LIPIODOL® ULTRA FLUID

Ethyl ester of iodized fatty acids of poppy seed oil

The only oil-based contrast agent indicated for HSG

INFERTILITY EVALUATION

TUBAL IMAGING

UTERINE IMAGING

Guerbet

Contrast for Life
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

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

P 4  Lipiodol® Ultra Fluid for Hysterosalpingography (HSG)
P 5  Reasons for performing HSG
P 6  The female reproductive system
P 7  When to perform HSG
P 8  HSG steps
P 9  Lipiodol® HSG: Findings
P 10 Lipiodol® HSG: Endorsement by international clinical practice guidelines
P 11 Lipiodol® HSG: Safety
P 12 Lipiodol® HSG: Pain
P 13 Lipiodol® HSG: Features & Benefits
P 14 Bibliography
Lipiodol® Ultra Fluid for Hysterosalpingography (HSG)

- Hysterosalpingography: 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:

  **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
Reasons for performing HSG

- Infertility work-up
- Sterilization procedure follow-up
- Pelvic pain
- Irregular menstrual cycles
- Congenital abnormalities/anatomic variants
- Postoperative uterine cavity
- Uterine fibroids
- Thickened/irregular endometrium
- Ectopic pregnancy sequelae
- Pre/post-surgery

HSG – Most commonly used in infertility evaluation

Example for CHINA
- 95% infertility evaluation
- 5% other evaluations (Surgical follow-up, dysfunctional uterine bleeding…)

Country % of using HSG in infertility evaluation
- UK 100%
- Germany 100%
- Japan 100%
- France 92%
- USA 85%
- Spain 84%
- Italy 83%
- Korea 83%
- Brazil 97%
- China 95%
- Spain 84%
- Italy 83%
- Korea 83%
- Brazil 97%
- China 95%
The female reproductive system

**Fallopian tubes:** transport eggs from ovaries to 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

HSG – Procedure performed after bleeding period & before ovulation (approximately between the 7th and 10th day of the menstrual cycle)
HSG steps

PATIENT PREPARATION
- Patient lies on table on her back under fluoroscope, bringing legs up into «frog position»
- External genitals must be cleaned with an antiseptic
- Vaginal speculum gently inserted for visualization of cervix

HSG PROCEDURE

1. Contrast medium injected slowly through catheter/cannula into uterine cavity (under fluoroscopy)

2. Images taken of uterine cavity and Fallopian tubes for tubal patency & uterine environment investigations

3. Instruments removed from cervix & vagina
Lipiodol® HSG: Findings

Normal HSG

Lipiodol® HSG showing normal peritoneal cavity & patent tubes

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

Lipiodol® HSG showing Müllerian duct anomalies

Lipiodol® – Accurate tubal & uterus imaging
Lipiodol® HSG: Endorsement by international clinical practice guidelines

American Society for Reproductive Medicine (ASRM) 12
«...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) 13
«...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...»

NICE Guidelines 14
«...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

World Endometriosis Society (WES) 15
«...Emerging therapies for infertility in women with endometriosis: ... (64) Lipiodol® hysterosalpingogram improves live birth rates in women with endometriosis, but otherwise unexplained infertility, who are attempting natural conception...»
Consensus grading γ, (majority, 50 – 80% agreed)

International Federation of Gynecology and Obstetrics (FIGO) 16
«...Use oil soluble contrast: there is evidence based support for a therapeutic effect [Luttjebroer, 2007] in contrast to water soluble contrast [Lindgren, 2009]...»
Lipiodol® HSG: Safety

✔ No evidence of difference between OSCM Lipiodol® & WSCM groups

- 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...”


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

Lipiodol® for HSG – A safe procedure
Lipiodol® HSG: Pain

✓ Procedural pain level: No significant difference between OSCM & WSCM group

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

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

✓ Post-procedural pain reported less frequently in OSCM than in WSCM group

Review: Tubal flushing for subfertility
Comparison: 3 WSCM versus OSCM
Outcome: Any postprocedural pain (dichotomous variable)

Lipiodol® for HSG – A well-tolerated procedure
Lipiodol® HSG: Features & Benefits

Features

- Tube & uterus visualizer
- Convenient

Benefits

- Both tubes & uterine cavity visualization
- Accurate image quality \(^1,17,18\)
- Simple
- Safe - No difference in adverse events rate compared to WSCM group \(^6,7,17\)
- 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
Bibliography

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 (**): In diagnostic radiology - Hysterosalpingography - Ascending urethrogramy - Lymphography - Sialography - Fistulography and exploration of abscesses - Exploration of frontal sinuses - Pre and post-operative cholangiography. In 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 - Selective embolization in combination with Histocryl 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. 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. Contraindications: Hypersensitivity to LIPIODOL ULTRA-FLUID - Confirmed hyperthyroidism - Patients with traumatic injuries, recent haemorrage or bleeding – Hysterosalpingography during pregnancy or acute pelvic inflammation – Bronchography. In interventional radiology (Trans-Arterial Chemo-Embolization), Administration in liver areas with dilated bile ducts unless drainage has been performed. Special warnings and special 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: can cause hyperthyroidism in predisposed patients. Lymphography saturates the thyroid with iodine for several months and thyroid exploration should be performed before radiological examination. Chemo-Embolization: Trans-Arterial Chemo-Embolization is not recommended in patients with decompensated liver cirrhosis (Child-Pugh ≥ 8), advanced liver dysfunction, macroscopic 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. Interaction with other medicinal products and other forms of interaction (*): Metformin, Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, 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, vomiting, diarrhoea, nausea, fever, pain, dyspnea, cough, hypothyroidism, hyperthyroidism, thyroiditis, pulmonary embolism, cerebral embolism, retinal vein thrombosis, lymphoedema aggravation, hepatic vein thrombosis, granuloma. 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: April 24th, 2018. (*) For complete information please refer to the local Summary of Product Characteristics (SPC). (**) Indications, volumes 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. This brochure is not intended for US Healthcare Professionals.