Guerbet

November 3, 2017

Dear Healthcare Professional,

Guerbet LLC

821 Alexander Rd - Suite 204
Princeton, NJ 08540
Tel: 812-333-0059
Fax: 609-919-0495
www.guerbet-us.com

Due to recent manufacturing issues we would like to inform you of a critical shortage of **LIPIODOL® (ETHIODIZED OIL) INJECTION.** Guerbet is coordinating with the U.S. Food and Drug Administration (FDA) to increase the availability of **LIPIODOL® (ETHIODIZED OIL) INJECTION** for patients in the United States.

During this interim period, Guerbet is initiating a temporary importation of **LIPIODOL® ULTRA-FLUIDE**, ethyl esters of iodized fatty acids of poppy seed oil, Lot # 17LU607A to the United States market. **LIPIODOL® ULTRA-FLUIDE** contains the same drug components as **LIPIODOL® (ETHIODIZED OIL) INJECTION** (manufactured by Jubilant HollisterStier, Canada). **LIPIODOL® ULTRA-FLUIDE** is manufactured in compliance with European Good Manufacturing Practice (GMP) regulations by Delpharm Tours (France) for Guerbet. Delpharm Tours's manufacturing facility is FDA inspected. The FDA has not approved this product in the United States.

At this time, no other entity except Guerbet is authorized by the FDA to import or distribute **LIPIODOL® ULTRA-FLUIDE**.

Effective immediately, and during this temporary period, Guerbet will offer the following version:

LIPIODOL® ULTRA-FLUIDE **48% Iodine w/vol (i.e 480 mg Iodine/mL)** (ethyl esters of iodized fatty acids of poppy seed oil)	
10mL glass ampoule	Authorization #3400930621608 Box of 1 ampoule

LIPIODOL® ULTRA-FLUIDE formulation is the same as LIPIODOL (Ethiodized Oil) Injection®.

The active substance of LIPIODOL® ULTRA-FLUIDE and LIPIODOL (ETHIODIZED OIL) INJECTION is the same (ethyl esters of iodized fatty acids of poppy seed oil, stabilized with 1% of poppy seed oil).

The barcode used on **LIPIODOL® ULTRA-FLUIDE** is an international pharmaceutical manufacturing code and will likely not be recognized by scanning systems used in the United States. Institutions should confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

For questions regarding **LIPIODOL® ULTRA-FLUIDE** in the United States, please contact Guerbet LLC at 1-877-729-6679 between the hours of 8 a.m. and 5 p.m. (ET), or email at info-us@guerbet.com.

Please click here for prescribing information: **LIPIODOL® ULTRA-FLUIDE Prescribing Information** and **LIPIODOL® (ETHIODIZED OIL) INJECTION Prescribing Information.**

Guerbet

The product comparison table below also highlights the differences between **LIPIODOL® ULTRA-FLUIDE** and **LIPIODOL® (ETHIODIZED OIL) INJECTION**.

Prescribing physicians are advised to refer to the package insert for the FDA-approved product for full prescribing information, including a Boxed Warning for risk of pulmonary and cerebral embolism, which can result from inadvertent intravascular injection or intravasation of Lipiodol, and Instructions for Use available at http://www.guerbet-us.com/products/lipiodol.html or

- **Customers can order directly from Guerbet LLC by contacting Customer Service at 1-877-729-6679, between the hours of 8 a.m. and 5 p.m. (ET).**
- **LIPIODOL® ULTRA-FLUIDE is not refundable and not for resale.**

Guerbet will make reasonable attempts to fill your orders. Guerbet will be closely monitoring the distribution of **LIPIODOL® ULTRA-FLUIDE** to help manage the supply.

If you have additional questions, please contact Customer Service at 1-877-729-6679, Monday through Friday, between the hours of 8 a.m. and 5 p.m. (ET), or email customer.service-us@guerbet.com. This communication and updated product information is available on the Guerbet website at http://www.guerbet-us.com as well as on the FDA Drug Shortage website at http://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm.

To report adverse events among patients administered, please call 1-877-729-6679 between the hours of 8 a.m. and 5 p.m. (ET), or email medical.liaison@guerbet.com.

Adverse events or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting Program either online, or regular mail, or by fax:

- Complete and submit the report **Online**: www.fda.gov/medwatch/report.htm
- Regular mail or Fax: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

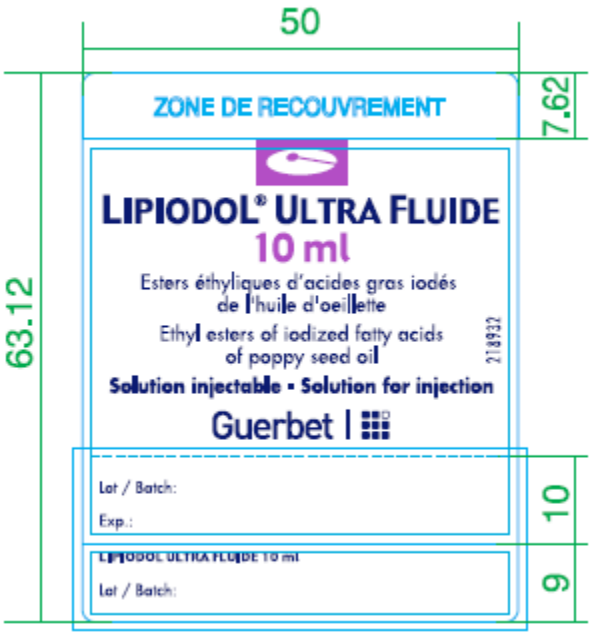
We urge you to contact our Medical Information Department at 1-877-729-6679 between the hours of 8 a.m. and 5 p.m. (ET), or email medical.liaison@guerbet.com if you have any questions about the information contained in this letter or the safe and effective use of **LIPIODOL® ULTRA-FLUIDE.**

Sincerely,

Alice Lorenzo

Alice Lorenzo, MJ, MBe, RAC
Compliance Officer, Head of North American Regulatory and Quality

Comparison Table

LIPIODOL® ULTRA-FLUIDE ampoule label	LIPIODOL® (ETHIODIZED OIL) Injection ampoule label
	
LIPIODOL® ULTRA-FLUIDE carton label	**LIPIODOL® (ETHIODIZED OIL) Injection carton label**
	

LIPIODOL® ULTRA-FLUIDE (ethyl esters of iodized fatty acids of poppy seed oil)	**LIPIODOL® (ETHIODIZED OIL) INJECTION** (ethyl esters of fatty acids of poppy seed oil)
Indications and contraindications	
See Summary of Product Characteristics (SmPC) **Please note: see SmPC sections 4.1 Therapeutic indications, 4.2 Posology and method of administration, 4.3 Contraindications, and 4.4 Special warning and precautions for use.**	**LIPIODOL®** is an oil-based radio-opaque contrast agent indicated for: • hysterosalpingography in adults • lymphography in adult and pediatric patients • selective hepatic intra-arterial use for imaging tumors in adults with known hepatocellular carcinoma (HCC) **LIPIODOL®** is contraindicated in patients with hypersensitivity to Lipiodol, hyperthyroidism, traumatic injuries, recent hemorrhage or bleeding. **Hysterosalpingography** Lipiodol hysterosalpingography is 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. **Lymphography** Lipiodol Lymphography is 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, radiation therapy to the examined area. **Selective Hepatic Intra-arterial Use Patients with HCC** Lipiodol use is contraindicated in areas of the liver where the bile ducts are dilated unless external biliary drainage was performed before injection.
Barcode	
Barcode use by **LIPIODOL® ULTRA-FLUIDE** may not register accurately in the United States scanning systems. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.	A unit of use barcode is on individual ampoules.
How supplied	
Box of 1 ampoule Authorization# 34009 306 216 0 8: 10 mL glass ampoule, single-unit box	Lipiodol is supplied in a box of one 10 mL ampoule, NDC 67684-1901-1.
Additional information	
Contains a patient information leaflet	N/A

PACKAGE LEAFLET: INFORMATION FOR THE PATIENT

LIPIODOL ULTRA-FLUID (480 mgI/ml), solution for injection

Ethyl esters of iodized fatty acids of poppy seed oil

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions or doubts, ask your doctor or pharmacist for more information.
- This medicinal product was prescribed specifically for you. Do not pass it on to others. It may harm them, even if the signs of illness are the same as yours.
- If any of the side effects becomes serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

In this leaflet:

1. WHAT LIPIODOL ULTRA-FLUID IS AND WHAT IT IS USED FOR

What Lipiodol Ultra-Fluid is

Lipiodol Ultra-Fluid belongs to the class of iodinated contrast agents. Lipiodol Ultra-Fluid enhances the contrast of images obtained during these examinations, which improves the visualisation and delineation of the contours of certain parts of the body.

When it is used

This medicinal product is used:
- During radiological examinations.
- During surgery.
- To prevent disorders related to iodine deficiency when iodinated salt or supplemented drinking water cannot be used.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE LIPIODOL ULTRA-FLUID

Do not use Lipiodol Ultra-Fluid

- If you are allergic to the active substance (ethyl esters of iodized fatty acids of poppy seed oil).
- During radiological examinations, you must not receive an injection of this medicinal product:
  - if you have elevated serum levels of thyroid hormones (hyperthyroidism),
  - if you have or recently have had wounds with significant bleeding,
  - if you are scheduled for bronchography (radiological examination of the bronchia during which the contrast agent is administered directly to the lungs).
- During surgery, this medicinal product must not be injected if you have a blood clot in a liver vein.
- If you have iodine deficiency, you must not take this medicinal product:
  - if you have elevated serum levels of thyroid hormones (hyperthyroidism),
  - if you have a swollen neck due to a thyroid disorder (large multinodular goiter) and are over 45 years of age,
  - if you are breastfeeding.

This medicinal product must not be injected into large arteries, veins or the vertebral column.

Warnings and precautions

Talk to your doctor before using Lipiodol Ultra-Fluid if:
- You have, or have had, an allergic disorder such as:
  - allergy to this medicinal product that occurred in particular during previous radiological examinations,
  - allergy to iodine,
  - any other kind of allergy (dietary or medicinal),
  - hives,
  - red patches that itch (eczema),
  - asthma,
  - hay fever.
- You have heart or lung disease (heart or respiratory failure, cardiac malformation).
- You have kidney disease (renal failure).
- You are diabetic.
- You have high levels of blood cholesterol (hypercholesterolaemia).
- You are currently under treatment or have recently been treated for cancer with medicines (chemotherapy) and/or with radiation (radiotherapy).
- You have a thyroid disorder.
- You are scheduled for a thyroid examination or treatment with radioactive iodine.

If you are being treated for iodine deficiency:
- You must not use other products containing iodine (iodized salt or drinking water containing iodine). This could increase the risk of overloading your thyroid.

You should avoid using this medicinal product if you are over 45 years of age.

Other medicines and Lipiodol Ultra-Fluid

Tell your doctor if you are taking, have recently taken or might take:
- A medicine to treat heart disease or high blood pressure (beta-blockers, diuretics).
- A medicine to treat diabetes (metformin).
- Interleukin-2, a medicine to treat cancer or reinforce the immune system.

If you are taking or have recently taken any other medicines, including those that do not require a medical prescription, inform your doctor or pharmacist.

Lipiodol Ultra-Fluid with food and drink

Reactions between Lipiodol Ultra-Fluid and food or drink have not been reported. However, you should ask your doctor if you should not eat or drink before receiving this medicinal product.

Pregnancy

Ask your doctor or pharmacist for advice before taking any medicine.
If necessary, your doctor may prescribe iodine during pregnancy.

Breastfeeding

Ask your doctor or pharmacist for advice before taking any medicine.
You should stop breastfeeding if you have to take this medicinal product.

Driving and using machines

Lipiodol Ultra-Fluid should not affect your ability to drive or use machines. However, if you do not feel well after taking this medicinal product, you should not drive or use machines.

3. HOW TO USE LIPIODOL ULTRA-FLUID

Dose

The dose depends on the reason for which it is being used.
Your doctor will determine the dose to be injected.

Route and method of administration

A health professional will prepare and inject this product before carrying out the examination.
The route and method of injection depend on the reason for which the medicinal product is being administered.

Duration of treatment

This medicine is administered only once.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Lipiodol Ultra-Fluid may cause side effects, although not everybody gets them.

Allergic reactions may occur. They are indicated by the following signs:

Flushing, pimples, itching and/or sudden swelling of the face, eyelids, lips or throat that may result in difficulties in breathing or swallowing. Other possible signs of an allergic reaction are: wheezing, plugged nose, sneezing, coughing, dry throat, hives.
In exceptional cases, the reaction may be serious. If any of these signs occur, you should immediately contact your doctor.

Other possible side effects are:

- High fever in the hours following the examination.
- Gastrointestinal disorders such as nausea, vomiting, diarrhoea.
- Signs of an overactive thyroid such as weight loss, faster heartbeat and intestinal transit, nervousness and insomnia.
- Pains.
- Blockage of certain blood vessels in the lungs or brain.

If you get any side effects, talk to your doctor or pharmacist. This includes any possible effects not listed in this leaflet.

5. HOW TO STORE LIPIODOL ULTRA-FLUID

Keep this medicine out of the sight and reach of children.
Do not use Lipiodol Ultra-Fluid after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Store protected from light.
Do not throw away medicinal products via wastewater or with household waste.
Ask your pharmacist how to throw away medicinal products you no longer use. These measures will help protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Lipiodol Ultra-Fluid contains

The active substance is: ethyl esters of iodized fatty acids of poppyseed oil (iodine content: 48%, i.e. 480 mg/mL).
Lipiodol Ultra-Fluid does not contain any other ingredients than the active substance.

What Lipiodol Ultra-Fluid looks like and contents of the pack

This medicinal product is a solution for injection in 5 or 10 ml ampoules.

MA holder / Distributor / Manufacturer

Guerbet
BP 57400
95943 ROISSY CDG Cedex
France

This leaflet was last revised in January 2013.
Detailed information on this medicinal product is available on the ANSM website (France).

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY

Take special care with Lipiodol Ultra-Fluid

An early polymerization reaction may exceptionally occur between Lipiodol Ultra-Fluid and certain surgical glues, or even certain batches of glue. Before using new batches of Lipiodol Ultra-Fluid or surgical glue, the compatibility of Lipiodol Ultra-Fluid and the glue must be tested in vitro.

Method and route of administration

This product must be administered using a glass syringe.

In diagnostic radiology:
Lymphography:
STRICT INTRALYMPHATIC USE

Diagnosis of hepatic lesions:
STRICT SELECTIVE INTRA-ARTERIAL USE

In interventional radiology:
Embolization with surgical glues
STRICT SELECTIVE INTRA-ARTERIAL USE

In iodine deficiency:
STRICT INTRAMUSCULAR USE

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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LIPIODOL ULTRA-FLUID (480 mg I/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

One 5 mL ampoule contains ..... 2400 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

- Lymphography
- Diagnosis of liver lesions

Diagnosis of the spread of malignant lesions, whether hepatic or not, by selective hepatic arterial injection.

In interventional radiology

- Visualisation, localisation and vectorisation during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma at intermediate stage, in adults.
- Embolization with surgical glues

In association with surgical glues during vascular embolizations.

In endocrinology

The use of Lipiodol in prevention of iodine deficiency disorders should exclusively be reserved to countries in which other methods of supplementation, particularly iodization of salt and/or drinking water, cannot be undertaken.

4.2. Posology and method of administration

LIPIODOL ULTRA-FLUID must be administered by slow injection or by catheter, using an appropriate glass syringe and a catheter (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 subject), 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.

- Diagnosis of hepatic lesions

Strict intra-arterial route.

The usual dose varies depending on the size of the lesions, ranging from 2 to 10 mL per patient. LIPIODOL ULTRA-FLUID is sometimes mixed with small quantities of water-soluble iodinated contrast agents. Imaging must be carried out 7 to 15 days after selective injection to allow LIPIODOL ULTRA-FLUID to be eliminated from the non-tumoural liver.

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:

- Trans-Arterial Chemo-Embolisation 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 Trans-Arterial Chemo-Embolisation 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.

- Embolisation with surgical glues

Exclusive selective arterial catheterization.

The dose of LIPIODOL ULTRA-FLUID per embolisation session is determined depending on the size of the lesions. The proportion of LIPIODOL ULTRA-FLUID versus the liquid embolising agent can vary from 20 to 80% but is usually a 50/50 mixture.

The injection volume must not exceed 15 mL.

In endocrinology:

Strict intramuscular route.

- Adults and children over 4 years of age: 1 mL every three years.
- Children under 4 years of age : 0.5 mL every two years without exceeding 3 mL.

In patients with thyroid nodules, the dose is 0.2 mL.

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.

- Embolisation with surgical glues

There are no particular contraindications apart from those of embolization, particularly in patients with portal vein thrombosis.

Contraindications specific to the use in endocrinology:

- Large multinodular goiter in patients over 45 years of age, because of the high risk of hyperthyroidism,
- During breastfeeding.

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.

4.4.1 Warnings

4.4.1.1. 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.

4.4.1.2. 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.

4.4.1.3. 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.

4.4.1.4. Trans-Arterial Chemo-Embolisation

Trans-Arterial Chemo-Embolisation 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 Trans-Arterial Chemo-Embolisation procedure.

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

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

4.4.1.5. Embolisation with surgical glues

An early polymerisation reaction may exceptionally occur between LIPIODOL ULTRA-FLUID and certain surgical glues, or even certain batches of glue. Before using new batches of LIPIODOL ULTRA-FLUID or surgical glue, the compatibility of LIPIODOL ULTRA-FLUID and the glue must be tested *in vitro*.

4.4.2 Precautions for use

4.4.2.1. 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).

4.4.2.2. 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.

4.4.2.3. Trans-Arterial Chemo-Embolisation / 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 Trans-Arterial Chemo-Embolisation procedure.

4.4.2.4. 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 medicinal products 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 Trans-Arterial Chemo-Embolisation, metformin must be discontinued 48 hours before the procedure and resumed no earlier than two days after the procedure.

Combinations requiring caution

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

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.

- Diagnosis of hepatic lesions

A temperature increase is often observed. Other more rare complications may occur, i.e. nausea, vomiting and diarrhoea.

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.

- Embolisation with surgical glues

Specific adverse reactions directly related to LIPIODOL ULTRA-FLUID have not been reported.

- In endocrinology:

Hyperthyroidism (see Section 4.4).

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	Undetermined frequency: hyperthyroidism.
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 via the national declaration system - Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) and Regional Centers of Pharmacovigilance network – Web site: www.ansm.sante.fr

4.9. Overdose

Overdose can cause respiratory, cardiac or cerebral complications, which can be fatal. The frequency of micro-embolisms may be increased after an 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

(V: Other)

Used in Trans-Arterial Chemo-Embolisation 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, Trans-Arterial Chemo-Embolisation 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 intramuscular injection

A portion of the oil accumulates in the muscle and adjacent tissues. Another portion is deiodinated via the metabolic route, the iodine being used to compensate for the iodine losses of the thyroid.

Urinary iodine excretion is massive and occurs rapidly (within the first few hours after the injection) but continues over the following months.

Urinary iodine excretion falls to 50 µg/day in adults within 3 to 5 years.

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 Trans-Arterial Chemo-Embolisation 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

Plastic is not suitable for the storage of LIPIODOL ULTRA-FLUID. In the absence of any specific compatibility studies, plastic containers and syringes should not be used.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store protected from light.

6.5. Nature and contents of container

5 or 10 mL glass (type 1) ampoules.

All pack sizes may not be marketed.

6.6. Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Guerbet

BP 57400

F-95943 Roissy CdG cedex

FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 306 217-7 or 34009 306 217 7 6: 5 mL glass ampoule, 4-unit box
- 306 216-0 or 34009 306 216 0 8: 10 mL glass ampoule, single-unit box
- 560 350-7 or 34009 560 350 7 6: 5 mL glass ampoule, 100-unit box
- 560.351-3 or 34009 560 351 3 7: 10 mL glass ampoule, 50-unit box

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

28 March 1978 / 30 September 2007.

10. DATE OF REVISION OF THE TEXT

August 2014.

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR THE PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I

Medicinal product subject to medical prescription

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LIPIODOL safely and effectively. See full prescribing information for LIPIODOL.

LIPIODOL® (Ethiodized Oil) Injection

Initial U.S. Approval: 1954

WARNING: FOR INTRALYMPHATIC, INTRAUTERINE AND SELECTIVE HEPATIC INTRA-ARTERIAL USE ONLY

See Full Prescribing Information for complete Boxed Warning

Pulmonary and cerebral embolism can result from inadvertent intravascular injection or intravasation of Lipiodol. Inject Lipiodol slowly with radiologic monitoring; do not exceed recommended dose (5.1).

RECENT MAJOR CHANGES

Indications and Usage (1)	4/2014
Dosage and Administration, Dosage Guidelines (2.1)	4/2014
Contraindications (4)	4/2014
Warnings and Precautions (5)	4/2014

INDICATIONS AND USAGE

Lipiodol is an oil-based radiopaque contrast agent indicated for:
- hysterosalpingography in adults
- lymphography in adult and pediatric patients
- selective hepatic intra-arterial use for imaging tumors in adults with known hepatocellular carcinoma (HCC) (1)

DOSAGE AND ADMINISTRATION

Use a glass syringe to draw and inject Lipiodol. (2)

• Hysterosalpingography

Inject increments of 2 mL of Lipiodol into the endometrial cavity until tubal patency is determined; stop the injection if the patient develops excessive discomfort. Inject with radiologic monitoring.

• Lymphography

Inject Lipiodol into a lymphatic vessel with radiologic monitoring.

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

Pediatric patients:
- Inject a 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.

• Selective Hepatic Intra-arterial Use

Inject 1.5 to 15 mL of Lipiodol slowly under continuous radiologic monitoring. Do not exceed 20 mL total dosage.

DOSAGE FORMS AND STRENGTHS

Each mL of Lipiodol contains 480 mg Iodine organically combined with ethyl esters of fatty acids of poppy seed oil. (3)

CONTRAINDICATIONS

Hypersensitivity to Lipiodol, hyperthyroidism, traumatic injuries, recent hemorrhage or bleeding. (4)
- **Lipiodol Hysterosalpingography is 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 Lymphography is contraindicated in:** 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.
- **Lipiodol Selective Hepatic Intra-arterial Injection is contraindicated in:** the presence of dilated bile ducts unless external biliary drainage was performed before injection.

WARNINGS AND PRECAUTIONS

- Pulmonary and cerebral embolism: avoid use in patients with severely impaired lung function, cardiorespiratory failure or right-sided cardiac overload (5.1)
- Hypersensitivity reactions: avoid use in patients with a history of sensitivity to other iodinated contrast agents, bronchial asthma or allergic disorders because of an increased risk of a hypersensitivity reaction to Lipiodol (5.2)
- Exacerbation of chronic liver disease (5.3)
- Thyroid dysfunction (5.4)

ADVERSE REACTIONS

Adverse reactions caused by Lipiodol include hypersensitivity reactions, pulmonary embolism, pulmonary dysfunction, exacerbation of liver disease, procedural complications, abdominal pain, fever, nausea, vomiting, and thyroid dysfunction. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GUERBET LLC at 1-877-729-6679 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Revised: 5/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.**

FULL PRESCRIBING INFORMATION

WARNING: FOR INTRALYMPHATIC, INTRAUTERINE AND SELECTIVE HEPATIC INTRA-ARTERIAL USE ONLY

Pulmonary and cerebral embolism can result from inadvertent intravascular injection or intravasation of Lipiodol. Inject Lipiodol slowly with radiologic monitoring; do not exceed recommended dose (5.1).

1 INDICATIONS AND USAGE

Lipiodol is an oil-based radio-opaque contrast agent indicated for:
- hysterosalpingography in adults
- lymphography in adult and pediatric patients
- selective hepatic intra-arterial use for imaging tumors in adults with known hepatocellular carcinoma (HCC)

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Guidelines

Draw Lipiodol into a glass syringe.

Use the smallest possible amount of Lipiodol according to the anatomical area to be visualized.

Hysterosalpingography

Using aseptic technique inject Lipiodol into the endometrial cavity with fluoroscopic control. Inject increments of 2 mL of Lipiodol until tubal patency is determined; stop the injection if patient develops excessive discomfort. Re-image after 24 hours to establish whether Lipiodol has entered the peritoneal cavity.

Before using Lipiodol exclude the presence of these conditions: pregnancy, uterine bleeding and endocervicitis, acute pelvic inflammatory disease, the immediate pre-or postmenstrual phase or within 30 days of curettage or conization.

Lymphography

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

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

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

Selective Hepatic Intra-arterial Injection

Determine the dose depending on the tumor size, local blood flow in the liver and in the tumor(s).
- Inject from 1.5 to 15 mL slowly under continuous radiologic monitoring. Stop the injection when stagnation or reflux is evident. Limit the dose to only the quantity required for adequate visualization. The total dose of Lipiodol administered should not exceed 20 mL.

2.2 Drug Handling

Inspect Lipiodol 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 is a clear, pale yellow to amber colored oil; do not use if the color has darkened.

Draw Lipiodol into a glass syringe and use promptly. Discard any unused portion of Lipiodol.

3 DOSAGE FORMS AND STRENGTHS

Each milliliter of Lipiodol contains 480 mg/mL of Iodine organically combined with ethyl esters of fatty acids of poppy seed oil.

4 CONTRAINDICATIONS

Lipiodol is contraindicated in patients with hypersensitivity to Lipiodol, hyperthyroidism, traumatic injuries, recent hemorrhage or bleeding.

Hysterosalpingography

Lipiodol hysterosalpingography is 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.

Lymphography

Lipiodol Lymphography is 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, radiation therapy to the examined area.

Selective Hepatic Intra-arterial Use Patients with HCC

Lipiodol use is contraindicated in areas of the liver where the bile ducts are dilated unless external biliary drainage was performed before injection.

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary and Cerebral Embolism

Pulmonary embolism may occur immediately or after a few hours to days from inadvertent systemic vascular injection or intravasation of Lipiodol and cause decreased pulmonary diffusing capacity and pulmonary blood flow, pulmonary infarction, acute respiratory distress syndrome and fatalities. Embolization of Lipiodol to brain and other major organs may occur. Avoid use of Lipiodol in patients with severely impaired lung function, cardiorespiratory failure, or right–sided cardiac overload. Perform radiological monitoring during the Lipiodol injection. Do not exceed the recommended maximum dose and rate of injection of Lipiodol. During lymphography to minimize the risk of pulmonary embolism obtain radiographic confirmation of intralymphatic (rather than venous) injection, and terminate the procedure when Lipiodol becomes visible in the thoracic duct or lymphatic obstruction is observed.

5.2 Hypersensitivity Reactions

Anaphylactoid and anaphylactic reactions with cardiovascular, respiratory or cutaneous manifestations, ranging from mild to severe, including death, have uncommonly occurred following Lipiodol administration. Avoid use in patients with a history of sensitivity to other iodinated contrast agents, bronchial asthma or allergic disorders because of an increased risk of a hypersensitivity reaction to Lipiodol. Administer Lipiodol 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. Most hypersensitivity reactions to Lipiodol occur within half an hour after administration. 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 administration.

5.3 Exacerbation of Chronic Liver Disease

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

5.4 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. As Lipiodol may remain in the body for several months, thyroid diagnostic results can be affected for up to two years after lymphography.

6 ADVERSE REACTIONS

6.2 Postmarketing Experience

The following adverse reactions (Table 1) have been identified during post approval use of Lipiodol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions are described in more detail in other sections of the prescribing information:
Pulmonary and cerebral embolism [*see Warnings and Precautions (5.1)*]
Hypersensitivity reactions [*see Warnings and Precautions (5.2)*]
Exacerbation of chronic liver disease [*see Warnings and Precautions (5.3)*]

Table 1: Adverse Reactions in the Postmarketing Experience

System Organ Class	Adverse Reaction
Endocrine disorders	hypothyroidism, hyperthyroidism, thyroiditis
Eye disorders	retinal vein thrombosis
Gastrointestinal disorders	nausea, vomiting, diarrhea
General disorders and administration site conditions	fever, pain, granuloma
Hepatobiliary disorders	hepatic vein thrombosis
Immune system disorders	hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Nervous system disorders	cerebral embolism
Respiratory, thoracic and mediastinal disorders	pulmonary embolism, dyspnea, cough, acute respiratory distress syndrome
Urinary system disorders	renal insufficiency

Hysterosalpingography

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

Lymphography

Cardiovascular collapse, lymphangitis, thrombophlebitis, edema or exacerbation of preexisting 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, and vomiting are the most common reactions; other reactions include hepatic ischemia, liver enzymes abnormalities, transitory decrease in liver function, liver decompensation and renal insufficiency. Procedural risks include vascular complications and infections.

7 DRUG INTERACTIONS

7.1 Interference with Iodine-Based Diagnostic Tests and Iodine-Based Radiotherapy

Following Lipiodol administration, ethiodized oil remains in the body for several months, and may interfere with thyroid function testing for up to two years. Ethiodized oil 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of Lipiodol effects in pregnant women. Use Lipiodol during pregnancy only if clearly needed.

Human Data

It is not known whether Lipiodol can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.
The use of Lipiodol during pregnancy causes iodine transfer which may interfere with the thyroid function of the fetus and result in brain damage and permanent hypothyroidism. Institute thyroid function testing and careful medical monitoring of the neonate exposed to Lipiodol in utero.

Animal Data

Animal reproduction studies have not been conducted using the indicated routes of administration of Lipiodol. Lipiodol was not embryotoxic or teratogenic in rats after oral administration of up to 110 mg Iodine/kg each day between gestation days 6 to 17, or in rabbits after 4-5 intermittent (once every three days) oral administrations of 12.5 mg Iodine/kg between gestation days 6 to 18.

8.2 Nursing Mothers

No nonclinical lactation studies of Lipiodol have been reported.

Lipiodol is excreted in human milk. Avoid use of Lipiodol in a nursing woman because of risk of hypothyroidism in nursing infants.
If breastfeeding is continued the neonate's thyroid function should be monitored.

8.3 Pediatric Use

For lymphography 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. Administer the smallest possible amount of Lipiodol according to the anatomical area to be visualized.

8.4 Geriatric Use

There are no studies conducted in geriatric patients.

8.5 Renal Impairment

Prior to an intra-arterial administration of Lipiodol screen all patients for renal dysfunction by obtaining history and/or laboratory tests.
Consider follow-up renal function assessments for patients with a history of renal dysfunction.

10 OVERDOSAGE

Overdose may lead to respiratory, cardiac or cerebral complications, which can potentially be fatal. Microembolisms to multiple organs may occur more frequently after overdose. Promptly initiate symptomatic treatment and support of vital functions.

11 DESCRIPTION

Lipiodol, ethiodized oil injection, is a sterile injectable radio-opaque agent. Each milliliter contains 480 mg of Iodine organically combined with ethyl esters of fatty acids of poppy seed oil. The precise structure of Lipiodol is unknown.

Lipiodol is a sterile, clear, pale yellow to amber colored oil. Lipiodol has a viscosity of 34 – 70 mPa·s at 20°C, and a density of 1.28 g/cm^3 at 20°C.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ethiodized oil is an iodinated poppy seed oil based contrast agent.

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential, or whether Lipiodol can affect fertility in males or females. Lipiodol did not demonstrate mutagenic potential in bacterial reverse mutation assays (*in vitro*), in a chromosomal aberration test in the mouse lymphoma assay (*in vitro*), and was negative in an *in vivo* micronucleus test in rats after intravenous injection of 479 mg I/kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

Lipiodol is supplied in a box of one 10 mL ampoule, NDC 67684-1901-1.

Store at controlled room temperature 15°-30°C (59°-86°F) [see USP, Controlled Room Temperature (CRT)].
Protect from light. Remove from carton only upon use.

℞ only

Guerbet

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