AUSTRALIAN PRODUCT INFORMATION

LIPIODOL ULTRA FLUID (IODISED OIL) SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Iodised oil

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lipiodol Ultra Fluid, 480 mg I/mL, solution for injection is an iodinated, non-water-soluble contrast agent.

Lipiodol Ultra Fluid is for diagnostic use only.

It is an opaque medium for use in certain radiological investigations, where it is desired to outline a viscus or other structure with directly instilled radio-opaque material. It is slowly absorbed from most sites in the body, but from the peritoneal cavity (after hysterosalpingography) absorption is relatively rapid.

Each ampoule contains 10 mL of the active, ethyl esters of iodised fatty acids of poppy seed oil corresponding to an iodine content of 480 mg/mL. This medicine does not contain any excipients.

Viscosity at 15^0C: 70 cP (centipoises)
Viscosity at 37^0C: 25 cP
Relative density at 15^0C: 1.280
ATC code: V08AD01 (V: other).

3 PHARMACEUTICAL FORM

Solution for injection.

Lipiodol Ultra Fluid is a clear, bright pale yellow, sterile oil in a glass ampoule.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

In diagnostic radiology:

Hysterosalpingography; lymphangiography; urethrography; radiography of the seminal vesicles, vas deferens and epididymis; nasal sinuses (for which purpose dilution to one-half or one-third strength with liquid paraffin or a suitable vegetable oil is generally advised); dacryocystography; sialography and the exploration of sinuses, fistulae, etc. It has also been used in the form of a 20% emulsion for the X-ray examination of empyema cavities.

In interventional radiology:

As an imaging agent for visualisation and localisation during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma (HCC) at intermediate stage in adults (see section 4.3 - Contraindications and Section 4.4 Special Warnings and Precautions for Use).

4.2 DOSE AND METHOD OF ADMINISTRATION

Lipiodol Ultra Fluid is for administration using glass syringe or other compatible administration system by slow injection or cannulation (see section 6.2 - Incompatibilities).

After the administration of Lipiodol Ultra Fluid, the patient must be kept under observation for at least 30 minutes.

In diagnostic radiology:

Hysterosalpingography

Administration is by slow injection into the uterine cervical cannula via syringe and suitable cannula.

Care is needed to avoid the risk of venous intravasation. The injection must therefore not be made either during the first few days after a menstrual period or in the few days before a menstrual period is due. When the injection is made by means of a cannula, direct trauma to the uterine mucosa must be avoided. Excessive pressure should not be used in making the injection, which should be avoided entirely when the endometrium and the cervix have been recently subjected to surgical trauma.

On account of the disadvantages and potential dangers (very rare instances of oil emboli and iodism) associated with the use of Lipiodol Ultra Fluid in hysterosalpingography, etc, many radiologists prefer to use water soluble contrast agents.

Lymphangiography

Administration is by lymphatic cannulation. The lymph vessels should first be rendered visible with a subcutaneous injection of Patent Blue V. Lipiodol Ultra Fluid is then injected by means of an automatic infusion machine at a rate of 1 mL every ten minutes.

The usual dosage to visualise the lymphatic system of the leg in the adult patient is 8 mL; in the arm, 3 to 4 mL is usually adequate to show the axillary glands. For bilateral examinations a total of 15 mL usually gives adequate filling of inguinal, iliac and para-aortic glands.

Paediatric population

In children, dosage is reduced according to bodyweight using approximately 0.25 mL/kg.

The procedure is usually carried out under local analgesia. Exposures are made at the end of the infusion; further films are taken 24 and 48 hours later.

The lymph glands retain Lipiodol Ultra Fluid for several weeks or months and changes in their appearance may be followed by serial radiographs for example, after a course of chemo- or radiotherapy.

Elderly

The product should be administered with caution in patients over 65 years of age presenting with underlying pathologies of the cardiovascular, respiratory or neurological system.

In elderly patients with cardiorespiratory failure, the dose should be adapted or the examination itself cancelled, since a portion of the product will temporarily embolise the pulmonary capillaries.

In interventional radiology:

Trans-Arterial Chemo-Embolisation (TACE)

The dose of Lipiodol Ultra Fluid depends on the extent of the lesion but should usually not exceed a total dose of 15 mL in adults.

Procedures involving the use of Lipiodol Ultra Fluid in HCC patients should be conducted by interventional radiologists with prerequisite training and a thorough knowledge of the procedure to be performed.

The administration is by selective intra-arterial catheterisation of the hepatic artery. The procedure should be performed within a typical interventional radiology setting with the appropriate equipment.

Lipiodol Ultra Fluid for TACE can be mixed with anticancer medications for HCC in accordance with the applicable clinical guidelines.

Instructions and precautions for use of the anticancer medications must be strictly followed.

Instructions for preparation of the mixture of Lipiodol Ultra Fluid with an anticancer medicine:

- Prepare two syringes large enough to contain the total volume of mixture. The first syringe contains the anticancer solution, the second syringe contains Lipiodol Ultra Fluid.
- Connect the two syringes to a 3-way stopcock.
- Perform 15 to 20 back and forth movements between the two syringes to obtain a homogeneous mixture. It is recommended to start by pushing the syringe with the anticancer medicine first.
- The mixture is to be prepared at the time of use and must be used promptly after preparation (within 3 hours). If necessary during the interventional radiology procedure, the mixture can be re-homogenised as described above.
- When the adequate mixture is obtained, use a 1 to 3 mL syringe to inject in the micro-catheter.

The procedure can be repeated every 4 to 8 weeks according to tumour response and patient conditions.

Paediatric population

The efficacy and safety of the use of Lipiodol Ultra Fluid for Trans-Arterial Chemo-Embolisation of hepatocellular carcinoma have not been established in children.

Elderly

Lipiodol Ultra Fluid must be administered with special care in patients over 65 years of age with underlying diseases of the cardiovascular, respiratory or nervous systems.

Renal Impairment

Lipiodol Ultra Fluid must be administered cautiously in patients with impaired renal function or pre-existing renal failure (see section 4.4 - Special warnings and precautions). Dosage adjustment is not recommended for patients with renal impairment.

4.3 CONTRAINDICATIONS

- Hypersensitivity to Lipiodol Ultra Fluid (ethyl esters of iodised fatty acids of poppy seed oil)
- Lipiodol Ultra Fluid is unsuitable for bronchography
- Recent haemorrhage in the region of investigation
- Hysterosalpingography during pregnancy or acute pelvic inflammation
- Iodine idiosyncrasy: It is strongly recommended that the patient be tested for iodine idiosyncrasy before the administration of Lipiodol Ultra Fluid in other than small amounts. Simple and reliable tests can be effected by painting an area of the skin with iodine solution or by giving potassium iodine orally for a few days. Iodism occurs more frequently with Lipiodol Ultra Fluid than with organic salts of iodine.
- Documented hyperthyroidism
- Lipiodol Ultra Fluid must not be administered by systemic intra-arterial (apart for selective catheterisation) or intravenous injection.
- To prevent the occurrence of biloma, in the context of TACE procedure, Lipiodol Ultra Fluid must not be administered in liver areas with dilated bile ducts unless drainage has been performed.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Lipiodol Ultra Fluid must not be administered intravenously, intra-arterially (apart from selective catheterisation) or intrathecally.

Hypersensitivity

There is a risk of hypersensitivity regardless of the dose administered.

All iodinated contrast agents can lead to minor or major hypersensitivity reactions, which can be life threatening. They can be immediate (occurring within 60 minutes) or delayed (not occurring until up to 7 days later). Anaphylactic reactions are immediate and can be fatal.

The risk of a major reaction means that the equipment needed for emergency resuscitation must be immediately at hand.

Patients who have already experienced a reaction after a previous administration of Lipiodol Ultra Fluid or who have a history of iodine hypersensitivity are at increased risk of another reaction on re-administration of the product (see section 4.3 - Contraindications).

The injection of this medicine may aggravate symptoms of a pre-existing asthma. In patients whose asthma is not controlled by treatment, the decision to administer Lipiodol Ultra Fluid requires careful prior review of the risk/benefit ratio.

Lymphography

Pulmonary embolism occurs in the majority of patients undergoing lymphography with Lipiodol Ultra Fluid injection since a fraction of the product temporarily embolises the pulmonary capillaries. Evidence of such embolisation is infrequent, usually immediate however possibly delayed from a few hours to days and usually of a transient nature. For this reason, the doses should be adjusted or the examination cancelled in patients presenting with impaired respiratory function, cardiorespiratory insufficiency or pre-existing right cardiac overload, particularly if the patient is elderly. Patients should be warned about the possible signs of pulmonary embolism and to contact their doctor or hospital if any symptoms emerge.

Thyroid

Iodinated contrast media can affect thyroid function because of the free iodine content and can cause hypothyroidism, or hyperthyroidism in predisposed patients. Patients at risk are those with latent hyperthyroidism and those presenting with functional thyroid autonomy. Iodism occurs more frequently with Lipiodol Ultra Fluid than with water soluble organic iodine derivatives. Thyroid disorders may be adequately monitored with thyroid function tests after treatment has been initiated.

Lymphography saturates the thyroid with iodine for several months and any thyroid function tests should therefore be conducted prior to the radiological examination.

Trans-Arterial Chemo-Embolisation

Trans-Arterial Chemo-Embolisation is not recommended in patients with decompensated liver cirrhosis (Child-Pugh score ≥ 8), advanced liver dysfunction, macroscopic invasion and/or extra-hepatic spread of the tumour.

The uncontrolled migration of Lipiodol Ultra Fluid into the arterio-venous system may induce the temporary obliteration of small vessels (oil embolism) in various organs. Evidence of such embolisation is infrequent, usually immediate but can also be delayed occurring after a few hours or days and is usually transient. Most reported localizations of such an event include pulmonary embolisms, cerebral embolisms and skin embolisms (which could lead to skin necrosis). Patients should be warned of the possible signs of embolism and should contact their doctor or hospital if any symptoms emerge.

Hepatic intra-arterial procedures can cause an irreversible liver insufficiency in patients with serious liver malfunction and/or undergoing close multiple sessions. More than 50% liver replacement with tumour, bilirubin level greater than 2 mg/dL, lactate dehydrogenase level greater than 425 mg/dL,

aspartate aminotransferase (AST) level greater than 100 units/L and decompensated cirrhosis have been described as associated with increased post-procedural mortality.

Oesophageal varices must be carefully monitored as they can rupture immediately after treatment. If a risk of rupture is demonstrated, endoscope sclerotherapy/ligature should be performed before the Trans-Arterial Chemo-Embolisation procedure.

Iodinated contrast agent induced renal insufficiency must be systematically prevented by correct rehydration before and after the procedure.

The risk of superinfection in the treated area is normally prevented by administration of antibiotics.

Renal Impairment

Iodinated contrast agents can induce a transient deterioration of renal function or exacerbate pre-existing renal failure. The preventive measures are as follows:

- Identify patients at risk, i.e. patients who are dehydrated or who have renal failure, diabetes, severe heart failure, monoclonal gammopathy (multiple myeloma, Waldenstrom's macroglobulinemia), a history of renal failure after administration of iodinated contrast agents, children under one year of age and elderly atheromatous patients.
- Hydrate the patient before and after the examination.
- Avoid combinations with nephrotoxic medicines. If such a combination is necessary, laboratory monitoring of renal function must be intensified. The medicines concerned are in particular the aminoglycosides, organoplatinums, high doses of methotrexate, pentamidine, foscarnet and certain antiviral agents [aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir], vancomycin, amphotericin B, immunosuppressors such as cyclosporine or tacrolimus, ifosfamide)
- Allow at least 48 hours between radiological examinations or interventions with iodinated contrast agent injections, or delay further examinations or interventions until renal function returns to baseline.
- Check for lactic acidosis in diabetics treated with metformin, by monitoring serum creatinine. Normal renal function: discontinue metformin before and for at least 48 hours after contrast agent administration or until renal function returns to baseline. Abnormal renal function: metformin is contraindicated. In emergencies, if the examination is required, precautions must be taken, i.e. discontinue metformin, hydrate the patient, monitor renal function and test for signs of lactic acidosis.
- Cardiovascular and/or pulmonary co-morbidities should be assessed before initiation of a Trans-Arterial Chemo-Embolisation procedure.

Miscellaneous

The injection of Lipiodol Ultra Fluid into certain fistulae should be conducted with great care in order to avoid penetration of vascular channels and the possibility of oil emboli.

Care should be taken not to inject the product into an area affected by haemorrhage or trauma.

Lipiodol Ultra Fluid has been shown to dissolve polystyrene. Disposable syringes made from the latter must not be used. The product should be administered using a glass syringe.

Effects on laboratory tests

As Lipiodol Ultra Fluid remains in the body for several months, the results of thyroid diagnostic tests may be incorrect for up to 2 years after lymphography.

Paediatric use

Infants - Thyroid function in infants exposed to iodinated contrast media (ICM) should be evaluated and monitored. Decreased levels of thyroxine (T4) and triiodothyronine (T3) and increased level of thyroid stimulating hormone (TSH) were reported after exposure to ICM in infants, especially preterm infants, which remained for up to a few weeks or more than a month. Thyroid function in infants exposed to ICM should therefore be evaluated and monitored until thyroid function is normalised. Some patients were treated for hypothyroidism.

Use in the elderly

See section 4.2 - Dose and Method of Administration, *Elderly*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with other medicines

- Metformin

In diabetic patients, intra-arterial administration of Lipiodol Ultra Fluid may cause lactic acidosis induced by diminished renal function. In patients undergoing a Trans-Arterial Chemo-Embolisation, metformin must be discontinued 48 hours before the procedure and resumed no earlier than two days after the procedure.

Combinations requiring caution

- Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers.

These medicines reduce the effectiveness of the cardiovascular mechanisms that compensate for blood-pressure disturbances.

- Interleukin II (IV)

There is an increased risk of reaction to contrast media in the event of recent interleukin II administration (IV route): skin rash or more rarely hypotension, oliguria or even renal failure.

- Diuretics

There is an increased risk of acute renal failure with diuretics as these may cause dehydration, particularly when high doses of contrast agents are administered.

Precautions for use: rehydration before intra-arterial administration of Lipiodol Ultra Fluid for embolisation.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
No data available.

Use in pregnancy
Pregnancy Category C

The safety of Lipiodol Ultra Fluid during pregnancy has not been demonstrated and therefore should only be used in pregnancy if absolutely necessary and under strict medical supervision.

It must not be used for hysterosalpingography when pregnancy is suspected or confirmed.

Infants born to women who received iodinated contrast media while pregnant should have testing for hypothyroidism in the neonatal period. Some patients were treated for hypothyroidism. See section 4.4 - Special warnings and precautions for use, *Paediatric use*.

Animal reproduction studies have not been conducted using the indicated routes of administration of Lipiodol Ultra Fluid. Lipiodol Ultra Fluid was not embryotoxic or teratogenic in rats after oral administration of 50 mg iodine/kg/day during gestation days 6 to 17, or in rabbits after 4-5 intermittent (once every three days) oral administration of 12.5 mg iodine/kg during gestation days 6 to 18. In rats, increased incidences of dilated renal pelvis and ureter were observed at oral doses of 110 and 250 mg iodine/kg/day and increased incidence of kinked ureter at 250 mg/kg/day.

Use in lactation
Pharmacokinetic studies have shown significant secretion of iodine in breast milk after intramuscular administration of Lipiodol Ultra Fluid. It has been demonstrated that the iodine enters the vascular system of the breastfed infant via the gastrointestinal tract and this could interfere with thyroid function. Consequently, breastfeeding should be discontinued if Lipiodol Ultra Fluid must be used.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of Lipiodol Ultra Fluid on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Most adverse reactions are dose related and consequently the dose should be as low as possible.

Severe allergic reactions have occurred in patients with a hypersensitivity to iodine so adrenaline and oxygen should be available at the time of administration and the patient pre-tested for allergy. Other dangers include oil embolism and venous intravasation.

In diagnostic radiology:

Lymphography

A large increase in temperature followed by a fever of 38 to 39°C may occur within 24 hours following the examination.

Fat micro-embolisms may occur, with or without symptoms. In very rare cases, they may resemble embolisms originating in the body, in terms of their appearance and size. They usually appear as punctiform opacities on radiographic images of the lungs. Transient increases in temperature are possible. Fat micro-embolisms usually occur following an overdose of contrast agent or excessively rapid infusion. Anatomic anomalies such as lymphovenous fistulas or a decrease in the capacity of lymph nodes to retain the contrast agent (in elderly patients or after radiotherapy or cytostatic therapy) favour their occurrence.

Patients with a right-to-left cardiac shunt and those with a massive pulmonary embolism are particularly at risk for fat micro-embolisms in the brain.

In interventional radiology:

Trans-Arterial Chemo-Embolisation

Most adverse reactions are not caused by Lipiodol Ultra Fluid but are due to anticancer medications or the embolisation itself. Procedural risks associated with catheterisation include vascular complications and infections.

The most frequent adverse reactions associated with Lipiodol Ultra Fluid in the context of Trans-Arterial Chemo-Embolisation are post embolisation syndrome (fever, abdominal pain, nausea, vomiting) and transitory changes in liver function tests.

The worsening of a pre-existing hepatocellular insufficiency can occur following the use of Lipiodol Ultra Fluid in the context of Trans-Arterial Chemo-Embolisation and may exceptionally lead to the occurrence of serious and potentially fatal complications such as hepatic encephalopathy, liver abscess, hepatic infarction, ascites, pancreatitis, or even necrotising pancreatitis.

Further serious adverse events associated with uncontrolled dissemination of Lipiodol Ultra Fluid in various organs includes pulmonary, cerebral or skin embolisms.

Post marketing adverse effects

The adverse effects (regardless of indication) are presented in the table below, by system organ class and by frequency using the following categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000), unknown (cannot be estimated from the available data).

System organ class	Frequency: Adverse reactions
Immune system disorders	Unknown: hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Endocrine disorders	Uncommon: hypothyroidism* Unknown: hyperthyroidism, thyroiditis
Nervous system disorders	Unknown: cerebral embolism, hepatic encephalopathy
Skin and subcutaneous tissue disorders	Unknown: skin necrosis
Eye disorders	Unknown: retinal vein thrombosis
Vascular disorders	Unknown: Lymphoedema aggravation
Respiratory, thoracic and mediastinal disorders	Unknown: pulmonary embolism, dyspnoea, cough, pulmonary oedema, pleural effusion, acute respiratory distress syndrome, pneumonitis
Gastrointestinal disorders	Unknown: vomiting, diarrhoea, nausea, pancreatitis, ascites
Hepatobiliary disorders	Unknown: hepatic vein thrombosis, cholecystitis, biloma, hepatic failure, hepatic infarction
Infections and infestations	Unknown: liver abscess
General disorders and administration site conditions	Unknown: granuloma, fever, pain

*Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose may lead to respiratory, cardiac or cerebral complications, which can potentially be fatal. Microembolisms may occur more frequently in the context of overdose.

Management of overdose consists in initiating symptomatic treatment and maintaining vital functions in the shortest possible timeframe.

Sites performing contrast medium examinations must be equipped with medicines and equipment for emergency aid.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Used in Trans-Arterial Chemo-Embolisation (TACE) by selective intra-arterial hepatic injection, Lipiodol Ultra Fluid allows visualisation and control of the procedure due to its opacifying properties. In literature reports, after close-arterial injection to the liver, selective retention of Lipiodol Ultra Fluid within HCC nodules has been shown for up to 6 to 12 months on computed tomography scans.

5.2 PHARMACOKINETIC PROPERTIES

After selective intra-arterial injection

The iodine is eliminated mainly in the urine. After selective intra-arterial injection into the hepatic artery for the diagnosis of hepatic lesions or in Trans-Arterial Chemo-Embolisation of hepatocellular carcinoma, Lipiodol Ultra Fluid is significantly more concentrated in the tumour than in the healthy liver tissue.

Following intra-arterial administration of Lipiodol Ultra Fluid, ethiodised oil retained in normal hepatic parenchyma is phagocytised by the Kupffer cells of the liver and washed out via the hepatic lymphatic system in about 2 to 4 weeks. In HCC, retention in the liver tumour is prolonged, allowing re-imaging of the tumour for four weeks or longer.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Lipiodol Ultra Fluid is non-genotoxic based on negative results in a bacterial reverse mutation assay (*in vitro*), a mouse lymphoma forward mutation assay (*in vitro*), and an *in vivo* micronucleus bone marrow assay in rats after intravenous injection of LIPIODOL at 479 mg iodine/kg.

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Lipiodol Ultra Fluid.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

None

See section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Lipiodol Ultra Fluid does not keep well in plastic containers. Therefore, Lipiodol Ultra Fluid must be administered using glass syringes or other administration system proven to be compatible with it.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25^0C. Protect from light.

If the product becomes opaque or dark amber in colour (approximately the colour of a 1% solution of potassium dichromate), it should not be used.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mL Type I glass ampoule. Pack size of 1.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

The drug substance is a mixture of ethyl esters of iodised and non- iodised fatty acids.

CAS number

8002-46-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled.

8 SPONSOR

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9 DATE OF FIRST APPROVAL

18 December 1991

10 DATE OF REVISION

14 May 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.1, 4.2. 4.3. 4.4, 4.8, 5.1 and 5.2	Added new information pertaining to the TACE indication
4.4, 4.5	Added new safety information for consistency with global prescribing documents
All	Minor editorial changes to adopt consistent wording with global prescribing documents.