NEW ZEALAND DATA SHEET

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 iodised 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 ULTRA FLUID is used in lymphography, hysterosalpingography in women undergoing infertility workup 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

Inject increments of 2 mL of LIPIODOL ULTRA FLUID into the endometrial cavity under fluoroscopic control until tubal patency is determined. The total volume to be injected depends on the volume of the uterine cavity, usually not exceeding 15 mL. The dose of LIPIODOL ULTRA FLUID for hysterosalpingography should be kept as low as possible to minimize the potential risk of thyroid dysfunction.

Administration in hysterosalpingography is by slow injection into the uterine cervical canal via a suitable catheter or cannula. Stop the injection if the patient develops excessive discomfort. The examination should be preferably carried out during the follicular phase of the menstrual cycle.

- 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.

In elderly patients with cardiorespiratory failure scheduled for a lymphography, 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:

- 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.

Limiting the injected dose will also prevent non-targeted pulmonary embolism which might occur in the course of a hepatic chemoembolisation.

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):

Intra-arterial administration of chemotherapy.

LIPIODOL ULTRA FLUID for treatment of hepatocellular carcinoma may lead to both ischemic and toxic effects to the bile ducts. Therefore, the treatment is contraindicated in areas of the liver where the bile ducts are dilated, unless post-procedural drainage can be performed.

Contraindications specific to the use in hysterosalpingography:

Hysterosalpingography during pregnancy, acute pelvic inflammation, marked cervical erosion, endocervicitis and intrauterine bleeding, within 30 days of curettage or conisation, or in patients with known or suspected reproductive tract neoplasia (due to the risk of peritoneal spread of neoplasm).

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

All Indications

Hypersensitivity

All iodinated contrast agents can lead to minor or major hypersensitivity reactions which can be life-threatening. These hypersensitivity reactions may be either of an allergic nature (known as anaphylactic reactions if they are serious) or a non-allergic nature. 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. They are dose-independent, can occur from the first administration of the product, and are often unforeseeable.

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 increased risk of another reaction on re-administration of the product and are thus regarded as at-risk patients.

Injection of LIPIODOL ULTRA FLUID may aggravate symptoms of an existing asthma. In patients with asthma unbalanced by treatment, the decision to use LIPIODOL ULTRA FLUID must be made after careful evaluation of the benefit-to-risk ratio.

Thyroid dysfunction

Iodinated contrast mediacan affect thyroid function because of the free iodine they contain and cause hyperthyroidism in predisposed patients. Patients at risk are those with latent hyperthyroidism and those with functional thyroid autonomy. Iodism occurs more frequently with LIPIODOL ULTRA FLUID than with water-soluble organic iodine derivatives.

Embolic and thrombotic complications

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 localisations of such an event include pulmonary embolisms, cerebral embolisms (which could lead to cerebral infarction) 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.

Specific warning related to 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. The occurrence of 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.

Lymphography saturates the thyroid with iodine for several months and may induce thyroid dysfunction. Any thyroid function tests must be performed before the radiological examination.

Specific warning related to Hysterosalpingography

Intravasation of LIPIODOL ULTRA FLUID may occur in the course of a hysterosalpingography procedure and may result in serious pulmonary or cerebral embolic complications in the next hours following the procedure. The hysterosalpingography procedure should be immediately interrupted in case of suspected or confirmed intravasation of LIPIODOL ULTRA FLUID. The patient should be closely monitored for embolic complication in a care setting deemed appropriate by the treating clinician.

When used in hysterosalpingography in patients considered at risk for hypothyroidism, thyroid function should be monitored closely for several months after the examination to observe potential development of hypothyroidism. The dose of LIPIODOL ULTRA FLUID should be kept as low as possible to minimise the potential risk of thyroid dysfunction.

Specific warnings related to Trans-Arterial Chemo Embolisation

TACE is not recommended in patients with decompensated liver cirrhosis (Child-Pugh ≥8), advanced liver dysfunction, macroscopic portal vein 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 through precise questioning 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, it is necessary to ensure the following:

- medical monitoring
- maintenance of venous access.

After the examination:

- After administration of a contrast agent, the patient must be kept under observation for at least 30 minutes, as most serious adverse reactions occur within this period.The patient must be warned of the possibility of delayed reactions occurring up to 7 daysafter administration (see Section 4.8 - Undesirable effects).

Thyroid dysfunction

To prevent any metabolic disorder, possible thyroid risk factors must be determined. If administration of an iodinated contrast agent is planned in such patients at risk, thyroid function must be determined before the examination.

Chemoembolisation/Vascular embolisation

Iodinated contrast agents can induce a transient alteration in renal function or worsen pre-existing renal insufficiency. Preventive measures include:

- Identify patients at risk, i.e. patients who are dehydrated or who have renal insufficiency, 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 patients with atheroma.
- Hydrate the patient before and after the procedure.
- Avoid combinations with nephrotoxic medicines. If this cannot be avoided, laboratory monitoring of renal function must be intensified. The medicines concerned include aminoglycosides, organoplatinum compounds, high doses of methotrexate, pentamidine, foscarnet and certain antiviral agents [aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir], vancomycin, amphotericin B, immunosuppressants such as cyclosporine or tacrolimus, ifosfamide).
- Allow at least 48 hours between two radiological examinations or procedures with iodinated contrast agent injections, or delay further examinations or procedures until renal function returns to baseline.
- Prevent lactic acidosis in diabetics treated with metformin, by monitoring serum creatinine levels. 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 case of emergency: if the examination is mandatory, 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.

Miscellaneous

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

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

Indications for the use of LIPIODOL ULTRA FLUID must be carefully assessed in patients with primary lymph oedema, as the oedema can be exacerbated.

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. For patients scheduled to undergo embolisation 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 medicines reduce the efficacy of cardiovascular mechanisms that compensate for blood pressure disturbances. The physician must be aware of this before administering LIPIODOL ULTRA FLUID andhave resuscitation equipment available.

- **Diuretics**

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

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

- **Interleukin 2**

Reactions to contrast agents may be increased if the patient has recently been treated with interleukin 2 (i.v.route), i.e. skin rash 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 results can be falsified for up to two years after lymphography.

4.6. Fertility, pregnancy and lactation

Pregnancy

The safety of LIPIODOL ULTRA FLUID during pregnancy has not been demonstrated.

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. Although this anomaly is transitory it produces the potential risk of brain damage and permanent hypothyroidism, and therefore requires supervision of thyroid function and careful medical monitoring of the neonate.

Also, LIPIODOL ULTRA FLUID must not be used for hysterosalpingography when pregnancy is suspected or confirmed.

The occurrence of maternal hypothyroidism after hysterosalpingography procedure (see Section 4.4 – Specific warnings related to Hysterosalpingography) and the possible long half-life of the product in the event of a successful pregnancy requires a surveillance of the newborns thyroid function.

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.

Fertility

In women who underwent hysterosalpingography with LIPIODOL ULTRA FLUID for infertility workup, a significantly higher rate of pregnancy has been observed, compared to women who did not undergo any

hysterosalpingography or who underwent hysterosalpingography with water-soluble iodinated contrast agents (see section 5.1 Pharmacodynamics).

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

Undesirable effects not related to a specific indication

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

The 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 previously damaged or hypoplastic lymph nodes, these changes can exacerbate the existing lymphostasis.

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.

Undesirable effects related to a specific indication

- Lymphography:

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

Oil micro-emboli can occur, with or without clinical symptoms. In very rare cases, they may resemble organic emboli in terms of their appearance and size. They appear as punctiform or flat opacities on radiographic images of the lungs.

Oil micro-emboli usually occur following an overdose of contrast agent or excessively rapid infusion. They are favoured by anatomic abnormalities such as lympho-venous fistulas or decreased lymph node uptake capacity (e.g. in elderly patients or after radiotherapy or cytostatic therapy).

Patients with a right-to-left cardiac shunts and those with massive pulmonary embolism are particularly at risk or cerebral oil micro-emboli.

- Hysterosalpinography

Transitory fever reactions usually between 37 and 38°C accompanied by pelvic pain are frequent.

Episodes of salpingitis or pelvic peritonitis have been reported after the examination in case of latent infection. Granuloma type tissue reactions are rare but could be serious as they produce a risk of perforation.

Hypothyroidism may also occur especially in patient with subclinical hypothyroidism. Following maternal exposure with LIPIODOL ULTRA FLUID, foetal thyroid disorders including foetal goitre were also reported. Intravasation of LIPIODOL ULTRA FLUID may occur in the course of hysterosalpingography procedure and may result in serious pulmonary or cerebral embolic complications.

- Sialography

A secondary inflammation reaction can sometimes occur with functional glandular paralysis (salivary duct inflammation) which disappears within 48 hours.

- 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 part of the post embolisation syndrome

(fever, abdominal pain, nausea, vomiting and transitory changes in liver function tests). These reactions may also be induced by the anticancer medications or by the procedure itself.

Further serious adverse events associated with uncontrolled dissemination of LIPIODOL ULTRA FLUID in various organs include pulmonary, cerebral (which could lead to cerebral infarction) or skin embolisms (which could lead to skin necrosis) may also occur. Massive pulmonary embolism has been associated with serious complications including dyspnoea, pulmonary oedema, pleural effusion, acute respiratory distress syndrome, and pneumonitis.

Frequencies of Undesirable effects The adverse effects 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), not known (cannot be estimated from the available data).

System organ class	**Frequency: adverse reactions**
Immune system disorders	Frequency not known: Hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Endocrine disorders	Frequency not known: Transient hypothyroidism, hyperthyroidism, thyroiditis, goitre[b]
Nervous system disorders	Frequency not known: Cerebral embolism, celebral infarction, hepatic encephalopathy[a]
Eye disorders	Frequency not known: Retinal vein thrombosis
Vascular disorders	Frequency not known: Lymphoedema aggravation
Respiratory, thoracic and mediastinal disorders	Frequency not known: Pulmonary embolism, dyspnoea, cough, pulmonary oedema[a], pleural effusion[a], acute respiratory distress syndrome[a], pneumonitis[a]
Gastrointestinal disorders	Frequency not known: Vomiting, diarrhoea, nausea, pancreatitis[a], ascites[a]
Hepatobiliary disorders	Frequency not known: Hepatic vein thrombosis, cholecystitis[a], biloma[a], hepatic failure[a], hepatic infarction[a]
General disorders and administration site conditions	Frequency not known: granuloma, fever, pain.
Infections and infestations	Frequency not known: Liver abscess[a]
Skin and subcutaneous tissue disorders	Frequency not known: Skin necrosis[a]
Injury, poisoning and procedural complications	Rare: spinal cord injury. Undetermined frequency: fat embolism Frequency not known venous intravasation[b]

[a] In the context of TACE
[b] In the context of hysterosalpingography.

Adverse reactions in children

The expected nature of the adverse reactions to LIPIODOL ULTRA FLUID are the same as those reported in adults. Their frequency cannot be estimated from the 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 may lead to respiratory, cardiac or cerebral complications, which can potentially be fatal. Microembolisms may occur more frequently in the context of overdose.

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

The treatment of overdose is directed toward a prompt initiation of symptomatic treatment and support of all vital functions. Sites performing contrast medium examinations must be equipped with medicines and equipment for emergency aid.

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.

Used in hysterosalpingography, in women with infertility for more than 1 year randomly assigned to hysterosalpingography with LIPIODOL ULTRA FLUID (n=73) or no hysterosalpingography (n=85), the pregnancy rate at 6 months follow-up was 38.4% (28/73) and 16.5% (14/85), respectively (p=0.002) and the live birth rate was 31.5% (23/73) and 12.9% (11/85), respectively (p=0.005).

In women with infertility for more than 1 year randomly assigned to hysterosalpingography with LIPIODOL ULTRA FLUID (n=554) or hysterosalpingography with water soluble iodinated contrast agent (n=554), the pregnancy rate at 6 months follow-up was 39.7% (220/554) and 29.1% (161/554), respectively (p<0.001) and the live birth rate was 38.8% (214/552) and 28.1% (155/552), respectively (p=0.005).

A meta-analysis of randomized controlled trials showed an overall odds ratio (OR) for pregnancy within 6 months after the procedure significantly in favor of hysterosalpingography with LIPIODOL ULTRA FLUID: OR of 3.47 [95%CI: 1.98; 6.08] when compared to no hysterosalpingography (p<0.001, 3 studies, 382 women) and OR of 1.59 [95%CI: 1.28; 1.98] when compared to hysterosalpingography with water soluble iodinated contrast agent (p<0.001, 4 studies, 1510 women).

The mechanisms underlying these differences are not well characterized. The following hypotheses have been proposed:

- mechanical effect: tubal flushing of debris out of the Fallopian tubes
- endometrial bathing effect
- immunologic effect: inhibition of peritoneal macrophages.

5.2. Pharmacokinetic properties

<u>After intralymphatic injection</u>

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.

After intrauterine injection

After intrauterine injection in rats, LIPIODOL ULTRA FLUID migrates through the Fallopian tubes to the peritoneal cavity from which it is resorbed. The Tmax in plasma is reached around 8 hours post-administration. Half-life in plasma was about 18 hours. After 7 days, 48% of injected dose was eliminated (37% in urine, 11% in faeces).

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
P.O. Box 26511
Epsom, AUCKLAND 1344

Telephone: (09) 630 3456
Toll Free: 0800 656 239

Fax: (09) 630 9009
www.obex.co.nz

Supplied by:

Guerbet

Guerbet
16-24 rue Jean Chaptal
93600 Aulnay-sous-Bois
FRANCE

9. DATE OF FIRST APPROVAL

31 December 1969

10. DATE OF REVISION OF TEXT

14 March 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Addition of the contraindication “hysterosalpingography in patients with known or suspected reproductive tract neoplasia.