Vectorio® efficacy & safety for improved cTACE mixing & delivery

UNBREAKABLE | USER-FRIENDLY | SHARP
Primary liver cancer epidemiology

- 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

- Incidence of primary liver cancer
  - 782,000 new cases worldwide in 2012
  - 554,000 cases in men
  - 228,000 cases in women

- Mortality
  - 746,000 deaths in 2012
  - 95% mortality rate (out of 782,000 cases)
Lipiodol® indication in HCC

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 particles

- Tumor necrosis & size reduction

BCLC staging system & treatment strategy (2)

- BCLC = Barcelona Clinic Liver Cancer

LIPIODOL® – INDICATED TO FIGHT HCC

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4-5
Dual arterial & venous perfusion for efficient cTACE (3)

- Radiological evidence of dual vascularization of HCC

PERIBILIARY PLEXA ALLOW LIPIODOL®-DRUG DROPLETS SHUNTING FROM HEPATIC ARTERY TO PORTAL VEIN

Overall survival data (2, 4)

Significant improvement of stage B HCC patient overall survival

Mean survival with no treatment

Mean survival with cTACE

16 months

20 months

4 months

29 months

37 months

45 months

Best case scenario with cTACE

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

Arterial enhancement of the tumor

Early venous enhancement thanks to the peribiliary vascular plexus

Full visualization of the arterioportal vascular bed

Grades 0, 1, 2

Arterial enhancement

Early venous enhancement

Full visualization of the arterioportal vascular bed

Grades 0, 1, 2

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6-7
**VECTORIO**® intened use

**LIPIODOL® Resistant Mixing & Injection System for conventional Trans-Arterial Chemo-Embolization (cTACE)**

- Lipiodol® Ultra Fluid – anticancer mixture should be performed with VECTORIO®
- Mixture preparation recommendations
  - Anticancer drug should be first pushed towards the syringe containing Lipiodol®
  - Anticancer drug volume should be lower than Lipiodol® volume, ideally 1 drug volume to 2 Lipiodol® volumes
  - Vigorous mixing of Lipiodol® & anticancer drug via the stopcock
- Lipiodol® Ultra Fluid may be associated with various anticancer drugs

<table>
<thead>
<tr>
<th>Anticancer drugs that may be associated with Lipiodol® Ultra Fluid</th>
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<td>Cisplatin</td>
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**VECTORIO**® compounds

- Raw materials of Vectorio® have been validated for resistance to Lipiodol® up to 24h

- A & B 20 mL mixing syringes (x2)
- C Particle filter for Lipiodol® Ultra Fluid withdrawal (x1)
- D Lipiodol® Ultra Fluid ampoule withdrawing straw (x1)
- E Lipiodol® Ultra Fluid vial spike (x1)
- F 3-way stopcock with 4 connections (x1)
- G Connector (x1)
- H 1 mL injection syringe (x1)
- I 3 mL injection syringe (x1)

The system does not contain:
- Lipiodol® Ultra Fluid ampule or vial
- Anticancer drug
- Microcatheter

* Guerbet recommends the use of Vectorio® to prepare and inject the mixture of Lipiodol® and anticancer drug
***The instructions and precautions for use relating to anticancer drugs must be strictly followed

* Guerbet project under progress
Mixing syringes (20 mL)
Design Aim – Making multiple mixes easy & safe

- Plunger – Ergonomic convex shape, rotatable,atraumatic for the palm & fingers
- Backstop (Patented) – Prevents accidental release & uncontrolled drug exposure
- Rotary finger support – Adjustable working position after connection
- O-ring design – Sealing function
- Elimination of the elastic zone – Tactile feedback improvement, direct transmission of forces from hand to mixture

Injection syringe (1 mL & 3 mL)
Design Aim – Making injection easy & safe

- Plunger – Ergonomic design for optimal grip and easy injection
- Backstop (Patented) – Prevents accidental release & uncontrolled drug exposure
- Rotary finger support – Obtain more suitable working position
- O-ring design – Sealing function
- Elimination of the elastic zone – Tactile feedback improvement, direct transmission of forces from hand to emulsion
3-way stopcock with 4 connections—(Patented)
Design Aim – Easy & safe to perform operation

Raw materials - Strong & Resistant for cTACE use

- Connects 2 mixing syringes, injection syringe & catheter
- The "L" channel & Rotary handle enable to choose which two ports can be connected
- Mix, inject, refill or remix No need to disconnect

Foolproof Luer lock connection
- Vectorio® mixing syringes can’t be connected to injection port
- Mixing ports can’t communicate with the patient

Catheter/patient line connection

Particle filter for withdrawing Lipiodol®

- 15µm filter retain glass particles that may be released when breaking ampoule

Double female connector

Design Aim – Easy & safe to perform preparation

Transfer drug from the pharmaceutical preparation syringe to the mixing syringe of Vectorio®
**Lipiodol® Ultra Fluid – anticancer drug mixture preparation using VECTORIO**

**STEP I: WITHDRAWING**
- Withdraw Lipiodol® Ultra Fluid and anticancer drug into the 2 mixing syringes
- Connect the mixing syringes to the 4 ports 3 way stopcock

**STEP II: MIXING**
- Anticancer drug should be first pushed towards the syringe containing Lipiodol®
- Perform 20 vigorous back & forth movements to obtain an homogeneous mixture

**STEP III: INJECTING**
- Connect stopcock to the microcatheter
- Lipiodol® Ultra Fluid + anticancer drug mixture ready to inject
- Possibility of remixing, refill within closed system (on-table mixing)

THE MIXTURE SHOULD BE EXTEMPORANEOUSLY PREPARED AND SHOULD BE USED IMMEDIATELY AFTER PREPARATION
**LIPIODOL® ULTRA-FLUID**: Iodine values of oil and fatty acids of游离 (18-19), corresponding to an iodine content of 480 mg/mL. Indications:**

- **Radiography**:
  - Angiography:
    - Intravenous angiography and selective angiography: visualization and demonstration of the site of the lesion.
    - Trans-Arterial Chemo-Embolization (TACE): detection, localization and indication for treatment of hepatocellular carcinoma, especially in cases of early-stage disease or in cases where surgery is contraindicated.
    - Computed tomography (CT): visualization and demonstration of the site of the lesion.
  - Intravenous and intra-arterial use during CT: visualization and demonstration of the site of the lesion in the liver.

- **Urography**:
  - Intravenous urography: visualization of the kidneys, ureters, and bladder.
  - Intravenous pyelography: visualization of the renal pelvis and ureters.

- **Intramuscular use during CT**:
  - Visualization of the muscles and tendons.

- **Contraindications**:
  - Hypersensitivity to any of the components of LIPIODOL® ULTRA-FLUID.
  - Known or suspected iodine sensitivity.
  - 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.

Effects on ability to drive and to use machines:

- The effects on ability to drive and to use machines have not been investigated.

**Special warnings and special precautions for use**: There is a risk of hypersensitivity regardless of the dose administered.

**Adverse effects**: The most common adverse reactions are dose-related and dosage should therefore be kept as low as possible.

**Overdose**: The total dose of LIPIODOL® ULTRA-FLUID administered must not exceed 20 mL.

**Precautions**:

- Special warnings and special precautions for use:
  - There is a risk of hypersensitivity regardless of the dose administered.
  - Adverse effects:
    - The most common adverse reactions are dose-related and dosage should therefore be kept as low as possible.
  - Overdose: The total dose of LIPIODOL® ULTRA-FLUID administered must not exceed 20 mL.

**Interactions**:

- Metformin, Beta blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonists, Diuretics, Interleukin II.

**Reporting of suspected adverse reactions**: 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.

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

**Countries in which TACE indication is registered**: France, South Korea, Austria, Peru, Turkey, Hungary, Czech Republic, Mongolia, Argentina, The Netherlands, Vietnam, Mexico, Canada, New Zealand, Thailand, Taiwan & Brazil.
Device functionality verified up to 24h in contact with Lipiodol®