Guerbet

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February 27, 2012

Dear Healthcare Professional,

Due to the current critical shortage of **ETHIODOL®, Brand of Ethiodized Oil Injection**, Guerbet is coordinating with the FDA to increase the availability of the ethyl esters of iodized fatty acids of poppy seed oil product.

Guerbet has acquired the Ethiodol® NDA from Nycomed US Inc. effective May 7, 2010 and is working with the FDA to resume manufacturing of Ethiodol in the near future to ensure continued availability for the US patients. During this interim period, Guerbet, in conjunction with the FDA, is initiating a temporary importation of **LIPIODOL® ULTRA-FLUIDE**, ethyl esters of iodized fatty acids of poppy seed oil, to the United States market. **LIPIODOL® ULTRA-FLUIDE** contains the same drug components as **ETHIODOL®, Brand of Ethiodized Oil Injection,** (previously manufactured and marketed in the United States by Savage Laboratories, a subsidiary of Nycomed). **LIPIODOL® ULTRA-FLUIDE** is manufactured in compliance with European Good Manufacturing Practice (GMP) regulations by Delpharm Tours (France) for Guerbet.

At this time, no other entity except Guerbet is authorized by the FDA to import or distribute **LIPIODOL® ULTRA-FLUIDE**. Any sales of **LIPIODOL® ULTRA-FLUIDE** ampoules from any entity other than Guerbet will be considered in violation of the Federal Food, Drug and Cosmetic Act and may be subject to enforcement action by the FDA.

Effective immediately, 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# 306 216.0 Box of 1 ampoule

LIPIODOL® ULTRA-FLUIDE formulation is similar to ETHIODOL®.

The active substance of LIPIODOL® ULTRA-FLUIDE and ETHIODOL is the same (ethyl esters of iodized fatty acids of poppy seed oil, stabilized with 1% of poppy seed oil). It is important to note that there are some key labeling differences between the international marketed **LIPIODOL® ULTRA-FLUIDE** and the United States marketed **ETHIODOL®** that you need to be aware:

- **The difference in label claim is due to the unit used to express the Iodine content: the unit for ETHIODOL® is 37% Iodine w/w = weight/weight, while the unit for LIPIODOL ULTRA-FLUIDE® is 48% Iodine w/vol= weight/volume. When converting one unit to another (w/w or w/vol), the Iodine content of ETHIODOL® and LIPIODOL® ULTRA-FLUIDE are similar.**

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. (EST), or email at info-us@guerbet-group.com.

The product comparison table below also highlights the differences between **LIPIODOL® ULTRA-FLUIDE** and **ETHIODOL®**.

Please click here for package inserts: Guerbet **LIPIODOL® ULTRA-FLUIDE** (Patient Information Leaflet and/or Summary of Product Characteristics) and Savage Laboratories **ETHIODOL®**

- **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. (EST).**
- **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. (EST), or email customer.service-us@guerbet-group.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. (EST), or email medical.liaison@guerbet-group.com.

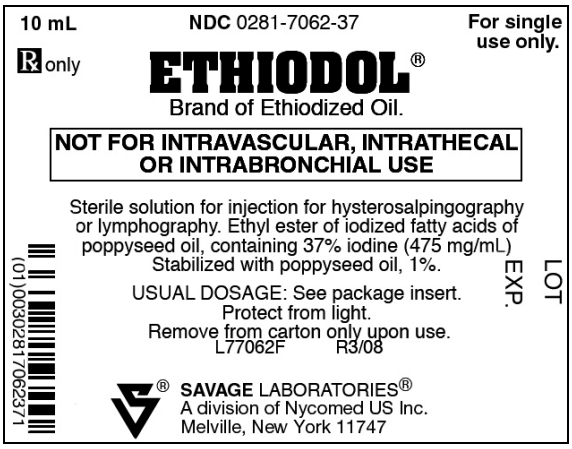
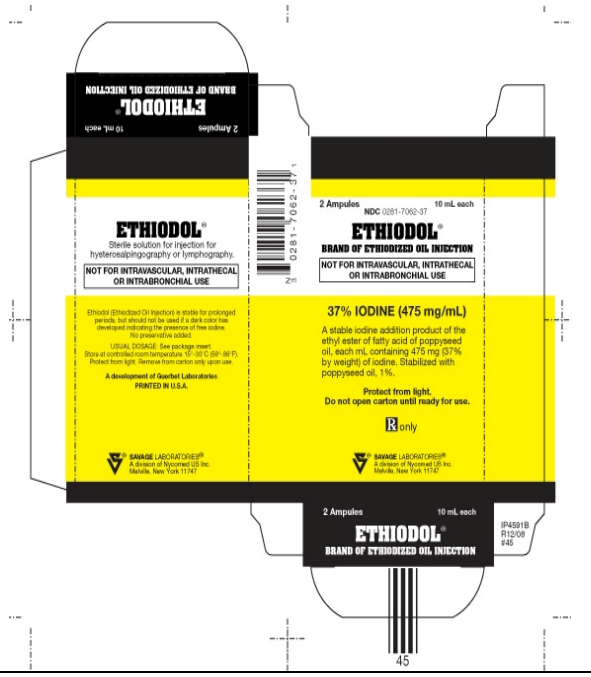
Alternatively, any adverse events that may be related to the use of these products should be reported to the FDA's Med Watch Program by fax at 1-800-FDA-0178, by mail at Med Watch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20852-9787, or on the Med Watch website at http:www.fda.gov/safety/medwatch/default.htm.

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. (EST), or email medical.liaison@guerbet-group.com if you have any questions about the information contained in this letter or the safe and effective use of **LIPIODOL® ULTRA-FLUIDE.**

Sincerely,

Corina Harper
Head of North America Scientific Office, Guerbet LLC

Comparison Table

LIPIODOL® ULTRA-FLUIDE ampoule label	ETHIODOL® ampoule label
	
LIPIODOL® ULTRA-FLUIDE carton label	**ETHIODOL® carton label**
	

LIPIODOL® ULTRA-FLUIDE (ethyl esters of iodized fatty acids of poppy seed oil)	**ETHIODOL®** (ethyl esters of iodized fatty acids of poppy seed oil)
Iodine label claim	
48% w/vol Iodine (480 mg/mL)	**37% w/w Iodine (475 mg/mL)**
Indications and contraindications	
See package insert **Please note: see package insert sections 4.2 Method of administration, 4.3 Contraindications, and 4.4 Special warning and precautions for use.**	**ETHIODOL®** is indicated for use as a radio-opaque medium for hysterosalpingography and lymphography. See package insert for contraindications.
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# 306 216.0	Box of 2 ampoules NDC# 0281-7062-37
Additional information	
Contains a patient information leaflet	N/A

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.

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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

APPENDIX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE 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.

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

<u>In diagnostic radiology</u>

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

<u>In interventional radiology</u>

- Embolization with surgical glues

In association with surgical glues during vascular embolizations.

<u>In endocrinology</u>

- Prevention of iodine deficiency disorders.

This treatment should only be used when other methods of supplementation, particularly iodization of salt and/or drinking water, cannot be undertaken.

4.2. Posology and route of administration

In diagnostic radiology

- Lymphography

5 to 7 ml by intralymphatic injection only for opacification of a limb (the dose being adapted to the height of the patient), i.e. 10 to 14 ml for bilateral pedal lymphography.

- Diagnosis of liver lesions

Intra-arterial route only.

The standard dose depends on lesion size and can vary from 2 to 10 ml per patient. LIPIODOL ULTRA-FLUIDE is sometimes mixed with small amounts of water-soluble iodinated contrast agents. The CT scan should be performed 7 to 15 days after the selective injection to allow the LIPIODOL ULTRA-FLUIDE to be eliminated from the non-tumoral liver tissue.

In interventional radiology

- Embolization with surgical glues

Selective arterial catheterization only.

The dose of LIPIODOL ULTRA-FLUIDE administered at each embolization session depends on lesion size. The Lipiodol and liquid embolizing agent mixture may vary from 20 to 80% but usually consists of a 50/50 mixture.
The volume injected should not exceed 15 ml.

In endocrinology

Intramuscular injection only.

- Adults and children aged over 4 years: 1 ml every 3 years.
- Children aged under 4 years: 0.5 ml every 2 years without exceeding 3 ml.

In patients with thyroid nodules, the dose is 0.2 ml.
This product must be administered using a glass syringe.

4.3. Contraindications

In diagnostic radiology

This product must not be administered by intra-arterial, intravenous or intrathecal injection.
In the diagnosis of liver lesions, there are no particular contraindications to the examination, apart from those associated with selective arteriography.

In interventional radiology

- Embolization with surgical glues

There are no particular contraindications apart from those related to embolization, in particular the presence of portal thrombosis.

In endocrinology

This medicinal product is CONTRAINDICATED in the following situations:
- hyperthyroidism,
- large, multinodular goiters in persons aged over 45 years, due to the high risk of hyperthyroidism,
- during breast-feeding.

4.4. Special warnings and special precautions for use

This medicinal product should be used with caution in patients with a history of allergy.

Care should be taken to avoid vascular structures due to the risk of fat embolisms and not to inject the product into an area affected by haemorrhage or trauma, except in the specific cases described below:

In diagnostic radiology

- lymphography

Intralymphatic injection only.

After chemotherapy or radiotherapy, the lymph nodes decrease substantially in size and only retain small amounts of contrast agent. The dose injected must therefore be reduced.

Overdoses can be avoided by radiological or radioscopic monitoring during the injection.

In subjects with cardiorespiratory failure, particularly elderly patients, the doses should be adapted or the examination itself cancelled, since a portion of the product will temporarily embolize the pulmonary capillaries.

Any thyroid explorations should be performed before the radiological examination, as lymphography saturates the thyroid with iodine for several months.

- Diagnosis of liver lesions

Intra-arterial injection only

Special care should be taken in cirrhotic patients.
The examination should only be performed if it contributes to therapeutic decision-making.

In interventional radiology

- Embolization with surgical glues

Selective arterial catheterization only

Vascular embolization with liquid agents is a complex and delicate technique which should only be performed by trained physicians in an appropriate medicosurgical setting.

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.

In endocrinology

Intramuscular injection only.

Do not associate other methods of iodine supplementation. The risk of thyrotoxicosis is increased if the treatment is associated with other methods of iodine supplementation, particularly iodization of foodstuffs.

Because of the risk of hyperthyroidism:

- it is advisable to avoid administering this treatment to subjects over the age of 45 years,
- and to reduce the dose in patients with thyroid nodules (see Posology and Route of Administration).

4.5. Interactions with other medicinal products and other forms of interaction

Associations requiring precautions for use

* Beta-blockers

In the event of shock or hypotension due to iodinated contrast agents, reduction of compensatory cardiovascular reactions by treatment with beta-blockers.
Treatment with beta-blockers should be stopped, whenever possible, before the radiological investigation. When continuation of treatment is essential, adequate resuscitation equipment must be available.

* Diuretics

In the event of dehydration provoked by diuretics, the risk of acute renal failure is increased, especially when high doses of iodinated contrast agents are used.
Precautions for use: re-hydration before administration of the iodinated contrast agent.

* Metformin

Lactic acidosis triggered by impaired renal function induced by the radiological investigation in diabetic patients.
Treatment with metformin must be suspended 48 hours before the investigation and only restarted 2 days after the radiological examination.

Associations to be taken into account

* Interleukin II

The risk of developing a reaction to the contrast agents is increased in the event of previous treatment with interleukin II (IV route): skin rash or, more rarely, hypotension, oliguria, or even renal failure.

4.6. Pregnancy and lactation

In endocrinology

It appears that in populations with moderate to severe iodine deficiency, it can be beneficial for pregnant women to receive iodine supplementation.

This medicinal product is highly concentrated in the maternal milk. Due to the risk of hypothyroidism in neonates, Lipiodol is contraindicated during breast-feeding.

4.7. Effects on ability to drive and use machines

Not applicable.

4.8. Undesirable effects

Allergic-like reactions may occur.

In diagnostic radiology

- Lymphography

A fever of 38-39°C may be observed in the 24 hours following the examination.
A transient lipiodol miliary is often observed on radiological images, particularly following a high or inappropriate dose. This usually remains clinically silent. In exceptional cases, pulmonary or cerebral embolism may be observed.
Spinal cord accidents are rare.

- Diagnosis of liver lesions

Fever is often observed. Other rarer complications may occur: nausea, vomiting and diarrhoea.

In interventional radiology

- Embolization with surgical glues

No undesirable effects directly related to LIPIODOL ULTRA FLUIDE have been specifically described.

In endocrinology

Hyperthyroidism (see Precautions for use).

4.9. Overdose

In radiology

Following intralymphatic injection, cardiorespiratory and central venous complications are proportional to the dose of LIPIODOL ULTRA-FLUIDE injected.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

NON-WATER-SOLUBLE CONTRAST AGENTS, Code ATC: V08AD01
(V: Other)

5.2. Pharmacokinetic properties

After intralymphatic injection

Lipiodol 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. The iodinated contrast agent is significantly more concentrated in the tumour than in the surrounding tissue, especially in the case of hepatocellular carcinomas.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. Incompatibilities

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

6.2. Shelf-life

3 years.

6.3. Special precautions for storage

Store protected from light.

6.4. Nature and contents of container

5 ml or 10 ml type I glass ampoule.

7. PRESENTATION AND MARKETING AUTHORISATION NUMBERS

306 217.7 - 5 ml glass ampoule, box of 4
306 216.0 - 10 ml glass ampoule, box of 1
560 350-7 - 5 ml glass ampoule, box of 100
560 351-3 - 10 ml glass ampoule, box of 50

8. LEGAL STATUS

Not applicable.

9. MARKETING AUTHORISATION HOLDER

Guerbet
BP 57400
F-95943 Roissy CdG cedex
FRANCE

10. DATE OF REVISION

November 3, 2005

ETHIODOL®

BRAND OF ETHIODIZED OIL INJECTION

A Low Viscosity Radio-Opaque Diagnostic Agent

NOT FOR INTRAVASCULAR, INTRATHECAL OR INTRABRONCHIAL USE

℞ Iy

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.

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