**TRANSPARENCY COMMITTEE**  
**Opinion**  
**18 December 2013**

**LIPIODOL ULTRA-FLUIDE 480 mg/ml, solution for injection**  
1 10 ml glass ampoule (CIP: 34009 306 216 0 8)  
Applicant: GUERBET

<table>
<thead>
<tr>
<th>INN</th>
<th>Fatty acid ethyl esters</th>
</tr>
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<tbody>
<tr>
<td>ATC Code (2013)</td>
<td>V08AD01 (iodinated contrast medium)</td>
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</table>

**Reasons for the review**  
- Re-assessment of the actual benefit at the request of the Committee (pursuant to Article R 163-21 of the French Social Security Code)  
- Extensions of indication:  
  - Diagnosis of liver lesions: diagnosis of the spread of malignant lesions, whether hepatic or not, by selective hepatic arterial injection.  
  - Embolisation with surgical glues: in association with surgical glues during vascular embolisations"

**List concerned**  
Hospital use (French Social Security Code L.5123-2)

**Indications concerned**  
- **In diagnostic radiology:**  
  o Lymphography  
  o Diagnosis of liver lesions: Diagnosis of the spread of malignant lesions, whether hepatic or not, by selective hepatic arterial injection.  
- **In interventional radiology:**  
  o Embolisation with surgical glues: In association with surgical glues during vascular embolisations."
01 ADMINISTRATIVE AND REGULATORY INFORMATION

| Marketing Authorisation (procedure) | Date of the initial Marketing Authorisation (national procedure): 28 March 1978  
Extension of indication: 13 April 2001 |
<table>
<thead>
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<tr>
<td>Prescribing and dispensing conditions</td>
<td>List I</td>
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<table>
<thead>
<tr>
<th>ATC Classification</th>
<th>Description</th>
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<tr>
<td>2013</td>
<td>Various</td>
</tr>
<tr>
<td>V</td>
<td>X-ray contrast media</td>
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<tr>
<td>V08</td>
<td>Contrast media, iodinated</td>
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<tr>
<td>V08AD</td>
<td>Non-water soluble X-ray contrast media</td>
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<tr>
<td>V08AD01</td>
<td>Ethyl esters of iodised fatty acids</td>
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</table>

02 BACKGROUND

LIPIODOL, ethyl esters of iodised fatty acids of poppy seed oil, is a non water soluble contrast medium. It differs from other iodinated contrast media by its non-water soluble nature and its administration route, lymphatic or intra-arterial only.

This review concerns the re-assessment of actual benefit in just its diagnostic indications, following the re-assessment of the risk/benefit ratio by the ANSM [French National Security Agency of Medicines and Health Products] in iodinated contrast media started at the end of 2011. Furthermore, the company has requested inclusion of LIPIODOL in the diagnosis of liver lesions and in embolisation, in association with biological glues (MA obtained in 2001).

Note that all the indications for LIPIODOL ULTRA-FLUID correspond to procedures listed in the CCAM (French Joint Classification Of Medical Procedures).

03 INDICATIONS

"In diagnostic radiology:
- Lymphography
- Diagnosis of liver lesions: diagnosis of the spread of malignant lesions, whether hepatic or not, by selective hepatic arterial injection.

In interventional radiology:
- Embolisation with surgical glues
  In association with surgical glues during vascular embolisations.

In endocrinology:
- Prevention of iodine deficiency disorders.
- This treatment should only be used when other methods of supplementation, particularly iodisation of salt and/or drinking water, cannot be undertaken."
"Lipiodol ultra-fluide must be administered by slow injection or catheterisation using a suitable glass syringe and a catheter.

In diagnostic radiology:

**Lymphography**

LIPIODOL ULTRA FLUIDE must be administered by lymphatic catheterisation. This may be preceded by injection of a dye to locate the lymphatic vessels.

The usual dose is 5 to 7 ml by intralymphatic injection only for opacification of a limb (the dose being adapted to the height of the patient), i.e. 10 to 14 ml for bilateral pedal lymphography. The dose should be reduced proportionally in children. In infants 1 to 2 years old, a dose of 1 ml per limb is sufficient.

**Diagnosis of liver lesions**

Intra-arterial route only.

The standard dose depends on lesion size and can vary from 2 to 10 ml per patient. Lipiodol Ultra-Fluide is sometimes mixed with small amounts of water-soluble iodinated contrast agents. The CT scan should be performed 7 to 15 days after the selective injection to allow the Lipiodol Ultra-Fluide to be eliminated from the non-tumoural liver tissue.

**Paediatric population**

The dose should be reduced proportionally in children.

**Patients who are underweight**

The dose should be reduced proportionally in this population.

**Elderly**

The product should be administered with caution in patients over 65 years old with underlying diseases of the cardiovascular, respiratory or neurological systems. In subjects with cardio-respiratory failure, particularly elderly patients, the doses should be adapted or the examination itself cancelled, since a portion of the product will temporarily embolise the pulmonary capillaries.

**In interventional radiology:**

**Embolisation with surgical glues**

Selective arterial catheterisation only.

The dose of Lipiodol Ultra-Fluide administered at each embolisation session depends on lesion size. The Lipiodol and liquid embolising agent mixture may vary from 20 to 80% but usually consists of a 50/50 mixture.

The volume injected should not exceed 15 ml."
**05 THERAPEUTIC NEED**

**05.1 Lymphography**

Lymphography is the opacification of lymphatic channels and lymph nodes by injection of an iodinated contrast medium such as LIPIODOL into a lymph vessel. Indications for lymphography have become exceptional, in particular, this examination, and therefore LIPIODOL is no longer used in lymphoma staging. The Société Française de Radiologie (French Society of Radiology, SFR), in its guide,\(^1\) does not recommend lymphography in any indication.

Lymphomas are currently staged by ultrasound and, with more precision than lymphography, by PET/CT (positron emission tomography) chest, abdomen and pelvic scan with FDG, neck scan, which is indicated in localised forms (stage I-II) and in anticipation of radiotherapy in Hodgkin's lymphoma. Note that ultrasound is indicated in the testes and if there is any question of a liver or spleen location. MRI is indicated in cerebral, meningeal and cardiac locations and if there is any question of bone marrow involvement.

A whole-body acquisition with diffusion weighting can complement conventional sequences. According to expert opinion, lymphography would still be useful in rare indications: traumatic injury of the thoracic duct and lymphatic channel occlusion.

**05.2 Liver lesions**

Characterisation (number, size, vascular extension) of liver lesions is vital to the therapeutic, and especially surgical, management of liver tumours. According to the characteristics identified, patient treatment will be different: surgery, primary or adjuvant chemotherapy. The first-line examination is MRI. Liver ultrasound is used only in certain cases. CT scan is a second-line examination, in the majority of cases, if MRI is not possible. CT scan combined with LIPIODOL may be used, exceptionally, in the diagnosis and pre-surgical staging of hepatocellular carcinomas, especially small lesions.

**05.3 Interventional radiology**

Arterial embolisation and embolisation of arteriovenous fistulas are done with solid implants, implants made up of synthetic particles or a combination of biological glue and LIPIODOL. Embolic implants may be:

- **Solid embolic implants**
  - Non-absorbable embolic implants:
    - Microcoils are metal implants, most often made of stainless steel or platinum, possibly combined with fibres. They come in different sizes, diameters, shapes and materials in order to be suitable for different morphological configurations of vessels to be occluded.
    - The mechanisms for detaching microcoils may be mechanical, electric or thermoelectric or hydraulic. They may have a simple or complex shape (microcoil forming a 3D cage after being deployed).
    - Synthetic particles (in polyvinyl acetate (PVA)), particles containing animal derivatives. These particles are either spherical or non-spherical.
    - Intracranial stents.
  - Absorbable embolic implants (gelatin).

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\(^{1}\) Guide de bon usage des examens d'imagerie. SFR 2013 http://gbu.radiologie.fr/
• Liquid embolic implants
These implants act by two different mechanisms of action: by polymerisation (cyanoacrylate glues) or by precipitation.
Embolic implants are used in many indications, regardless of the trade name.

- CEREBRAL
  - Intracranial aneurysms
  - Cerebral arteriovenous malformations
  - Dural arteriovenous fistulas
  - Post-traumatic and spontaneous carotid-cavernous arteriovenous fistulas
  - Hypervascular tumours
- SPINAL CORD (dura mater)
  - Spinal arteriovenous malformations
  - Dural arteriovenous fistulas
- SPINE
  - Hypervascular tumours of the spine (symptomatic vertebral angiomas, aneurysmal cysts, metastases, osteoblastomas, etc.)
- ENT and digestive system
  - Haemostasis indications
  - Tumours
  - Malformations
  - Traumatic vascular lesions

Embolisation may also be used in treating severe pulmonary arteriovenous malformations and varicoceles. The choice of the embolic implant depends on the size of the lesion and its location (cerebral or peripheral).2
LIPIODOL may be used in association with biological glues for arterial embolisation in cases of gastrointestinal bleeding, or bleeding originating from trauma, ulcer or tumour.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

LIPIODOL is the only non-water soluble contrast medium.

06.2 Other health technologies

6.2.1 Lymphography

In the examination of lymph nodes for pelvic tumours, ultrasound, CT and MRI are all first-line examinations.

6.2.2 Liver lesions

In the examination of liver lesions, the first-line examination is MRI. Ultrasound and CT are second-line examinations.

6.2.3 Interventional radiology

Arterial embolisation with solid implants or implants made of synthetic particles are alternatives to the association of biological glue + LIPIODOL. These products (glues, coils, non-absorbable particles) are medical devices. Stereotactic radiotherapy is also used in the treatment of intracranial dural arteriovenous fistulas.

The embolic implants used for treating arteriovenous fistulas are liquid embolic agents or glues, non-absorbable particles either based on PVA or particles made up of an acrylic polymer and gelatin of pig origin and coils (mentioned above).

> Conclusion

The alternatives listed are all clinically relevant.

For diagnosis, the relevant comparators are imaging techniques such as MRI, ultrasound and CT scan.

For embolisation, the relevant comparators are synthetic particles, solid implants and radiotherapy.
### International Information on the Medicinal Product

<table>
<thead>
<tr>
<th>Country</th>
<th>Marketing Authorisation</th>
<th>Indications and special condition(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>United Kingdom</td>
<td>Yes (03/06/1996)</td>
<td>Hysterosalpingography/lymphography/sialography</td>
</tr>
<tr>
<td>Austria</td>
<td>Yes (18/02/1966)</td>
<td>No information</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Yes (10/01/2001)</td>
<td>Lymphangiography/fistulography</td>
</tr>
<tr>
<td>Germany</td>
<td>Yes (18/10/1963)</td>
<td>Lymphography</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>Yes (21/03/1996)</td>
<td>Lymphography/interventional radiology</td>
</tr>
<tr>
<td>Hungary</td>
<td>Yes (17/12/2003)</td>
<td>No information</td>
</tr>
<tr>
<td>Portugal</td>
<td>Yes (14/03/2001)</td>
<td>Lymphography/prevention of iodine deficiencies</td>
</tr>
<tr>
<td>Ireland</td>
<td>Yes (07/05/1996)</td>
<td>No information</td>
</tr>
<tr>
<td>Denmark</td>
<td>Yes (08/09/1967)</td>
<td>Lymphography/hysterosalpingography</td>
</tr>
<tr>
<td>Belgium</td>
<td>Yes (01/06/1962)</td>
<td>Lymphography/interventional radiology</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Yes (14/08/1964)</td>
<td>Lymphography/hysterosalpingography</td>
</tr>
<tr>
<td>Italy</td>
<td>Yes (13/12/1980)</td>
<td>Hysterosalpingography/urethrography/lymphography/sialography/ examination of the frontal sinus/pre and post-operative cholangiography/chemoembolisation for hepatocellular carcinoma/selective embolisation combined with glues</td>
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<tr>
<td>USA</td>
<td>Yes (31/03/1954)</td>
<td>Lymphography/hysterosalpingography</td>
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</tbody>
</table>

### Summary of Previous Assessments

**For the lymphography indication**

<table>
<thead>
<tr>
<th>Date of opinion (reason for request)</th>
<th>22 April 2000</th>
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<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Lymphography</td>
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<tr>
<td><strong>AB (wording)</strong></td>
<td>Moderate</td>
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<tr>
<td><strong>IAB (wording)</strong></td>
<td>Not applicable</td>
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<tr>
<td><strong>Studies requested</strong></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
**09 ANALYSIS OF AVAILABLE DATA**

**09.1 Efficacy**

In support of its application, the company submitted several studies resulting from a literature search in different indications for the product, discussed below.

**9.1.1 Lymphography**

Since the Committee's last opinion, four studies were identified in lymphography.\(^3\,4\,5\,6\) These studies were not described due to their methodological limits (case studies).

**9.1.2 Liver lesions**

Since 2000, the date of the Committee's last opinion, two studies evaluating the role of scanning with LIPIODOL\(^7\,8\) were identified in the literature. For the first study, including 24 patients with liver cirrhosis, there was no significant difference between the two methods (helical CT and CT with LIPIODOL) to detect nodules of more than 10 mm, in terms of sensitivity. The gold standard diagnostic test is liver biopsy. Helical CT was more sensitive than CT with LIPIODOL for nodules of less than 10 mm (47 vs. 27; \(p<0.001\)).

The second study aimed to compare the diagnostic performances of helical CT, digital subtraction angiography and CT with injection of LIPIODOL in the detection of hypervascular hepatocellular carcinoma; 28 patients were included. The three imaging techniques had the same sensitivity for detecting nodules >20 mm in diameter. There was no significant difference in sensitivity among the three techniques for nodules of 10-20 mm in diameter. For nodules of diameter <10 mm, helical CT identified 58 nodules, CT with LIPIODOL identified 27 nodules, including 6 not identified by helical CT, and angiography showed 16.

As a reminder, before 2000, 11 published studies (n=524 patients) evaluated the contribution of LIPIODOL in diagnosis of liver lesions in reference to other imaging techniques (MRI, angiography, digital CT scan, ultrasound) or histopathology, leading to obtaining a marketing authorisation in this indication.

**9.1.3 Interventional radiology**

A total of 31 studies including 6,739 patients were identified in the literature, in the indication of vascular embolisation. Among these, only two comparative studies were conducted.

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The first study\(^9\) compared the treatment of cerebral arteriovenous malformations by surgery alone (n=41) with the combination of surgery and embolisation by N-Butyl cyanoacrylate, LIPIODOL and tantalum powder (n = 30). This study showed that embolisation plus surgery had the best results one week after surgery (p<0.05) and also over the long-term (p=0.057) based on the Glasgow scale.\(^{10}\) No significant difference was demonstrated postoperatively (fewer than 24 hours) in Glasgow score between the two groups.

The second study\(^{11}\) compared arterial embolisation in potentially fatal upper GI bleeding by two different embolisation techniques: one (n=23) using metal springs and gelfoam powder, the other (n=7) consisting of injecting N-Butyl cyanoacrylate and LIPIODOL. This study showed that the LIPIODOL-N-Butyl cyanoacrylate mixture was more effective than the other method of embolisation; 18 of 23 patients that did not receive the cyanoacrylate-LIPIODOL mixture and 6 of 7 patients who received the mixture were completely cured without new bleeding. The time until bleeding stopped was significantly shorter for patients who received the cyanoacrylate-LIPIODOL mixture (p = 0.0095) than for the others.

Regarding studies recently published in the literature, since the Committee's last opinion, the company submitted the following:

- One study on cerebral embolisation.\(^{12}\) This study pertained to embolisation with a biological glue using LIPIODOL as a "diluent", but only evaluated complications related to this procedure.
- A randomised, prospective, double-blind study comparing the efficacy of two biological glues, LIPIODOL being used as a "diluent" for these biological glues.\(^{13}\) The two glues showed comparable efficacy in terms of occluding the spermatic vein and blocking reflux (94.7% and 100%). This study did not evaluate the efficacy of LIPIODOL, but rather the glue associated with LIPIODOL.
- In the embolisation of gastrointestinal bleeding: two studies pertaining to embolisation combining a biological glue with LIPIODOL.\(^{14,15}\) The haemostasis at 1 week was 94.4%. The rebleeding rate was 23.3%. In the second study, rebleeding from gastric varices was observed in 5% of patients from 0 to 72 hours, in 6.5% of patients after 72 hours to 3 months and in 17% of patients after 3 months to 1 year.
- In the embolisation of ovarian veins in pelvic congestion syndrome.\(^{16}\) Transcatheter embolisation of ovarian veins resolved the symptoms in 58% of cases, in this prospective, non-comparative study.
- One study in the paediatric population in the treatment of oesophageal varices in children.\(^{17}\) This study only included 8 patients and was not comparative. All of these studies published since 2000 are described in Table 1.


\(^{10}\) Scale for evaluating consciousness, ranging from 3 (deep coma) to 15 (someone fully conscious).


<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Objective</th>
<th>Numbers</th>
<th>Population studied / inclusion criteria</th>
<th>Diagnostic schemes</th>
<th>Primary efficacy endpoint</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Comparative study</td>
<td>To evaluate the role of hepatic arterial phase CT in comparison with CT with LIPIODOL in the diagnosis of nodular hepatocellular carcinomas.</td>
<td>N=24</td>
<td>Cirrhosis patients.</td>
<td>Hepatic arterial phase CT 25 seconds after injection of the iodinated medium and portal phase 70 seconds after. All the patients underwent hepatic angiography and injection of 10 to 15 ml of LIPIODOL via the hepatic artery. The slides from the LIPIODOL CT were taken 3 to 4 weeks after injection.</td>
<td>Percentage of detection of hepatic nodules.</td>
<td>There was no significant difference between the two methods for detecting nodules of more than 10 mm. Helical CT was more sensitive than CT with LIPIODOL for nodules of less than 10 mm (47 vs. 27; p&lt;0.001).</td>
</tr>
<tr>
<td>Detection of hypervascular hepatocellular carcinoma: comparison of multi-detector CT with digital subtraction angiography and Lipiodol CT.</td>
<td>Comparative study</td>
<td>Comparison of the diagnostic precision of multi-detector CT, digital subtraction angiography and CT with LIPIODOL in the detection of hypervascular hepatocellular carcinoma (HCC).</td>
<td>N=28</td>
<td>Patients with nodular HCC. Mean age: 49; 24 men, 4 women.</td>
<td>CT with LIPIODOL was performed with 8 to 15 ml of LIPIODOL injected by coeliac route into the focal branch vascularising the tumour; CT was performed 3 to 4 weeks after the injection.</td>
<td>Detection of liver nodules.</td>
<td>CT with LIPIODOL permitted detecting at least 1 liver nodule in 26 of 28 patients, for a total of 66 nodules. The remaining two patients showed two nodules with multi-detector CT (arterial phase). Multi-detector CT identified 92 nodules. 60 nodules were detected by both these techniques, 6 were only detected by CT with LIPIODOL and 32 only by multi-detector CT (arterial phase). The 53 nodules detected by digital subtraction angiography were detected by CT with LIPIODOL and multi-detector CT. The three techniques have the same sensitivity for detecting nodules of more than 20 mm.</td>
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**CT: computed tomography**

In diameter, multi-detector CT and LIPIODOL CT have compatible sensitivities for detecting nodules whose diameter is comprised between 10 and 20 mm. For nodules of less than 10 mm, some are detected by CT and others only by LIPIODOL CT.
### 9.1.4 Diseases justifying vascular embolism

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Objective</th>
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<th>Population studied / inclusion criteria</th>
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<th>Primary efficacy endpoint</th>
<th>Results</th>
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<tr>
<td><strong>Cerebral arteriovenous malformation</strong></td>
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<tr>
<td>Embolization of cerebral arteriovenous malformations with n-butyl-2-cyanoacrylate.</td>
<td>Noncomparative study</td>
<td>To determine the safety and efficacy of cAVM embolisation by N-butyl-2-cyanoacrylate (NBCA).</td>
<td>N=103</td>
<td>103 patients undergoing cerebral arteriovenous embolisation aged 12 to 56.</td>
<td>Mixture of 25% to 50% N-butyl-2-cyanoacrylate and LIPIODOL. If necessary: addition of tantalum powder (0.5 g/ml) and injection of the mixture in association with microcoils. In this study, LIPIODOL is used as a vector for the biological glue.</td>
<td>Evaluation of embolisation efficacy according to the percentage of stopping preoperative stroke.</td>
<td>Endovascular treatment of cAVM with a mixture of NBCA and LIPIODOL permitted: 75 to 99% obliteration in 39 patients, 74 to 50% in 33 patients, and less than 50% obliteration in 13 patients. Two patients died during the operation and 7 others had serious complications.</td>
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<td><strong>Varicoceles</strong></td>
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<tr>
<td>Efficacy and safety of two different n-butyl-2-cyanoacrylates for the embolization of varicoceles: a prospective, randomized, blinded study.</td>
<td>Prospective, randomised and blinded study</td>
<td>To compare the safety and efficacy of two surgical glues (N-butyl-2-cyanoacrylate) for varicocele embolisation.</td>
<td>N=83</td>
<td>83 men with spermatic venous insufficiency.</td>
<td>Embolisation by the mixture of: - either 1 ml of N-butyl-2-cyanoacrylate + 1.2 ml of LIPIODOL - or 1 ml of N-butyl-2-cyanoacrylate/methacryloxy sulfonolane + 1 ml of LIPIODOL, the higher concentration being justified by the higher polymerisation rate of this acrylic glue. The surgeon received a syringe with 1.8 ml of mixture.</td>
<td>Efficacy judged by venographic check of the internal spermatic vein and the renal vein 30 min after embolisation.</td>
<td>The populations of each treatment group were comparable in terms of age and clinical characteristics. The two glues had a comparable efficacy in terms of occlusion of the spermatic vein and blocking reflux (94.7% and 100%) in terms of embolisation of an equal number of veins (70.7% and 83.3%).</td>
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<td><strong>Gastrointestinal bleeding</strong></td>
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<tr>
<td>Endoscopic treatment of bleeding gastric varices by n-butyl-2-cyanoacrylate (histoacryl) injection: long-term efficacy and safety.(^5)</td>
<td>Open-label uncontrolled study</td>
<td>To evaluate the long-term safety and efficacy of treating bleeding gastric varices by embolisation.</td>
<td>N=90</td>
<td>Patients with bleeding gastric varices.</td>
<td>Embolisation by 1 to 2 ml, depending on the appearance of the varice and the mixture of N-butyl-2-cyanoacrylate + LIPIODOL (dilution 1:1).</td>
<td>Haemostasis in gastric varices over one week.</td>
<td></td>
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<tr>
<td>Enbucrilate for gastric varices: extended experience in 92 patients.(^5)</td>
<td>Open-label, uncontrolled study</td>
<td>To evaluate the safety and efficacy of the mixture of LIPIODOL and cyanoacrylate in bleeding gastric varices.</td>
<td>N=92</td>
<td>92 patients with portal hypertension, primarily due to cirrhosis or thrombosis of the splenic vein, accompanying gastric varices that were often bleeding.</td>
<td>Embolisation by 1 ml of n-butyl-2-cyanoacrylate + LIPIODOL mixture. 1:1 dilution.</td>
<td>In the ITT group, the reappearance of bleeding from gastric varices was observed in 5% of patients from 0 to 72 hours, in 6.5% of patients after 72 hours to 3 months and in 17% of patients after 3 months to 1 year. The authors concluded that the mixture of cyanoacrylate + LIPIODOL is effective in treating gastric varices.</td>
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**Other diseases**
<table>
<thead>
<tr>
<th>Study</th>
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<th>Objective</th>
<th>Numbers</th>
<th>Population studied / inclusion criteria</th>
<th>Diagnostic schemes</th>
<th>Primary efficacy endpoint</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian vein embolization for the treatment of pelvic congestion syndrome: long-term technical and clinical results.</td>
<td>Prospective study</td>
<td>To evaluate the safety, efficacy and long-term clinical results of embolisation of the ovarian vein or veins for pelvic congestion syndrome.</td>
<td>N=41 F</td>
<td>41 women aged 30 to 58 with pelvic congestion syndrome.</td>
<td>Embolisation by 2 ml of a mixture of 0.5 ml n-butyl-2-cyanoacrylate and 0.4 ml of LIPIODOL.</td>
<td>Embolisation success rate.</td>
<td>After the procedure, embolisation worked in 98% of the patients. At 20 months on average (from 1 to 61) transcatheter embolisation of ovarian veins resolved the symptoms in 58% of cases.</td>
</tr>
<tr>
<td>Endoscopic treatment of gastroesophageal varices in young infants with cyanoacrylate glue: a pilot study.</td>
<td>Prospective pilot study for procedure performed under endoscopic control</td>
<td>To evaluate the feasibility, efficacy and safety of embolisation with glue in the treatment of gastro-oesophageal varices.</td>
<td>N=8</td>
<td>8 children under 2 years old and less than 10 kg with portal hypertension and gastro-oesophageal varices.</td>
<td>Embolisation with the mixture of butyl /methacryloxyisulfolane + LIPIODOL without exceeding 1 ml per injection. Dilution = 1:1.</td>
<td>Evaluation of the appearance of bleeding following treatment.</td>
<td>The mean age and weight of the patients were 1.3 ± 0.42 years (range from 0.8 to 1.9 years) and 8.5 ± 1.6 kg (range from 5.5 to 10 kg). The glue was injected successfully in all the infants. The mean injected volume was 1.15 ± 0.62 ml (range from 0.5 to 2 ml). A bleeding ulcer was observed in 1 case. A relapse with bleeding varices was observed in 3 of 8 patients after a mean of 12.5 ± 10.6 weeks (range from 5-20 weeks). Patients with recurrent bleeding varices were treated again. The varices were eradicated in all cases, after a mean of 1.4 ± 0.52 sessions.</td>
</tr>
</tbody>
</table>

* cAVM: Cerebral Arteriovenous Malformation
These studies, of low-quality methodology, did not permit conclusions regarding the efficacy of LIPIODOL in its new indications.
09.2 Safety/Adverse effects

The latest periodic safety update report (PSUR) for LIPIODOL ULTRA FLUIDE 480 mg/ml covered the period from 1/02/2010 to 31/07/2012. In this period, 1,920,456 doses of LIPIODOL UF were used, corresponding to that many patients exposed to the product. In all:
- 94 cases (including the literature) were reported, corresponding to 206 adverse effects;
- The reporting rate over the period was 4.9 per 100,000 patients.

Out of the 206 adverse effects, 7 were considered serious (3.41%) and probably linked to LIPIODOL UF. Nine deaths were reported, including 7 for an off-label use of LIPIODOL UF (chemoembolisation of a liver tumour by arterial approach).

In France, in the context of embolisation, the serious cases were:
- one gastric ulcer in a 62-year-old patient, following embolisation for treatment of left gastric artery aneurysm with LIPIODOL UF and N-butyl 2-cyanoacrylate
- one bleeding duodenal ulcer
- one stroke
- One case of acute renal failure, respiratory failure, one pleural effusion, one biloma and one fever
- one pleural effusion
- one cardiovascular collapse, one case of hypoxaemia and one case of intravascular coagulation
- one embolism, one case of hypotension and one case of hypoxia.

Concerning the use in diagnosing liver lesions, one serious case was collected. This was a 62-year-old patient who had anaphylactic shock, urticaria, hypotension and increased pulmonary arterial pressure after portography using LIPIODOL and HEXABRIX. This was a serious case with a favourable outcome and in which an attribution to LIPIODOL is improbable. Co-administered anaesthetics were also considered as suspect medicines.

09.3 Usage/prescription data

During the period covered by the PSUR, 31,944 units were sold, for all uses (that many patients exposed to the product).
Since the product was not prescribed in private practice, it does not appear in EPPM panels.

09.4 Summary & discussion

LIPIODOL has been used for many years as a contrast medium for lymphography, CT scan in characterising liver lesions and in association with biological glues in arterial embolisation or embolisation of arteriovenous fistulas.

In the indication of diagnosis by lymphography, there is no new relevant clinical data.

In the diagnosis of liver lesions, the studies presented by the company are from a literature search. These studies involved small numbers of participants. Among these, only two comparative studies were conducted. A study including 24 patients with cirrhosis of the liver and using liver biopsy as the gold standard diagnostic method showed that there was no significant difference between helical CT and LIPIODOL CT for detecting nodules of more than 10 mm, in terms of sensitivity. In contrast, helical CT was more sensitive than CT scan with LIPIODOL for nodules of less than 10 mm (58 vs. 27; p<0.001).

The second study aimed to compare the diagnostic performances of helical CT, digital subtraction angiography and CT scan with injection of lipiodol in the detection of hypervascular hepatocellular carcinoma; 28 patients were included. The three imaging techniques had the same sensitivity for detecting nodules >20 mm in diameter. There was no significant difference in sensitivity among the
three techniques for nodules of 10-20 mm in diameter. For nodules <10 mm diameter, six nodules <10 mm diameter were detected only by lipiodol CT.

In embolisation, 31 studies including 6,739 patients were identified in the literature. Among these, only two comparative studies were conducted. The first study compared the treatment of cerebral arteriovenous malformations by surgery alone (n=41) with the combination of surgery and embolisation by N-Butyl cyanoacrylate, LIPIODOL and tantalum powder (n = 30). This study showed that embolisation plus surgery had the best results one week after surgery (p<0.05) based on the Glasgow scale. The second study compared arterial embolisation in potentially fatal upper GI bleeding by two different embolisation techniques: one (n=23) using metal springs and gelfoam powder, the other (n=7) consisting of injecting N-Butyl cyanoacrylate and LIPIODOL. This study showed that the LIPIODOL-N-Butyl-cyanoacrylate mixture was more effective than the other embolisation method on the occurrence of new bleeding.

These studies, with a low level of evidence, provide information on the efficacy of LIPIODOL in its new indications. The use of LIPIODOL in embolisation remains an established usage.

The safety data resulting from the PSUR do not show any new adverse effect and confirm the favourable safety profile already known for this medicinal product.

**010 THERAPEUTIC USE**

Situations in which a contrast medium is recommended appear in the “Guide de bon usage des examens d'imagerie médicale” (Good use guide for imaging examinations) (ANAES [French National Health Accreditation and Assessment Agency], 2005), updated in 2013.¹

### 010.1 Lymphography

LIPIODOL is the only contrast medium that can be used for lymphography. Lymphography is no longer used in lymphoma staging because, currently, ultrasound (in some cases only), CT scan, positron emission tomography and MRI are used as first-line examinations before lymphography. According to expert opinion, lymphography would still be useful in rare indications: traumatic injury of the thoracic duct and lymphatic channel occlusion.

### 010.2 Diagnosis of liver lesions

Most often, liver tumour diagnosis is raised during an ultrasound conducted as part of the monitoring of a chronic liver disease. In addition to this situation, ultrasound is ordered when there is a clinical suspicion of hepatocellular carcinoma (HCC). In the case of a strong suspicion of HCC associated with a normal ultrasound or with a questionable image, the diagnosis of tumour should not be ruled out. An MRI should then be conducted. If MRI is contraindicated, CT scan with or without injection of iodinated contrast medium (LIPIODOL) can be performed.

### 010.3 Interventional radiology

The primary application of embolisation with biological glues concerns vascular occlusion of arteriovenous shunts in brain and spinal cord angiomas. Based on the “Guide du bon usage des examens d'imagerie médicale”¹ the clinical situations that could require vascular embolisation are the following:
- **Varicocele**
  Varicocele is a varicose vein of the spermatic cord (located in the bursa, above and around each testicle).
  It may cause pain, testicular atrophy or sterility problems. Embolisation is the first-line treatment (expert opinion).

- **Cerebral arteriovenous malformations (AVM)**
  Cerebral arteriovenous malformations (AVM) are relatively rare and generally congenital. The major risk of an arteriovenous malformation is the occurrence of a rupture with cerebral haemorrhage, the neurological consequences of which will depend on the size of the initial haemorrhage. In some cases, they can be fatal for the patient. AVM treatment aims to obliterate the malformation in order to prevent or avoid the risk of bleeding. Several therapeutic modalities may be used: microsurgery, endovascular embolisation or radiosurgery, but most often, it is a treatment combining these different modalities. According to the scientific literature, LIPIODOL embolisation is not the first-line treatment. For experts, lipiodol is commonly used in interventional neurology due to its ease of use and low cost.

- **Pulmonary arteriovenous malformations**
  These rare malformations are defined as congenital arteriovenous connections. There can be many of these AVMs, in particular in hereditary haemorrhagic telangiectasia. Surgical treatment, for a location in the lung, often consists of a lobectomy or segmentectomy. This is still a difficult procedure, with a high operative mortality (6% of cases). It is currently limited to localized forms with high flow and large calibre.
  For several years, and thanks to advances in superselective catheterisation, it has been possible to treat these diseases by percutaneous embolisation by endovascular approach. This is a first-line examination (Grade C). Releasable balloons and metal coils are the most often used materials.
  Biological glues + LIPIODOL are second-line embolisation techniques.

- **Gastrointestinal bleeding**
  The use of embolisation by biological glue associated with LIPIODOL depends on the location. For experts, LIPIODOL is commonly used in interventional gastroenterology due to its ease of use and low cost.

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18 HAS, Révision de catégories de dispositifs médicaux Implants d’embolisation artérielle (indications craniocoéphaliques et vertébro-médullaires), Rapport d’évaluation technologique 2011.
20 HAS, 2011 Irradiation intracrânienne en conditions stéréotaxiques : les malformations artério-veineuses – Short text of Volume IV.
In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

011.1 Actual benefit

11.1.1 Lymphography

- Lymphography is an examination that can diagnose serious diseases.
- LIPIODOL is an iodinated contrast medium used for diagnostic purposes.
- This medicinal product used in lymphography has exceptional indications, particularly traumatic lesions of the thoracic duct and lymphatic channel occlusion.
- Alternatives for lymphatic system investigation are MRI, CT, PET and ultrasound.
- The diagnostic efficacy/adverse effects ratio of this contrast medium in this indication is low.

Consequently, given the limited role of lymphography in diagnosis of diseases which may nevertheless be serious, the Committee considers that the actual benefit of LIPIODOL is low.

11.1.2 Diagnosis of liver lesions

- Liver tumours can be life-threatening for the patients who have them.
- LIPIODOL is used as part of a CT examination for diagnostic purposes.
- The diagnostic efficacy/adverse effects ratio of this contrast medium in this indication is low.
- This medicinal product is a last resort product.
- There are alternatives: the first-line examination is MRI. Liver ultrasound is used only in certain cases.

Consequently, given its limited role in the diagnosis of liver lesions, the Committee considers that the actual benefit of LIPIODOL is low.

11.1.3 Interventional radiology

- Bleeding related to arteriovenous malformations requiring embolisation can be life-threatening for patients. Gastrointestinal bleeding is life-threatening. Varicocele is a varicose vein of the spermatic cord (located in the bursa above and around each testicle) which can cause pain, testicular atrophy or sterility problems.
- Embolisation is a curative therapy.
- The efficacy/adverse effects ratio is high.
- The therapeutic use of this product is either as a first or second-line treatment, depending on the location of the arteriovenous malformations.
- There are alternatives: glue alone, solid implants or stereotactic radiotherapy.

Consequently, the Committee considers that the actual benefit of LIPIODOL is substantial.

The Committee recommends inclusion on the list of medicines approved for hospital use in the indications of interventional radiology and liver lesion diagnosis and recommends continued inclusion for lymphography on the list of medicinal products approved for hospital use.
011.2 Improvement in actual benefit (IAB)

LIPIODOL ULTRA-FLUIDE 480 mg/ml, solution for injection does not provide any improvement in actual benefit (IAB V, non-existent) compared with existing alternatives in the diagnosis of liver lesions and vascular embolisation.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging
Appropriate for the prescribing conditions according to the indications of the marketing authorisation.