1. NAME OF THE MEDICINAL PRODUCT

LIPIODOL ULTRA FLUIDE 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 iodised fatty acids of poppy seed oil per.....1 ml
Each 10 ml ampoule contains ……4,800 mg of iodine
Viscosity at 15 °C: 70 cP (centipoises)
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.

In interventional radiology:
Visualisation, locating and vectoring during transarterial chemoembolisation of intermediate-stage hepatocellular carcinoma in adults.

4.2. Posology and method of administration

Posology

In diagnostic radiology:

- Lymphography

8mL max per extremity

Paediatric population
In children, the dosage is reduced according to bodyweight with an average dosage of 0.20 mL/kg.

Elderly subjects
The product must be administered with caution to patients over 65 years of age with underlying cardiovascular, respiratory or nervous system conditions. Given that part of the product temporarily embolises the pulmonary capillaries, cardiorespiratory failure in an elderly patient may require adaptation of the dose following assessment of the benefit-risk ratio.

In interventional radiology:

- Transarterial chemoembolisation of hepatocellular carcinoma

The dose of LIPIODOL ULTRA FLUIDE depends on the extent of the lesion but generally must not exceed a total dose of 15 ml in adults.

Paediatric population:

The safety and efficacy of LIPIODOL ULTRA FLUIDE in transarterial chemoembolisation of hepatocellular carcinoma in children have not yet been established.

Elderly people:
The product must be administered with caution to patients over 65 years of age with underlying cardiovascular, respiratory or nervous system conditions.
The injected dose must not exceed 10 ml in order to prevent a possible untargeted pulmonary embolism occurring during hepatic chemoembolisation.

Method of administration
LIPIODOL ULTRA FLUIDE must be administered by slow injection or catheterisation using a suitable glass syringe or other delivery devices where compatibility with LIPIODOL ULTRA FLUIDE has been demonstrated. The instructions on use for such devices must be followed (see section 6.2).

In diagnostic radiology:
- Lymphography

Administration takes the form of lymphatic catheterisation. It may be preceded by the injection of a dye to locate the lymphatic vessels.

In interventional radiology:
- Transarterial chemoembolisation of hepatocellular carcinoma

Administration is by intra-arterial selective catheterisation of the hepatic artery. The procedure must be performed in an interventional radiology room with the appropriate equipment.
LIPIODOL ULTRA FLUIDE may be mixed with anti-cancer medicines such as cisplatin, doxorubicin, epirubicin and mitomycin.
The instructions and precautions for use regarding anti-cancer medicines must be strictly adhered to.
Instructions for preparing the mixture of LIPIODOL ULTRA FLUIDE with an anti-cancer medicine:
- Prepare two syringes large enough to hold the total mixture volume: the first syringe containing the anti-cancer medicine solution, and the second syringe containing LIPIODOL ULTRA FLUIDE.
- Connect the two syringes to a three-way valve.
- Shake back and forth between the two syringes 15 to 20 times to obtain a homogeneous mixture. It is recommended that the syringe containing the anti-cancer medicine be pushed first.
- The mixture must be prepared immediately before use and must be used immediately after preparation (within 3 hours). If necessary, the mixture may be homogenised again as described above during the interventional radiology procedure.
- Once the correct mixture has been obtained, use a 1 ml to 3 ml syringe for injection into the micro-catheter.

The procedure may be repeated every 4 to 8 weeks depending on the tumour response and the patient's condition.

4.3. Contraindications

- Hypersensitivity to LIPIODOL ULTRA FLUIDE (ethyl esters of iodised fatty acids of poppy seed oil).
- Pregnant women.
- Proven hyperthyroidism.
- Trauma injuries, haemorrhages or recent bleeding episodes (risk of extravasation or embolism).
- Bronchography (the product would quickly flood the bronchioles and alveoli).

Contraindications specific to use in interventional radiology:

- Transarterial chemoembolisation:

Mixing with LIPIODOL ULTRA FLUIDE to treat hepatocellular carcinoma may cause both ischaemic and toxic effects for the gallbladder. Administration is therefore contraindicated in hepatic areas where the bile ducts are dilated, unless post-procedure drainage is possible.

- Intra-arterial injection of LIPIODOL ULTRA FLUIDE may cause total obstruction of the hepatic artery and total suppression of arterial flow. This should only be considered after having made sure, via imaging or angiography, that there is at least partial portal vascular flow.

4.4. Special warnings and precautions for use

LIPIODOL ULTRA FLUIDE is not suitable for intravenous, intra-arterial (excluding selective catheterisation) or intrathecal administration.
There is a risk of hypersensitivity, regardless of the dose administered.

Warnings

Lymphography

A pulmonary embolism occurs in most patients undergoing a lymphography with injection of LIPIODOL ULTRA FLUIDE, as part of the product temporarily embolises the pulmonary capillaries. This embolism rarely manifests clinically; in such cases, the signs are immediate (they may, however, also appear several hours or even days after administration) and usually temporary. For this reason, doses must be adjusted or the examination cancelled for subjects with impaired respiratory function, cardiorespiratory failure or pre-existing right ventricular overload, particularly 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 with radiological or fluoroscopic guidance. Pulmonary invasion can be reduced to a minimum via radiological confirmation that the injection is strictly intralymphatic (and not intravenous) and by stopping the examination as soon as the contrast agent becomes visible in the thoracic duct or as soon as any lymphatic obstruction is observed.

Hypersensitivity

All iodinated contrast agents may cause minor or major hypersensitivity reactions that may be life-threatening. These hypersensitivity reactions may be allergic (known as anaphylactic reactions if serious) or non-allergic. These reactions 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 means that emergency resuscitation equipment must be immediately available.
Patients who have already had a reaction to a previous administration of LIPIODOL ULTRA FLUIDE or who have a history of iodine hypersensitivity are at greater risk of another reaction if the product is administered again. They are therefore considered to be at-risk patients.
Injection of LIPIODOL ULTRA FLUIDE may exacerbate existing asthma symptoms. In patients whose asthma is not controlled by treatment, the decision to use LIPIODOL ULTRA FLUIDE must be based on careful consideration of the benefit-risk ratio.

Thyroid

Due to their free iodine content, iodinated contrast agents may alter thyroid function and therefore produce hyperthyroidism or hypothyroidism in patients who are predisposed to this condition. At-risk patients are those with latent hyperthyroidism and those with thyroid autonomy. Iodism occurs more commonly with LIPIODOL ULTRA FLUIDE 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.

Transarterial chemoembolisation

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

A hepatic intra-arterial procedure may cause irreversible liver failure in patients with severe hepatic impairment and/or treated over several sessions close together. Tumour invasion of the liver of more than 50%, 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 must be monitored closely, as they may rupture immediately after treatment. If a risk of rupture is identified, endoscopic sclerotherapy/ligation must be performed prior to the transarterial chemoembolisation procedure.

The risk of kidney failure caused by iodised contrast agents must be prevented by systematic hydration before and after the procedure.

The risk of superinfection in the treated area, including the occurrence of liver abscess, can be prevented via the administration of antibiotics for 3 to 5 days.

Precautions for use

Hypersensitivity

Before the examination:

Identify at-risk patients by taking a detailed history.

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

During the examination, it is important to ensure:

- medical monitoring
- maintenance of a venous line

After the examination:

After administration of a contrast agent, the patient must be monitored for at least 30 minutes since the majority of serious adverse reactions occur within this period.

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-related risk factors to prevent any metabolic complications. If use of an iodinated contrast agent is planned for such at-risk patients, thyroid function must be assessed before the examination.

Transarterial chemoembolisation / Embolisation

Subjects with impaired respiratory function, cardiorespiratory failure or pre-existing right ventricular overload, particularly if the patient is elderly.

Iodinated contrast agents can induce temporary deterioration of renal function or exacerbate pre-existing renal impairment. Preventive measures include:

- Identifying at-risk patients, i.e. patients with dehydration or renal failure, diabetes, severe heart failure, monoclonal gammopathy (multiple myeloma, Waldenström's macroglobulinaemia), 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 drugs. If this cannot be avoided, closer biological monitoring of renal function is required. The medicinal products concerned include aminoglycosides, organoplatinum compounds, high-dose methotrexate, pentamidine, foscarnet, and certain antiviral agents (aciclovir, ganciclovir, valacyclovir, adefovir, cidofovir, tenofovir), vancomycin, amphotericin B and immunosuppressants such as ciclosporin, tacrolimus and ifosfamide.
- Allow at least 48 hours between radiological examinations or procedures with injection of iodinated contrast agents, or delay further examinations or procedures until renal function returns to baseline.
- Prevent lactic acidosis in diabetic patients 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 an examination is required, precautions must be taken including stopping metformin administration, hydration, monitoring of renal function and looking for signs of lactic acidosis.
- The cardiovascular and/or pulmonary risk factors must be assessed before initiating a transarterial chemoembolisation procedure.

Other

Injection into certain fistulas requires the utmost caution to avoid any vascular penetration, taking into account the risk of fat embolism.

Care should be taken not to inject the product into areas of bleeding or trauma.

The instructions on use for LIPIODOL ULTRA FLUIDE must be carefully assessed in patients with primary lymphoedema, as the oedema may be exacerbated.

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

Drug interaction

- Metformin

In diabetic patients, the intra-arterial administration of LIPIODOL ULTRA FLUIDE may cause lactic acidosis triggered by functional renal failure. In patients scheduled for transarterial chemoembolisation, treatment with metformin must be suspended 48 hours before the procedure and only be resumed 2 days after.

Combinations to be taken into consideration

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

These medicinal products reduce the efficiency of the cardiovascular compensation mechanisms in blood-pressure disorders: the doctor must be informed before administering LIPIODOL ULTRA FLUIDE and have resuscitation equipment 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 FLUIDE for embolisation.

- Interleukin 2

The risk of developing a reaction to contrast agents is increased in the case of recent treatment with interleukin 2 (intravenous route): rash or, more rarely, hypotension, oliguria or even renal failure.

Interference with diagnostic examinations

As LIPIODOL ULTRA FLUIDE stays in the body for several months, the results of thyroid tests may be distorted up to two years after a lymphography.

4.6. Fertility, pregnancy, and lactation

Pregnancy

LIPIODOL ULTRA FLUIDE must not be used in pregnant women due to the transplacental transfer of iodine over long periods, which is likely to interfere with the foetus' thyroid function with a potential risk of brain damage and permanent hypothyroidism. Consider thyroid function testing in infants whose mothers were exposed to LIPIODOL ULTRA FLUIDE before and during pregnancy or if clinically indicated.

Breast-feeding

Pharmacokinetic studies have shown that a large amount of iodine is excreted in breast milk following intramuscular administration of LIPIODOL ULTRA FLUIDE. It was demonstrated that the iodine entered the vascular system of the breast-fed infant through the digestive tract and that this could interfere with its thyroid function. Breast-feeding should therefore be stopped if LIPIODOL ULTRA FLUIDE must be used. If breastfeeding is continued, the infant's thyroid function should be monitored.

4.7. Effects on ability to drive and use machines

The effects of LIPIODOL ULTRA FLUIDE 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.

Using LIPIODOL ULTRA FLUIDE causes a foreign-body reaction with the formation of macrophages and foreign-body giant cells, as well as sinus catarrh, plasmocytosis and subsequently alterations to the lymph nodes' connective tissue. Healthy lymph nodes are able to withstand the resulting reduction in transport capacity. In patients with lymph node lesions or hypoplasia, these changes may exacerbate existing lymph stasis.

Hypersensitivity reactions are possible. These reactions include one or more effects, appearing simultaneously or sequentially, which are most often cutaneous, respiratory and/or cardiovascular in nature. Each one may be a warning sign of shock and, in very rare cases, may result in death.

In diagnostic radiology:

- Lymphography:

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

Fat micro-emboli may occur with or without symptoms. In very rare cases, they may resemble organic emboli in their appearance and size. They most commonly present as punctiform opacities on lung X-rays. Temporary increases in temperature are possible. Fat micro-emboli usually occur following an overdose of contrast agent or excessively rapid infusion. Anatomical abnormalities 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) make their occurrence more likely. Patients with a right-to-left cardiac shunt and those with a massive pulmonary embolism are particularly at risk for fat micro-emboli in the brain.

In interventional radiology:

- Transarterial chemoembolisation:

Most adverse reactions are not caused by LIPIODOL ULTRA FLUIDE but rather by anti-cancer medicines or the embolisation itself.
The most common adverse reactions to treatment by transarterial chemoembolisation are post-embolisation syndrome (fever, abdominal pain, nausea, vomiting) and temporary changes in liver function tests.
Pre-existing hepatocellular deficiency may be exacerbated following use of Lipiodol as part of a hepatic intra-arterial procedure and result in serious and potentially fatal complications such as hepatic encephalopathy, ascitic oedematous decompensation, hepatic necrosis, liver abscess, pancreatitis or even necrotising pancreatitis.

Adverse reactions are shown in the table below according to system organ class and frequency, using the following classification: 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 (frequency cannot be estimated from the available data).

System organ class	**Frequency: adverse reaction**
Immune system disorders	Frequency not known: Hypersensitivity, anaphylactic reaction
Endocrine disorders	Frequency not known: Hyperthyroidism, hypothyroidism
Nervous system disorders	Frequency not known: Cerebral embolism, hepatic encephalopathy[a]
Respiratory, thoracic and mediastinal disorders	Frequency not known: Pulmonary embolism, pulmonary oedema, pleural effusion, acute respiratory distress syndrome, pneumonitis[a]
Gastrointestinal disorders	Frequency not known: Vomiting, diarrhoea, nausea, pancreatitis[a], ascites[a]
Hepatobiliary disorders	Frequency not known: Cholecystitis[a], biloma[a], liver 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 chemoembolisation

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 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

An overdose may result in respiratory, cardiac or cerebral complications that may be fatal. The frequency of micro-embolisms may be increased after an overdose.
The total dose of LIPIODOL ULTRA FLUID administered must not exceed 20 ml.
An overdose should be managed by treating the symptoms and ensuring that vital functions are maintained as quickly as possible. Establishments performing examinations with contrast agents must have emergency medicines and equipment available.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: "NON-WATERSOLUBLE X-RAY CONTRAST MEDIA", ATC Code: V08AD01

In conventional chemoembolisation by selective hepatic intra-arterial injection, LIPIODOL ULTRA FLUID is used, as an oily contrast agent, to view and monitor the procedure thanks to its opacifying properties; as a vehicle, to transport and elute anti-cancer medicines in hepatocellular carcinoma nodules and, as a transient embolic agent, to contribute to vascular embolisation induced during the procedure. As it is a selective procedure by hepatic intra-arterial injection, conventional chemoembolisation combines the effect of a targeted anti-cancer medicine at the local/regional level with ischaemic necrosis caused by double arterioportal embolisation. The opacifying properties and 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 intra-lymphatic injection

LIPIODOL ULTRA FLUID is released into the blood and captured by the liver and the lungs, where the lipid droplets are broken down in the pulmonary alveoli, the spleen and adipose tissue.
Resorption can take from a few days to several months or years after the product has been captured in the retaining tissues and organs. The process is continuous and steady, and the presence of iodide can be detected in the patient's urine for as long as an opaque spot remains on X-rays.

After selective intra-arterial injection

The iodine is again mainly eliminated in the patient's urine. Following selective injection into the hepatic artery for the transarterial chemoembolisation of hepatocellular carcinoma, LIPIODOL ULTRA

FLUID is significantly more concentrated in the tumour than in the surrounding healthy hepatic tissue.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

This medicinal product does not contain any excipients.

6.2. Incompatibilities

LIPIODOL ULTRA FLUID does not keep well in plastic containers. Only use plastic delivery devices if their compatibility with LIPIODOL ULTRA FLUID has been demonstrated, and in strict compliance with their instructions on use.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

Store protected from light.
Store below 30°C.

6.5. Nature and contents of container

10 ml glass ampoule (type I). Box of 1 or 50.
Self-breaking ampoules.
Not all pack sizes may be marketed.

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.

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