Product Monograph

Including Patient Medication Information

LIPIODOL® ULTRA FLUID

Ethiodized Oil Injection

Solution for injection, 38% w/w (380 mg iodine/g or 480 mg iodine/mL)

For Parenteral and Intracavitary use

V08AD01 non-water-soluble X-ray contrast media

House Standard

For professional use only

Guerbet

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France

Date of Authorization:
2017-07-13

Date of Revision:

2026-03-12

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Control Number: 302675

Recent Major Label Changes

2. Contraindications	2026-03
7. Warnings and Precautions, Cardiovascular	2026-03
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Part 1: Healthcare Professional Information

1. Indications

LIPIODOL ULTRA FLUID (ethiodized oil) is an X-ray contrast media indicated for:

Adult patients:

- Lymphography
- Hysterosalpingography
- Sialography
- Fistulography
- Selective hepatic intra-arterial use for imaging tumors in patients with known hepatocellular carcinoma (HCC)

LIPIODOL ULTRA FLUID should be administered by health professional experienced in the respective imaging procedure in a controlled clinical setting where adequate facilities and expertise for the management of serious adverse events are readily available.

1.1. Pediatrics

Pediatrics (<18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of LIPIODOL ULTRA FLUID in pediatric has been established. Therefore, Health Canada has authorized the following indication for pediatric use: lymphography.

1.2. Geriatrics

Geriatrics (>65 years): Evidence from clinical experience suggests that use in elderly patients with diseases of the cardiovascular, respiratory or nervous systems is associated with an increased risk of serious adverse reactions (see 7 Warnings and Precautions). LIPIODOL ULTRA FLUID must be administered with caution in these patients, based on individual benefit-risk evaluation

2. Contraindications

- Hypersensitivity reaction to ethiodized oil or iodine
- Manifest hyperthyroidism
- Traumatic injuries, recent hemorrhage or bleeding (risk of extravasation or embolism)
- Bronchography
- Intravenous, intra-arterial (apart from authorized selective use) or intrathecal administration
- LIPIODOL ULTRA FLUID hysterosalpingography is also contraindicated in pregnancy, acute pelvic inflammatory disease, marked cervical erosion, endocervicitis and intrauterine bleeding, in the immediate pre-or postmenstrual phase, or within 30 days of curettage or conization.
- LIPIODOL ULTRA FLUID lymphography is also contraindicated in patients with a right to left cardiac shunt, advanced pulmonary disease, tissue trauma or hemorrhage, advanced neoplastic disease

with expected lymphatic obstruction, previous surgery interrupting the lymphatic system, or radiation therapy to the examined area.

- Sialography with LIPIODOL ULTRA FLUID is also contraindicated in case of acute parotiditis.
- LIPIODOL ULTRA FLUID for selective hepatic intra-arterial use for imaging tumors may lead to both ischemic and toxic effects to the bile ducts. Therefore, LIPIODOL ULTRA FLUID selective hepatic intra-arterial use is also contraindicated in areas of the liver where the bile ducts are dilated (unless external biliary drainage was performed before injection), in case of advanced liver failure (Child-Pugh Class C), macroscopic vascular invasion of the main portal vein (right, left or common trunk) or hepatic vein or vena cava, and/or extensive extra-hepatic metastasis of the tumor.

3. Serious Warnings and Precautions Box

Serious Warnings and Precautions

- LIPIODOL ULTRA FLUID should be administered by health professional experienced in the respective imaging procedure in a controlled clinical setting where adequate facilities and expertise for the management of serious adverse events are readily available. LIPIODOL ULTRA FLUID should be administered slowly with radiologic monitoring without exceeding the recommended dose.
- Serious or fatal pulmonary or cerebral embolism has been reported following intralymphatic and selective intra-arterial use, and after inadvertent systemic intravascular injection or intravasation. See 7 Warnings and Precautions
- Serious or fatal cases of exacerbation of chronic liver disease and related conditions have been reported after the selective intra-arterial administration of LIPIODOL ULTRA FLUID. See 7 Warnings and Precautions

4. Dosage and Administration

4.1. Dosing Considerations

- Lipiodol Ultra Fluid is for intralymphatic, intracavitary and selective intra-arterial use.
- Use the smallest possible amount of LIPIODOL ULTRA FLUID according to the anatomical area to be visualized.
- Inspect LIPIODOL ULTRA FLUID visually for particulate matter and discoloration before administration. Do not use the solution if particulate matter is present or if the container appears damaged.
- LIPIODOL ULTRA FLUID is a clear, pale yellow to amber colored oil; do not use it if the color has darkened.
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4.2. Recommended Dose and Dosage Adjustment

Hysterosalpingography

Inject increments of 2 mL of LIPIODOL ULTRA FLUID until tubal patency is determined

Lymphography

Start the injection of LIPIODOL ULTRA- FLUID into a lymphatic channel at a rate not to exceed 0.2 mL per minute. Inject the total dose of LIPIODOL ULTRA FLUID in no less than 1.25 hours.

Adults:
- unilateral lymphography of the upper extremities 2 to 4 mL
- unilateral lymphography of the lower extremities 6 to 8 mL
- penile lymphography 2 to 3 mL
- cervical lymphography 1 to 2 mL

After chemotherapy or radiotherapy, the lymph nodes shrink significantly and retain only a small amount of the contrast agent. Doses must then be reduced.

Pediatric Patients:
Use a dose of minimum of 1 mL to a maximum of 6 mL according to the anatomical area to be visualized. Do not exceed 0.25 mL/kg. The dose should be proportionally decreased in children: in infants between 1 and 2 years of age, a dose of 1 mL per extremity is sufficient.

Sialography

Inject LIPIODOL ULTRA FLUID until the gland fills. Do not exceed 5 mL.

Fistulography

Inject LIPIODOL ULTRA FLUID until fistulae fills. Do not exceed 5 mL.

Selective Hepatic Intra-arterial Use

The dose depends on the tumor size, and local blood flow in the liver and in the tumor.

Limit the dose to only the quantity required for adequate visualization.

Inject from 1.5 to 15 mL slowly under continuous radiologic monitoring. The total dose of LIPIODOL ULTRA FLUID administered should not exceed 15 mL.

Limiting the injected dose may lower the risk of pulmonary embolism which might occur in the course of a hepatic artery catheterization. (See 4.1 Dosing Considerations).

4.5. Administration

Draw LIPIODOL-ULTRA FLUID into a glass syringe and use promptly. Use the smallest possible amount of LIPIODOL ULTRA FLUID according to the anatomical area to be visualized. Discard any unused portion of LIPIODOL ULTRA FLUID.

Hysterosalpingography

Using aseptic technique, inject LIPIODOL ULTRA FLUID into the endometrial cavity with fluoroscopic control. Stop the injection if patient develops excessive discomfort. Re-image after 24 hours to

establish whether LIPIODOL ULTRA FLUID has entered the peritoneal cavity. The examination should be carried out on the 10th day following the start of the menstrual period and must be carried out no later than the 12th day.

Lymphography

Inject LIPIODOL ULTRA FLUID into a lymphatic vessel under radiologic guidance to prevent inadvertent venous administration or intravasation.

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The following method is recommended for lymphography of the upper or lower extremities. Start the injection of LIPIODOL ULTRA- FLUID into a lymphatic channel at a rate not to exceed 0.2 mL per minute. Inject the total dose of LIPIODOL ULTRA FLUID in no less than 1.25 hours. Use frequent radiologic monitoring to determine the appropriate injection rate and to follow the progress of LIPIODOL ULTRA FLUID within the lymphatics. Interrupt the injection if the patient experiences pain. Terminate the injection if lymphatic blockage is present to minimize introduction of LIPIODOL ULTRA FLUID into the venous circulation via lymphovenous channels. Terminate the injection as soon as LIPIODOL ULTRA FLUID is radiographically evident in the thoracic duct to minimize entry of LIPIODOL ULTRA FLUID into the subclavian vein and pulmonary embolization. A radiographic or fluoroscopic control during injection allows to avoid overdosing. Obtain immediate post-injection images. Re-image at 24 or 48 hours to evaluate nodal architecture.

Sialography

Inject LIPIODOL ULTRA FLUID until the gland fills. Do not exceed 5 mL.

Fistulography

Inject LIPIODOL ULTRA FLUID until fistulae fills. Do not exceed 5 mL.

Selective Hepatic Intra-arterial Use

Administration is by selective intra-arterial catheterization of the hepatic artery. Inject from 1.5 to 15 mL slowly under continuous radiologic monitoring. Stop the injection when stagnation or reflux is evident. The total dose of LIPIODOL ULTRA FLUID administered should not exceed 15 mL.

5. 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. Promptly initiate symptomatic treatment and support of all vital functions for overdose.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

LIPIODOL ULTRA FLUID is available in self-breaking ampoules of 10 mL.

LIPIODOL ULTRA FLUID is a water insoluble iodinated contrast media. (i.e., ethyl esters of iodized fatty acids of poppy seed oil).

One gram of LIPIODOL ULTRA FLUID contains 0.38 g of iodine.

One milliliter of LIPIODOL ULTRA FLUID contains 0.48 g of iodine.

Table 5 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Intralymphatic, Intracavitary and selective intra-arterial use	Solution for injection, 380 mg iodine/g (38% w/w), 480 mg iodine/mL	None

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box

Cardiovascular

Embolization of the lung, brain and other major organs

Pulmonary embolism may occur immediately or a few hours to days following lymphography, intra-arterial use, or inadvertent systemic vascular injection or intravasation of LIPIODOL ULTRA FLUID, causing decreased pulmonary diffusing capacity and pulmonary blood flow, pulmonary infarction, acute respiratory distress syndrome, or fatalities.

Embolization of the brain and less commonly other major organs has been reported.

LIPIODOL ULTRA FLUID is not recommended in patients with impaired lung function, cardiorespiratory failure, or pre-existing right-sided cardiac overload, in particular elderly patients. Radiological monitoring should be performed during the LIPIODOL ULTRA FLUID injection. Do not exceed the recommended maximum dose and rate of injection of LIPIODOL ULTRA FLUID.

During lymphography to minimize the risk of pulmonary embolism, obtain radiographic confirmation of intralymphatic (rather than venous) injection, and terminate the procedure when Lipiodol Ultra Fluid Lipiodol Ultra Fluid becomes visible in the thoracic duct or lymphatic obstruction is observed.

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 embolization 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 (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 healthcare professional if any symptoms emerge.

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.

Endocrine and Metabolism

Thyroid dysfunction

Iodinated contrast media can affect thyroid function because of the free iodine content and can cause hyperthyroidism or hypothyroidism in predisposed patients. Patients at risk are those with latent hyperthyroidism and those with Hashimoto thyroiditis, or history of thyroid irradiation. Iodism occurs more frequently with Lipiodol Ultra Fluid than with water-soluble organic iodine derivatives. Iodism (iodine toxicity or poisoning) is a syndrome caused by iodine or any iodine compound and manifested by loss of appetite, sickness, tachycardia, headache, abdominal pain, intestinal transit disorder, extreme tiredness, taste disturbance, corysa, skin irritation, depression, parotid gland swelling.

As LIPIODOL remain in the body for several months, thyroid diagnostic results can be affected for up to two years.

In patients at risk, the thyroid function must be assessed before LIPIODOL ULTRA FLUID administration. LIPIODOL ULTRA FLUID is contraindicated in manifest hyperthyroidism (see 2 Contraindications).

When used in hysterosalpingography in patients at risk of hypothyroidism, close monitoring of thyroid function and follow-up of hypothyroidism should be undertaken several months after examination. The LIPIODOL ULTRA FLUID dose should be as low as possible to minimize the potential risk of thyroid dysfunction.

Hepatic/Biliary/Pancreatic

Exacerbation of chronic liver disease

LIPIODOL ULTRA FLUID selective hepatic intra-arterial administration can exacerbate the following conditions: portal hypertension causing variceal bleeds due to obstruction of intrahepatic portal channels by opening a pre-sinusoidal anastomosis, hepatic ischemia with liver enzyme elevations, fever and abdominal pain, hepatic failure resulting in ascites and encephalopathy. Hepatic vein thrombosis, irreversible liver insufficiency and fatalities have been reported. Procedural risks include vascular complications and infections.

LIPIODOL ULTRA FLUID use is contraindicated in areas of the liver where the bile ducts are dilated (unless external biliary drainage was performed before injection), advanced liver failure (Child-Pugh Class C), macroscopic vascular invasion of the main porta vein (right, left or common trunk or hepatic vein or vena cava), and/ or extensive extra-hepatic metastasis of the tumor (see 2 Contraindications). Patients with esophageal varices should be carefully monitored for rupture during the procedure.

Immune

Hypersensitivity

Anaphylactic and anaphylactoid reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following LIPIODOL ULTRA FLUID administration, independent of the dose. Most hypersensitivity reactions to LIPIODOL ULTRA FLUID occur within half an hour after administration.

Avoid use in patients with a history of sensitivity to other iodinated contrast agents (see 2 Contraindications), bronchial asthma or allergic disorders because of an increased risk of a hypersensitivity reaction to LIPIODOL ULTRA FLUID. Administer LIPIODOL ULTRA FLUID only in situations where trained personnel and therapies are promptly available for the treatment of hypersensitivity reactions, including personnel trained in resuscitation; ensure continuous medical monitoring and maintain an intravenous access line. Delayed reactions can occur up to several days after administration. Observe patients for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following LIPIODOL ULTRA FLUID administration and warn patients of the possibility of delayed reactions.

Circulatory

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In patients with primary lymphoedema, healthcare professionals should carefully assess the benefit–risk of using LIPIODOL ULTRA FLUID, as it may exacerbate the underlying lymphoedema

Renal

Iodinated contrast agents can induce a transient deterioration of renal function or exacerbation of persisting renal insufficiency. Acute renal failure, including fatal cases has been reported in patients following selective intra-arterial use of LIPIODOL ULTRA FLUID. Patients at risk of contrast media-induced nephrotoxicity include those with pre-existing renal impairment, diabetes mellitus, sepsis, hypotension, dehydration, cardiovascular disease, older age, multiple myeloma, hypertension, and hyperuricemia, children under one year of age and elderly patients with atheroma and co-administered nephrotoxic medications (see 9 Drug Interactions).

Prior to the intra-arterial administration, all patients should be screened for renal dysfunction by obtaining history and/or laboratory tests. Preventative measures in patients at risk include adequate hydration, avoidance of nephrotoxic medications, and temporary interruption of metformin to manage the risk of lactic acidosis triggered by dehydration in diabetic patients (see 9 Drug Interactions). Consider follow-up renal function assessments for patients with a history of renal dysfunction.

Respiratory

LIPIODOL ULTRA FLUID administration may aggravate symptoms of an existing asthma. In patients with uncontrolled asthma, LIPIODOL ULTRA FLUID should be used with caution, based on individual benefit-risk evaluation.

7.1. Special Populations

7.1.1. Pregnancy

There are no adequate and well-controlled studies of LIPIODOL ULTRA FLUID in pregnant women.

LIPIODOL ULTRA FLUID hysterosalpingography is contraindicated in pregnancy (see 2 Contraindications). Limited clinical data is available for LIPIODOL ULTRA FLUID during pregnancy for other procedures; however, administration of LIPIODOL ULTRA FLUID causes iodine transfer which may

interfere with the thyroid function of the fetus and result in brain damage and permanent hypothyroidism. LIPIODOL ULTRA FLUID must only be used in pregnancy if absolutely necessary.

Cumulatively to date (2017), twenty-two cases of drug exposure during pregnancy based on spontaneous reporting have been reported. In the vast majority of the overall 22 case reports (77%), the mother received LIPIODOL ULTRA FLUID for hysterosalpingography for infertility before getting pregnant (n=16) or accidentally at the very beginning of an unknown pregnancy (n=1). Among the 17 reports fetal drug exposure were reported in mothers received LIPIODOL ULTRA FLUID for hysterosalpingography, there were six case reports of fetal goiter, three cases of hypothyroidism in the neonate and one report each of missed abortion, abortion and premature delivery.

Neonates exposed to LIPIODOL ULTRA FLUID in utero should be tested for thyroid function and receive careful medical monitoring.

The occurrence of maternal hypothyroidism after hysterosalpingography procedure and the possible long half-life of the product in the event of a successful pregnancy requires a surveillance of fetal goiter and of the newborns thyroid function. Reports of fetal goiter occurring in mothers who received LIPIODOL ULTRA FLUID for hysterosalpingography included cases where conception occurred several months after the procedure.

7.1.2. Breastfeeding

LIPIODOL ULTRA FLUID is excreted in human milk. Iodine has been shown to pass into the vascular bed via the digestive tract of infants and could interfere with the thyroid function.

LIPIODOL ULTRA FLUID use should be avoided in a nursing woman because of risk of hypothyroidism in nursing infants. If breastfeeding is continued, the neonate's thyroid function should be monitored.

7.1.3. Pediatrics

Pediatrics (<18 years): See 4.2 Recommeded Dose or Dosage Adjustment

7.1.4. Geriatrics

There are no studies conducted in geriatric patients. Evidence from clinical experience suggests that use in elderly patients with cardiovascular, respiratory or nervous systems is associated with an increased risk of serious adverse reactions. LIPIODOL ULTRA FLUID must be administered with caution in these patients, based on individual benefit-risk evaluation.

8. Adverse Reactions

8.1. Adverse Reaction Overview

Several adverse effects are dose-related, and dosage should therefore be kept 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 subsequent connective tissue changes in the lymph nodes. 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 (see 2 Contraindications and 7 Warnings and Precautions, Hypersensitivity).

8.2. Clinical Trial Adverse Reactions

Clinical efficacy and safety evidence supporting LIPIODOL ULTRA FLUID indications are based on published literatures.

8.5. Post-Market Adverse Reactions

The following adverse reactions have been identified in the literature and based on spontaneous reporting in the post-market setting and are presented by MedDRA preferred term. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Table 1: Post-Market Adverse Reactions experience

System organ class	Adverse reaction
Endocrine disorders	hypothyroidism, hyperthyroidism, thyroiditis, goitre[b]
Eye disorders	retinal vein thrombosis
Gastrointestinal disorders	nausea, vomiting, diarrhoea, pancreatitis[a], ascites[a]
General disorders and administration site conditions	fever, pain, granuloma
Hepatobiliary disorders	hepatic vein thrombosis, cholecystitis[a], biloma[a], hepatic failure[a], hepatic infarction[a]
Infections and infestations	liver abscess[a]
Injury, poisoning and procedural complications	venous intravasation[b]
Immune disorders	hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Nervous system disorders	cerebral embolism, cerebral infarction, hepatic encephalopathy[a]
Respiratory, thoracic and mediastinal disorders	pulmonary embolism, dyspnea, cough, acute respiratory distress syndrome[a], pulmonary oedema[a], pleural effusion[a], pneumonitis[a]
Renal and urinary disorders	renal failure
Skin and subcutaneous tissue disorders	skin necrosis[a]

Vascular system disorders	lymphoedema aggravation

[a]: in the context of hepatic intra-arterial use for imaging tumors in patients with known HCC

[b]: in the context of hysterosalpingography

Serious adverse reactions are described in more detail in WARNINGS AND PRECAUTIONS section:

Adverse reactions specific to the condition of use are as follows:

Sialography

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

Hysterosalpingography

Abdominal pain, foreign body reactions, exacerbation of pelvic inflammatory disease.

Following maternal exposure with LIPIODOL ULTRA FLUID, fetal thyroid disorders including fetal 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.

Lymphography

Cardiovascular collapse, lymphangitis, thrombophlebitis, edema or exacerbation of pre-existing lymphedema, dyspnea and cough, fever, iodism (headache, soreness of mouth and pharynx, coryza and skin rash), allergic dermatitis, lipogranuloma, delayed healing at the site of incision.

Selective Hepatic Intra-arterial Injection

Fever, abdominal pain, nausea, vomiting and diarrhoea are the most common reactions; other reactions include blood glucose abnormalities, blood pressure increased, cholecystitis, carcinoid crisis, hepatic ischemia, liver enzymes abnormalities, transitory decrease in liver function, liver decompensation or failure, hepatic encephalopathy, biloma, hepatic abscess, bacteraemia, sepsis, renal insufficiency or failure, gastrointestinal bleeding due to ruptured varices or ulcer. Procedural risks include vascular complications, ascites and access site injuries and infections.

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 dyspnea, pulmonary oedema, pleural effusion, acute respiratory distress syndrome, and pneumonitis.

9. Drug Interactions

9.4. Drug-Drug Interactions

Beta blockers

Patients on beta blockers including ophthalmic beta blockers may be at risk of treatment-refractory anaphylaxis due to reduced response to adrenaline.

Other vasoactive substances that may potentially reduce the effectiveness of the sympathomimetic drugs and the beta-adrenergic effects of adrenaline include angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers.

It is important to be familiar with the practice of emergency measures so that prompt action may be taken in the event of hypersensitivity reactions. To permit immediate countermeasures to be taken in emergencies, appropriate drugs and instruments, e.g., endotracheal tube and ventilator, should be readily available.

Diuretics

In the event of dehydration provoked by diuretics, the risk of acute renal failure is increased, especially when high doses of iodinated contrast agents are used.
Patients should be received re-hydration before intra-arterial administration of LIPIODOL ULTRA FLUID.

Interleukin II

Interleukins are associated with an increased prevalence of delayed hypersensitivity/ anaphylactoid reactions after iodinated contrast agent administration. These reactions include flu-like symptoms, fever, chills, nausea, vomiting, pruritus, rash, diarrhea, hypotension, edema, oliguria, and joint pain.

Metformin

Lactic acidosis triggered by impaired renal function may be induced by intra-arterial administration of LIPIODOL ULTRA FLUID in diabetic patients. For patients scheduled to undergo examination, treatment with metformin must be suspended 48 hours before the investigation and only restarted 2 days after the radiological examination.

Nephrotoxic medications

Iodinated contrast agents can induce a transient deterioration of renal function or exacerbation of persisting renal insufficiency. Avoid combinations with nephrotoxic medicines (e.g., aminoglycosides, organoplatinum compounds, high doses of methotrexate, pentamidine, foscarnet and certain antiviral agents [e.g., aciclovir, ganciclovir, valaciclovir, adefovir, cidofovir, tenofovir], vancomycin, amphotericin B, immunosuppressants such as cyclosporine or tacrolimus, ifosfamide).

If such a combination is necessary, laboratory monitoring of renal function must be intensified.

9.7. Drug-Laboratory Test Interactions

Following LIPIODOL ULTRA FLUID administration, the product remains in the body for several months and may interfere with thyroid function testing for up to two years. LIPIODOL ULTRA FLUID interferes with radioactive iodine uptake by thyroid tissue for several weeks to months and may impair visualization of thyroid scintigraphy and reduce effectiveness of iodine 131 treatment.

10. Clinical Pharmacology

10.1. Mechanism of Action

LIPIODOL ULTRA FLUID is a radio-opaque, iodinated poppy seed oil-based contrast agent.

10.3. Pharmacokinetics

Following an injection administered through lymphatic vessels, LIPIODOL ULTRA FLUID is transported by the blood to the liver and lungs where the lipid droplets are broken down in the pulmonary alveoli, the spleen and adipose tissues. LIPIODOL ULTRA FLUID can be retained for several weeks or months following lymphography.

When given into the hepatic artery, LIPIODOL ULTRA FLUID has been found to remain selectively in the neovasculature and extravascular tissues of the HCC for several weeks to over a year, while it is cleared from normal liver parenchyma within a few days (7 days is commonly cited).

LIPIODOL ULTRA FLUID releases iodine which is eliminated by the urine in the form of iodide.

11. Storage, Stability, and Disposal

LIPIODOL ULTRA FLUID should be protected from light. Store at room temperature up to 30°C.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance(s): Ethyl esters of iodized fatty acids of poppy-seed oil

Chemical name: Ethyl esters of iodized fatty acids of poppy-seed oil (EEIFA). Ethiodized oil injection is an iodine addition product of the ethyl ester of the fatty acids of poppy-seed oil.

Structural formula: The drug substance is a mixture of ethyl esters of iodized and non-iodized fatty acids. The indicative proportions of the main compounds of this mixture are given in the table below.

Table 2: Indicative proportions of the main compounds of EEIFA Drug Substance

Name	Abbreviation	Molecular formula	Mw (g/mol)	%w/w
Ethyl palmitate	Ethyl C16:0	$C_{18}H_{36}O_2$	284	4.6 to 6.7
Ethyl stearate	Ethyl C18:0	$C_{20}H_{40}O_2$	312	0.8 to 1.9
Ethyl monoiodostearate	Ethyl C18:I:0	$C_{20}H_{39}IO_2$	438	11.3 to 15.3
Ethyl diiodostearate	Ethyl C18:I2:0	$C_{20}H_{38}I_2O_2$	564	73.5 to 82.8

Physicochemical properties: EEIFA is a pale yellow liquid. It's density at 20° C is 1.280. EEIFA is practically insoluble in water. One gram of EEIFA contains 0.38 g of iodine. One milliliter of EEIFA contains 0.48 g of iodine.

14. Clinical Trials

14.1. Clinical Trials by Indication

Selective hepatic intra-arterial use for imaging tumors in patients with known hepatocellular carcinoma (HCC)

Clinical efficacy evidence supporting LIPIODOL ULTRA FLUID for selective intra-arterial use for imaging tumors in adults with known hepatocellular carcinoma (HCC) is based on published literatures. Two studies were identified as pivotal, based on sensitivity and specificity results compared with other imaging modalities.

Lipiodol Computerized Tomography: How Sensitive and Specific is the Technique in the Diagnosis of Hepatocellular Carcinoma? (Ngan H, 1990)
This study was performed to analyze the pattern of uptake of Lipiodol in the liver on computed tomography (CT), to study the sensitivity and specificity of Lipiodol-CT (compared with angiography) and to evaluate if Lipiodol-CT can detect an HCC while it is still small and therefore improve respectability rate.

This was a single center, prospective, single arm study. Lipiodol-CT was performed in 60 patients with either persistently raised serum AFP levels above 20 ng/mL or abnormalities in ultrasound (US) of the liver. Data was collected over a 4 years period. The series included 53 men and 7 women with ages ranging from 16 to 78 years. Most of these patients were hepatitis-B surface antigen positive and were

closely followed up at 3-6 monthly intervals because of chronic active hepatitis, cirrhosis or a history of hepatic resection for HCC. A conventional hepatic angiogram was performed prior to Lipiodol-CT. Then 2-5 mL of Lipiodol was selectively infused into the common hepatic artery or into the celiac axis if selective catheterization of the common hepatic artery was not possible. CT of the upper abdomen was performed 6-13 days after the injection of Lipiodol. Information about image evaluation (blinded/unblinded; one reader/consensus reads) is not available. The true standard for diagnosis of HCC is composited of persisted high AFP, ultrasound and/or histology confirmation after hepatic resection.

HCC was present in 34 out of 60 patients. Lipiodol-CT had an overall sensitivity of 97.1%, an accuracy of 88.3% and a specificity of 76.9% in the diagnosis of HCC. A total of 33 HCCs were correctly diagnosed by Lipiodol-CT (true positive). There were, however, 6 false positives: 2 lesions turned out to be focal nodular hyperplasia, 2 hemangioma, 1 was a metastasis and 1 was a regenerative nodule. HCC was correctly excluded in 20 patients. Conventional hepatic angiography detected the HCCs with certainty in 25 patients (sensitivity, 73.6%). US was performed on 21 patients with HCCs and detected the tumors in only 10 patients (sensitivity, 47.6%).

Table 3: Summary of results of sensitivity and specificity

Imaging Modality	True Positive+ False Negative	True Positive	Sensitivity Estimate	True Negative + False Positive	True Negative	Specificity Estimate
Lipiodol-CT	34	33	97.06	26	20	76.92
US	21	10	47.62			
Angiography	34	25	73.53			

MRI of Small Hepatocellular Carcinoma: Comparison with US, CT, DSA, and Lipiodol-CT (De Santis M et al., 1992)

This study was conducted to compare the diagnostic value of magnetic resonance imaging (MRI) with that of US, pre- and post-contrast CT, digital subtraction angiography (DSA) and CT after injection of Lipiodol (Lipiodol-CT) in the diagnosis of small HCC (< 3 cm).

This was a single center, intra-individual comparative study. A total of 30 cirrhotic patients who developed HCC were examined and 13 patients (10 men and 3 women, 52-69 years old) who demonstrated the presence of at least one HCC nodule < 3 cm in size, were included in study. HCC was diagnosed by percutaneous tissue-core biopsy under US in 11 patients and by combined findings of various imaging techniques in the remaining two patients.

Real-time sonography was performed using a convex scanner (3.5 MHZ). MR was performed using 1.5 T system. Pre- and post-contrast CT were performed in 12 of 13 patients with Iopamiron (200-250 mL) administered intravenously for contrast-enhanced CT. DSA was performed and the contrast material (30 mL) for DSA was injected at the rate of 4-5 mL/s. Following angiography, 4-8 mL of Lipiodol was injected in the common hepatic artery (7 patients) and proper hepatic artery (6 patients). Lipiodol-CT was performed 1-2 weeks after DSA in all patients, except one patient who was examined on the same

day as DSA and 23 days later. A repeat Lipiodol-CT was performed in 4 patients 1-3 months after DSA and 2 of them were re-examined 6 months later. One patient was re-examined one month after DSA.

All the techniques employed (US, MR, CT, DSA, and Lipiodol-CT) enabled 27 small HCCs to be detected in the 13 patients. The detection rate (sensitivity) for HCC nodules was 63% by MR, 67% by US, 50% by CT, 74% by DSA and 93% by Lipiodol-CT.

Table 4: De Santis study - Detection Rates (Sensitivity) of Various Imaging Techniques for Small Hepatocellular Carcinomas

Technique	Number of Patients	Number of Tumors Detected	Total Tumors Examined	Sensitivity (%)
Lipiodol-CT	13	25	27	92.59
CT	12	12	24	50.00
MR	13	17	27	62.96
US	13	18	27	66.67
DSA	13	20	27	74.07

16. Non-Clinical Toxicology

General toxicology

Genotoxicity

A battery of in vitro and in vivo genotoxicity tests performed with Lipiodol proved to be negative:

- In vitro bacterial reverse mutation test performed on Salmonella Typhimurium strains TA1535, TA1537, TA98, TA102, and TA100 at tested concentrations up to 240 mg/plate, by both pre-incubation and plate-incorporation methods with or without metabolic activation,
- In vitro cytogenetic evaluation of chromosomal damages (L5178Y mouse lymphoma cells TK+/), conducted at concentrations up to 5000 µg/mL with or without metabolic activation
- In vivo chromosomal damage assay in bone marrow of rats (micronucleus test) by the intravenous route at 48, 240, and 479 mg/kg.

LIPIODOL ULTRA FLUID can be thus considered to be devoid of genotoxic potential.

Reproductive and developmental toxicology

There is no available data on potential effects of Lipiodol on fertility and reproductive performance.

Embryo-fetotoxic potential and teratogenic effects of Lipiodol Ultra Fluid have been evaluated in rats and rabbits after oral administration:

- Female rats were dosed daily with Lipiodol from gestation days 6 to 17 at doses of 50, 110, and 250 mg iodine/kg/day. The fetuses were removed on gestation day 20 by cesarean section.
- Female rabbits were dosed daily with Lipiodol from gestation days 6 to 18 at doses of 12.5, 25, and 50 mg iodine/kg/day (study 1), and every 3 days from gestation days 6 to 18 at a dose of

12.5 mg iodine/kg/day (study 2). The fetuses were removed on gestation day 29 by cesarean section.

In both species, mortality, clinical signs, food consumption, gestation body weight were regularly noted until the foetuses were removed by cesarean section. Gestation parameters were recorded (number of implantation, corporea lutea, pre/post implantation losses, fetal weight, sex ratio). An external examination of maternal organs and foetuses was conducted. Foetuses were examined for visceral and skeletal abnormalities

LIPIODOL ULTRA FLUID is neither embryofetotoxic nor teratogenic in rats and rabbits after oral administration.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

LIPIODOL® ULTRA FLUID

Ethiodized Oil Injection, House Std

This Patient Medication Information is written for the person who will be taking **LIPIODOL® ULTRA FLUID**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **LIPIODOL® ULTRA FLUID**, talk to a healthcare professional.

Serious Warnings and Precautions

LIPIODOL ULTRA FLUID is given by a doctor who knows how to treat life threatening reactions. Your doctor will watch your health before, during and after the exam. They know what safety measures to take. They are aware of the possible complications. They are experienced in doing X-ray tests. This drug is only used at sites with drugs, equipment and staff that can handle serious emergencies. They will monitor you for at least 30 minutes after the drug is given. Each patient must have an intravenous line open for use. LIPIODOL ULTRA FLUID should be given slowly with X-ray monitoring. The doctor should not exceed the recommended dose.

Serious or fatal events can occur when LIPIODOL ULTRA FLUID is used. They include:

- Blockage of certain blood vessels in the brain (**cerebral embolism**) or in the lung (**pulmonary embolism**)
- **Worsening chronic liver disease** which may last over a period of six months

What LIPIODOL ULTRA FLUID is used for:

It is a drug used in X-ray tests.

- Lymphography: to see lymphatic vessels and lymph nodes in adults and children
- Hysterosalpingography: to see the uterus and fallopian tubes in adult women.
- Sialography: to see the salivary glands in adults.
- Fistulography: to see fistulas, a kind of abnormal channel in the body, in adults.
- Selective hepatic intra-arterial use for imaging tumors in adults with known hepatocellular carcinoma (HCC): to see tumors in the liver, in adults.

How LIPIODOL ULTRA FLUID works:

LIPIODOL ULTRA FLUID helps tissue to appear darker or brighter depending on the test. This makes it

easier for the doctor to detect any abnormalities. Your doctor performs the test immediately after using LIPIODOL ULTRA FLUID. Your doctor may need to repeat the test after 24-48 hours.

The ingredients in LIPIODOL ULTRA FLUID are:

Medicinal ingredient(s): Ethyl esters of iodized fatty acids of poppy-seed oil.

Non-medicinal ingredients: None

LIPIODOL ULTRA FLUID comes in the following dosage form(s):

- a solution for injection
- supplied as 380 mg iodine/g (38% w/w), corresponding to 480 mg iodine/ mL
- packaged in a self-breaking 10 mL ampoule

Do not use LIPIODOL ULTRA FLUID if:

- you ever had an allergic reaction to Lipiodol Ultra Fluid or to any other iodine product. This can also be called **Allergic Disorders**
- you have **hyperthyroidism,**
- you have traumatic injuries or recent bleeding,
- you have **acute parotiditis** (swelling of the salivary gland) and are imaging salivary glands,
- you are undergoing **bronchography.** This is a type of X-ray exam of the lung,
- you are pregnant or have disease, infection, bleeding or recent surgical procedures of the genital organs. This applies if you need to have an exam of the uterus and fallopian tubes (hysterosalpingography),
- you suffer from heart or lung disease; you have a tumor, recent surgery or radiation therapy that blocks lymph nodes. This applies if you will receive **lymphography**.
- you have a liver disease and you have blocked bile ducts, unless a drainage tube is in place before the test; you have advanced liver failure or cancer in veins of the liver; or you have cancer spread from the liver. These apply if you will receive Lipiodol Ultra Fluid in your liver.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LIPIDOL ULTRA FLUID. Talk about any health conditions or problems you may have, including if you:

- you suffer or have suffered from an allergy (eg, hay fever, hives) or asthma,
- you suffer from lung or cardiac diseases,
- you have an over-active thyroid,
- you have diabetes,
- you have uterine bleeding and infection,
- you have pelvic inflammation,
- you are pregnant or planning to get pregnant. LIPIODOL ULTRA- FLUID can result in brain damage and permanent hypothyroidism (overactive thyroid gland)in the baby. Your healthcare

professional may monitor you or your baby for signs of hyperthyroidism and goitre (Swelling of the thyroid gland) for some time after you are given LIPIODOL ULTRA- FLUID,
- you are breastfeeding. LIPIODOL ULTRA- FLUID can pass through breast milk. It can result in hypothyroidism in the baby,
- you are in the a few days before or immediately after your monthly period,
- you have a disease of the kidney,
- you suffer from an accumulation of fluid in your body,
- you plan to have an examination of the thyroid,
- you are over 65 years old,
- you have problems with swelling in your lymph nodes.

Other warnings you should know about:

- A decrease in how well your kidneys work
- Existing kidney problems to get worse
- An increase in thyroid gland volume (goitre)
- Liver damage which can make your liver not work properly. This can cause side effects such as accumulation of fluid in the abdomen (ascites), not enough blood supply in the liver (hepatic infarction), changes in the level of consciousness possibly associated with other neurological symptoms (hepatic encephalopathy),
- An inflammation of the Fallopian tubes or of the peritoneum (lining of the stomach and pelvis),
- A temporary fever following hysterosalpingography (X-ray test to see the uterus and fallopian tubes) , with pain in the pelvic area is often noted as well as the possibility of salpingitis (inflammation of fallopian tubes) or pelvioperitonitis (inflammation of peritonium) if there is a latent state of infection,
- Small amounts of LIPIODOL ULTRA FLUID may enter into the blood supply and end up in other parts of the body such as blood vessels or arteries. This can cause serious reactions such as pulmonary, cerebral, and skin embolisms (Please see symptoms of these side effects in the Serious side effects and what to do about them table below). Your healthcare professional may monitor your symptoms after your X-ray test.

It can also cause:

1. Thyroid dysfunction
    - Hyperthyroidism: an over-active thyroid gland
    - Hypothyroidism: an under-active thyroid gland
    - Thyroiditis: inflammation of the thyroid gland

2. Allergic Disorders including hypersensitivity, anaphylactic or anaphylactoid reactions
   These are uncommon and can be mild to severe including death. Most allergic disorders occur within 30 minutes. Reactions can also occur for up to several days. Your doctor should discuss symptoms of delayed allergic reactions with you.

3. Cerebral Embolism and Blockages to Other Organs
   Blockage of certain blood vessels in the brain

4. Pulmonary Embolism

Blockage of certain blood vessels in the lung. It usually occurs right away but can be delayed for hours to days. It may result in excess fluid accumulation in and around the lung, critical respiratory failure, inflammation of the lungs.

5. Worsening Chronic Liver Disease
   Disease of the liver which lasts over a period of six months. It can cause heart problems, infection, irreversible liver damage and death.

6. Lymphoedema Aggravation

An accumulation of fluid in a body part. It is caused by a block of the lymph flow

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LIPIODOL ULTRA FLUID:

- beta-blockers, diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers: these are drugs to treat eye disease, heart disease or high blood pressure,
- interleukin II drugs: These are drugs to treat cancer or to reinforce your immune system, i.e. your internal defence system,
- metformin: Drugs to treat diabetes. Your doctor should stop this drug 48 hours before the exam. It can be restarted 2 days after the exam,
- drugs that may cause damage to the kidney.

How to take LIPIODOL ULTRA FLUID:

Your doctor will prepare and inject this product before the exam. The route and method of injection depend on the reason the drug is being used.

Usual dose:
These depend on the reasons why LIPIODOL ULTRA FLUID is being used.
Your doctor will determine the dose to inject.

Overdose:

If you think you, or a person you are caring for, have taken too much LIPIODOL ULTRA FLUID, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using LIPIODOL ULTRA FLUID:

These are not all the possible side effects you may have when taking LIPIODOL ULTRA FLUID. If you experience any side effects not listed here, tell your healthcare professional.

Side effects can include:

- Shortness of breath and cough
- Injection site pain and redness
- LIPIODOL ULTRA FLUID can cause abnormal blood test results. Your doctor will decide when to preform blood tests and will interpret the results.
- LIPIODOL ULTRA FLUID may interfere with thyroid diagnostic tests. It can cause changes to how the thyroid gland works. You may need to have a blood test to check the thyroid gland before using it. Thyroid blood test results can be affected for up to two years after taking LIPIODOL ULTRA FLUID.

Serious side effects and what to do about them

Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Thyroid Dysfunction: **<u>Hypothyroidism:</u>** fatigue,increased sensitivity to cold, constipation, dry skin, weight gain, puffy face, hoarseness, muscle weakness, slowed heart rate, depression, impaired memory **<u>Hyperthyroidism:</u>** difficulty concentrating, frequent bowel movements, goiter (visibly enlarged thyroid gland) or thyroid nodules, hair loss, hand tremor, heat intolerance, increased sweating, nervousness, weight loss, high blood pressure, bulging eyes **<u>Thyroiditis:</u>** feeling of fullness or pain in the neck, other symptoms similar to those of hypothyroidism or hyperthyroidism		✓	
Nausea, vomiting, diarrhoea, inflammation of the pancreas and gallbladder causing abdominal pain and fever, accumulation of bile in the abdomen (biloma) causing abdominal pain		✓	
Fever, general pain throughout your body and/or pain in the pelvis (lower abdomen)		✓	

Granuloma: pain or tenderness in the lower abdominal area, vaginal infection		✓	
Hepatic vein thrombosis: vomiting blood, black stools, enlarged spleen, swelling of lower limbs, abdominal pain (mainly in the upper right part of the abdomen), jaundice (yellowing of the skin and eyes).		✓	
Allergic Disorder: rash or hives, flushing, pimples, itching and/or sudden swelling of the face, eyelids, lips, tongue or throat. Difficulty breathing or swallowing, wheezing, plugged nose, sneezing, coughing, dry throat, fever, chills, nausea, vomiting, diarrhoea, low blood pressure, and joint pain. Decreased urine output.		✓	
Cerebral Embolism and Blockages to Other Organs: severe headache, blurred vision, fainting, loss of consciousness, drowsiness, convulsion, confusion.		✓	
Pulmonary Embolism: shortness of breath, fast or difficult breathing, cough.		✓	
Lymphoedema Aggravation: swelling, heaviness, fullness and aching of body parts. Full or heavy sensation in the limb(s), tightness of the skin or tissue, decreased flexibility in the hand/wrist/foot/ankle, difficulty fitting into clothing in one specific area, or ring/wristwatch/bracelet tightness		✓	
Worsening Chronic Liver Disease: fever, chills, swollen or painful abdomen. Jaundice with yellow color to skin, eyes and dark urine, pus-filled mass inside the liver. Increased blood pressure, headache and dizziness.		✓	

Retinal Vein Thrombosis (Blood clot in the eye): sudden loss of all or part of your vision or double vision.		✓	
Salivary Duct Inflammation: Abnormal or foul tastes, decreased ability to open the mouth, dry mouth, fever, mouth or facial pain, especially when eating, swelling of the face		✓	
Decreased kidney Function: Fatigue, lethargy, weakness, swelling, shortness of breath and confusion		✓	
Worsening existing asthma: Cough, wheezing, shortness of breath, chest pain or pressure		✓	
Skin damage (necrosis)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Protect from light. Store at room temperature up to 30°C.

Keep out of reach and sight of children.

If you want more information about LIPIODOL ULTRA FLUID:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the importer's website www.methapharm.com; or by calling 1-800-287-7686 ext. 7804.

This leaflet was prepared by Guerbet.

Date of Revision: 2026-03-12