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

100% iodised ethyl-esters of the fatty acids of poppy-seed oil containing approximately
480 mg I/ml organically combined iodine.

This product does not contain any excipient.

3 PHARMACEUTICAL FORM

Solution for injection.
A pale yellow, clear oily liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In diagnostic radiology:
Lipiodol Ultra Fluid is an X-ray contrast medium for use in certain radiological investigations where it is desired to outline a viscous or other structure with directly instilled radio-opaque material.

Lipiodol Ultra Fluid is used in hysterosalpingography in women undergoing infertility workup.

From most sites in the body it is slowly absorbed, but from the peritoneal cavity (after hysterosalpingography) absorption is relatively rapid. On account of its low viscosity Lipiodol Ultra Fluid is suitable for introduction into narrow channels and may therefore be used in ducts and sinuses.

In interventional radiology:
Visualisation, localisation and carrier of cytotoxic medicine during Trans-Arterial Chemo- Embolisation (TACE) of hepatocellular carcinoma at intermediate stage, in adults (see sections 4.2 and 5.1).

In interventional radiology procedures for peripheral and central vascular embolisation with cyanoacrylate-based surgical glues compatible with Lipiodol Ultra Fluid and approved for endovascular use, to allow visualisation of the procedure and adjustment of polymerisation time.

4.2 Posology and method of administration

In diagnostic radiology:
The volume to be administered depends on the particular requirements of the technique and the size of the patient.

Recommended dosages
- Lymphography: 3 to 10 mL (maximum 20 mL)
- Hysterosalpingography:

Inject increments of 2 mL of Lipiodol Ultra Fluid into the endometrial cavity under fluoroscopic control until tubal patency is determined.

The total volume to be injected depends on the volume of the uterine cavity, usually not exceeding 15 mL.

The dose of Lipiodol Ultra Fluid for hysterosalpingography should be kept as low as possible to minimize the potential risk of thyroid dysfunction; this is important as women undergoing HSG are likely to be trying to conceive. *See Section 4.4 and 4.6*.

- Sialography: Until the gland fills, maximum 5 mL

Special populations:

Paediatric population:
The dose for lymphography should be proportionally decreased in children depending on the weight of the patients. In infants between 1 and 2 years of age, a dose of 1 mL per extremity is sufficient.

Underweight patients:
The dose should be proportionally decreased in this population.

Elderly:
The drug must be administered cautiously in patients over 65 years presenting with underlying pathologies of the cardiovascular, respiratory or neurological system.

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.

Ininterventional radiology-TACE of hepatocellular carcinoma:
Use of Lipiodol Ultra Fluid during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma at intermediate stage, in adults should only be carried out by specialists with relevant expertise in this area.

Adults:
The dose used in TACE should be adjusted according to tumour and patient characteristics and should not exceed 15 ml due to risk of pulmonary adverse events when higher volume is used (see section 4.9).

Most adverse effects are dose related and dosage should therefore be kept as low as possible
(see section 4.8).

Lipiodol Ultra Fluid has been used with a number of chemotherapeutic agents in the TACE procedure, and prescribers are advised to consult local guidance or treatment guidelines (see section 5.1).

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

Practices can vary across specialist centres therefore current published guidance or protocols and individual specialist centres should be consulted for specific regimens and dosages of specific anticancer drugs and embolic agents used with Lipiodol Ultra Fluid as part of the TACE procedure.

The final step in the TACE procedure is the administration of an embolic agent in line with established protocols.

If necessary, the procedure can be repeated according to tumour response and patient clinical status, in consultation with specialist centres and in line with currently established guidelines and local protocols (see sections 4.4 and 4.8).

Special populations:

Paediatric population:

The efficacy and safety of Lipiodol Ultra Fluid in TACE of hepatocellular carcinoma have not been established in the paediatric 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.

Limiting the injected dose will also prevent non-targeted pulmonary embolism which might occur in the course of a hepatic chemoembolisation.

Renal impairment:
In patients with renal failure, no adjustment of dose is required; only sufficient hydration must be ensured (see section 4.4).

Hepatic impairment:
The safety and efficacy of Lipiodol Ultra Fluid has not been established in patients with significant underlying liver disorders.

Patients with liver decompensation or more advanced liver failure should be excluded from

TACE since this can lead to severe or fatal adverse hepatic events (see sections 4.4 and 4.8).

Method of administration
Lipiodol Ultra Fluid must not to be administered by intravenous or intrathecal route.

The use of these contrast media should be carried out under the supervision of trained personnel whose experience qualifies them in the safe conduct of such examinations as may be required.

Equipment and medications appropriate for emergency treatment of reactions should always be immediately available.

Lipiodol Ultra Fluid should be administered via a suitable glass syringe and cannula by slow injection or cannulation.

Administration in lymphography is by lymphatic cannulation. It may be preceeded by the injection of a dye to locate the lymph collectors.

Administration in hysterosalpingography is by slow injection into the uterine cervical canal via a suitable catheter or cannula.

Stop the injection if the patient develops excessive discomfort.

The examination should be preferably carried out during the follicular phase of the menstrual cycle.

Administration in sialography is by cannulation of salivary duct.

Administration in TACE is by selective intra-arterial catheterisation of the hepatic artery. The procedure should be performed within a typical interventional radiology setting with the appropriate equipment, in eligible patients after a multidisciplinary team assessment of the staging of hepatocellular carcinoma and the assessment of the patients general condition.

Instructions for preparation of the mixture of Lipiodol Ultra Fluid with anticancer medicine(s) (see sections 6.3 and 6.6):

- Prepare two syringes, made from compatible plastic material (i.e: polyamide, polypropylene, polysulfone), large enough to contain the total volume of 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 promptly after preparation (within 3 hours). In exceptional cases, an early phase separation may be observed during the interventional radiology procedure, in this case 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.

Air embolism, resulting from accidental arterial injections of air bubbles after improper preparation of mixture (Lipiodol Ultra Fluid with chemotherapeutic agent) can potentially be fatal and can lead to respiratory, cardiac or cerebral complications.

Peripheral and central vascular embolisation:
The procedure must be performed by a physician trained in the use of Lipiodol Ultra Fluid and glue mixture for endovascular embolization and in an interventional radiology department with the proper equipment. The ratio of glue to Lipiodol Ultra Fluid may vary from 1:1 to 1:8 allowing for the adjustment of the polymerisation time depending on whether a proximal or distal embolisation is to be performed.

For proximal targets, the ratio is more frequently 1:1 to 1:3 while higher dilutions (1:4 to 1:8) are used for distal target lesions.

By adjusting the ratio of glue to Lipiodol Ultra Fluid, the glue polymerization time can be adjusted to take into account the diameter of the target vessel and blood flow velocity.

The injected volume of Lipiodol Ultra Fluid must not exceed 15 mL.

The recommendations of the Instructions For Use of the surgical glue must be strictly followed.

Method of administration
Administration for vascular embolisation with surgical glues is by selective intravascular catheterisation or percutaneous administration in the lesion to be embolised.

Instructions for preparation of the mixture of Lipiodol Ultra Fluid with cyanoacrylate-based surgical glues:

- When preparing the mixture, great care must be taken to avoid contamination with ionic solutions, such as blood or normal saline, as this may accelerate polymerization and lead to excessively proximal glue deposition and/or an increased risk of catheter retention. The injection should be stopped immediately in this case.
- The mixture is prepared by injecting the glue into the desired volume of Lipiodol Ultra Fluid in a compatible syringe. The two components are then thoroughly mixed using a 3-way stopcock until a homogenous mixture is obtained.
- The preparation must be administered immediately, using a catheter that has been flushed thoroughly with 5% dextrose to completely clear ionic solutions from its lumen.

Elderly patients
The medicinal product should be administered with caution in patients over 65 years of age with underlying cardiovascular, respiratory or neurological pathology.

Paediatric patients
Limited data are available regarding the efficacy and safety of Lipiodol Ultra Fluid in vascular embolization in paediatric patients.

4.3 Contraindications

Hypersensitivity to Lipiodol Ultra Fluid (esters of iodised fatty acids of poppy-seed oil)

- Manifest hyperthyroidism
- Patients with traumatic injuries, recent haemorrhage or bleeding (risk of extravasation or embolism)
- Hysterosalpingography during pregnancy, acute pelvic inflammation, marked cervical erosion, endocervicitis and intrauterine bleeding, within 30 days of curettage or conization
- Bronchography (it would rapidly fill the bronchioles and alveoli)

Additional contraindication specificto usein TACE:
- 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.

In peripheral and central vascular embolisation:
The contraindications mentioned in the Instructions For Use of the surgical glue must be taken into account.

4.4 Special warnings and precautions for use

Lipiodol Ultra Fluid must not to be administered via systemic intravascular or intrathecal route. There is a risk of hypersensitivity, regardless of the dose administered.

Warnings

Lymphography
Pulmonary embolisation occurs in a majority of patients following lymphography with Lipiodol Ultra Fluid, due to a portion of the product temporarily embolising the pulmonary capillaries. Clinical evidence of such embolization is infrequent, usually immediate however possibly delayed from a few hours to days, and usually of a transient nature. For this reason the doses should be adapted or the examination itself cancelled in subjects with impaired lung function, cardiorespiratory failure, or pre-existing right –sided cardiac overload, in particular elderly patients. The injected dose of Lipiodol Ultra Fluid must be also

reduced after chemotherapy or radiotherapy, as the lymph nodes will be considerably reduced in volume and will only take up a small amount of the contrast medium. Radiological or radioscopic monitoring during the injection is recommended. 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.

Hypersensitivity
All iodinated contrast agents can lead to minor or major hypersensitivity reactions, which can be life-threatening. These hypersensitivity reactions are of an allergic nature (known as anaphylactic reactions if they are serious) or a non-allergic nature. They can be immediate (occurring within 60 min) or delayed (not occurring until up to 7 days later). Anaphylactic reactions are immediate and can be fatal. They are dose-independent, can occur right from the first administration of the product, and are often unforeseeable.

The risk of a major reaction means that the equipment needed for emergency resuscitation must be immediately to hand.

Patients who have already experienced a reaction after a previous administration of Lipiodol Ultra Fluid or who have a history of iodine hypersensitivity are at increased risk of another reaction on readministration of the product. Therefore, the use of Lipiodol Ultra Fluid in these patients is contraindicated (see section 4.3).

The injection of Lipiodol Ultra Fluid may aggravate symptoms of an existing asthma. In patients with asthma unbalanced by the treatment, the decision to use Lipiodol Ultra Fluid must be made after careful evaluation of the risk/benefit ratio.

Thyroid
Iodinated contrast media can affect thyroid function because of the free iodine content and can cause hyperthyroidism in predisposed patients. Patients at risk are those with latent hyperthyroidism and those with functional thyroid autonomy. Hyperthyroidism occurs more frequently with Lipiodol Ultra Fluid than with water-soluble organic iodine derivatives. Lymphography saturates the thyroid with iodine for several months and any thyroid exploration should be performed before the radiological examination.

To prevent any metabolic disorder, possible thyroid risk factors must be determined. If administration of an iodised contrast agent is planned in such patients at risk, thyroid function must be determined before the examination.

Thyroid function following hysterosalpingography.
When Lipiodol Ultra Fluid is used in hysterosalpingography in women who are trying to conceive, women should be advised to have their thyroid function monitored in the months after the examination to observe potential development of hypothyroidism or subclinical hypothyroidism, and especially if the woman has a history of thyroid dysfunction.

The dose of Lipiodol Ultra Fluid should be kept as low as possible to minimize the potential risk of thyroid dysfunction. In the event of a successful pregnancy after the hysterosalpingography it is recommended to monitor the woman and fetus for any indication of thyroid dysfunction, and also to monitor the newborn's thyroid function. *See also Section 4.6*.

TACE
There is variation in the choice of chemotherapeutic agents and regimens used in current clinical practice in the management of intermediate stage hepatocellular carcinoma with TACE (see sections 4.2 and 5.1).

As per current guidelines TACE should be performed in patients with well-preserved liver function (mostly Child-Pugh A or B without ascites) and asymptomatic multinodular tumors without macroscopic portal vein invasion invasion or extrahepatic spread (see sections 4.1 and 4.2) following multidisciplinary diagnosis and assessment in a specialist centre experienced in performing TACE.

Patients with liver decompensation or more advanced liver failure should be excluded from TACE since this can lead to severe adverse events (see section 4.8).

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 TACE procedure.

Iodinated contrast agent induced renal insufficiency must be systematically prevented by correct rehydration before and after TACE of hepatocellular carcinoma.

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

Peripheral and central vascular embolisation:
Off-target embolisation of various parts of the body may also occur in the context of selective embolisation in combination with surgical glue (See Embolic and thrombotic complications). The intrinsic properties of the glue (polymerisation capacity and resorption time) must be taken into account in the embolisation process. Patients should be closely monitored for embolic complication in a care setting deemed appropriate by the treating clinician.

The safety risks mentioned in the Instructions For Use of the surgical glue must be taken into account.

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. 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 foruse

Hypersensitivity

Before the examination:

- identify patients at risk through precise questioning about their history.

- Corticosteroids and H1 antihistamines have been proposed as premedication in patients at greatest risk of intolerance reactions (those known to be intolerant to a contrast agent). They do not prevent the occurrence of severe or fatal anaphylactic shock, however.

Throughout the examination, it is necessary to ensure the following:

- medical monitoring
- maintenance of venous access

After the examination:

- After administration of a contrast agent, the patient must be kept under observation for at least 30 min, as most of the serious undesirable effects occur within this period.

The patient must be warned of the possibility of delayed reactions (occurring up to 7 days after administration) (see section 4.8).

TACE
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 procedure.

Avoid combinations with nephrotoxic medicines (see section 4.5). If such a combination is necessary, laboratory monitoring of renal function must be intensified.

Allow at least 48 hours between radiological examinations or interventions with iodinated contrast agent injections. Alternatively 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: 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 TACE procedure.

Hysterosalpingography
Intravasation of Lipiodol Ultra Fluid may occur in the course of a hysterosalpingography procedure and may result in serious pulmonary or cerebral embolic complications in the next hours following the procedure. The hysterosalpingography procedure should be immediately interrupted in case of suspected or confirmed intravasation of Lipiodol Ultra Fluid. The patient should be closely monitored for embolic complication in a care setting deemed appropriate by the treating clinician.

Miscellaneous
When injected into certain fistulae, great care should be taken to avoid penetration of vascular channels with the risk of oil embolism.

Care should be taken not to inject the product into an area affected by haemorrhage or trauma.

Indications for the use of Lipiodol Ultra-Fluid must be carefully assessed in patients with primary lymph oedema, as the oedema can be exacerbated.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions with other medicines

- Metformin: in diabetic patients, intra-arterial administration of Lipiodol Ultra Fluid may cause lactic acidosis induced by diminished renal function. In patients undergoing TACE, metformin must be discontinued before the examination and resumed no earlier than two days after the procedure.

Combinations that need to be taken into account

- Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers: these medicines reduce the effectiveness of the cardiovascular mechanisms that compensate for blood-pressure disturbances: the doctor should be informed about these prior to the administration of Lipiodol Ultra Fluid and have resuscitation equipment at hand.

- 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 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.

Interference with diagnostic tests
As Lipiodol Ultra Fluid remains in the body for several months, thyroid diagnostic results can be affected for up to two years after lymphography.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Lipiodol Ultra Fluid during pregnancy has not been demonstrated. The use of

Lipiodol Ultra Fluid during pregnancy causes iodine transfer which probably interferes with the thyroid function of the foetus. Although this anomaly is transitory it produces the potential risk of brain damage and permanent hypothyroidism, and therefore requires supervision of thyroid function and careful medical monitoring of the neonate. Consequently, Lipiodol Ultra Fluid must only be used in pregnancy if absolutely necessary and under strict medical supervision.

Also Lipiodol Ultra Fluid must not be used for hysterosalpingography when pregnancy is suspected or confirmed.

If a woman conceives in the months following hysterosalpingography the pregnant woman and fetus should be monitored for any indication of thyroid dysfunction, and there should also be surveillance of the newborn's thyroid function (See Sections 4.4 and 4.8)

Lactation
Pharmacokinetic studies show significant excretion of iodine in breast milk following intramuscular administration of Lipiodol Ultra Fluid. Iodine has been shown to pass into the vascular bed via the digestive tract of breastfeeding infants and this could interfere with their thyroid function. Consequently, if Lipiodol Ultra Fluid is to be used, breastfeeding should be interrupted or the neonate's thyroid function should be checked more frequently.

4.7 Effects on ability to drive and use machines

The effects on the ability to drive and to use machines have not been investigated.

4.8 Undesirable effects

The undesirable effects 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<1/10), uncommon (<1/1000 to 1<1/100), rare (<1/10,000 to <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Data are presented separately for diagnostic radiology and TACE procedure reflecting the different profile of adverse reactions observed

Diagnostic radiology
Incidence of adverse reactions from post-marketing experience are:

System organ class	Frequency: undesirable effect
Immune system disorders	Unknown: hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Endocrine disorders	Unknown: hypothyroidism, hyperthyroidism, thyroiditis, goitrea
Nervous system disorders	Unknown: Cerebral embolism, cerebral infarction
Eye disorders	Unknown: Retinal arterial embolism
Vascular disorders	Unknown: Lymphoedema aggravation
Respiratory, thoracic and mediastinal disorders	Unknown: Pulmonary embolism, dyspnea, cough
Gastrointestinal disorders	Unknown: Vomiting, diarrhoea, nausea
Hepatobiliary disorders	Unknown: Hepatic vein thrombosis
General disorders and administration site conditions	Unknown: Granuloma, fever, pain
Injury, poisoning and procedural complications	Unknown: Venous intravasation[a]

[a]: in the context of hysterosalpingography (HSG)

TACE
Adverse reactions and their incidence were determined based on meta-analysis of data from selected published studies.

System organ class	Frequency: undesirable effect
Blood and lymphatic system disorders	Very common: Hematotoxicity

Gastrointestinal disorders	Unknown: pancreatitis Common: Gastrointestinal haemorrhage
Hepatobiliary disorders	Very common: Hepatic enzyme abnormal Common: Hepatic failure Common: Hepatic encephalopathy Common: Hepatic infarction Common: Ascites Uncommon: Biloma Uncommon: Cholecystitis
Infections and infestations	Uncommon: Abscess, including liver abscesses
Injury poisoning and procedural complications	Very common: Post embolisation syndrome Common: Post procedural complication
Renal and urinary disorders	Uncommon: Renal failure
Respiratory, thoracic and mediastinal disorders	Uncommon: Acute respiratory distress syndrome, pneumonitis Common: Pulmonary oedema Common: Pleural effusion
Skin and subcutaneous tissue disorders	Unknown: Skin necrosis

Most adverse effects are dose related and dosage should therefore be kept 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 reduced transport capacity. In previously damaged or hypoplastic lymph nodes, these changes can exacerbate the existing lymphostasis.

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 lymphography
An increase of temperature followed by fever with temperature of 38 to 39°C may be observed during the 24 hours after the exam.

Oil microemboli can occur with or without clinical symptoms. In very rare cases, they may resemble organic emboli in appearance and size. They appear as punctiform or flat opacities on X-ray images of the lungs. Transient increases in temperature may occur. Oil microemboli occur more frequently after overdose of the contrast agent or excessively rapid infusion. They are favoured by anatomic abnormalities such as lymph-venous fistulae or decreased lymph node uptake capacity (in the elderly or after radiotherapy or cytostatic therapy).

Patients with cardiac right-to-left shunt and those with a massive pulmonary embolism are particularly at risk of cerebral oil microemboli.

In hysterosalpinography
Transitory fever reactions, usually below 38°C accompanied by pelvic pain are frequent. Episodes of salpingitis or pelvic peritonitis have been reported after the exam in case of latent infection. Granuloma type tissue reactions are rare but could be serious during the exam as they produce a risk of perforation.

Hypothyroidism may also occur especially in patients with subclinical hypothyroidism.

Following maternal exposure with Lipiodol Ultra Fluid, including maternal exposure before pregnancy, fetal thyroid disorders including fetal goitre were also reported. *See also Sections 4.4 and 4.6*.

Intravasation of Lipiodol Ultra-Fluid may occur in the course of hysterosalpingography procedure and may result in serious pulmonary or cerebral embolic complications.

In peripheral and central vascular embolisation:
No adverse reactions specifically related to Lipiodol Ultra Fluid have been described. However, serious thromboembolic adverse events, which might be fatal, have been associated with uncontrolled dissemination of the mixture containing Lipiodol

Ultra Fluid and surgical glue. The causal role of Lipiodol Ultra Fluid as a component of the mixture should therefore be taken into consideration (see section 4.4).

In sialography
A secondary inflammation reaction can sometimes occur with functional glandular paralysis (salivary duct inflammation) which disappear within 48 hours.

In TACE
The most frequent adverse reactions of TACE treatment are post-embolisation syndrome (fever, abdominal pain, nausea and vomiting) and transient changes in liver function tests. This can last for a few hours to few days. This syndrome is usually self-limiting and is treated symptomatically.

Adverse reactions may also be due to anticancer medicines or the procedure itself.

As with any medical procedure there are specific procedural risks and complications that can occur:

iatrogenic dissection of hepatic artery, puncture site hematomas, peritoneal bleeding due to wire penetration in branch of gastric artery, subcapsular hematomas.

Other important complications which may be common:

- Alteration of liver function tests and liver failure, especially in patients with liver dysfunction, larger tumour size or in patients receiving large doses of cytotoxic/Lipiodol or undergoing multiple TACE sessions. Amongst the liver related complications: hepatic decompensation/deterioration of hepatic function, hepatic encephalopathy with coma and hepatic infarction
- Renal failure which is frequently associated with diabetes, number of treatment sessions, severity of liver disease.
- Pulmonary complications including ARDS/pulmonary embolization, pulmonary edema and pleural effusion
- Also ischemic complications of TACE appear and can lead to hepatic and splenic abscesses, acute cholecystitis and bilomas.
- Ascites and Gastrointestinal bleeding due to rupture of varices may occur.

Further serious adverse events associated with uncontrolled dissemination of Lipiodol Ultra Fluid 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.

Hematologic toxicity such anemia, leukopenia, neutropenia and thrombopenia have been reported within TACE and related to anti-cancer agent used, for more information please refer to the corresponding Summary of Product Characteristics.

Potential reactivation of hepatitis B/C virus following TACE may occur.

Undesirable effects in children
The expected nature of the undesirable effects connected with Lipiodol Ultra Fluid is the same at 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: HPRA Pharmacovigilance.
Website: www.hpra.ie

4.9 Overdose

Overdose may lead to respiratory, cardiac or cerebral complications, which can potentially be fatal. Microembolisms may occur more frequently in the context of overdose.

The total therapeutic 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 support of all vital functions. Sites performing contrast medium examinations must be equipped with medicines and equipment for emergency aid.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: non-water-soluble contrast agent, ATC code: V08AD01. Lipiodol Ultra Fluid is an X-ray contrast medium.

Used in TACE by selective intra-arterial hepatic injection, Lipiodol Ultra Fluid 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 (such as, doxorubicin, epirubicin and mitomycin) into hepatocellular carcinoma nodules and, as a transient embolic, it contributes to the vascular embolisation induced during the procedure.

As a selective intra-arterial hepatic injection procedure, TACE 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 Fluid'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.

Used in hysterosalpingography, in women with infertility for more than 1 year randomly assigned to hysterosalpingography with Lipiodol Ultra-Fluid (n=73) or no hysterosalpingography (n=85), the pregnancy rate at 6 months follow-up was 38.4% (28/73) and 16.5% (14/85), respectively (p=0.002) and the live birth rate was 31.5% (23/73) and
12.9% (11/85), respectively (p=0.005).

When analysed separately, the increase in pregnancy rate was statistically significant at 6- month follow-up for the subgroup of women with endometriosis (48% vs 11%, p=0.001) and not statistically significant for the subgroup of women with pure unexplained infertility (33% vs 21%, p=0.168), while it was the opposite at 24 months follow-up: statistically significant increase in women with pure unexplained infertility (60% vs 40%, p=0.04) while the increase in pregnancy rate was no longer statistically significant in women with endometriosis (56% vs 43%, p=0.32).

In a multicentre, randomised, open-label study, women between 18 and 39 years, with infertility for more than 1 year and low risk of tubal disease were randomly assigned to either hysterosalpingography with Lipiodol Ultra-Fluid (n=554) or hysterosalpingography with water soluble iodinated contrast agent (n=554). After a follow-up of 6 months, the pregnancy rate was 39.7% (220/554) and 29.1% (161/554), respectively (p<0.001) and the live birth rate was 38.8% (214/552) and 28.1% (155/552), respectively (p=0.005).

A meta-analysis of randomized controlled trials showed an overall odds ratio (OR) for pregnancy within 6 months after the procedure significantly in favor of hysterosalpingography with Lipiodol Ultra-Fluid: OR of 3.47 [95%CI: 1.98; 6.08] when compared to no hysterosalpingography (p<0.001, 3 studies, 382 women) and OR of 1.59 [95%CI: 1.28; 1.98] when compared to hysterosalpingography with water soluble iodinated contrast agent (p<0.001, 4 studies, 1510 women).

Live birth rate was reported as a secondary criterion in some studies with various follow-up durations. The overall OR was also in favor of hysterosalpingography with Lipiodol Ultra- Fluid but without reaching statistical significance: 2.1 [95%CI: 0.87; 5.17] when compared to no hysterosalpingography (p=0.100, 3 studies, 1692 women) and 1.45 [95%CI: 0.99; 2.12], when compared to hysterosalpingography with water soluble iodinated contrast agent (p=0.055, 5 studies, 3281 women).

<u>In peripheral and central vascular embolisation:</u>
When mixed with a cyanoacrylate-based surgical glue, Lipiodol Ultra Fluid is used as a radiopaque polymerising retardant. Upon contact with body fluids or tissue, the surgical glue polymerises into a solid material. The amount of Lipiodol Ultra Fluid used will vary the time of polymerisation. Lipiodol Ultra Fluid, as an oily contrast agent, allows the visualisation and control of the procedure due to its opacifying properties.

A systematic review and analysis of the literature showed a consistently high rate of technical success for vascular embolisation with Lipiodol Ultra Fluid combined to cyanoacrylate glue in various settings (such as active bleeding, tumor, vascular anomalies). A meta-analysis including 150 studies and over 8900 patients showed an overall technical success rate of **95.8%**

[95% Confidence interval: 95.4%; 96.3%] when using Lipiodol in association with glue for vascular embolisation. This rate was either significantly higher than or similar to that of other embolisation techniques (ligation, shunt, sclerotherapy, and microparticles) reported in 7 randomised controlled trials.

5.2 Pharmacokinetic properties

Lipiodol Ultra Fluid can remain in the body for several weeks or months after lymphography. Following intralymphatic administration, Lipiodol Ultra Fluid is transported in blood to the liver, to the lungs where the lipid droplets are rapidly dispersed in the pulmonary alveoli, to the spleen and to adipose tissue. Disappearance of droplets in the lungs or other tissues proceeds slowly. During metabolism, iodine is released which is eliminated in urine as iodine.

After selective intra-arterial injection into the hepatic artery TACE of hepatocellular carcinoma, Lipiodol Ultra Fluid is significantly more concentrated in the tumour than in the healthy liver tissue.

After intrauterine injection in rats, Lipiodol Ultra Fluid migrates through the Fallopian tubes to the peritoneal cavity from which it is resorbed. The Tmax in plasma is reached around 8 hours post-administration. Half-life in plasma was about 18 hours. After 7 days, 48% of injected dose was eliminated (37% in urine, 11% in faeces).

5.3 Preclinical safety data

There are no findings from preclinical testing of Lipiodol Ultra Fluid which could be of relevance for the prescriber in recognizing the safety of this product used for the authorized indications, and which is not already included in other sections of this SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Lipiodol Ultra Fluid has been shown to dissolve polystyrene; for this reason disposable syringes made from this material must not be used to administer this preparation. Only equipment made from compatible materials, as described in section 6.6, should be used to administer Lipiodol Ultra Fluid.

Lipiodol Ultra Fluid must not be mixed with other medicinal products except those mentioned in section 6.6.

Medicinal products containing liposomal formulations should not be mixed with Lipiodol Ultra Fluid.

6.3 Shelf life

3 years.

Once opened, use immediately and discard any unused content.

When mixed with other compatible medicinal products (see sections 4.2 and 6.6), the mixture is to be prepared at the time of use and must be used promptly after preparation (within 3 hours).
For chemoembolisation procedures of hepatocellular carcinoma, the storage time of mixture with anticancer medicines at a temperature of 25°C should normally not exceed 3 hours.

6.4 Special precautions for storage

Do not store above 25°C.
Keep in outer carton
For storage conditions following mixing with compatible medicinal products listed in section 6.6, refer to section 6.3.

6.5 Nature and contents of container

Clear type I glass ampoules of 10 ml.
Box of 1 ampoule.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

If the product becomes opaque or dark amber in colour it should not be used. For single use only. Discard any remaining contents after use.

Only equipment made from compatible plastic materials (i.e: polyamide, polypropylene, polysulfone) should be used to administer Lipiodol Ultra Fluid.

Lipiodol Ultra Fluid can be mixed with medicinal products containing the following anticancer drugs: doxorubicin, epirubicin and mitomycin (see section 4.2).

Medicinal products containing liposomal formulations should not be mixed with Lipiodol Ultra Fluid.

Preparation of the mixture of Lipiodol with anticancer drugs must take place in a controlled and validated aseptic environment. Special precautions for disposal and other handling of the anticancer drugs must be strictly followed.

Lipiodol Ultra Fluid can be mixed with cyanoacrylate-based surgical glues. Instructions For Use of the surgical glue used for vascular embolisation must be strictly followed.

7 MARKETING AUTHORISATION HOLDER

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BP 57400
95943 Roissy CdG cedex
France

8 MARKETING AUTHORISATION NUMBER

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