LIPIODOL ULTRA-FLUIDE (480 mg I/ml), solution for injection.

Composition
Ethyl esters of iodized fatty acids of poppy seed oil* qs ad for one ampoule
* Iodine content: 48 %, i.e. 480 mg per ml.
Solution for injection in 5 ml or 10 ml ampoules.

Pharmaco-therapeutic class
Contrast agent.

Guerbet
BP 57400
95943 ROISSY CdG Cedex - FRANCE

When to use this medicinal product (therapeutic indications)
This medicinal product is an iodinated contrast agent. It has been prescribed to you for a radiological examination which is to be performed for diagnostic purposes or during a surgical procedure.
It can also be used to prevent iodine deficiency disorders when iodization of salt or drinking water cannot be undertaken.

WARNINGS !

When not to use this medicinal product (contraindications)
In radiology
This product MUST NOT BE ADMINISTERED by general intra-arterial, intravenous or intrathecal injection (injection of the product via the same route as for lumbar puncture).

In the treatment of iodine deficiency

This medicinal product MUST NOT BE USED in the following situations:
- if you suffer from hyperthyroidism,
- if you have a large, multinodular goiter and are aged over 45 years, due to the high risk of hyperthyroidism,
- if you are breast-feeding,

Special warnings
In diagnostic or interventional radiology
You should inform the doctor who is to perform the injection if you have or have had any problems of an allergic nature:
  - allergic reactions to iodinated products, particularly during previous radiological examinations with contrast agents,
  - food or drug-related allergies,
  - urticaria,
  - eczema,
  - asthma,
  - hay fever.
- Or if you suffer from cardiac or respiratory insufficiency.
- Or if you have a liver (cirrhosis) or thyroid disorder.

In iodine deficiency
Do not associate with other methods of iodine supplementation (iodization of salt or drinking water) which could increase the risk of hyperthyroidism.
It is advisable to avoid using this medicinal product in persons over the age of 45 years.

IF IN DOUBT, ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE

Precautions for use
A premature polymerisation reaction may exceptionally occur between Lipiodol Ultra-Fluide and certain glues or batches of glues. Prior to any use of new batches of Lipiodol Ultra-Fluide or glue, it is mandatory to verify in vitro the compatibility between the glue used and Lipiodol Ultra-Fluide.

IF IN DOUBT, ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE

Interactions with other medicinal products and other forms of interaction
IN ORDER TO AVOID ANY INTERACTIONS BETWEEN DIFFERENT MEDICINAL PRODUCTS, YOU MUST ALWAYS INFORM YOUR DOCTOR OR PHARMACIST OF ANY OTHER TREATMENT YOU ARE TAKING especially any treatment for hypertension or diabetes.

Pregnancy - Lactation
In iodine deficiency
If you are pregnant, your doctor may prescribe you iodine supplementation.
Due to the risk of hypothyroidism in neonates, Lipiodol is contraindicated during breast-feeding.

IF IN DOUBT, ASK YOUR DOCTOR OR PHARMACIST FOR ADVICE

AS A GENERAL RULE, IF YOU ARE PREGNANT OR BREAST-FEEDING, YOU SHOULD ALWAYS ASK THE ADVICE OF YOUR DOCTOR OR PHARMACIST BEFORE TAKING ANY MEDICINAL PRODUCT.

HOW TO USE THIS MEDICINAL PRODUCT

Dosage
Dosage varies according to the indication and is determined by the doctor performing the injection.

Method and route of administration
This product must be administered using a glass syringe.

In diagnostic radiology
Lymphography: intralymphatic injection only
Diagnosis of liver lesions: selective intra-arterial injection only

In interventional radiology
Embolization with surgical glues: selective intra-arterial injection only

In iodine deficiency
Intramuscular injection only

Duration of treatment
This medicinal product will be administered to you in a single dose.

UNDESIRABLE EFFECTS

AS WITH ALL ACTIVE PRODUCTS, THIS MEDICINAL PRODUCT MAY CAUSE SOME UNDESIRABLE EFFECTS OF VARIABLE INTENSITY IN CERTAIN PERSONS:
possible onset of allergic reactions.

In diagnostic radiology
You may experience transient fever during the first few hours following the examination.
You may experience gastrointestinal disorders (nausea, vomiting or diarrhoea)

In iodine deficiency
You may presents signs of hyperthyroidism (weight loss, accelerated heart rate, increased intestinal transit rate, anxiety, insomnia, etc.).

PLEASE REPORT ANY UNDESIRABLE EFFECT WHICH IS NOT MENTIONED IN THIS LEAFLET TO YOUR DOCTOR OR PHARMACIST.

STORAGE

Do not use the product after the expiry date indicated on the outer packaging.

Special precautions for storage
Store protected from light.

DATE LEAFLET LAST REVISED
03/11/2005.

212129

Guerbet

ETHIODOL®

BRAND OF ETHIODIZED OIL INJECTION

A Low Viscosity Radio-Opaque Diagnostic Agent

NOT FOR INTRAVASCULAR, INTRATHECAL OR INTRABRONCHIAL USE

℞ only

DESCRIPTION: Ethiodol, brand of ethiodized oil, is a sterile injectable radio-opaque diagnostic agent for use in hysterosalpingography and lymphography. It contains 37% iodine (475 mg/mL) organically combined with ethyl esters of the fatty acids (primarily as ethyl monoiodostearate and ethyl diiodostearate) of poppyseed oil. Stabilized with poppyseed oil, 1%. The precise structure of Ethiodol is unknown at this time. Ethiodol is a straw to amber colored, oily fluid, which because of simplified molecular structure, possesses a greatly reduced viscosity (1.280 specific gravity at 15°C yields viscosity of 0.5 - 1.0 poise). This high fluidity provides a new flexibility for radiographic exploration.

CLINICAL PHARMACOLOGY: There has been little detailed investigation of the metabolic fate of Ethiodol in either man or animals. However, the fate of Ethiodol following lymphangiography in dogs has been reported.[1] Koehler et al. employed I^{131}–tagged Ethiodol for lymphangiography in dogs and analyses of individual organs at various time intervals were done. The investigators reported an average of only 25% of the injected medium was retained in the lymphatics at the end of three days. An average of 50% was recovered from the lungs. They found the remainder of injected activity was fairly uniformly distributed throughout the body. Urinary excretion in the form of inorganic iodine was revealed as the chief mode of iodine loss from the system.

INDICATIONS: Ethiodol is indicated for use as a radio-opaque medium for hysterosalpingography and lymphography.

IN HYSTEROSALPINGOGRAPHY

CONTRAINDICATIONS: Ethiodol is contraindicated in patients hypersensitive to it. Ethiodol should not be injected intrathecally or intravascularly, or used in bronchography. A history of sensitivity to iodine contraindicates the use of Ethiodol; iodine is split off from fatty compounds and becomes free iodine in the body. Hysterosalpingography is contraindicated in intrauterine pregnancy, acute pelvic inflammatory disease, marked cervical erosion, endocervicitis in the presence of intrauterine bleeding, in the immediate pre-or postmenstrual phase, or within 30 days of curettage or conization.

WARNINGS: Ethiodol is not intended for use in bronchography and, therefore, is not to be introduced into the bronchial tree. A history of sensitivity to iodine or to other contrast materials is not an absolute contraindication to Ethiodol, but calls for extreme caution. All procedures utilizing contrast media carry a definite risk of adverse reactions. While most reactions are minor, life threatening and fatal reactions may occur without warning. The risk/benefit factor should always be carefully evaluated. At all times a fully equipped emergency cart and resuscitation equipment should be readily available, and personnel competent in recognizing and treating reactions of all severity should be on hand.

PRECAUTIONS:
General: Since iodine-containing contrast materials may alter the results of certain thyroid function tests, such tests, if indicated, should be performed prior to the administration of this drug. Pulmonary embolization of the contrast material may occur if hysterosalpingography is performed under conditions which may lead to intravasation of the contrast materials. These conditions include uterine bleeding, recent curettage or conization and injection of the contrast material under excessive pressure.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether Ethiodol can affect fertility in males or females.

Pregnancy Category C: Animal reproduction studies have not been conducted with Ethiodol. It is also not known whether Ethiodol can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ethiodol should be administered to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Ethiodol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: Hypersensitivity reactions, foreign body reactions and exacerbation of pelvic inflammatory disease, although infrequent, have been reported. In an occasional patient, abdominal pains may occur. Such pains may be the result of tubal torsion, or possibly due to too rapid a rate of instillation or excessive pressure, or both. The condition is usually only transitory, lasting one or two hours at most, and may be relieved by the administration of any of the commonly used analgesics.

DOSAGE AND ADMINISTRATION: The hysterosalpingogram is preferably taken during the patient's preovulatory phase (as determined from her basal body temperature record) and not less than two days after cessation of her menstrual flow. It has been frequently observed that some bleeding will occur during or after the onset of pregnancy which cannot be distinguished by the patient from a normal menstrual period. In such cases a basal body temperature record will reveal a sustained high temperature phase, and thus enable an operator to avoid hysterosalpingography when a pregnancy may exist. Salpingography should not be performed if the blood is exuding from the cervical os (which occasionally occurs without the patient being aware of it) or if any gross evidence of endocervicitis exists.

Careful aseptic technique should be employed as for any operative procedure in which the uterus is entered. A self-retaining cannula should be used thereby permitting removal of the vaginal speculum so that the outline of the cervical canal may be seen in the film. The use of a radio-opaque aluminum speculum may be employed in patients where a lacerated or patulous cervix does not permit the use of a retaining cannula.

The radio-opaque agent is introduced under pressure and preferably with fluoroscopic control. A preliminary film is exposed and a skiagram is made after the injection of 5 mL of the agent. The pressure is raised to 80-90 mm Hg. In cases of normal bilateral tubal patency, the pressure falls immediately to below 60 mm Hg. The wet film may be viewed immediately and if both tubes are seen to "fill", the apparatus is removed and the procedure is finished, except for the 24 hour follow-up to establish whether or not "spill" into the peritoneal cavity has occurred.

Increments of 2 mL of the agent are injected and successive films exposed until tubal patency is established or until the patient's limit of tolerance to discomfort is reached. Few patients will complain of discomfort at pressures under 200 mm Hg.

IN LYMPHOGRAPHY

CONTRAINDICATIONS: Ethiodol is contraindicated in patients hypersensitive to it. Ethiodol should not be injected intrathecally or intravascularly or introduced into the bronchial tree. Patients with known sensitivity to iodine should not have lymphography performed. Iodine is split off from fatty compounds and becomes free iodine in the body. Lymphography is contraindicated in patients with a right to left cardiac shunt, in patients with advanced pulmonary disease, especially those with alveolar-capillary block, and in patients who have had radiotherapy to the lungs.

WARNINGS: The use of intralymphatic Ethiodol presents a significant hazard in patients with pre-existing pulmonary disease characterized by a decrease in pulmonary diffusing capacity and/or pulmonary blood flow. A few fatalities have been noted in such patients. With reference to this potential complication, recent studies indicate a significant decrease in both pulmonary diffusing capacity and pulmonary capillary blood flow following Ethiodol lymphography without appreciable concomitant clinical manifestations. Also, care should be exercised in patients with other types of pulmonary disease in view of the more frequent incidence of overt pulmonary complications such as pulmonary infarction, in these groups. However, it is to be noted that pulmonary infarction, although rare, has occurred in patients without evidence of pre-existing pulmonary disease.

The safety of intralymphatic Ethiodol has not been established in pregnant women, and accordingly, its use should be restricted to such situations where it is deemed necessary.

PRECAUTIONS:
General: Although subclinical pulmonary embolization occurs in a majority of patients following Ethiodol lymphography, clinical evidence of such embolization is infrequent and is usually of a transient nature. Such clinical manifestations are usually immediate, but may be delayed from a few hours to days. It would appear that it is advantageous to use the smallest volume of Ethiodol necessary for radiographic visualization. For this reason, and to prevent inadvertent venous administration, radiographic monitoring of patients is recommended during the injection of Ethiodol.

The timing and choice of anesthesia following Ethiodol injection may be influenced by consideration of the above noted decrease in pulmonary and capillary blood flow and diffusing capacity. It should be noted that although an average of 2 to 3 days was required for complete reversibility for such tests, an occasional patient required up to 12 days to return to baseline values.

PBI determination of thyroid uptake studies should be carried out prior to the lymphographic procedure because interference with these tests may be anticipated for as long as one year. In the presence of known iodine sensitivity, Ethiodol lymphography should be carried out with greatest precaution.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential, mutagenesis, or whether Ethiodol can affect fertility in males or females.

Pregnancy Category C: Animal reproduction studies have not been conducted with Ethiodol. It is also not known whether Ethiodol can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ethiodol should be administered to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Ethiodol, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS: The occasional observation of pulmonary Ethiodol embolization (infarction) several hours after injection has been reported. This was noticed more frequently when excessive amounts of Ethiodol have been injected, in the presence of marked lymphatic obstruction or through accidental intravenous injection. Radiologic manifestations are fine, granular stippling throughout both lung fields. The clinical symptoms usually noted have been mild, consisting of moderate temperature elevation, dyspnea, and cough. However, severe acute symptoms developed in two patients both of whom were severely ill and required extensive care.[2] Fuchs[3] experienced 1 severe and 3 minor complications in a series of 20 bilateral procedures. Two are described by the author as cardiovascular collapse occurring at two hours respectively following the completion of the procedure. It was postulated that minute emboli may have been causative. Recovery was rapid and complete in both instances.

The occurrence of pulmonary invasion may be minimized if radiographic confirmation of intralymphatic (rather than venous) injection is secured, and the procedure discontinued when the medium becomes visible in the thoracic duct or the presence of lymphatic obstruction is noticed.

While rare, other side effects reported include transient fever, lymphangitis, iodism (headache, soreness of mouth and pharynx, coryza and skin rash), allergic dermatitis, and lipogranuloma formation. Delayed wound healing at the site of incision and secondary infection are occasionally seen, and can be prevented or minimized by adhering to a strict sterile technique.

Transient edema or temporary exacerbation of preexisting lymphedema, as well as thrombophlebitis have also been reported. In the extremely rare presence of concomitant lymphatic and

inferior vena cava obstruction the contrast medium may be shunted partially to the liver, resulting in hepatic embolization. Also, when accidental intravenous administration of Ethiodol results in a considerable amount of this medium entering the circulation, embolization other than pulmonary may occur as reported in 2 cases[4]. Both cases developed a transient, psychotic-like manifestation, which in all probability stemmed from the entrance of fine oil droplets into the cerebral circulation. Recovery was uneventful and complete without evidence of neurological sequelae.

DOSAGE AND ADMINISTRATION: This method applies for both the upper and lower extremities. A lymphatic vessel is selected for cannulization.

The patient should be comfortably arranged in a supine position on a portable stretcher or an x-ray table. When available, a radiolucent pad will add to the patient's comfort during the one to two hours required for completion of the examination. It is important that the patient be in a cooperative state. Premedication might be advisable in the unusually apprehensive patient.

In the unusually restless patient, the extremities should be immobilized during the entire procedure to prevent displacement of the needle. Thomas splints have been satisfactorily employed for the legs and simple arm boards for the upper extremities. The cut-down and injection instruments and materials include the following:

Sterile pediatric cut-down set

Sterile towels for draping, sponges, etc.

Local anesthetic, such as procaine hydrochloride, and a syringe

Bactericidal painting solution

20 mL syringe containing 15 mL of Ethiodol with an 18 inch catheter to which is affixed a 27 or 30 gauge needle. (If bilateral lymphography is scheduled, two syringes should be prepared.)

A manually driven or motorized unit (a pressure regulated pump) to provide for slow injection.

Under local infiltration anesthesia, a transverse, curvilinear or longitudinal small skin incision should be made near the ankle or wrist (just lateral and distal to the first metatarsal head on the dorsum of the foot, or just over the "snuff-box" in the dorsum of the hand).

Upon superficial dissection (but not penetrating the subcutaneous layer of tissue) lymph vessels will be noted in the immediate subcutaneous tissue, while larger lymph vessel trunks are found in the extrafascial plane. The deeper lymph trunks will be easier to cannulate.

One lymph vessel is then exposed, avoiding circumferential dissection. The less manipulation performed, the better the results that will be obtained. The lymphatic, thus isolated, is then cannulated with a 27 or 30 gauge 5/8 inch needle, depending upon the size of the lymphatic selected for injection. It is rarely possible to cannulate with a needle greater than 27 gauge. Insertion of the needle through the skin flap before cannulating the lymphatic serves to reduce the movement of the needle within the vessel. Additional security of the needle in the lymphatic is obtained by strapping, with sterile tape, the polyethylene tubing to the patient's foot.

The injection should be started at a slow rate, i.e., 0.1 mL to 0.2 mL per minute. Radiographic monitoring either by fluoroscopy or serial radiographs after 1 mL to 2 mL has been injected, will confirm the proper intralymphatic placement of the needle, rule out accidental intravenous injection or extravasation of the medium by perforation or rupture of the lymphatic. Monitoring will also permit prompt termination of the procedure in the event that lymphatic blockage is present. In such situations, continuation of the injection will result in unnecessary introduction of contrast material in the venous system via the lymphovenous communication channels. If the injection is satisfactory, approximately 6 to 8 mL, are then injected. However, as soon as it becomes radiographically evident that Ethiodol has entered the thoracic duct, the procedure should be terminated to minimize entry of the contrast material into the subclavian vein. Two to four mL of Ethiodol injected into the upper extremity will suffice to demonstrate the axillary and supraclavicular nodes. In penile lymphography approximately 2 to 3 mL of Ethiodol is required. In infants and children, a minimum of 1 mL to a maximum of 6 mL should be employed.

The rate of speed at which the contrast material may be introduced varies and is dependent upon receptivity of the lymphatics in the individual patient. If the injection is proceeding at too rapid a rate, extravasation will be noted and the patient may refer to pain in the foot, leg or arm.

At the completion of the injection, anteroposterior roentgenograms are obtained of the legs or arms, thighs, pelvis, abdomen and chest (dorsal spine technique). Lateral or oblique views as well as laminograms are obtained when indicated. Follow-up films at 24 or 48 hours provide better demonstration of lymph nodes and permit more concise evaluation of nodal architecture.

As a general rule, the smallest possible amount of Ethiodol should be employed according to the anatomical area to be visualized. Therefore, and to prevent inadvertent venous administration, fluoroscopic monitoring or serial radiographic guidance of patients is recommended during the injection of Ethiodol.
Average dose in the adult patient for unilateral lymphography of the upper extremities is 2 to 4 mL; of lower extremities, 6 to 8 mL; of penile lymphography, 2 to 3 mL; of cervical lymphography, 1 to 2 mL.

In the pediatric patient, a minimum of 1 mL to a maximum of 6 mL may be employed according to the anatomical area to be visualized.

SUMMARY OF STEPS TO AVOID COMPLICATIONS IN LYMPHOGRAPHY [5]

1. Contraindicate patients:
   A. With a known hypersensitivity to Ethiodol
   B. With a right to left cardiac shunt
   C. With advanced pulmonary disease, especially those with alveolar-capillary block. Pulmonary gas diffusion studies should be done if in doubt.
   D. Who have had radiation therapy to the lungs

2. Proceed with caution:
   A. Patients having markedly advanced neoplastic disease with expected lymphatic obstruction.
   B. Patients having undergone previous surgery interrupting the lymphatic system.
   C. Patients having had deep radiation therapy to the examined area.

If in those cases in which extreme caution should be exercised, lymphography is still necessary, a smaller dose of oily contrast medium with protracted injection time with less pressure and careful monitoring is required.

3. Skin testing should be done on all patients before submitting them to lymphography. Be aware of possible hypersensitivity to local anesthetics and skin disinfectants. Careful history taking is important.

4. Technique of cannulation: extravasation is to be avoided and/or detected early. The injection site should be included on the "scout film" or observed under image amplification fluoroscopy. The needle tip must remain visible in the incision wound.

5. Oily contrast materials: once opened, ampules should be discarded. Ampules of Ethiodol should not be used if the color has darkened or if particulate matter is present. The average dose for each foot in an adult is 5 to 6 mL; one-half as much for the upper extremity. The amount for children should be determined by careful monitoring. It should stay below 0.25 mL/kg.

6. Injection pressure should be regulated to deliver the average dose in no less than 1 1/4 hours. Continuous monitoring helps to determine the speed most appropriate for each individual. Sensation of pain is a warning of too high pressure.

7. Scout roentgenograms: if scout roentgenograms are used for monitoring, they should be developed and viewed immediately in order to apply corrective measures when needed; e.g., discontinuation of the study when one sees intravenous injection or lymphatico-venous anastomosis. Reduction of injection speed is needed if evidence of collateral circulation occurs or if the higher abdomino-aortic nodes do not opacify in spite of the usual injection pressure. This is highly suggestive of lymphatic obstruction. Scout roentgenograms should be taken more frequently in such cases.

8. Surgical technique: strict aseptic surgical technique is followed including the wearing of a face mask. Before suturing the incision wound, the remnants of the lymphatic vessels and loose tissue are removed and the wound well washed with saline to remove any possible oil. In case of reflux type lymphedema, the cannulated large lymphatic vessel may have to be closed by catgut to avoid development of a lymphocyst.

The patient is instructed to elevate the legs as often as possible to promote healing.
The sutures are removed from the feet on the 10th day, and on the 5th or 6th from the hands.

HOW SUPPLIED: Ethiodol (ethiodized oil for injection) is supplied in a box of two 10 ml ampules, NDC 0281-7062-37.

Store at controlled room temperature15°-30°C (59°-86°F). Protect from light. Remove from carton only upon use.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Ethiodol brand of ethiodized oil for injection is straw to amber color under normal conditions. (See **DESCRIPTION**).

A development of Guerbet Laboratories.

BIBLIOGRAPHY

1. P. Ruben Koehler, M.D. et al.:"Body Distribution of Ethiodol Following Lymphangiography", Radiology, 1964, 82, 5 866-871.
2. Bronk, et. al.:"Oil Embolism in Lymphography",Radiation, 80:194, February 1963.
3. Fuchs, S.A.,"Complications in Lymphography With Oily Contrast Media", Acta Radiol., 57:247, November 1962.
4. Viamonte, M. Jr., University of Miami, Jackson Memorial Hospital, Miami, Florida, Private Communication.
5. Kuisk, H., "Techniques of Lymphography and Principles of Interpretation",1971, Warren H. Green, Inc.,St. Louis, Missouri, 63105.

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Melville, New York 11747

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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: 04/2014

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

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