SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LIPIODOL ULTRA-FLUID

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 for.....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

- Lymphography.
- Visualisation, localisation and vectorisation during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma, in adults.

4.2. Posology and method of administration

Posology

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. Given that part of the product temporarily embolises the pulmonary capillaries, the dose must be adjusted in elderly patients with cardiorespiratory insufficiency or the examination must be cancelled.

In interventional radiology

- Trans-Arterial Chemo-Embolisation of hepatocellular carcinoma:

The dose of LIPIODOL ULTRA-FLUID depends on the extent of the lesion, but should usually not exceed a total dose of 15 mL in adults.

Paediatric population

The efficacy and safety of the use of LIPIODOL ULTRA-FLUID for Trans-Arterial Chemo-Embolisation of hepatocellular carcinoma have not been established in children.

Elderly

The product must be administered with special care in patients over 65 years of age with underlying diseases of the cardiovascular, respiratory or nervous systems.

Method of administration

LIPIODOL ULTRA-FLUID must be administered by slow injection or by catheterization, using a suitable glass syringe or other delivery devices for which compatibility with LIPIODOL ULTRA FLUIDE has been demonstrated. The instructions on use for such devices must be followed (see section 6.2).

In interventional radiology:

- Trans-arterial chemo-embolisation of hepatocellular carcinoma

  The administration is by selective intra-arterial catheterization of the hepatic artery. The procedure should be performed within a typical interventional radiology setting with the appropriate equipment.

LIPIODOL ULTRA-FLUID can be mixed with anticancer drugs such as cisplatin, doxorubicin, epirubicin and mitomycin.

Instructions and precautions for use of the anticancer drugs must be strictly followed.

Instructions for preparation of the mixture of LIPIODOL ULTRA-FLUID with an anticancer drug:

- Prepare two syringes large enough to contain the total volume of the mixture. The first syringe contains the anticancer drug solution, the second syringe contains LIPIODOL ULTRA-FLUID.

- Connect the two syringes to a 3-way stopcock.

- Perform 15 to 20 back and forth movements between the two syringes to obtain a homogeneous mixture. It is recommended to start by pushing the syringe with the anticancer drug first.

- The mixture is to be prepared at the time of use and must be used immediately after preparation (within 3 hours). If necessary, during the interventional radiology procedure, the mixture may be re-homogenized as described above.

- When the adequate mixture is obtained, use a 1 to 3 mL syringe to inject in the micro-catheter.

The procedure may be repeated every 4 to 8 weeks according to tumor response and the patient's condition.

4.3. Contraindications

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

- Hypersensitivity to LIPIODOL ULTRA-FLUID (ethyl esters of iodised fatty acids of poppyseed oil).
- Pregnant women
- Proven hyperthyroidism.
- Traumatic injuries, recent haemorrhage or bleeding (risk of extravasation or embolism).
- Bronchography (the product would rapidly flood bronchioles and alveoli).

Specific contraindications for use in interventional radiology:

Transarterial chemoembolisation:

Lipiodol Ultra Fluid mixture for treatment of hepatocellular carcinoma may lead to both ischemic and toxic effects to the bile duct. Therefore, the administration is contraindicated in liver areas where the bile ducts are dilated, unless post-procedural drainage can be performed.

Intra-arterial injection of LIPIODOL ULTRA-FLUID may lead to a complete hepatic artery obliteration and complete suppression of arterial flow. It should only be performed after having made sure, via CT scan or angiography, that there is the presence of at least a partial portal vascular flow.

4.4. Special warnings and precautions for use

LIPIODOL ULTRA-FLUID should not be administered by systemic intravascular or intrathecal administration.

There is a risk of hypersensitivity, regardless of the dose administered.

Warnings

Warnings common to all therapeutic indications

Hypersensitivity

All iodinated contrast agents may cause minor or major hypersensitivity reactions that may be life-threatening. These hypersensitivity reactions may be allergic (so-called anaphylactic reactions if severe) or non-allergic. They can occur immediately (within 60 minutes) or may be delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, may occur from the first administration of the product, and are often unpredictable.

The risk of major reactions implies having necessary emergency resuscitation equipment immediately available.

Patients who have already had a reaction with a previous administration of LIPIODOL ULTRA-FLUID or have a history of iodine hypersensitivity are at increased risk of another reaction in case of repeat administration of the product. They are therefore considered to be at-risk patients.

Injection of LIPIODOL ULTRA-FLUID may aggravate the symptoms of existing asthma. In patients whose asthma is not controlled with treatment, the decision to use LIPIODOL ULTRA-FLUID must be based on a careful consideration of the benefit- risk ratio.

Disturbed thyroid function

Due to their free iodine content, iodinated contrast agents may alter thyroid function and thus cause hyperthyroidism in predisposed patients. Patients at risk are those with latent hyperthyroidism and those with thyroid autonomy. Iodism occurs more frequently with LIPIODOL ULTRA FLUIDE than with water-soluble organic derivatives of iodine.

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been reported following iodinated contrast media administration to adult and paediatric patients, including infants. Some patients were treated for hypothyroidism. See also section on Paediatric population.

Paediatric population:

Thyroid Dysfunction in Pediatric Patients 0 to 3 Years of Age

Thyroid dysfunction characterized by hypothyroidism or transient thyroid suppression has been reported after both single exposure and multiple exposures to iodinated contrast media (ICM) in pediatric patients 0 to 3 years of age.

Younger age, very low birth weight, prematurity, underlying medical conditions affecting thyroid function, admission to neonatal or pediatric intensive care units, and congenital cardiac conditions are associated with an increased risk of hypothyroidism after ICM exposure. Pediatric patients with congenital cardiac conditions may be at the greatest risk given that they often require high doses of contrast during invasive cardiac procedures.

An underactive thyroid during early life may be harmful for cognitive and neurological development and may require thyroid hormone replacement therapy. After exposure to ICM, individualize thyroid function monitoring based on underlying risk factors, especially in term and preterm neonates.

See also section 4.4, “Specific warnings for lymphography”.

Embolic and thrombotic complications

The uncontrolled migration of Lipiodol Ultra Fluid into the arterio-venous system may induce the temporary obliteration of small vessels (oil embolism) in various organs. Signs of such embolism are infrequent and generally immediate, but they may also be delayed and appear after a few hours or days. They are usually transient. However, cases of pulmonary embolism and cerebral embolism (possibly associated with a cerebral infarction) that are life-threatening or fatal have been reported with LIPIODOL ULTRA-FLUID in all its therapeutic indications. Patients should be informed of possible signs of embolism and should contact their doctor or hospital if any symptoms appear. The benefit/risk balance should be carefully evaluated prior to examination, particularly in patients with a known right-to-left cardiac shunt or a known intratumoral vascular shunt. The recommended dose should not be exceeded and the administration procedures should be followed.

Specific warnings for Lymphography

A Pulmonary embolism occurs in most patients undergoing lymphography with injection of LIPIODOL ULTRA-FLUID, as part of the product temporarily embolises pulmonary capillaries. For this reason, doses should be adjusted or the examination cancelled in subjects with impaired respiratory function, cardiorespiratory insufficiency, or pre-existing right heart overload, especially if the patient is elderly. The doses must also be reduced after anti-cancer chemotherapy or radiotherapy, as the lymph nodes shrink considerably and therefore do not retain much contrast agent. It is recommended that the injection be carried out under radiological or radioscopic guidance.

Pulmonary embolisation can be reduced to a minimum via radiological confirmation that the injection is strictly intralymphatic (and not intravenous) and by interrupting the examination as soon as the contrast agent becomes visible in the thoracic duct or if lymphatic obstruction is observed.

Lymphography saturates the thyroid with iodine for several months and it is therefore necessary to perform a thyroid assessment prior to the radiological examination.

Special warnings for transarterial chemoembolisation

Transarterial chemoembolisation is not recommended in patients with decompensated cirrhosis of the liver (Child-Pugh ≥ 8), severe hepatic dysfunction, macroscopic portal vein invasion, portal thrombosis (partial or total), and/or extrahepatic tumour dissemination.

An intra-arterial hepatic procedure may cause irreversible liver failure in patients with severe hepatic dysfunction and/or treated over several sessions close together. Tumour invasion of greater than 50% of the liver, bilirubin levels over 2 mg/dl, lactate dehydrogenase levels over 425 mg/dl, aspartate aminotransferase levels over 100 IU/l and decompensated cirrhosis have been described as being associated with an increase in the post-procedure mortality rate.

Oesophageal varices should be monitored carefully as they may rupture immediately after treatment. If a risk of rupture is identified, an endoscopic sclerotherapy/ligation should be performed prior to the transarterial chemoembolisation procedure.

Iodinated contrast-induced renal failure risk should be prevented by systematic hydration before and after the procedure.

The risk of superinfection in the treated area can be prevented by the administration of antibiotics.

Precautions for use

Hypersensitivity

Before the examination:

identify patients at risk in a detailed interview on their history.

Corticosteroids and H1 antihistamines have been proposed as pre-medication for patients with the highest risk of intolerance reactions (those with known intolerance to a contrast agent). However, they do not prevent the occurrence of severe or fatal anaphylactic shock.

During the examination, the following should be maintained:

- medical monitoring
- an indwelling intravenous catheter.

After the examination:

After contrast agent administration, the patient must be observed for at least 30 minutes, as the majority of serious adverse reactions occur within this time frame.

The patient must be informed of the possibility of delayed reactions (up to 7 days after administration) (see Section 4.8 - Undesirable effects).

Thyroid

It is essential to look for any thyroid risk factors to prevent any metabolic disorders. If administration of an iodinated contrast agent is planned for such at risk patients, an assessment of thyroid function should be performed before the examination.

Transarterial chemoembolisation/Embolisation

Iodinated contrast agents may cause temporary deterioration of renal function or aggravate pre-existing renal impairment. Preventive measures include:

- Identifying at-risk patients, i.e. patients with dehydration or renal insufficiency, diabetes, severe heart failure, monoclonal gammopathy (multiple myeloma, Waldenstrom's macroglobulinemia), subjects with a history of renal failure after administration of iodinated contrast agents, infants under one year of age and elderly subjects with atheroma.
- Hydrating before and after the procedure.
- Avoiding combining nephrotoxic medicinal products. If this is necessary, increase renal function monitoring. The medicinal products concerned include 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.
- Allowing at least 48 hours between radiological examinations or interventions with iodinated contrast agent injections, or delaying further examinations or interventions until renal function returns to baseline.
- Preventing lactic acidosis in diabetics treated with metformin by monitoring serum creatinine levels. Normal renal function: treatment with metformin must be stopped at least 48 hours before injection of the contrast agent or until normal renal function has been restored. Abnormal renal function: metformin is contraindicated. In an emergency, if the examination is required, precautions must be taken, i.e. discontinuation of metformin, hydration, renal function monitoring and looking for signs of lactic acidosis.
- Cardiovascular and/or pulmonary risk factors should be evaluated prior to initiating a transarterial chemoembolisation procedure.

Other

Injection into certain fistulas requires the utmost caution to avoid any vascular penetration, considering the risk of fat embolisms.

Care should be taken not to inject the product into a haemorrhagic or traumatized area.

Indications for the use of LIPIODOL ULTRA-FLUID should be carefully assessed in patients with primary lymph oedema, as the oedema can be exacerbated.

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

Drug interactions

Metformin

In diabetic patients, intra-arterial administration of LIPIODOL ULTRA-FLUID is likely to cause lactic acidosis triggered by functional renal failure. For patients scheduled to undergo embolisation or Trans-Arterial Chemo-Embolisation, metformin treatment should be suspended 48 hours before the procedure and should only be resumed 2 days after the procedure.

Combinations to be taken into consideration

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

These medicinal products lead to a decrease in the effectiveness of the cardiovascular mechanisms that compensate for blood-pressure disturbances: the doctor must be informed before the administration of LIPIODOL ULTRA-FLUID and have resuscitation equipment to hand.

+ Diuretics

Since diuretics are likely to cause dehydration, the risk of acute renal failure is increased, particularly when contrast agents are administered at high doses.

Precautions for use: rehydration before intra-arterial administration of LIPIODOL ULTRA-FLUID for embolisation.

+ Interleukin ll

There is a risk of increased reaction to contrast agents in case recent treatment with interleukin-ll (intravenous route): rash or, more rarely, hypotension, oliguria, and even renal failure.

Interference with diagnostic tests

Since LIPIODOL ULTRA-FLUID remains in the body for several months, results of thyroid diagnostic tests may be distorted for up to two years after a lymphography.

4.6. Fertility, pregnancy and lactation

Pregnancy

LIPIODOL ULTRA-FLUID must not be used in pregnant women due to the transplacental transfer of iodine over a long periods, which is likely to interfere with the foetus' thyroid function with a potential risk of brain damage and permanent hypothyroidism.

Breastfeeding

Pharmacokinetic studies have shown significant excretion of iodine in breast milk after intramuscular administration of LIPIODOL ULTRA-FLUID. It has been demonstrated that iodine passes into the vascular system of the breastfed infant via the gastrointestinal tract and this could interfere with thyroid function. Consequently, breastfeeding should be discontinued if LIPIODOL ULTRA-FLUID must be used.

4.7. Effects on ability to drive and use machines

Effects of LIPIODOL ULTRA-FLUID on the ability to drive and use machines have not been studied.

4.8. Undesirable effects

Most of the adverse reactions are dose-related and consequently the dose should be as low as possible.

The use of LIPIODOL ULTRA-FLUID causes a foreign body reaction, with the formation of macrophages and foreign body giant cells and the occurrence of sinus catarrh, plasmacytosis and subsequent connective tissue changes in the lymph nodes. Healthy lymph nodes tolerate the resulting decrease in transport capacity. In case of lesions or hypoplasia of the lymph nodes, these changes may exacerbate existing lymphostasis.

Hypersensitivity reactions are possible. These reactions include one or more effects with a concomitant or successive onset, most often including cutaneous, respiratory and/or cardiovascular manifestations, which can each be a warning of an early state of shock and, in very rare cases, can even prove fatal.

Cases of pulmonary embolism and cerebral embolism (possibly associated with a cerebral infarction) that are life-threatening or fatal have been reported with LIPIODOL ULTRA-FLUID, for all its therapeutic indications.

Diagnostic radiology:

- Lymphography:

A sharp increase in temperature followed by a fever of 38 to 39°C may occur within 24 hours following the examination.

Fat microemboli may occur, with or without symptoms. In very rare cases, they may resemble emboli of organic origin due to their appearance and size. They most often present as punctiform opacities on radiographic images of the lungs.
Transient temperature increases are possible. Fat microemboli often occur following an overdose of contrast agent or excessively rapid infusion. Anatomic abnormalities such as lympho-venous fistulas or a decrease in the capacity of the lymph nodes to retain the contrast medium (in elderly patients, or after radiotherapy or cytostatic therapy) make their occurrence more likely.
Patients with a right-left cardiac shunt and those with massive pulmonary embolism are particularly exposed to the occurrence of fat microemboli in the brain.

Interventional radiology:

- Trans-Arterial Chemo-Embolisation:

Most adverse reactions are not caused by LIPIODOL ULTRA-FLUID but are due to anticancer drugs or the embolisation itself.
The most common adverse reactions of transarterial chemoembolisation treatment are post embolisation syndrome (fever, abdominal pain, nausea, vomiting) and transient changes in liver function tests.

Worsening of pre-existing hepatocellular failure may occur following the use of LIPIODOL ULTRA-FLUID in a hepatic intra-arterial procedure and may lead to serious and potentially fatal complications such as hepatic encephalopathy, oedematous ascitic decompensation, hepatic necrosis, liver abscess, pancreatitis, and even necrotising pancreatitis.

The adverse reactions are presented in the table below by System Organ Class and by frequency using the following categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

System organ class	**Frequency: adverse reactions**
Immune system disorders	Frequency not known: hypersensitivity, anaphylactic reaction.
Endocrine disorders	Frequency not known: hyperthyroidism.
Nervous system disorders	Frequency not known: cerebral embolism, cerebral infarction, hepatic encephalopathy[a]
Respiratory, thoracic and mediastinal disorders	Frequency not known: pulmonary embolism, pulmonary oedema, pleural effusion, acute respiratory distress syndrome, pneumonitis
Gastrointestinal disorders	Frequency not known: vomiting, diarrhoea, nausea, pancreatitis[a], ascites[a]
Hepatobiliary disorders	Frequency not known: cholecystitis[a], biloma[a], hepatic failure[a], hepatic infarction[a]
General disorders and administration site conditions	Frequency not known: fever, pain.
Injury, poisoning and procedural complications	Rare: spinal cord injury. Frequency not known: fat embolism.
Infections and infestations	Frequency not known: liver abscess[a]

Skin and subcutaneous tissue disorders	Frequency not known: skin necrosis[a]

[a]: in the context of transarterial chemoembolization (TACE) and transarterial embolisation.

Adverse reactions in children

The nature of the expected adverse reactions related to LIPIODOL ULTRA-FLUID is identical to that of the effects reported in adults. Their frequency cannot be estimated from the available data.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/
In addition, suspected adverse events can be reported to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9. Overdose

An overdose may result in respiratory, cardiac or cerebral complications that may be fatal. The frequency of microemboli may be increased in the context of overdose.

The total dose of LIPIODOL ULTRA-FLUID administered must not exceed 20 mL.

The treatment of overdose is directed toward a prompt initiation of symptomatic treatment and ensure the maintenance of vital functions as quickly as possible. Facilities performing examinations with contrast agents must have the necessary medicinal products and equipment for emergency care.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Non-water-soluble X-ray contrast media; ATC code: V08AD01

When used in conventional chemoembolisation by selective hepatic intra-arterial injection, LIPIODOL ULTRA-FLUID allows, as an oily contrast agent, to visualise and control the procedure thanks to its opacifying properties; as a vehicle, to carry and elute anticancer drugs into hepatocellular carcinoma nodules; and as an agent of transient embolism, to contribute to the vascular embolisation induced during the procedure.
As it is a selective procedure by hepatic intra-arterial injection, conventional chemoembolisation combines the effect of a loco-regional targeted anticancer drug with the effect of an ischemic necrosis induced by dual arterio-portal embolisation. The opacifying properties and the tropism for hepatic tumours of LIPIODOL ULTRA-FLUID make it possible to perform post procedure imaging for several months to ensure effective monitoring of the patient.

5.2. Pharmacokinetic properties

After intralymphatic injection

LIPIODOL ULTRA-FLUID is released into the blood and captured by the liver and lungs, where the lipid droplets are broken down in the pulmonary alveoli, spleen and adipose tissue.

After being taken up by the tissues and storage organs, resorption varies from a few days to several months or years. It is continuous and regular and it is possible to detect the presence of iodine in the urine as long as an opaque mark persists on imaging.

After selective intra-arterial injection

Iodine remains primarily eliminated in the urine. After selective injection into the hepatic artery for the diagnosis of liver damage or after transarterial chemoembolisation of hepatocellular carcinomas, LIPIODOL ULTRA-FLUID is significantly more concentrated in the tumour than in surrounding healthy liver tissue.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity and reproductive and developmental functions.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

This medicinal product does not contain any excipients.

6.2. Incompatibilities

LIPIODOL ULTRA-FLUID does not store well in plastics. Only use plastic delivery devices if they have been demonstrated to be compatible with LIPIODOL ULTRA-FLUID and their instructions for use are followed rigorously.

6.3. Shelf life

The expiry date of the product is indicated on the packaging.

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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION NUMBERS

056-03-21367-00

8. MANUFACTURER

Guerbet,

BP 57400, F-95943 Roissy CdG Cedex, FRANCE.

9. MARKETING AUTHORISATION HOLDER

Promedico Ltd.,
Hashiloach 6, POB 3340, Petach Tikva.

Revised in January 2024.