	CCSI section 4.6, adequately reflected in SmPC and PIL.	

Part VI: Summary of the risk management plan

This is a summary of the risk management plan (RMP) for Lipiodol Ultra-Fluid. This RMP details important risks of Lipiodol, and how additional information will be obtained about the risks and uncertainties (missing information).

Moreover, Lipiodol summary of product characteristics (SmPC) and its package leaflet provide essential information to healthcare professionals and patients on how the product should be used.

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 in the EEA for various radiological diagnosis purposes (including hysterosalpingography), visualisation / localisation / chemoembolisation of HCC, and use in association with glues during vascular embolization. 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.

Moreover, in the context of this RMP, the following extensions of indication are applied for: Hysterosalpingography for tubal flushing in women undergoing infertility workup.

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
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.
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: CCSI section 4.3, 4.4 and 4.8, adequately reflected in the SmPC and in the PIL.

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.
Risk groups or risk factors	Patients with prior impaired respiratory function, cardiorespiratory failure, or pre-existing right-sided cardiac overload, in particular elderly patients.
Risk minimisation measures	Routine risk minimisation measures: CCSI section 4.3, 4.4 and 4.8, adequately reflected in the SmPC and in the PIL.

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: CCSI section 4.4 and 4.8, adequately reflected in the SmPC and in the PIL.

Important Identified Risk	**Hepatic failure**
Evidence for linking the risk to the medicine	Liver failure has been estimated to occur in about 2% of patients treated with hepatic chemoembolization. The risk of hepatic failure is dependent on baseline hepatic synthetic function. Treatment administered via liver arteries can progressively cause liver insufficiency in patients with pre-existing serious liver malfunction. More than 50% liver replacement with tumor, increase in markers of insufficient liver function and decompensated liver cirrhosis have been described as associated with unfavourable 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: CCSI section 4.4 and 4.8, adequately reflected in the SmPC and in the PIL.

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: CCSI section 4.4 and 4.8, adequately reflected in the SmPC and in the PIL.

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: CCSI section 4.6, adequately reflected in the SmPC and in the PIL.

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.