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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

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

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 – Incompatibilities).

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.

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.

4.3. Contraindications

This product must not be administered by intra-arterial, intravenous or intrathecal injection.

- Hypersensitivity to LIPIODOL ULTRA-FLUID (ethyl esters of iodised fatty acids of poppyseed oil).
- Confirmed hyperthyroidism.
- Traumatic lesions, haemorrhage or recent bleeding (risk of extravasation or embolism).
- Bronchography (the product rapidly inundates the bronchioles and alveoli).

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 intra-arterial, confirming radiologically that the injection is strictly intralymphatic (and not intravenous or intrathecal injection) 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. 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. 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.

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 embolisation, metformin must be discontinued 48 hours before the examination and resumed no earlier than two days after the examination.

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

The safety of LIPIODOL ULTRA-FLUID has not been demonstrated in pregnant women. The use of LIPIODOL ULTRA-FLUID during pregnancy increases the transplacental transfer of iodine, which probably interferes with thyroid function in the fœtus. Although transient, this abnormality may involve a risk of cerebral lesions and permanent hypothyroidism, calling for monitoring of thyroid function and close medical follow-up of the neonate.

Consequently, LIPIODOL ULTRA-FLUID should not be used in pregnant women unless it is absolutely necessary, and only with strict medical monitoring.

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, or else thyroid function should monitored more frequently in the neonate.

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.

A sharp 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.

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.

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)

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.

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

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 below 25ºC, protected from light.

6.5. Nature and contents of container

10 mL glass (type 1) ampoules.

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 NUMBERS

056-03-21367-00
056-03-21367-01

8. MANUFACTURER

Guerbet

BP 57400

F-95943 Roissy CdG cedex

FRANCE

9. MARKETING AUTHORISATION HOLDER

Promedico Ltd
6 Hashiloach St.
Petach- Tikva