Lipiodol® efficacy & safety for improved overall survival in HCC

Indications and dosage may vary from country to country. Countries in which cTACE indication is registered: France, Japan, South Korea, Austria, Peru, Turkey, Hungary, Czech Republic, Mongolia, Argentina, The Netherlands, Vietnam, Mexico, Thailand, Taiwan, Brazil, Cambodia, Portugal, Ireland, Hong Kong, Philippines, Iran & New Zealand.

For complete information please refer to country’s local SPC. For a copy of the SPC, please contact a member of Guerbet.

2. Lo C.M. et al. Randomized Controlled Trial of Transarterial Lipiodol Chemoembolization for Unresectable Hepatocellular Carcinoma Hepatology 2002; 35: 1164-1171
• 782,000 new cancer cases worldwide occurred in 2012\(^{(1)}\)
• 5th most common cancer in men (554,000 cases) and the 9th in women (228,000 cases)\(^{(1)}\)
• 2nd most common cause of death from cancer worldwide, 746,000 deaths in 2012\(^{(1)}\)
• HCC represents more than 90% of primary liver cancers\(^{(2)}\)
• Very poor prognosis
Visualization, Localization and Vectorization during Trans-Arterial Chemoembolization (TACE) of hepatocellular carcinoma (HCC) at intermediate stage, in adults

- HCC etiology
  - Hepatitis B & C
  - Prolonged alcohol abuse
  - Non alcoholic steato hepatitis (NASH)

- Conventional Trans Arterial Chemoembolization (cTACE)
  - cTACE = Lipiodol® TACE
  - Intratumor injection of Lipiodol® + anticancer agent
  - Complementary embolization with gelatin sponge or particules
**Lipiodol® mechanisms-of-action**

- Lipiodol®-drug droplets are deformable & heterogeneous in size\(^{(3-4)}\)

- Lipiodol®-drug droplets allow both proximal & distal anticancer drug delivery\(^{(3)}\)

- Lipiodol®-drug droplets achieve transient dual embolization (arterial & portal vessels)\(^{(5)}\)

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**LIPIODOL®—DRUG DROPLETS DEFORMABILITY & SIZE DIVERSITY FOR OPTIMAL DRUG DELIVERY & DUAL EMBOLIZATION**
Dual arterial & venous perfusion for efficient cTACE\(^{(6)}\)

Radiological evidence of dual vascularization of HCC

Grades of portal vein visualization & size of tumors treated with ultraselective cTACE

PERIBILIARY PLEXA ALLOW LIPIODOL\(^{®}\)–DRUG DROPLETS SHUNTING FROM HEPATIC ARTERY TO PORTAL VEIN
5 MAJOR RANDOMIZED CONTROLLED TRIALS & 1 META-ANALYSIS
Multicenter, randomized, controlled clinical trial.

112 patients with unresectable HCC (Child-Pugh class A or B)
- Arterial embolization group (TAE without cytotoxic drug): 37 patients
- Chemoembolization group (cTACE with Lipiodol® + doxorubicin): 40 patients
- Control group (conservative treatment): 35 patients.

1<sup>st</sup> endpoint = survival, 2<sup>nd</sup> endpoint = treatment response.

**Objective:**
“...to assess the survival benefit of regularly repeated arterial embolization (gelatin sponge) or chemoembolization (gelatin sponge plus doxorubicin) compared with conservative treatment.”

**Results:**
“...chemoembolization with gelfoam & doxorubicin improves survival in selected candidates with unresectable hepatocellular carcinoma.”

<table>
<thead>
<tr>
<th></th>
<th>TAE</th>
<th>cTACE</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year survival (%)</td>
<td>75</td>
<td>82</td>
<td>63</td>
</tr>
<tr>
<td>2-year survival (%)</td>
<td>50</td>
<td>63</td>
<td>27</td>
</tr>
<tr>
<td>3-year survival (%)</td>
<td>29</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Mean survival (mo)</td>
<td>25.3</td>
<td>28.7</td>
<td>17.9</td>
</tr>
<tr>
<td>Deaths</td>
<td>67%</td>
<td>52%</td>
<td>71%</td>
</tr>
<tr>
<td></td>
<td>25/37</td>
<td>21/40</td>
<td>25/35</td>
</tr>
</tbody>
</table>

**cTACE IMPROVED THE SURVIVAL OF PATIENTS WITH UNRESECTABLE HCC**
Efficacy
Lo C.M. et al. Hepatology (2002)\(^{(7)}\)

Single center, open-label, randomized, controlled clinical trial

79 Asian patients with unresectable HCC (Okuda I/II stage)
- Chemoembolization group (cTACE with cisplatin+Lipiodol\(^{®}\) repeated every 2-3 months): 40 patients
- Control group (symptomatic treatment): 39 patients

1\(^{st}\) endpoint = survival, 2\(^{nd}\) endpoints = tumor response, tolerance, liver function

Objective:
«... assessed the efficacy of transarterial Lipiodol\(^{®}\) (Lipiodol\(^{®}\) Ultrafluide, Laboratoire Guerbet, Aulnay-Sous-Bois, France) chemoembolization in patients with unresectable hepatocellular carcinoma. »

Results:
«... transarterial Lipiodol\(^{®}\) chemoembolization [...] prolongs the survival of a selected group of Asian patients with unresectable hepatocellular carcinoma & is an effective palliative treatment option. »

<table>
<thead>
<tr>
<th>Probability of survival</th>
<th>cTACE (%)</th>
<th>Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>57</td>
<td>32</td>
</tr>
<tr>
<td>2-year</td>
<td>31</td>
<td>11</td>
</tr>
<tr>
<td>3-year</td>
<td>26</td>
<td>3</td>
</tr>
</tbody>
</table>

Much higher probability of survival with cTACE rather than control.

\(P = 0.002\)

Fig. 2. Probability of survival in patients treated with chemoembolization & in patients of the control group (log-rank test, \(P = .002\)).

cTACE IMPROVED THE SURVIVAL OF ASIAN PATIENTS WITH UNRESECTABLE HCC
**BCLC staging system & treatment strategy**

**BCLC = Barcelona-Clinic Liver Cancer**

**Stage A-C**
- Very early stage (0) and Early stage (A)
  - Single nodules ≤ 3 cm
  - Portal pressure/bilirubin: Normal
  - Resection, RF/PEI, TACE, Sorafenib, Best supportive care
  - Median OS > 60 mo; 5-yr survival: 40-70%

**Stage D**
- Intermediate stage (B)
  - Multinodular, PS 0
  - Portal invasion, N1, M1, PS 1-2
  - TACE, Sorafenib, Best supportive care
  - Target: 20%
  - OS: 20 mo (45-14)

**Stage D**
- Advanced stage (C)
  - Portal invasion, N1, M1, PS 1-2
  - Target: 40%
  - OS: 11 mo (6-14)

**Stage D**
- Terminal stage (D)
  - Target: 10%
  - OS: < 3 mo

**cTACE: "STANDARD-OF-CARE" FOR STAGE B HCC PATIENTS**
Clinical practice guidelines for HCC management (2)

Recommendations on chemoembolization & transcatheter therapies (1)

« Chemoembolization (Lipiodol®) is recommended for patients with BCLC stage B, multinodular asymptomatic tumors without vascular invasion or extra hepatic spread (evidence 1iiA; recommendation 1A). »

« The use of drug-eluting beads has shown similar response rates than gelfoam-lipiodol® particles associated with less systemic adverse events (evidence 1D; recommendation 2B). »

cTACE STRONGLY RECOMMENDED FOR STAGE B HCC PATIENTS
STRONG LEVEL OF EVIDENCE OF IMPROVED OVERALL SURVIVAL

Strength of evidence according to study design

Level 1: Randomized controlled clinical trials or meta-analyses of randomized studies
  (i) Double-blinded
  (ii) Non-blinded treatment delivery
Level 2: Non-randomized controlled clinical trials
Level 3: Case series
  (i) Population-based, consecutive series
  (ii) Consecutive cases (not population-based)
  (iii) Non-consecutive cases

Strength of evidence according to end-points

A. Total mortality (or overall survival from a defined time)
B. Cause-specific mortality (or cause-specific mortality from a defined time)
C. Carefully assessed quality of life
D. Indirect surrogates
  (i) Event-free survival
  (ii) Disease-free survival
  (iii) Progression-free survival
  (iv) Tumor response rate

Grading of evidence

<table>
<thead>
<tr>
<th>Grading of evidence</th>
<th>Notes</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>High quality</td>
<td>Further research is very unlikely to change our confidence in the estimation of effect</td>
<td>A</td>
</tr>
<tr>
<td>Moderate quality</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate</td>
<td>B</td>
</tr>
<tr>
<td>Low or very low quality</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is uncertain</td>
<td>C</td>
</tr>
</tbody>
</table>

Grading recommendation

<table>
<thead>
<tr>
<th>Grading recommendation</th>
<th>Notes</th>
<th>Symbol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation warranted</td>
<td>Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost</td>
<td>1</td>
</tr>
<tr>
<td>Weaker recommendation</td>
<td>Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty: higher cost or resource consumption</td>
<td>2</td>
</tr>
</tbody>
</table>

STRONG GRADE OF RECOMMENDATION BASED ON HIGH-QUALITY EVIDENCE
cTACE endorsement by international clinical practice guidelines

American guidelines\(^{(9)}\)

« TACE is recommended as first line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extra hepatic spread (level I). »

« Chemotherapy has to be injected prior to arterial obstruction. It is usual to suspend chemotherapy in Lipiodol\(^\text{®} \), an oily contrast agent used for lymphographic studies. Lipiodol\(^\text{®} \) is selectively retained within the tumor and this expands the exposure of the neoplastic cells to chemotherapy… »

Chinese guidelines\(^{(10)}\)

« Superselective catheterization is preferred whenever possible, in combination with proper embolization agents. An emulsion mixture of super-liquid Lipiodol\(^\text{®} \) and chemotherapeutic agents is commonly used for this therapy. The dosage of iodized oil should depend on the size, blood supply, and tumor of feeding arteries of the tumor. »

Japanese guidelines\(^{(11)}\)

« Transcatheter arterial chemoembolization/TAE is recommended as treatment for advanced hepatocellular carcinoma with liver damage stages A and B (inoperable and not candidates for local ablation therapy)… (grade A). »

« Lipiodol\(^\text{®} -\text{TACE}\) taking account of hepatic functional reserve and the area of non-cancerous liver tissues to be chemoembolized is recommended for current TACE (grade B). […] »

\(^{(9)}\) TACE endorsement by international clinical practice guidelines worldwide

14-15
Overall survival data$^{(2, 12)}$:

- Mean survival with no treatment: 16 months
- Mean survival with cTACE: 20 months
- Best case scenario with cTACE: 37 to 45 months

Significant improvement of stage B HCC patient overall survival.
Objective:
«… this study describes & compares liver/biliary injuries encountered with TACE in tumours developed in cirrhotic [hepatocellular carcinoma (HCC) [… ] livers. »

Results:
« At least one liver/biliary injury was observed after 30.4-35.7% of DEB-TACE sessions while it occurred after 4.2-7.2% of Lipiodol®-TACE (p<0.001).
We suggest caution when using DEB-TACE in the non cirrhotic liver. »
Lipiodol®–drug mixture preparation*

1. Prepare a syringe containing Lipiodol® Ultra Fluid & a syringe containing the anticancer agent.

2. Connect both syringes to a three-way stopcock.

3. Perform 15 to 20 back & forth movements between the two syringes to obtain a homogeneous mixture.

4. Obtain a mixture of Lipiodol® Ultra Fluid + anticancer agent.

The mixture should be extemporaneously prepared & used immediately after preparation (within 3 hours).

Mixture preparation recommendation

- Anticancer drug should be first pushed towards the syringe containing Lipiodol®.[14]
- Volume of anticancer drug should be lower than the volume of Lipiodol®, ideally 1 volume of drug to 2 volume of Lipiodol®.[15]
- Vigorous mixing of the anticancer drug and Lipiodol® via a 3-way stopcock.[14]

* Example of a preparation with doxorubicin according to clinical practices. Guerbet pictures
Anticancer drugs associated with Lipiodol®

Several anticancer drugs may be associated with Lipiodol® Ultra Fluid

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>(7)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>(8)</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>(16)</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>(17)</td>
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</tbody>
</table>

The instructions & precautions for use relating to anticancer drug must be strictly followed according to local SmPC.

Lipiodol® Ultra Fluid

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>BENEFITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor visualizer &amp; localizer</td>
<td>- Immediate tumor visualization &amp; localization for real time procedure guiding&lt;sup&gt;(16)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Per-procedure complete tumor filling visual confirmation for patient prognosis&lt;sup&gt;(20)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chemotherapeutic drug vectorizer</td>
<td>- Proximal &amp; distal drug delivery thanks to droplets deformability &amp; size diversity&lt;sup&gt;(8)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Improved patient Overall Survival up to 45 months&lt;sup&gt;(2, 12)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Endorsed by international guidelines as Standard-of-Care&lt;sup&gt;(2, 9, 10, 11)&lt;/sup&gt;</td>
</tr>
<tr>
<td>Transient dual embolizer</td>
<td>- Index &amp; daughter nodules necrosis thanks to dual arteriportal embolization&lt;sup&gt;(19)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>- Transient occlusion authorizing repeated treatment&lt;sup&gt;(18)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

18-19


(7) Lo C.M. et al. Randomized Controlled Trial of Transarterial Lipiodol Chemoembolization for Unresectable Hepatocellular Carcinoma, Hepatology 2002; 5, 1164-1171.


(16) Chen M. et al. High Dose Iodized Oil Transcatheter Arterial Chemoembolization for Patients with Large Hepatocellular Carcinoma World. gastroenterol. 2002; 8: 74-78.


(19) Terayama N. et al. Accumulation of Iodized Oil Within the Non-Neoplastic Liver Adjacent to Hepatocellular Carcinoma via the Drainage Routes of the Tumor After Transcatheter Arterial Embolization CVIR 2001; 24:383-387

(20) Takayasu K. et al. Comparison of CT Findings with Resected Specimens After Chemoembolization with Iodized Oil for Hepatocellular Carcinoma AJR 2000;175:699–704
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 venography - Lymphography - Enterography - Phlebography and exploration of abscesses - Exploration of frontal sinuses - Pre and post-operative cholangiography - In interventional radiology - Vascularisation and localization (by selective intra-arterial use during CT) of liver lesions in adults with known or suspected hepatocellular carcinoma - Visualisation, localization and vectorisation during Trans-Arterial Chemo-Embolisation (TACE) 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 - Posology and method of administration (*): IV injections are contraindicated - 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 haemorrhage or bleeding - Hysterosalpingography during pregnancy or acute pelvic inflammation - Bronchography: In interventional radiology (Trans-Arterial Chemo-Embolisation). 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 intraarterial use of LIPIODOL ULTRA-FLUID. Perform radiological monitoring during LIPIODOL ULTRA-FLUID injection and avoid use in patients with severely impaired left 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. Throidal: 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 decompenated liver cirrhosis (Child-Pugh ≥ B). 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. Oesophaegus varices must be carefully monitored. Hepatic intra-arterial treatment can progressively cause irreversible liver insufficiency in patients with serious liver malnourition and/or undergoing close multiple sessions. This risk of super-infection 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 (*): Methotrexate, 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. LIPIODOL ULTRA-FLUID must be used. Effects on ability to drive and use machines: The effects on ability to drive and 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, diarrhea, nausea, fever, chills, hypotension, hypothermia, hyperthermia, thyrotoxicosis, hyperglycaemia, hypeleucocytosis, hyperlipidaemia, dyspnoea aggravation, hepatic 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, saturated. ATC code: V08A D01. Water-insoluble iodinated contrast medium. Presentation (**): 10 mL glass ampoules. 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
(**) 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.

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