SUMMARY OF THE RISK MANAGEMENT PLAN

FOR

Lipiodol Ultra-Fluid (480 mg Iodine per mL) solution for injection

(Ethyl esters of iodized fatty acids of poppy seed oil)

Marketing authorisation holder: Guerbet AG

RMP Version number: 3.0

Data lock point for this RMP: 31-Dec-2020.

Date of final sign off: 08-Jun-2021.

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Lipidol Ultra-fluide is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Lipidol Ultra-fluide in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Guerbet AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Lipidol Ultra-fluide.

I. The medicine and what it is used for

Lipiodol Ultra-Fluid contains ethyl esters of iodized fatty acids of poppy seed oil as the active substance and it is given by lymphatic route, locally by cannulation of salivary duct, locally by injection in uterine cervical canal, and by intra-arterial route of administration. It is authorised for lymphography and for intra-arterial application after previous catheterization of tumor-supporting branches of the A. hepatica (with water-soluble contrast media). It is used to enhance the contrast of structures or fluids within the body and is thus an essential key component in medical imaging. In general, the product is used in X-ray examinations, computed tomography, angiographies as well as in interventional radiology.

As regards its use in the treatment of inoperable liver tumors, Lipiodol combines the unique properties of a tumor-seeking compound, a drug-delivery system, and an embolic and X-ray radiopaque agent. Thus, Lipiodol is utilized as a vehicle to carry and localize anticancer agents inside liver tumors.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Lipiodol Ultra-Fluid, together with measures to minimise such risks and the proposed studies for learning more about Lipiodol risks, are outlined below.

Measures to minimise the risks identified for Lipiodol can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC and package leaflet addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Lipiodol is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Lipiodol Ultra-Fluid are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Lipiodol. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	- Thyroid disorders - Embolic and thrombotic events - Post-embolization syndrome - Hepatic failure - Liver abscess - Biloma - Cholecystitis - Granuloma (following hysterosalpingography)
Important missing information	- Use before and during pregnancy

II.B Summary of important risks

- **Risks relating to the active substance**

Important Identified Risk	Thyroid disorders
Evidence for linking the risk to the medicine	Iodinated contrast media can affect thyroid function because of the free iodine content and can cause an overactive thyroid gland (hyperthyroidism) in predisposed patients. Patients at risk are those with clinically concealed overactive thyroid gland (latent hyperthyroidism) and those with uncontrolled thyroid function (functional thyroid autonomy). Underactive thyroid (hypothyroidism) and inflammation of the thyroid (thyroiditis) have been reported as well. Iodine poisoning (iodism) occurs more frequently with Lipiodol than with water-soluble organic iodine derivatives. The use of Lipiodol during pregnancy causes iodine transfer which probably interferes with the thyroid function of the fetus. Although this anomaly is transitory, it produces the potential risk of permanent hypothyroidism and brain damage, and therefore requires supervision of thyroid function and careful medical monitoring of the neonate.
Risk factors and risk groups	Patients with a goiter or a history of dysthyroidism. Neonates who have received, or whose mother has received, an iodinated contrast agent.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3, 4.4 and 4.8.

Important Identified Risk	Embolic and thrombotic events
Evidence for linking the risk to the medicine	Occlusion of pulmonary blood vessels (pulmonary embolism) may occur in patients following lymphography with Lipiodol, due to a portion of the product temporarily blocking (embolizing) the pulmonary capillaries. In patients treated with hepatic chemoembolization, pulmonary artery oil embolus has been estimated to occur in <1%. Embolization may occur with or without clinical symptoms and is usually transient in nature. Temporary pulmonary, cerebral or skin embolization may occur in patients following Trans-Arterial Chemo-Embolisation or Selective embolisation in combination with Histoacryl glue. Intravasation of Lipiodol Ultra-Fluid may occur in the course of a hysterosalpingography procedure and may result in serious pulmonary or cerebral embolic complications.
Risk groups or risk factors	Patients with prior impaired respiratory function, cardiorespiratory failure, or pre-existing right-sided cardiac overload, in particular elderly patients. Overdose.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3, 4.4 and 4.8.

Important Identified Risk	Post-embolization syndrome (PES)
Evidence for linking the risk to the medicine	Post-embolization syndrome (fever, pain, increased white blood cell count) following the administration of Lipiodol together with anticancer drugs in patients with liver tumor has been reported to occur in 35 to 100% of patients. More severe forms requiring extended hospital stay or readmission were reported in about 4% of patients. A severe PES requiring treatment with analgesics for at least 7 days is associated with liver tumor size > 9 cm in diameter.
Risk groups or risk factors	Patients undergoing embolization (TAE, TACE). Severe PES requiring treatment with analgesics for at least 7 days is associated with tumor size > 9 cm in diameter.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8.

Important Identified Risk	Hepatic failure
Evidence for linking the risk to the medicine	Hepatic failure has been estimated to occur in about 2% of patients treated with hepatic chemoembolization. The risk of hepatic failure depends on the baseline hepatic synthetic function. When the mixture of Lipiodol with anticancer agents is administered into the hepatic arteries, it can progressively cause liver insufficiency in patients with pre-existing serious liver malfunction. More than 50% liver replacement with tumor, increase in

	markers of liver insufficiency, and decompensated liver cirrhosis have been described as associated with unfavorable outcome or even death.
Risk groups or risk factors	Portal vein thrombosis, high dose of anti-cancer drugs and Lipiodol, a high basal level of bilirubin, a prolonged prothrombin time and advanced Child-Pugh class.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8.

Important Identified Risk	**Liver abscess**
Evidence for linking the risk to the medicine	It is possible that dead (necrotic) tumor parts may become colonized by either enteric organisms or by bacteria introduced exogenously during the procedure. Liver abscess has been reported to occur in 0% to 15% of patients treated with hepatic chemoembolization.
Risk groups or risk factors	Patients who have chronic colonisation of the biliary tree with enteric flora are at significantly higher risk of hepatic abscess formation. This includes patients with a surgical bilioenteric anastomosis, seen commonly among patients with pancreatic neuroendocrine tumors, and previous intervention in the biliary system being prone to an ascending biliary infection.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8.

Important Identified Risk	**Biloma**
Evidence for linking the risk to the medicine	It has been suggested that Lipiodol can impair the blood flow in the vessels surrounding the bile ducts, and owing to the direct effect of concomitantly administered anticancer drugs which damage the cells of the hepatic arteries, death of bile duct cells can result. Consequently biloma (encapsulated collection of bile) is formed by the bile leaking out at the embolized areas. In addition, biloma seems to be associated to focal tightening of large bile ducts with the use of gelatin sponge particles. Biloma requiring drainage has been estimated to occur in <1% of patients treated with hepatic chemoembolization. Some risk factors of biloma have been suggested such as tumor size <5 cm, bile duct dilatation, proximal injection site, repeated injection with frequency of <3 months, and injection of a suspension of anticancer drugs.
Risk groups or risk factors	Tumor size of <5 cm, bile duct dilatation, proximal injection site, repeated injection with frequency of <3 months, and injection of a suspension of anticancer drugs.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 and 4.8.

Important Identified Risk	Cholecystitis
Evidence for linking the risk to the medicine	Cholecystitis requiring operation has been estimated to occur in <1% of patients treated with hepatic chemoembolization. Some risk factors of cholecystitis have been suggested such as unintentional blockage of the cystic artery during hepatic artery embolization, thus causing ischemic change to the gallbladder.
Risk groups or risk factors	None.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.8.

Important Identified Risk	Granuloma (following hysterosalpingography)
Evidence for linking the risk to the medicine	Underlying mechanism is still not fully resolved but literature data suggested the occurrence of fat granuloma: a nodule of necrotic, fatty tissue associated with granulomatous inflammation or a foreign-body reaction around a deposit of injected material containing an oily substance.
Risk groups or risk factors	Not available.
Risk minimisation measures	Routine risk minimisation measures: CCSI section 4.8 (not applicable in Switzerland).

Important missing information	Use before and during pregnancy
Potential mechanisms	Based on current knowledge, the use of Lipiodol during pregnancy causes iodine transfer which probably interferes with the thyroid function of the foetus. Although this anomaly is transitory, it produces the potential risk of permanent hypothyroidism and brain damage. Since the half-life of Lipiodol elimination following intrauterine administration was never assessed, it cannot be excluded that the foetus is exposed to Lipiodol from the date of the examination until the date of birth. In addition, the blood bioavailability in the pregnant mother via this route of administration has never been studied.
Evidence source	Post-marketing pharmacovigilance and literature data.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.6.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or any specific obligation with regards to Lipiodol.

II.C.2 Other studies in post-authorisation development plan

There are no post-authorisation development studies required for Lipiodol.