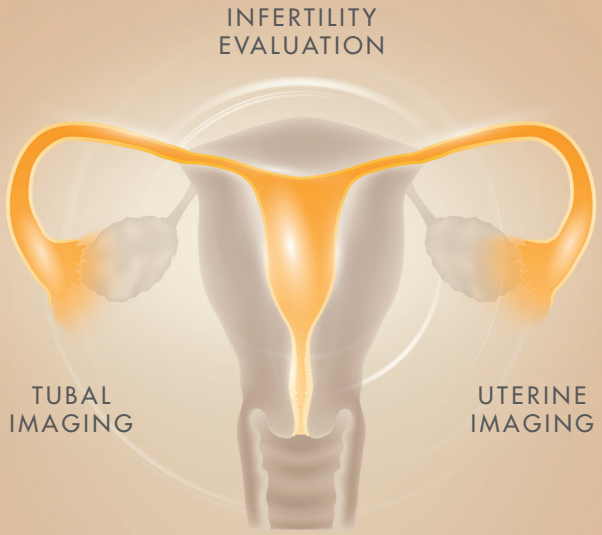
LIPIODOL® ULTRA FLUID

Ethyl ester of iodized fatty acids of poppy seed oil

The only oil-based contrast agent indicated for HSG[1-9]



Guerbet

LIPIODOL® ULTRA FLUID

FOR HYSTEROSALPINGOGRAPHY

Pharmaceutical form: Lipiodol® Ultra Fluid 480 mg Iodine per mL, solution for injection 10 mL, ethyl esters of iodized fatty acids of poppy-seed oil

Recommended dosage: Up to 20 mL, depending on the volume of the uterine cavity

Contents

Lipiodol® Ultra Fluid indication

Hysterosalpingography

- **Definition:** **radiological examination** to investigate the uterine cavity, Fallopian tubes & peritoneal cavity. It entails the injection of contrast medium and visualization under fluoroscopy.[10]

- CHARACTERIZATION OF HSG FINDINGS[11]

Tubal abnormalities

- Tubal occlusion
- Salpingitis isthmica nodosum
- Polyps
- Hydrosalpinx
- Peritubal adhesions

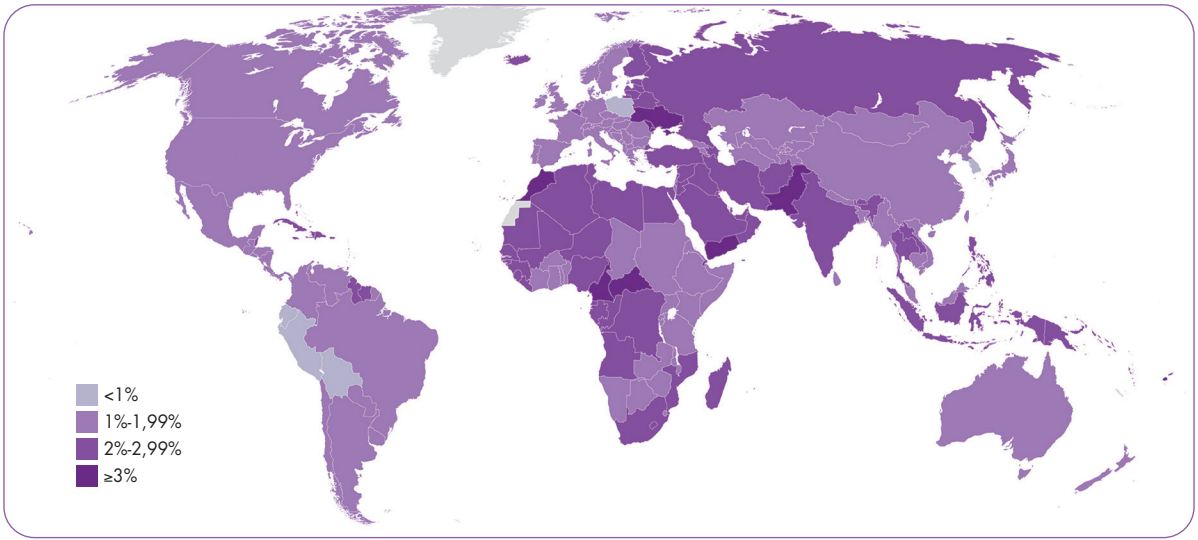
Uterine cavity abnormalities

- Congenital anomalies
- Polyps
- Leiomyomas
- Surgical changes
- Synechiae
- Adenomyosis
- Müllerian duct anomalies

HSG – Simple & accurate procedure for tubal patency & uterine investigation

Infertility prevalence

▸ PREVALENCE OF PRIMARY INFERTILITY AMONG WOMEN WHO SEEK A CHILD, IN 2010 [12]



Infertility – A huge clinical unmet need over the world

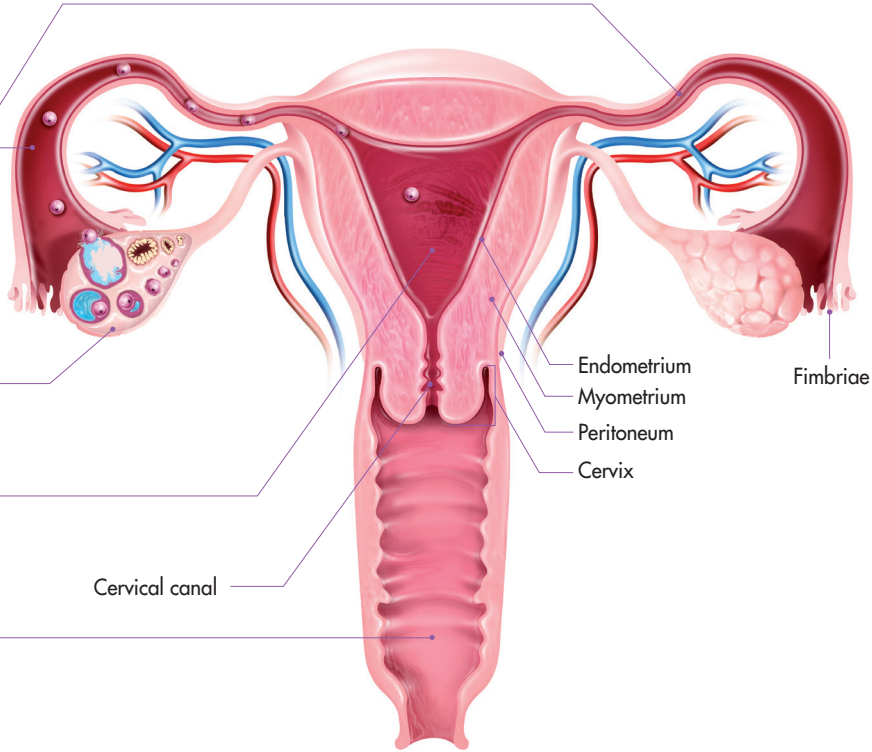
The female reproductive system

Fallopian tubes: transport sperm towards the egg for fertilization and then fertilized egg to the uterus

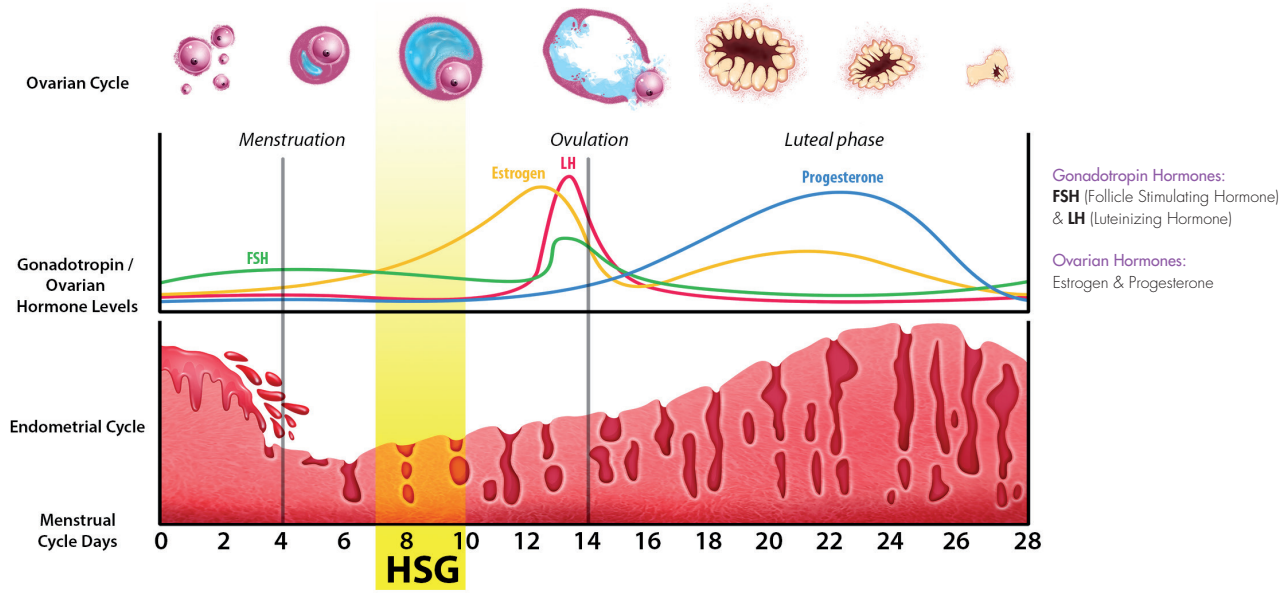
Ovaries: secrete estrogen & progesterone; produce eggs

Uterus: where foetus develops during pregnancy

Vagina: where semen enters the body; sperm can then travel up to the uterus and into the Fallopian tubes



When to perform HSG [13]

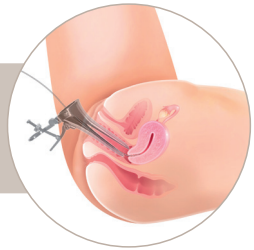


HSG – Procedure performed after bleeding period & before ovulation (ideally before the 12th day of the menstrual cycle for women with normal cycle length)

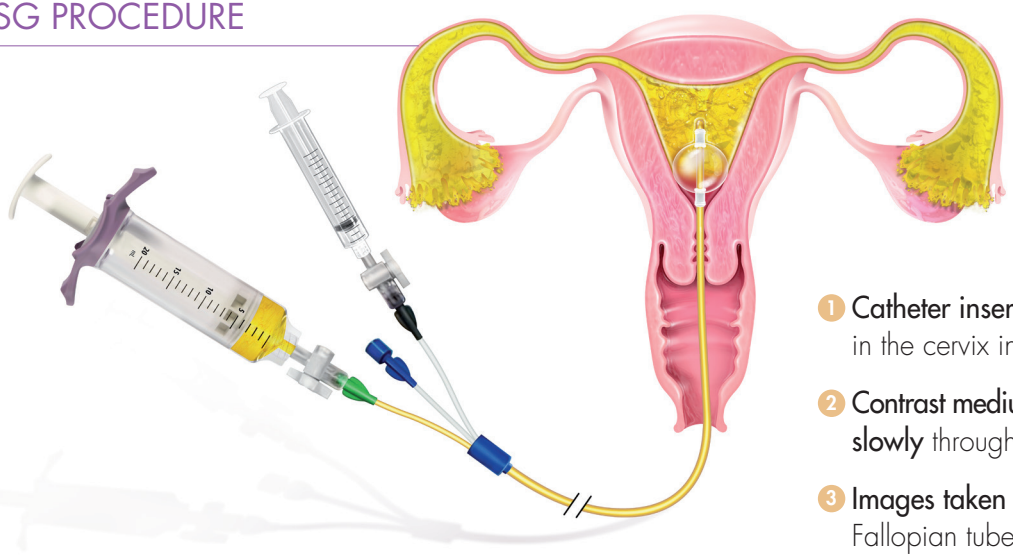
HSG steps

PATIENT PREPARATION

- ✓ The patient is **positioned on her back on a table** under a fluoroscope, bringing **legs up** into gynecological position
- ✓ Cervix must be **cleaned with an antiseptic**
- ✓ Vaginal **speculum** gently inserted for visualization of cervix



› HSG PROCEDURE



1. **Catheter inserted** through the opening in the cervix into the uterus
2. **Contrast medium (Lipiodol® Ultra Fluid) instilled slowly** through catheter into the uterine cavity
3. **Images taken** of the uterine cavity and Fallopian tubes

Lipiodol® HSG: Endorsement by international clinical practice guidelines

NICE Guidelines [14]

«…The potential therapeutic effect of diagnostic tubal patency testing has been debated for over 40 years. Tubal flushing might involve water- or oil-soluble media. A systematic review of eight RCTs showed a significant increase in pregnancy rates with tubal flushing using oil-soluble contrast media when compared with no treatment…Tubal flushing with oil soluble contrast media was associated with an increase in the odds of live birth…[Evidence level 1a]…»

**Hierarchy of evidence: 1a – Systematic review and meta-analysis of randomised controlled trials*

American Society for Reproductive Medicine (ASRM) [15]

«…Hysterosalpingography (HSG), using either a water- or lipid-soluble contrast media, is the traditional and standard method for evaluating tubal patency and may offer some therapeutic benefit…»

Canadian Fertility & Andrology Society (CFAS) [16]

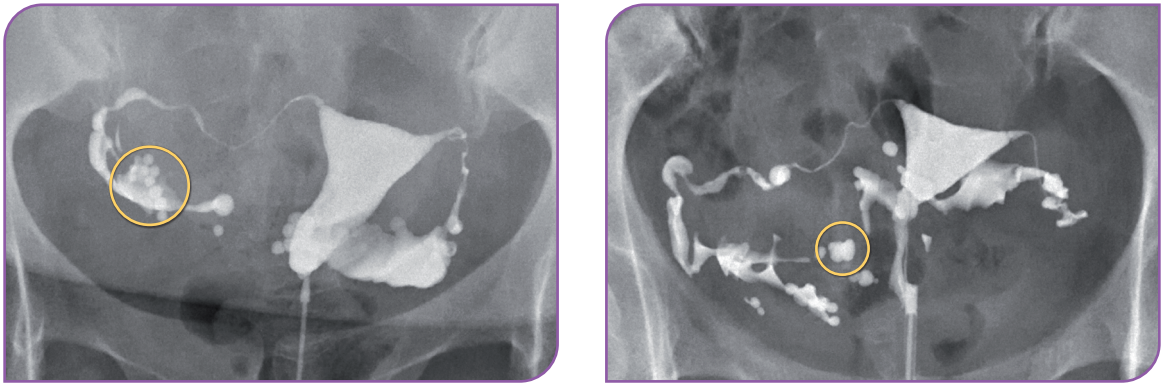
«…Hysterosalpingography…: Water-soluble or oil-based radio-opaque contrast material is used to delineate the uterine cavity…»

«…HSG is generally accepted as the traditional, least invasive and most cost effective method of evaluation of tubal patency in low-risk women…»

Lipiodol® HSG: Findings

Normal HSGs

Lipiodol® HSG showing normal uterine cavity & patent tubes

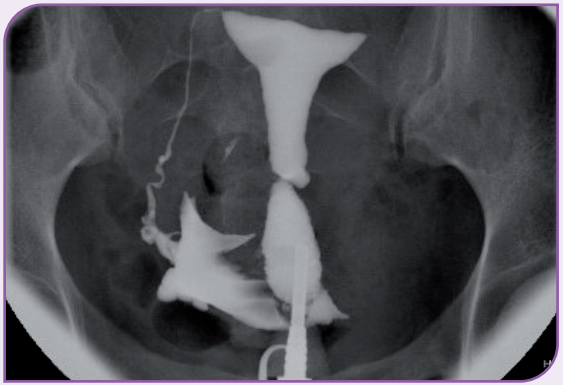


Courtesy: Pr. Velja Mijatovic & Dr. Kim Dreyer, Amsterdam University Medical Center (Netherlands)

Example of specific Lipiodol® droplets in the peritoneal cavity confirming tubal patency

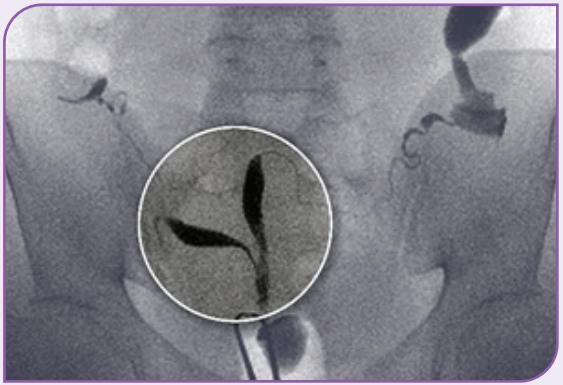
Abnormal findings

Lipiodol® HSG showing uterine cavity with a filling defect near the left tube due to an endometrial polyp & normal right tube with patency



Courtesy: Pr. Velja Mijatovic & Dr. Kim Dreyer, Amsterdam University Medical Center (Netherlands)

Lipiodol® HSG showing Müllerian duct anomalies



Courtesy: Dr. Naile Bolca Topal, Uludag University (Turkey)

Lipiodol® for HSG – Accurate tubal & uterus imaging

Lipiodol® HSG: Safety

✓ **No evidence of difference between OSCM Lipiodol® & WSCM groups** [6,7,17]

- Miscarriage
- Ectopic pregnancy
- Infection
- Haemorrhage

> ***«…There were no significant differences in miscarriage, ectopic pregnancy & infection rates between tubal flushing with oil or water, or between oil plus water media versus water media only…»***
>
> *NICE Clinical Guidelines 2013* [14]

OSCM: Oil Soluble Contrast Medium (Lipiodol® Ultra Fluid) I WSCM: Water Soluble Contrast Medium

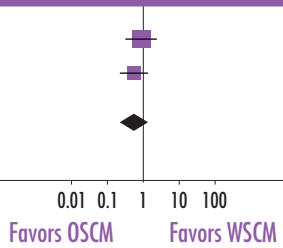
Rare HSG complications may occur

- Venous intravasation: Reported rate < 6.9% [2,18]
- Pulmonary embolism: Very rare cases which remained clinically asymptomatic (Reported rate 1.1%) [19]; No cases reported in a meta-analysis from 2019 [20]
- Lipogranuloma: Reported rate < 0.1% [21]
- Thyroid dysfunction (contraindicated in case of confirmed hyperthyroidism): Low risk of transient hypo/hyperthyroidism; when biochemically observed, no clinical consequences reported [22]

Lipiodol® for HSG – A safe procedure

Miscarriage [23]

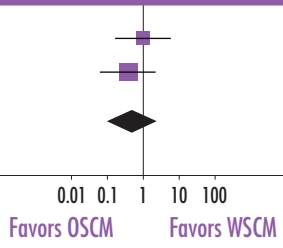
Study or subgroup	OSCM n/N	WSCM n/N	Odds Ratio M-H,Random,95% CI*	Weight	Odds Ratio M-H,Random,95% CI*
Dreyer 2017	29/554	31/554		58.8 %	0.93 [0.55, 1.57]
Spring 2000	19/273	25/260		41.2 %	0.70 [0.38, 1.31]
Total	**48/827**	**56/814**		**100 %**	**0.83 [0.56, 1.24]**



Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$, df = 1 (P = 0.50); I^2=0%
Test for overall effect: Z = 0.92 (P = 0.36)

Ectopic pregnancy [23]

Study or subgroup	OSCM n/N	WSCM n/N	Odds Ratio M-H,Random,95% CI*	Weight	Odds Ratio M-H,Random,95% CI*
Dreyer 2017	2/554	2/554		43 %	1.00 [0.14, 7.12]
Spring 2000	2/273	2/260		57 %	0.47 [0.09, 2.60]
Total	**4/827**	**6/814**		**100 %**	**0.65 [0.18, 2.36]**



Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.32$, df = 1 (P = 0.57); I^2=0%
Test for overall effect: Z = 0.65 (P = 0.52)

*M-H: Mantel-Haenszel, CI: Confidence Interval

Lipiodol® HSG: Pain

✓ **Procedural pain level: No significant difference between OSCM & WSCM group** [7]

	OSCM (Lipiodol® Ultra Fluid) N=554	WSCM (Telebrix Hystero®) N=554	P value
Median pain score on visual-analogue scale	4.8 (3.0-6.4)	5.0 (3.0-6.7)	0.28

✓ **Post-procedural pain reported less frequently in OSCM than in WSCM group** [6]

Study or subgroup	OSCM n/N	WSCM n/N	Odds Ratio M-H,Fixed,95% CI*	Weight	Odds Ratio M-H,Fixed,95% CI*
Rasmussen 1991	54/103	281/314		100 %	0.13 [0.08, 0.22]

*M-H: Mantel-Haenszel, CI: Confidence Interval

Lipiodol® for HSG – A well-tolerated procedure

Lipiodol® HSG: Features & Benefits

Features	Benefits
▸ **Tube & uterus visualizer**	• **Both tubes & uterine cavity visualization** • **Accurate image quality** [1,17,24]
▸ **Convenient**	• **Simple** • **Well-tolerated** - Less frequent post-procedural pain & no significant difference in pain level during the procedure compared to WSCM group [1,6,7,17] • **Minimally-invasive**

Lipiodol® efficacy & safety for tubal patency & uterine investigation

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LIPIODOL ULTRA-FLUID. Composition: Ethyl esters of iodized fatty acids of poppy seed oil 10 mL, corresponding to an iodine content of 480 mg/mL. **Indications (**):** For diagnostic radiology - Lymphography - Hysterosalpingography - Sialography - Ascending urethrography – Fistulography and exploration of abscesses - Exploration of frontal sinuses - Pre and post-operative cholangiography. For interventional radiology - Visualisation and localization (by selective intra-arterial use during CT) of liver lesions in adults with known or suspected hepatocellular carcinoma - Visualisation, localisation and vectorisation during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma at intermediate stage, in adults - Visualisation and localisation of hepatocellular carcinoma at intermediate stage in adults - Selective embolization in combination with Histoacryl glue (particularly for arteriovenous malformation or aneurysms) - Selective injections of LIPIODOL ULTRA-FLUID into the hepatic artery for diagnostic purposes where a spiral CT scan is not practical. In endocrinology - Prevention of severe cases of iodine deficiency. This treatment should only be used when other methods of supplementation, particularly iodization of salt and/or drinking water, cannot be undertaken. **Posology and method of administration (*) (**):** have to be adapted according to the type of examination, the territories explored, the age and weight of the patient. The volume to be administered depends on the particular requirements of the technique and the size of the patient. Lipiodol Ultra Fluid must be administered by slow injection or via a catheter, using a suitable glass syringe or other administration devices proven to be compatible with Lipiodol Ultra Fluid. The instructions for use of these devices must be followed. **Contraindications:** Hypersensitivity to LIPIODOL ULTRA-FLUID - Manifest hyperthyroidism - Patients with traumatic injuries, recent hemorrhage or bleeding – Hysterosalpingography during pregnancy or acute pelvic inflammation – Bronchography. Interventional radiology: Intra-arterial administration of chemotherapy / 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 (*):** There is a risk of hypersensitivity regardless of the dose administered. Lymphography: Pulmonary embolism may occur immediately or after few hours to days from inadvertent systemic vascular injection or intravasation of LIPIODOL ULTRA-FLUID: Perform radiological monitoring during LIPIODOL ULTRA-FLUID injection and avoid use in patients with severely impaired lung function, cardiorespiratory failure or right-sided cardiac overload. 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 unpredictable: avoid use in patients with a history of sensitivity to other iodinated contrast agents, bronchial asthma or allergic disorders because of an increased risk of a hypersensitivity reaction to LIPIODOL ULTRA-FLUID. Thyroid dysfunction: can cause hyperthyroidism in predisposed patients. Lymphography saturates the thyroid with iodine for several months and thyroid exploration should be performed before radiological examination. Visualisation / localisation / chemoembolisation of liver tumours: Trans-Arterial Chemo-Embolization 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. Renal insufficiency must be prevented by correct rehydration before and after the procedure. Oesophageal varices must be carefully monitored. Hepatic intra-arterial treatment can progressively cause an irreversible liver insufficiency in patients with serious liver malfunction and/or undergoing close multiple sessions. The risk of superinfection in the treated area is normally prevented by administration of antibiotics. Embolization with glue: An early polymerisation reaction may exceptionally occur between LIPIODOL ULTRA-FLUID and certain surgical glues, or even certain batches of glue. Before using new batches of LIPIODOL ULTRA-FLUID or surgical glue, the compatibility of LIPIODOL ULTRA-FLUID and the glue must be tested in vitro. Indications for the use of Lipiodol Ultra-Fluid 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 (*):** Metformin, Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, Diuretics, Interleukin II. **Fertility, pregnancy and lactation (*):** LIPIODOL ULTRA-FLUID must only be used in pregnant women if absolutely necessary and under strict medical supervision. Breastfeeding should be discontinued if LIPIODOL ULTRA-FLUID must be used **- Effects on ability to drive and use machines:** The effects on ability to drive and to use machines have not been investigated **- Undesirable effects (*):** Most adverse effects are dose-related and dosage should therefore be kept as low as possible: hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypothyroidism, hyperthyroidism, thyroiditis, cerebral embolism, hepatic encephalopathy [a], retinal vein thrombosis, lymphoedema aggravation, pulmonary embolism, dyspnea, cough, pulmonary oedema [a], pleural effusion [a], acute respiratory distress syndrome [a], pneumonitis [a], vomiting, diarrhea, nausea, pancreatitis [a], ascites [a], hepatic vein thrombosis, cholecystitis [a], biloma [a], hepatic failure [a], hepatic infarction [a], granuloma, fever, pain, liver abscess [a], skin necrosis [a]. **Overdose (*):** The total dose of LIPIODOL ULTRA-FLUID administered must not exceed 20 mL **- Pharmacodynamic properties (*):** Pharmacotherapeutic group: X-ray contrast media, iodinated; ATC code: V08A D01.

Water-insoluble iodinated contrast medium. **Presentation (**)**: 10 mL glass ampoule. **Marketing authorization holder (*)**: Guerbet - BP 57400 - F-95943 Roissy CdG cedex - FRANCE. Information: tel: 33 (0) 1 45 91 50 00. Revision: June 13th, 2019.

(a) in the context of TAE or TACE.

(*) For complete information please refer to the local Summary of Product Characteristics (SPC).

(**) These information are intended for an international audience or are provided during an international event. Be aware that indications, posology and presentations may differ from country to country.

Reporting of suspected adverse reactions is important as it helps to continuously assess the benefit-risk balance. Therefore, Guerbet encourages you to report any adverse reactions to your health authorities or to our local Guerbet representative.

Countries in which HSG indication is registered: USA, Canada, Argentina, UK, Ireland, The Netherlands, Denmark, Turkey, South-Africa, Japan, Taiwan, Thailand, Australia & New Zealand.

For a copy of the SPC, please contact a member of Guerbet.

Not intended for US Healthcare Professionals.

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