/inj | |
| | | selective coronary arteriography: 350 mg I/ml | 4 - 8 ml/inj | |
| | Children | 300 mg I/ml | Depending on age, weight and pathology (max 8 ml/kg) | |
| | | or 350 mg I/ml | | |
| **Digital subtraction angiography** | | 140 mg I/ml | 1 - 15 ml/inj | Depending on site of injection occasionally large volumes (up to 30 ml may be used) |
| | | or 200 mg I/ml | | |
| | | or 240 mg I/ml | | |
| | | or 300 mg I/ml | | |

**GUIDE FOR INTRATHECAL USE**

| INDICATION | | CONCENTRATION | VOLUME | COMMENTS |
|---|---|---|---|---|
| **Lumbar and thoracic myelography (lumbar injection)** | | 180 mg I/ml | 10 - 15 ml | |
| | | or 200 mg I/ml | 10 - 15 ml | |
| | | or 240 mg I/ml | 8 - 12 ml | |
| **Cervical myelography (lumbar injection)** | | 240 mg I/ml | 10 - 12 ml | |
| | | or 300 mg I/ml | 7 - 10 ml | |
| **Cervical myelography (lateral cervical injection)** | | 240 mg I/ml | 6 - 10 ml | |
| | | or 300 mg I/ml | 6 - 8 ml | |
| **CT cisternography (lumbar injection)** | | 180 mg I/ml | 5 - 15 ml | |
| | | or 200 mg I/ml | 5 - 15 ml | |
| | | or 240 mg I/ml | 4 - 12 ml | |
| **Paediatric myelography** | < 2 years | 180 mg I/ml | 2 - 6 ml | |
| | 2-6 years | 180 mg I/ml | 4 - 8 ml | |
| | > 6 years | 180 mg I/ml | 6 - 12 ml | |

To minimize possible adverse reactions a total dose of 3g iodine should not be exceeded.

**GUIDE FOR BODY CAVITIES**

| INDICATION | | CONCENTRATION | VOLUME | COMMENTS |
|---|---|---|---|---|
| **Arthrography** | | 200 mg I/ml | 5 - 20 ml | |
| | | or 240 mg I/ml | 5 - 20 ml | |
| | | or 300 mg I/ml | 5 - 15 ml | |
| | | or 350 mg I/ml | 5 - 10 ml | |
| **ERP/ERCP** | | 240 mg I/ml | 20 - 50 ml | |
| **Herniography** | | 240 mg I/ml | 50 ml | The dosage varies with the size of the hernia |
| **Hysterosalpingography** | | 240 mg I/ml | 15 - 50 ml | |
| | | or 300 mg I/ml | 15 - 25 ml | |
| **Sialography** | | 240 mg I/ml | 0.5 - 2 ml | |
| | | or 300 mg I/ml | | |
| **Gastro-intestinal (Oral use)** | **Adults** | 180 mg I/ml | individual | |
| | | or 200 mg I/ml | | |
| | | or 350 mg I/ml | | |
| | **Children (esophagus)** | 300 mg I/ml | 2 - 4 ml/kg bw | Max. dose 50 ml |
| | | or 350 mg I/ml | 2 - 4 ml/kg bw | Max. dose 50 ml |
| | **ventricle/ follow trough** | 140 mg I/ml | 4 - 5 ml/kg bw | |
| | **Prematures** | 350 mg I/ml | 2 - 4 ml/kg bw | |
| **Gastro-intestinal (Rectal use)** | **Children** | 140 mg I/ml or dilute with tapwater to 100-150 mg I/ml | 5 - 10 ml/kg bw | Example: Dilute Hovid Iohexol Solution for Injection U.S.P. 300mg I/mL or 350mg I/ml with water 1:1 or 1:2 |
| **CT - enhance-ment** | **Oral use (Adults)** | Dilute with water to ~6 mg I/ml | 800 – 2000 ml of the diluted solution over a period of time | Example: Dilute Hovid Iohexol Solution for Injection U.S.P. 300mg I/mL or 350mg I/ml with water 1:50 |
| | **Oral use (Children)** | Dilute with water to ~6mg I/ml | 15 – 20 ml/kg bw of the diluted solution | |
| | **Rectal use (Children)** | Dilute with water to ~6mg I/ml | Individual | |

Incompatibilities: Although no incompatibility had been found. Iohexol should not be directly mixed with other drugs. A separate syringe should be used.

Storage Condition: Store below 30°C. Protect from light. Do not freeze.

Presentation / Packing:
1 x 50mL vial (300mg I/mL)
1 x 50mL vial (350mg I/mL)

Product Registration Holder: **Hovid Berhad**
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Date of Revision: May 2024