LIPIODOL® ULTRA FLUIDE

NAME OF THE MEDICINAL PRODUCT

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

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.

PHARMACEUTICAL FORM

Solution for injection.

CLINICAL PARTICULARS

In diagnostic radiology
Lymphography

In interventional radiology

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

Posology and method of administration

LIPIODOL ULTRA FLUIDE must be administered by slow injection or via a catheter, using a suitable glass syringe and a catheter or other administration devices proven to be compatible with LIPIODOL ULTRA-FLUIDE. The instructions for use of these devices must be followed

In diagnostic radiology

- Lymphography

N.B. - One should rinse the syringe with ether immediately after use.

Dosage
8 ml. max. per extremity.

In interventional radiology

- Trans-Arterial Chemo-Embolisation of hepatocellular carcinoma

The administration is by selective intra-arterial catheterism of the hepatic artery. The procedure should be performed within a typical interventional radiology setting with the appropriate equipment. The dose of LIPIODOL ULTRA-FLUIDE depends on the extent of the lesion, but should usually not exceed a total dose of 15 mL in adults

LIPIODOL ULTRA-FLUIDE 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-FLUIDE with an anticancer drug:

- Prepare two syringes large enough to contain the total volume of mixture. The first syringe contains the anticancer drug solution, the second syringe contains LIPIODOL ULTRA-FLUIDE.
- 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 promptly after preparation (within 3 hours). If necessary during the interventional radiology procedure, the mixture can be re-homogenised as described above.
- When the adequate mixture is obtained, use a 1 to 3 mL syringe to inject in the micro-catheter.

The procedure can be repeated every 4 to 8 weeks according to tumour response and patient conditions.

Paediatric population

The efficacy and safety of the use of LIPIODOL ULTRA-FLUIDE 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.
In elderly patients with cardiorespiratory failure scheduled for a lymphography, the dose should be adapted or the examination itself cancelled, since a portion of the product will temporarily embolize the pulmonary capillaries.
Limiting the injected dose will also prevent non-targeted pulmonary embolism which might occur in the course of a hepatic chemoembolisation.

Contraindications

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

Contraindications specific to the use in interventional radiology:

- Trans-Arterial Chemo-Embolisation:

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

Special warnings and precautions for use

LIPIODOL ULTRA-FLUIDE must not be administered intravenously, intra-arterially (apart from selective catheterisation) or intrathecally.

There is a risk of hypersensitivity whatever the dose administered.

Warnings

Lymphography

Pulmonary embolism occurs in most patients undergoing lymphography with injection of LIPIODOL ULTRA-FLUIDE, 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 confirming radiologically that the injection is strictly intralymphatic (and not intravenous) 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.

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-FLUIDE 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-FLUIDE may exacerbate symptoms of asthma. In patients whose asthma is not controlled by treatment, the decision to use LIPIODOL ULTRA-FLUIDE must be based on a careful consideration of the benefit-to-risk ratio.

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-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.

Trans-Arterial Chemo-Embolisation

Trans-Arterial Chemo-Embolisation is not recommended in patients with decompensated liver cirrhosis (Child-Pugh ≥8), advanced liver dysfunction, macroscopic portal vein invasion and/or extra-hepatic spread of the tumour.

Hepatic intra-arterial procedures can cause an irreversible liver insufficiency in patients with serious liver malfunction and/or undergoing close multiple sessions. More than 50% liver replacement with tumour, bilirubin level greater than 2 mg/dL, lactate dehydrogenase level greater than 425 mg/dL, aspartate aminotransferase level greater than 100 IU/L and decompensated cirrhosis have been described as associated with increased post-procedural mortality.

Oesophageal varices must be carefully monitored as they can rupture immediately after treatment. If a risk of rupture is demonstrated, endoscope sclerotherapy/ligature should be performed before the Trans-Arterial Chemo-Embolisation procedure.

Iodinated contrast agent induced renal insufficiency must be systematically prevented by correct rehydration before and after the procedure.

The risk of superinfection in the treated area is normally prevented by administration of antibiotics.

Embolic and thrombotic complications

The uncontrolled migration of LIPIODOL ULTRA-FUIDE into the arterio-venous system may induce the temporary obliteration of small vessels (oil embolism) in various organs. Evidence of such embolisation is infrequent, usually immediate but can also be delayed occurring after a few hours or days and is usually transient. Most reported localizations of such an event include pulmonary embolisms, cerebral embolisms (which could lead to cerebral infarction) and skin embolisms (which could lead to skin necrosis). Patients should be warned of the possible signs of embolism and should contact their doctor or hospital if any symptoms emerge.

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 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 - Undesirable effects).

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.

Trans-Arterial Chemo-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.
- Cardiovascular and/or pulmonary co-morbidities should be assessed before initiation of a Trans-Arterial Chemo-Embolisation procedure.

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.

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

Interaction with other medicinal products and other forms of interaction

Interactions with other medicines

- Metformin

In diabetic patients, intra-arterial administration LIPIODOL ULTRA-FLUIDE may cause lactic acidosis induced by diminished renal function. In patients undergoing a Trans-Arterial Chemo-Embolisation, metformin must be discontinued 48 hours before the procedure and resumed no earlier than two days after the procedure.

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-FLUIDE 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-FLUIDE 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-FLUIDE remains in the body for several months, thyroid laboratory tests may be falsified for as long as two years after lymphography.

Pregnancy and lactation

Pregnancy

LIPIODOL ULTRA-FLUIDE must not be used in pregnant women because of the transplacental transfer of iodine, over a long period of time, which interferes probably with the thyroid function of the foetus, with a potential risk of cerebral lesions and permanent hypothyroidism.

Breastfeeding

Pharmacokinetic studies have shown significant secretion of iodine in breast milk after intramuscular administration of LIPIODOL ULTRA-FLUIDE. 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-FLUIDE must be used.

Effects on ability to drive and use machines

No studies on the effects of LIPIODOL ULTRA-FLUIDE on the ability to drive and use machines have been performed.

Undesirable effects

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

Use of LIPIODOL ULTRA-FLUIDE 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. These reactions may involve one or more effects, occurring concomitantly or successively, and usually including cutaneous, respiratory and/or cardiovascular manifestations, each of which can be a warning sign of incipient shock and, in very rare instances, can even prove fatal.

In diagnostic radiology:

- Lymphography:

A large 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.

In interventional radiology:

- In Trans-Arterial Chemo-Embolisation

Most of the adverse reactions are not caused by LIPIODOL ULTRA-FLUIDE itself but are due to anticancer drugs or the embolisation itself.

The most frequent adverse reactions of the TACE treatment are post embolisation syndrome (fever, abdominal pain, nausea, vomiting) and transitory changes in liver function tests.

Further serious adverse events associated with uncontrolled dissemination of LIPIODOL ULTRA-FLUIDE in various organs include pulmonary, cerebral (which could lead to cerebral infarction) or skin embolisms (which could lead to skin necrosis) may also occur. Massive pulmonary embolism has been associated with serious complications including dyspnea, pulmonary oedema, pleural effusion, acute respiratory distress syndrome, and pneumonitis.

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, cerebral infarction, hepatic encephalopathy[a]
Respiratory, thoracic and mediastinal disorders	Undetermined frequency: pulmonary embolism, pulmonary oedema[a], pleural effusion[a], acute respiratory distress syndrome[a], pneumonitis[a]
Gastrointestinal disorders	Undetermined frequency: vomiting, diarrhoea, nausea, pancreatitis[a], ascites[a]
Hepatobiliary disorders	Undetermined frequency: cholecystitis[a], biloma[a], hepatic failure[a], hepatic infarction[a]
General disorders and administration site conditions	Undetermined frequency: granuloma, fever, pain.
Infections and infestations	Undetermined frequency: liver abscess[a]
Skin and subcutaneous tissue disorders	Undetermined frequency: skin necrosis[a]
Injury, poisoning and procedural complications	Rare: spinal cord injury. Undetermined frequency: fat embolism.

[a]: in the context of TACE

Adverse reactions in children

The types of adverse reactions to LIPIODOL ULTRA-FLUIDE are the same as those reported in adults. Their frequency cannot be estimated on the basis of 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 declaration system.

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-FLUIDE 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

NON-WATER-SOLUBLE CONTRAST AGENTS, Code ATC: V08AD01

(V: Other)

Used in Trans-Arterial Chemo-Embolisation by selective intra-arterial hepatic injection, LIPIODOL ULTRA-FLUIDE allows, as an oily contrast agent, the visualisation and control of the procedure thanks to its opacifying properties. As a vehicle, it carries and elutes anticancer drugs into hepatocellular carcinoma nodules and, as a transient embolic agent, it contributes to the vascular embolisation induced during the procedure.

As a selective intra-arterial hepatic injection procedure, Trans-Arterial Chemo-Embolisation combines the effect of a loco-regional targeted anticancer drug with the effect of an ischemic necrosis induced by dual arterio-portal embolisation. LIPIODOL ULTRA-FLUIDE's opacifying properties and tropism for hepatic tumours continues for several months, so post procedure imaging can be performed for an effective patient follow-up.

Pharmacokinetic properties

<u>After intralymphatic injection</u>

LIPIODOL ULTRA-FLUIDE 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.

<u>After selective intra-arterial injection</u>

The iodine is eliminated mainly in the urine. After selective intra-arterial injection into the hepatic artery for Trans-Arterial Chemo-Embolisation of hepatocellular carcinoma, LIPIODOL ULTRA-FLUIDE is significantly more concentrated in the tumour than in the healthy liver tissue.

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.

PHARMACEUTICAL PARTICULARS

List of excipients

This medicinal product contains no excipients.

Incompatibilities

Plastic is not suitable for the storage of LIPIODOL ULTRA-FLUIDE. Only use plastic administration devices if their compatibility with LIPIODOL ULTRA-FLUIDE has been proven, and with the strictest adherence to their instructions for use.

Shelf life

3 years.

Special precautions for storage

Store protected from light and at temperature below 30°C.

Nature and contents of container

10 mL glass (type 1) ampoules.

Manufactured by

Guerbet

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