02/2022

רופא/ה ,רוקח/ת נכבד/ה,
חברת פרומדיקו בע"מ מקבוצת ניאופרם מבקשת להודיעך על תוספת התוויה אשר אושרה על ידי משרד הבריאות ועל עדכון העלון לרופא של התכשיר:

LIPIODOL ULTRA FLUID

SOLUTION FOR INJECTION

INTRA-ARTERIAL ,
INTRA-LYMPHATIC

החומר הפעיל וכמותו:
IODINE (AS ETHYL ESTERS OF IODIZED FATTY ACIDS OF POPPY SEED OIL) 480 MG/ML

שם היצרן וכתובתו: GUERBET, BP 57400,F-95943 ROISSY CdG,CEDEX, FRANCE

שם בעל הרישום וכתובתו: פרומדיקו בע"מ, השילוח 6, ת.ד. 3340, פתח תקווה

להלן נוסח ההתוויה המאושר לתכשיר:

- Lymphography.
- Visualisation, localisation and vectorisation during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma, in adults.

העדכונים המהותיים בעלון לרופא:

עדכוני בטיחות מודגשים בצהוב. תיקוני נוסח והסרת מידע ~~מסומנים בקו חוצה~~.

4.1. Therapeutic indications

Lymphography.

Visualisation, localisation and vectorisation during Trans-Arterial Chemo-Embolisation (TACE) of hepatocellular carcinoma, in adults.

4.2. Posology and method of administration

[…]
Posology
[…]

In interventional radiology

- Trans-Arterial Chemo-Embolisation of hepatocellular carcinoma:

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קשרי לקוחות מוסדיים טל: 03-9264280 1-800-23-23-03 פקס: 1-800-68-68-21 קשרי לקוחות פרטיים טל: 1-800-65-65-05 פקס:
Email: promedico@promedico.co.il www.promedico.co.il

The dose of LIPIODOL ULTRA-FLUID depends on the extent of the lesion, but should usually not exceed a total dose of 15 mL in adults.

Paediatric population

The efficacy and safety of the use of LIPIODOL ULTRA-FLUID for Trans-Arterial Chemo-Embolisation of hepatocellular carcinoma have not been established in children.

Elderly

The product must be administered with special care in patients over 65 years of age with underlying diseases of the cardiovascular, respiratory or nervous systems.

Method of administration

In interventional radiology:

- Trans-arterial chemo-embolisation of hepatocellular carcinoma

The administration is by selective intra-arterial catheterism of the hepatic artery. The procedure should be performed within a typical interventional radiology setting with the appropriate equipment.

LIPIODOL ULTRA-FLUID can be mixed with anticancer drugs such as cisplatin, doxorubicin, epirubicin and mitomycin.

Instructions and precautions for use of the anticancer drugs must be strictly followed.

Instructions for preparation of the mixture of LIPIODOL ULTRA-FLUID with an anticancer drug:

- Prepare two syringes large enough to contain the total volume of mixture. The first syringe contains the anticancer drug solution, the second syringe contains LIPIODOL ULTRA-FLUID.

- Connect the two syringes to a 3-way stopcock.

- Perform 15 to 20 back and forth movements between the two syringes to obtain a homogeneous mixture. It is recommended to start by pushing the syringe with the anticancer drug first.

- The mixture is to be prepared at the time of use and must be used promptly after preparation (within 3 hours). If necessary during the interventional radiology procedure, the mixture can be re-homogenized as described above.

- When the adequate mixture is obtained, use a 1 to 3 mL syringe to inject in the micro-catheter.

The procedure can be repeated every 4 to 8 weeks according to tumor response and patient conditions."

4.3. Contraindications

This product must not be administered by ~~intra-arterial~~, intravenous or intrathecal injection.

- Hypersensitivity to LIPIODOL ULTRA-FLUID (ethyl esters of iodised fatty acids of poppyseed oil).
- Pregnant women
- ~~Confirmed~~ Proven hyperthyroidism.
- Traumatic ~~lesions~~injuries, recent haemorrhage or ~~recent~~ bleeding (risk of extravasation or embolism).
- Bronchography (the product would rapidly ~~inundates the~~flood bronchioles and alveoli).

Specific contraindications for use in interventional radiology:

Transarterial chemoembolisation:

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Lipiodol Ultra Fluid mixture for treatment of hepatocellular carcinoma may lead to both ischemic and toxic effects to the bile duct. Therefore, the administration is contraindicated in liver areas where the bile ducts are dilated, unless post-procedural drainage can be performed.

Intra-arterial injection of LIPIODOL ULTRA-FLUID may lead to a complete hepatic artery obliteration and complete suppression of arterial flow. It should only be performed after having made sure, via CT scan or angiography, that there is the presence of at least a partial portal vascular flow.

4.4. Special warnings and precautions for use

[…]

Embolic and thrombotic complications

The uncontrolled migration of Lipiodol Ultra Fluid into the arterio-venous system may induce the temporary obliteration of small vessels (oil embolism) in various organs. Signs of such embolism are infrequent and generally immediate, but they may also be delayed and appear after a few hours or days. They are usually transient. However, cases of pulmonary embolism and cerebral embolism (possibly associated with a cerebral infarction) that are life-threatening or fatal have been reported with LIPIODOL ULTRA-FLUID in all its therapeutic indications. Patients should be informed of possible signs of embolism and should contact their doctor or hospital if any symptoms appear. The benefit/risk balance should be carefully evaluated prior to examination, particularly in patients with a known right-to-left cardiac shunt or a known intratumoral vascular shunt. The recommended dose should not be exceeded and the administration procedures should be followed.

Specific warnings for ~~4.4.1.1.~~ Lymphography

[…]

Lymphography saturates the thyroid with iodine for several months and it is therefore necessary to perform a thyroid assessment prior to the radiological examination.

Special warnings for transarterial chemoembolisation

Transarterial chemoembolisation is not recommended in patients with decompensated cirrhosis of the liver (Child-Pugh ≥ 8), severe hepatic dysfunction, macroscopic portal vein invasion, portal thrombosis (partial or total), and/or extrahepatic tumour dissemination.

An intra-arterial hepatic procedure may cause irreversible liver failure in patients with severe hepatic dysfunction and/or treated over several sessions close together. Tumour invasion of greater than 50% of the liver, bilirubin levels over 2 mg/dl, lactate dehydrogenase levels over 425 mg/dl, aspartate aminotransferase levels over 100 IU/l and decompensated cirrhosis have been described as being associated with an increase in the post-procedure mortality rate.

Oesophageal varices should be monitored carefully as they may rupture immediately after treatment. If a risk of rupture is identified, an endoscopic sclerotherapy/ligation should be performed prior to the transarterial chemoembolisation procedure.

Iodinated contrast-induced renal failure risk should be prevented by systematic hydration before and after the procedure.

The risk of superinfection in the treated area can be prevented by the administration of antibiotics.

[…]

Transarterial chemoembolisation/~~4.4.2.3.~~ Embolisation

Iodinated contrast agents ~~can~~ may ~~induce~~ cause ~~a transient~~temporary deterioration of renal function or ~~exacerbate~~ aggravate pre-existing renal ~~failure~~impairment. ~~The p~~Preventive measures ~~are as follows~~include:

[…]

- Cardiovascular and/or pulmonary risk factors should be evaluated prior to initiating a transarterial chemoembolisation procedure.

~~4.4.2.4.~~ Other

[…]

Indications for the use of LIPIODOL ULTRA-FLUID should be carefully assessed in patients with primary lymph oedema, as the oedema can be exacerbated.

4.6. Fertility, ~~P~~pregnancy and lactation

Pregnancy

~~The safety of LIPIODOL ULTRA-FLUID has not been demonstrated in pregnant women. The use of~~ LIPIODOL ULTRA-FLUID must not be used in ~~during pregnancy~~ pregnant women ~~because~~ due to ~~of~~ the ~~increases the~~ transplacental transfer of iodine~~,~~ over a long period~~s of time~~, which is likely to ~~probably~~ interfere~~s probably~~ with ~~thyroid function in of~~ the ~~foetus~~ foetus' thyroid function~~.~~, with a potential ~~. Although transient, this abnormality may involve a~~ risk of ~~cerebral lesions~~ brain damage and permanent hypothyroidism~~, calling for monitoring of thyroid function and close medical follow-up of the neonate.~~.

~~Consequently, LIPIODOL ULTRA-FLUID should not be used in pregnant women unless it is absolutely necessary, and only with strict medical monitoring.~~

Breastfeeding

Pharmacokinetic studies have shown significant ~~s~~excretion of iodine in breast milk after intramuscular administration of LIPIODOL ULTRA-FLUID. It has been demonstrated that the iodine ~~enters~~ passes into the vascular system of the breastfed infant via the gastrointestinal tract and this could interfere with thyroid function. Consequently, breastfeeding should be discontinued if LIPIODOL ULTRA-FLUID must be used~~, or else thyroid function should monitored more frequently in the neonate~~.

4.8. Undesirable effects

[…]

Hypersensitivity reactions are possible. These reactions ~~may involve~~ include one or more effects~~, occurring concomitantly or successively, and usually~~ with a concomitant or successive onset, most often including cutaneous, respiratory and/or cardiovascular manifestations, ~~each of~~ which can each be a warning ~~sign of incipient~~ of an early state of shock and, in very rare ~~instances~~cases, can even prove fatal.

Cases of pulmonary embolism and cerebral embolism (possibly associated with a cerebral infarction) that are life-threatening or fatal have been reported with LIPIODOL ULTRA-FLUID, for all its therapeutic indications.

~~*In i*~~*Interventional radiology:*

- ~~In~~ Trans-Arterial Chemo-Embolisation:

Most ~~of the~~ adverse reactions are not caused by LIPIODOL ULTRA-FLUID ~~itself~~ but are due to anticancer drugs or the embolisation itself.

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The most ~~frequent~~common adverse reactions of ~~the~~ TACE treatment are post embolisation syndrome (fever, abdominal pain, nausea, vomiting) and ~~transitory~~transient changes in liver function tests.

Worsening of pre-existing hepatocellular failure may occur following the use of Lipiodol in a hepatic intra-arterial procedure and may lead to serious and potentially fatal complications such as hepatic encephalopathy, oedematous ascitic decompensation, hepatic necrosis, liver abscess, pancreatitis, and even necrotising pancreatitis.

[…]

System organ class	Frequency: adverse reactions
Nervous system disorders	~~Undetermined frequency~~Frequency not known: cerebral embolism~~.~~, cerebral infarction, hepatic encephalopathy[a]
Respiratory, thoracic and mediastinal disorders	~~Undetermined frequency~~Frequency not known: pulmonary embolism~~.~~, pulmonary oedema, pleural effusion, acute respiratory distress syndrome, pneumonitis
Gastrointestinal disorders	~~Undetermined frequency~~Frequency not known: vomiting, diarrhoea, nausea~~.~~, pancreatitis[a], ascites[a]
Hepatobiliary disorders	Frequency not known: Cholecystitis[a], biloma[a], hepatic failure[a], hepatic infarction[a]
Infections and infestations	Frequency not known: Liver abscess[a]
Skin and subcutaneous tissue disorders	Frequency not known: Skin necrosis[a]

[a]: in the context of transarterial chemoembolization (TACE) and transarterial embolisation.

[…]

- השינויים המסומנים במכתב זה - הטקסט עם קו תחתון הוסף לעלון והסימונים בצהוב הינם החמרות במידע הבטיחותי.
- **העדכונים המשמעותיים ביותר מופיעים במכתב זה, אך קיימים עדכונים נוספים. יש לקרוא את העלון המעודכן במלואו.**
- העלון לרופא המעודכן נשלח למשרד הבריאות לצורך העלאתו למאגר התרופות שבאתר משרד הבריאות.
- ניתן לקבל את העלון מודפס על ידי פניה ישירה לבעל הרישום:
  פרומדיקו, רח' השילוח 6, ת.ד. 3340, פתח תקווה 4917001, טלפון: 03-9373737.

בברכה,

אבי ילצינדג
רוקח ממונה
בעל הרישום: פרומדיקו בע"מ