1. PRODUCT NAME

LIPIODOL ULTRA FLUID (480 mg iodine/ml), solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Corresponding to an iodine content of ..... 480 mg/mL

in the form of ethyl esters of iodized fatty acids of poppy seed oil per.....1 mL

One 10 mL ampoule contains .....4800 mg of iodine

Viscosity at 15°C: 70 cP (centipoise)

Viscosity at 37°C: 25 cP

Relative density at 15°C: 1.280

This medicinal product does not contain any excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In diagnostic radiology

LIPIODOL is used in lymphography, hysterosalpingography (however water soluble agents are preferred) and sialography.

In interventional radiology

Visualisation and localisation during Trans-Arterial Chemo Embolisation (TACE) of hepatocellular carcinoma (HCC) at intermediate stage in adults.

4.2. Dose and method of administration

LIPIODOL ULTRA FLUID must be administered by slow injection or by catheter, using glass syringes or other devices which have studies demonstrating the compatibility with LIPIODOL ULTRA FLUID. Instructions for use applicable to those devices should be followed (see Section 6.2).

In diagnostic radiology:

- Lymphography

Administer via a catheter inserted into a lymph duct. A dye can first be injected to locate the lymph ducts.

The usual dose is 5 to 7 mL via the strict lymphatic route to enhance contrast in an extremity (depending on the height of the patient), i.e. 10 to 14 mL for bilateral lymphography of the feet. The dose must be reduced proportionally in children. In infants 1 to 2 years of age, a dose of 1 mL per extremity is sufficient.

- Hysterosalpingography

The recommended dosage is 5-10mL.

- Sialography

The administered dose generally varies from 1 to 20 mL, depending on the requirements of the investigation.

Paediatric population

The dose must be reduced proportionally in children.

Patients with low weight

The dose must be reduced proportionally in this population.

Elderly
The product must be administered with special care in patients over 65 years of age with underlying diseases of the cardiovascular, respiratory or nervous systems. Keeping in mind that part of the product temporarily embolises the pulmonary capillaries, the dose must be adjusted in elderly patients with cardiorespiratory failure or the examination must be cancelled.

In interventional radiology:

- TACE of hepatocellular carcinoma

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

LIPIODOL ULTRA FLUID can be mixed with anticancer drugs such as cisplatin, doxorubicin, epirubicin and mitomycin. Instructions and precautions for use of the anticancer drugs must be strictly followed.

Instructions for preparation of the mixture of LIPIODOL ULTRA FLUID with an anticancer drug:

- Prepare two syringes large enough to contain the total volume of mixture. The first syringe contains the anticancer drug 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 drug 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 TACE of hepatocellular carcinoma have not been established in children.

Elderly
The product must be administered with special care in patients over 65 years of age with underlying diseases of the cardiovascular, respiratory or nervous systems.

4.3. Contraindications

- Hypersensitivity to LIPIODOL ULTRA FLUID (ethyl esters of iodised fatty acids of poppyseed oil).
- Pregnant women
- Confirmed hyperthyroidism.
- Traumatic lesions, haemorrhage or recent bleeding (risk of extravasation or embolism).
- Bronchography (the product rapidly inundates the bronchioles and alveoli).

Contraindications specific to the use in interventional radiology (Trans-Arterial Chemo Embolisation):

Administration 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.

There is a risk of hypersensitivity whatever the dose administered.

Warnings

Lymphography

Pulmonary embolism occurs in most patients undergoing lymphography with injection of LIPIODOL ULTRA-FLUID, as part of the product temporarily embolises the pulmonary capillaries. It is uncommon for this embolism to be manifested clinically; should this occur, the signs are immediate (though they may appear several hours or even several days after administration) and are usually transient. For this reason, doses must be adjusted or the examination cancelled in subjects with impaired respiratory function, cardiorespiratory failure or right ventricular overload, particularly if the patient is elderly. Doses must also be reduced after antineoplastic chemotherapy or radiotherapy because lymph nodes shrink significantly and retain very little contrast agent. The injection should be carried out with radiological or endoscopic guidance. Pulmonary invasion can be reduced to the minimum by confirming radiologically that the injection is strictly intralymphatic (and not intravenous) and by discontinuing the examination as soon as the contrast agent becomes visible in the thoracic duct or as soon as lymphatic obstruction is observed.

Hypersensitivity

All iodinated contrast agents may cause minor or major hypersensitivity reactions that may be life-threatening. These hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non-allergic. They may be immediate (within 60 minutes) or delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product, and are often unpredictable.

Emergency resuscitation equipment must be immediately available due to the risk of a major reaction.

Patients who have previously experienced a reaction during administration of LIPIODOL ULTRA FLUID or who have a history of hypersensitivity to iodine are at higher risk for another reaction if the product is again administered.

They are thus considered to be patients at risk.

Injection of LIPIODOL ULTRA FLUID may exacerbate symptoms of asthma. In patients whose asthma is not controlled by treatment, the decision to use LIPIODOL ULTRA FLUID must be based on a careful consideration of the benefit-to-risk ratio.

Thyroid

Because of the free iodine content in iodinated contrast agents, they may modify thyroid function and cause hyperthyroidism in predisposed patients. Patients at risk are those with latent hyperthyroidism or thyroid autonomy. Iodism occurs more commonly with LIPIODOL ULTRA FLUID than with water-soluble organic iodine derivatives.

Lymphography saturates the thyroid with iodine for several months and consequently thyroid function tests must be carried out before the radiological examination.

Trans-Arterial Chemo Embolisation

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

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 level greater than 100 IU/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 TACE 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.

Paediatric population
Transient hypothyroidism has been reported in premature infants, neonates and in other children after administration of iodinated contrast media. Premature infants are particularly sensitive to the effect of iodine. It is advisable to monitor thyroid function. Thyroid function should be checked in neonates during the first week of life, following administration of iodinated contrast agents to the mother during pregnancy. Repeat testing of thyroid function is recommended at 2 to 6 weeks of age, particularly in low birth weight newborn or premature newborn.

Precautions for use

Hypersensitivity

Before the examination:

Identify patients at risk in a detailed interview on their history.

Corticosteroids and H1 antihistamines have been proposed as premedication in patients at greatest risk for hypersensitivity reactions (patients with known hypersensitivity to a contrast agent). However, they do not prevent the occurrence of serious or fatal anaphylactic shock.

Throughout the examination, maintain:

- medical monitoring
- an indwelling intravenous catheter.

After the examination:

After contrast agent administration, the patient must be monitored for at least 30 minutes, as most serious adverse reactions occur within this time period.

The patient must be warned of the possibility of delayed reactions (for up to seven days) (see Section 4.8 - Undesirable effects).

Thyroid

Possible thyroid risk factors must be investigated to prevent metabolic disorders. If iodinated contrast agents are to be administered to patients at risk, thyroid function tests must be carried out before the examination.

Trans-Arterial Chemo Embolisation

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 subjects.
- 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 TACE procedure.

Other

Injection into certain fistulas requires the utmost caution to avoid any vascular penetration, taking into account the risk of fat embolisms.

Care should be taken not to inject the product into areas of bleeding or trauma.

4.5. Interaction with other medicines and other forms of interaction

Interactions with other medicines

- **Metformin**

In diabetic patients, intra-arterial administration LIPIODOL ULTRA FLUID may cause lactic acidosis induced by diminished renal function. In patients undergoing embolization or a TACE, 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 antagonists.**

These medicinal products reduce the efficacy of cardiovascular compensation mechanisms for blood pressure disorders. The physician must be aware of this before administering LIPIODOL ULTRA FLUID and emergency measures must be available.

- **Diuretics**

As diuretics may cause dehydration, the risk of acute renal failure is increased, particularly when high doses of contrast agents are administered.

Precautions for use: rehydration before intra-arterial administration of LIPIODOL ULTRA FLUID for embolisation.

- **Interleukin 2**

Reactions to contrast agents may be increased if the patient has recently been treated with interleukin 2 (i.v.), i.e. skin eruptions or more rarely hypotension, oliguria, or renal failure.

Interference with laboratory tests

As LIPIODOL ULTRA FLUID remains in the body for several months, thyroid laboratory tests may be falsified for as long as two years after lymphography.

4.6. Fertility, pregnancy and lactation

Pregnancy

LIPIODOL ULTRA FLUID must not be used in pregnant women because of the transplacental transfer of iodine, over a long period of time, which interferes probably with the thyroid function of the fœtus, with a potential risk of cerebral lesions and permanent hypothyroidism.

Breastfeeding

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.

Fertility:
There are no data on the impact of Lipiodol Ultra Fluid on fertility.

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. Undesirable effects

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

Use of LIPIODOL ULTRA FLUID causes a foreign body reaction, with the formation of macrophages and foreign-body giant cells and the occurrence of sinus catarrh, plasmacytosis and subsequently changes in lymph node connective tissue. Healthy lymph nodes tolerate the resulting decrease in transport capacity. In patients with lymph node lesions or hypoplasia, these changes may exacerbate lymph stasis.

Hypersensitivity reactions are possible. These reactions may involve one or more effects, occurring concomitantly or successively, and usually including cutaneous, respiratory and/or cardiovascular manifestations, each of which can be a warning sign of incipient shock and, in very rare instances, can even prove fatal.

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:

- In Trans-Arterial Chemo Embolisation

Most of the adverse reactions are not caused by LIPIODOL ULTRA FLUID itself but are due to anticancer drugs or the embolisation itself.

The most frequent adverse reactions of the TACE treatment are post embolisation syndrome (fever, abdominal pain, nausea, vomiting) and transitory changes in liver function tests.

Adverse reactions are given in the following table according to system organ class and frequency, using the following classification: 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), undetermined frequency (cannot be estimated on the basis of available data).

System organ class	**Frequency: adverse reactions**
Immune system disorders	Undetermined frequency: hypersensitivity, anaphylactic reaction.
Endocrine disorders	Transient hypothyroidism (frequency not known)
Nervous system disorders	Undetermined frequency: cerebral embolism.
Respiratory, thoracic and mediastinal disorders	Undetermined frequency: pulmonary embolism.
Gastrointestinal disorders	Undetermined frequency: vomiting, diarrhoea, nausea.
General disorders and administration site conditions	Undetermined frequency: fever, pain.
Injury, poisoning and procedural complications	Rare: spinal cord injury. Undetermined frequency: fat embolism.

Adverse reactions in children

The types of adverse reactions to LIPIODOL ULTRA FLUID are the same as those reported in adults. Their frequency cannot be estimated on the basis of available data.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 to https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Overdose can cause respiratory, cardiac or cerebral complications, which can be fatal. The frequency of micro-embolisms may occur more frequently in the context of overdose.

The total dose of LIPIODOL ULTRA FLUID must not exceed 20 mL.

The treatment of an overdose involves immediate symptomatic treatment and maintenance of vital functions. Establishments performing examinations with contrast agents must have emergency medicines and equipment available.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

NON-WATER-SOLUBLE CONTRAST AGENTS, Code ATC: V08AD01

(V: Other)

Used in TACE by selective intra-arterial hepatic injection, LIPIODOL ULTRA FLUID allows, as an oily contrast agent, the visualisation and control of the procedure thanks to its opacifying properties. As a vehicle, it carries and elutes anticancer drugs into hepatocellular carcinoma nodules and, as a transient embolic agent, it contributes to the vascular embolisation induced during the procedure.

As a selective intra-arterial hepatic injection procedure, TACE combines the effect of a loco-regional targeted anticancer drug with the effect of an ischemic necrosis induced by dual arterio-portal embolisation. LIPIODOL ULTRA FLUID's opacifying properties and tropism for hepatic tumours continues for several months, so post procedure imaging can be performed for an effective patient follow-up.

5.2. Pharmacokinetic properties

After intralymphatic injection

LIPIODOL ULTRA FLUID is released into the blood, taken up by the liver and lungs where the oily droplets are degraded in the pulmonary alveoli, spleen and adipose tissue.

After being taken up by the tissues and storage organs, reabsorption of Lipiodol occurs over a period lasting from a few days to several months or years. This is continuous and regular and the presence of iodides in the urine can be detected as long as contrast material is visible on the images.

After selective intra-arterial injection

The iodine is eliminated mainly in the urine. After selective intra-arterial injection into the hepatic artery for the diagnostic of hepatic lesions or in TACE of hepatocellular carcinoma, LIPIODOL ULTRA FLUID is significantly more concentrated in the tumour than in the healthy liver tissue.

5.3. Preclinical safety data

Preclinical data from conventional studies on pharmacological safety, single- and repeated-dose toxicology, genotoxicity and reproductive and developmental functions showed no particular risks for human subjects.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

This medicinal product contains no excipients.

6.2. Incompatibilities

LIPIODOL ULTRA FLUID must be administered using glass syringes or other devices which have studies demonstrating the compatibility with LIPIODOL ULTRA FLUID. Instructions for use applicable to those devices should be followed.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store below 30°C protected from light.

6.5. Nature and contents of container

1 x 10 mL glass (type 1) ampoule.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be discarded in accordance with current regulations.

7. MEDICINE SCHEDULE

General Sales Medicine

8. SPONSOR

Distributed in New Zealand by:

Obex Medical Limited
303 Manukau Road,
P.O. Box 26511
Epsom
AUCKLAND 1344

Phone: 09 630 3456 or 0800 656 239

Fax: 09 630 9009

www.obex.co.nz

Supplied by:

Guerbet

Guerbet
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93600 Aulnay-sous-Bois
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9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF TEXT

28 February 2018

SUMMARY TABLE OF CHANGES

Date of Revision	Section Changed	Summary of new information
08 November 2017	All 2 4.1 4.2 4.3 & 4.4 4.5 4.6 4.7 4.8, 4.9, 5, 6	• Updated to new Medsafe SPC template • Updated to reflect the current CCSI and the French SmPC • Addition of the TACE indication • Updated to reflect the current CCSI and the French SmPC. Addition of the TACE indication. • Updated to reflect the current CCSI and addition of the TACE indication. • Updated to reflect the current CCSI and the French SmPC • Updated to reflect the current CCSI and the French SmPC. Addition of fertility information. • Updated to reflect the current CCSI and the French SmPC. Addition of fertility information. • Updated to reflect the current CCSI and the French SmPC.
28 February 2018	4.4, 4.8	• Safety update due to possible risk of hypothyroidism in infants exposed to iodine-containing contrast agents.