SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lipiodol Ultra Fluid, 480 mg Iodine/mL, solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Ethyl esters of iodinated fatty acids of poppy seed oil	10 mL
Corresponding to an iodine content of	480 mg/mL

Viscosity at 15°C	70 cP (centipoises)
Viscosity at 37°C	25 cP
Relative density at 15°C	1.280

This product does not contain any excipients.

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lipiodol Ultra Fluid is an oily x-ray contrast medium for use in lymphography, hysterosalpingography in women undergoing infertility workup and sialography. On account of its low viscosity Lipiodol Ultra Fluid is suitable for introduction into narrow channels and may therefore be used in ducts, fistulae and sinuses.

This medicinal product is for diagnostic use only.

4.2 Posology and method of administration

Posology

Adults

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

Hysterosalpingography in women undergoing infertility workup: 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.

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

Paediatric population

The safety and efficacy of Lipiodol Ultra Fluid in children have not been specifically established for the indications of lymphography and sialography. No data are available.
There is no relevant use of Lipiodol Ultra Fluid in the paediatric population for the indication of hysterosalpingography.

Elderly population
The safety and efficacy of Lipiodol Ultra Fluid in the elderly have not been specifically established. Currently available data are described in section 4.4 but no recommendation on a posology can be made.

Method of administration
Lipiodol Ultra Fluid should be administered via a suitable syringe and cannula (see section 6.2 incompatibilities). The use of a glass syringe is recommended.

Administration in lymphography is by lymphatic cannulation.

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.

4.3 Contraindications

- - Hypersensitivity to the active substances or to any of the excipients listed in section 6.1. 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).

4.4 Special warnings and precautions for use

Lipiodol Ultra-Fluid must not to be administered by intravenous, intraarterial or intrathecal route.

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

4.4.1 Warnings

4.4.1.1 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 embolisation 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. Radiological or radioscopic monitoring during the injection is recommended. The occurrence of pulmonary invasion may be minimised 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.

4.4.1.2 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 re-administration of the product and are thus regarded as at-risk patients.

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.

4.4.1.3 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. Iodism 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.

When used in hysterosalpingography in patients considered at risk for hypothyroidism, thyroid function should be monitored closely for several months after the examination to observe potential development of hypothyroidism. The dose of Lipiodol Ultra Fluid should be kept as low as possible to minimize the potential risk of thyroid dysfunction.

4.4.1.4 Hysterosalpingography

Intravasation of Lipiodol 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. The patient should be closely monitored for embolic complication in a care setting deemed appropriate by the treating clinician.

4.4.2 Precautions for use

4.4.2.1 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) (cf. section 4.8 Undesirable effects).

4.4.2.2 Thyroid

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.

4.4.2.3 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.

4.5 Interaction with other medicinal products and other forms of interaction

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.
- 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 falsified 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.

Breastfeeding
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.

Fertility
In women who underwent hysterosalpingography with Lipiodol Ultra-Fluid for infertility workup, a higher rate of pregnancy has been observed, compared to women who did not undergo any hysterosalpingography or who underwent hysterosalpingography with water-soluble iodinated contrast agents.

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

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 increased 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 patient with subclinical hypothyroidism.

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

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).

System organ class	**Frequency: undesirable effect**
Immune system disorders	Unknown: hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Endocrine disorders	Unknown: hypothyroidism, hyperthyroidism, thyroiditis
Nervous system disorders	Unknown: Cerebral embolism
Eye disorders	Unknown: Retinal vein thrombosis
Vascular disorders	Unknown: Lymphoedema aggravation
Respiratory, thoracic and mediastinal disorders	Unknown: Pulmonary embolism, dyspnea, cough
Gastrointestinal disorders	Unknown: Vomiting, 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*

* In the context of hysterosalpingography.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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 agents, ATC code: V08AD01

Lipiodol Ultra Fluid is an X-ray contrast medium.

5.2 Pharmacokinetic properties

Distribution

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.

Elimination

Disappearance of droplets in the lungs or other tissues proceeds slowly. During metabolism, iodine is released which is eliminated in urine as iodine. Lipiodol Ultra Fluid can remain in the body for several weeks or months after lymphography.

5.3 Preclinical safety data

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).

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

Each ampoule contains 100% of iodised ethyl-esters of the fatty acids of poppy-seed oil.

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.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Protect from light. If the product becomes opaque or dark amber in colour it should not be used. Store below 25°C.

6.5 Nature and contents of container

Clear glass ampoules of 10 mL.

6.6 Special precautions for disposal

If the product becomes opaque or dark amber in colour it should not be used.

7 MARKETING AUTHORISATION HOLDER

Guerbet
BP 57400
95943 Roissy CdG Cedex
France

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