Part VI: Summary of the Risk Management Plan

Summary of Risk Management Plan for Cabazitaxel ratiopharm (cabazitaxel) 10 mg/ml concentrate for solution for infusion

This is a summary of the risk management plan (RMP) for Cabazitaxel ratiopharm (cabazitaxel) 10 mg/ml concentrate for solution for infusion. The RMP details important risks of Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion, how these risks can be minimised, and how more information will be obtained about Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion risks and uncertainties (missing information).

Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion should be used.

Important new concerns or changes to the current ones will be included in updates of Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion RMP.

I. The Medicine and What It is used for

Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion is authorised in combination with prednisone or prednisolone indicated for the treatment of adult patients with metastatic castration resistant prostate cancer previously treated with a docetaxel containing regimen. It contains Cabazitaxel as the active substance and it is given intravenously after dilution.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion , together with measures to minimise such risks and the proposed studies for learning more about Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC 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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion 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 Cabazitaxel ratiopharm 10 mg/ml concentrate for solution for infusion . 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);

Table 10: Summary of Safety Concerns

List of important risks and missing information	
Important identified risks	• Neutropenia and associated clinical events • Gastro-intestinal disorders • Renal failure • Peripheral neuropathy • Anemia • Respiratory disorders • Use in severe hepatic impairment
Important potential risks	• Cardiac arrhythmia • Hepatic disorders • Lens toxicity • Effect on male fertility • Use in non-evaluated conditions • Drug-drug interaction (concomitant administration with inducers or inhibitors of CYP3A) • Mild and moderate hepatic impairment • Teratogenicity • Drug preparation errors
Missing information	• Ethnicity other than Caucasian

II.B Summary of Important Risks

Table 11: Summary of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Important identified risk: Neutropenia and associated clinical events	
Evidence for linking the risk to the medicine	The risk is considered as important identified risk since adverse reactions such as neutropenia and neutropenia complications (febrile neutropenia, neutropenic infection, neutropenic sepsis, sepsis, septic shock) might require medical care or hospitalization if not detected and treated timely or even result in fatal outcome.
Risk factors and risk groups	Patients with high-risk clinical features (age > 65 years, poor performance status, previous episodes of febrile neutropenia, extensive prior radiation ports, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia.

Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.3, 4.8 and 5.1. SmPC section 4.4 where advice is given for monitoring of complete blood counts on a weekly basis during cycle 1 and before each treatment cycle thereafter so that the dose can be adjusted, if needed. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: Gastro-intestinal disorders	
Evidence for linking the risk to the medicine	The risk is considered as important identified risk since symptoms such as abdominal pain and tenderness, fever, persistent constipation, diarrhoea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly. Furthermore, gastrointestinal (GI) hemorrhage and perforation, ileus, colitis, including fatal outcome, have been reported in patients treated with cabazitaxel and exacerbation of adverse reactions as gastrointestinal disorders are the anticipated complications of overdose with cabazitaxel.
Risk factors and risk groups	Patients at risk of developing gastrointestinal complications: those with neutropenia, the elderly, patients who concomitantly use NSAIDs, anti-platelet therapy or anti-coagulants, and patients with a prior history of pelvic radiotherapy or gastrointestinal disease, such as ulceration and GI bleeding.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.8 and 5.1. SmPC section 4.4 where advice is given on appropriate measures to rehydrate patients and prompt evaluating symptoms such as abdominal pain and tenderness, fever, persistent constipation, diarrhoea, with or without neutropenia as well as monitoring and correction serum electrolyte levels, particularly potassium. SmPC section 4.9 where advice is given for close monitoring of patient with anticipated complications of overdose that would consist of gastrointestinal disorders. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: Renal failure	
Evidence for linking the risk to the medicine	The risk is considered as important identified risk since renal failure, including cases with fatal outcome, has been observed.
Risk factors and risk groups	Patients presenting end stage renal disease.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.8. SmPC section 4.2 where advice is given for ensuring adequate hydration of the patient throughout the treatment in order to prevent renal failure as well as recommendation for careful monitoring of patients presenting end stage renal disease. SmPC section 4.4 where advice is given for serum creatinine measurement

	at baseline, with each blood count and whenever the patient reports a change in urinary output. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: Peripheral neuropathy	
Evidence for linking the risk to the medicine	The risk is considered as important identified risk since cases of peripheral neuropathy, peripheral sensory neuropathy (e.g., paraesthesias, dysaesthesias) and peripheral motor neuropathy have been observed in patients receiving cabazitaxel.
Risk factors and risk groups	Patients under treatment with cabazitaxel, especially if they experience symptoms such as pain, burning, tingling, numbness, or weakness.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.8 and 5.1. SmPC section 4.4 where advice is given for assessing for the presence or worsening of neuropathy before each treatment. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: Anemia	
Evidence for linking the risk to the medicine	The risk is considered as important identified risk since in the EFC6193 study the most commonly (≥ 10%) occurring adverse reactions in all grades were anaemia (97.3%), leukopenia (95.7%), neutropenia (93.5%). The incidence of grade ≥ 3 anaemia, increased based on laboratory abnormalities was 10.5%, respectively.
Risk factors and risk groups	Patients on the treatment with cabazitaxel, patients experiencing blood loss, especially female patients.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.8 and 5.1 SmPC section 4.4 where advice is given on haemoglobin and haematocrit monitoring before treatment with cabazitaxel and if patients exhibit signs or symptoms of anaemia or blood loss. PL sections 2 and 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: Respiratory disorders	
Evidence for linking the risk to the medicine	The risk is considered as important potential risk since cases of interstitial pneumonia/pneumonitis and interstitial lung disease, sometimes fatal have been reported with an unknown frequency (cannot be estimated from the available data).
Risk factors and risk groups	Patients with history of respiratory disorders.

Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 and 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures None.
Important identified risk: Use in severe hepatic impairment	
Evidence for linking the risk to the medicine	In 3 patients with severe hepatic impairment (total bilirubin > 3 ULN), a 39% decrease in clearance was observed when compared to patients with mild hepatic impairment, indicating some effect of severe hepatic impairment on cabazitaxel pharmacokinetics. Maximum tolerated dose of cabazitaxel in patients with severe hepatic impairment was not established.
Risk factors and risk groups	Patients with severe hepatic impairment.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.3, 4.4 and 5.2. PL section 2. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Cardiac arrhythmia	
Evidence for linking the risk to the medicine	The risk is considered as important identified risk since cardiac arrhythmias have been reported, most commonly tachycardia and atrial fibrillation. Furthermore, one patient in the cabazitaxel group died from cardiac failure. Fatal ventricular fibrillation was reported in 1 patient (0.3%), and cardiac arrest in 2 patients (0.5%).
Risk factors and risk groups	Patients with cardiac disease, especially those diseases related to irregular or decreased cardiac rhythm.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4 and 4.8. PL section 4. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Hepatic disorders	
Evidence for linking the risk to the medicine	The risk is considered as important potential risk since adverse reactions not observed in clinical studies, but seen in dogs after single dose, 5 day and weekly administration at exposure levels lower than clinical exposure levels and with possible relevance to clinical use were arteriolar/periarterolar necrosis in the liver, bile ductule hyperplasia and/or hepatocellular necrosis.
Risk factors and risk groups	Patients with mild and moderate hepatic impairment.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3, 4.4, 4.8, 5.2 and 5.3. SmPC section 4.2 where advice is given on close monitoring of safety for the patient with mild hepatic impairment.

	PL section 2. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Lens toxicity	
Evidence for linking the risk to the medicine	The risk is considered as important potential risk since adverse reactions not observed in clinical studies, but seen in rats during repeat-dose toxicity studies at exposure levels higher than clinical exposure levels and with possible relevance to clinical use were eye disorders characterized by subcapsular lens fiber swelling/degeneration. These effects were partially reversible after 8 weeks.
Risk factors and risk groups	Patients treated with cabazitaxel, especially those with history of visual disturbances and eye disorders.
Risk minimisation measures	Routine risk minimisation measures SmPC section 5.3. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Effect on male fertility	
Evidence for linking the risk to the medicine	The risk is considered as important potential risk since, considering the pharmacological activity of taxanes, their genotoxic potential and effect of several compounds of this class on fertility in animal studies, effect on male fertility could not be excluded in human and in repeated-dose toxicity studies. Degeneration of seminal vesicle and seminiferous tubule atrophy in the testis were observed in rats, and testicular degeneration (minimal epithelial single cell necrosis in epididymis), was observed in dogs. Exposures in animals were similar or lower than those seen in humans receiving clinically relevant doses of cabazitaxel.
Risk factors and risk groups	Male patients treated with cabazitaxel as well as male healthcare personnel who participate in preparation and administration of cabazitaxel.
Risk minimisation measures	Routine risk minimisation measures SmPC section 5.3. SmPC section 4.6 where advice is given on using effective contraception throughout treatment and to continue this for up to 6 months after the last dose of cabazitaxel due to potential exposure via seminal liquid as well as as prevent contact with the ejaculate by another person throughout treatment. PL section 2 where advice is given not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because cabazitaxel may alter male fertility as well as recommendation for using efficient contraception. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Use in non-evaluated indications	
Evidence for linking the risk to the medicine	None.

Risk factors and risk groups	Not known.
Risk minimisation measures	Routine risk minimisation measures Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Drug-drug interaction (concomitant administration with inducers or inhibitors of CYP3A)	
Evidence for linking the risk to the medicine	Based on in vitro studies, the potential risk of inhibition by cabazitaxel at clinically relevant concentrations is possible towards medicinal products that are mainly substrate of CYP3A. However a clinical study has shown that cabazitaxel (25 mg/m2 administered as a single 1-hour infusion) did not modify the plasma levels of midazolam, a probe substrate of CYP3A. Therefore, at therapeutic doses, co-administration of CYP3A substrates with cabazitaxel to patients is not expected to have any clinical impact.
Risk factors and risk groups	Patients prescribed with CYP3A inducers or inhibitors.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.5 and 5.2 SmPC section 4.4 where advice is given for close monitoring for toxicity if co- administration with a strong CYP3A inhibitor cannot be avoided. PL section 2. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Mild and moderate hepatic impairment	
Evidence for linking the risk to the medicine	A dedicated study in 43 cancer patients with hepatic impairment showed no influence of mild (total bilirubin > 1 to ≤ 1.5 x ULN or AST > 1.5 x ULN) or moderate (total bilirubin > 1.5 to ≤ 3.0 x ULN) hepatic impairment on cabazitaxel pharmacokinetics. The maximum tolerated dose of cabazitaxel was 20 and 15 mg/m2, respectively.
Risk factors and risk groups	Patients with mild to moderate hepatic impairment.
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4 and 5.2. SmPC section 4.2 where advice is given for careful monitoring of patients presenting end stage renal disease (creatinine clearance (CLCR < 15 mL/min/1.73 m^2), due to their condition and the limited amount of data available. PL section 2. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Teratogenicity	
Evidence for linking the risk to the medicine	Cabazitaxel induced embryofoetal toxicity in female rats treated intravenously once daily from gestational days 6 through 17 linked with maternal toxicity and consisted of foetal deaths and decreased mean foetal weight associated with delay in skeletal ossification. Exposures in animals

	were lower than those seen in humans receiving clinically relevant doses of cabazitaxel. Cabazitaxel crossed the placenta barrier in rats.
Risk factors and risk groups	Women of childbearing potential.
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.6 and 5.3. PL section 2. Prescription only medicine. Additional risk minimisation measures None.
Important potential risk: Drug preparation errors	
Evidence for linking the risk to the medicine	Drug preparation errors, ie, reconstitution errors" is regarded as an identified risk for the reference product (Jevtana®, Sanofi). According to the DHPC for the reference product disseminated in August 2013 due to the risk of medication errors related to reconstitution error that could lead to overdose: "*The error in the administered dose occurred due to an inappropriate reconstitution in the first step where the nominal volume of the solvent vial (4.5 mL) was transferred to the concentrate vial, instead of the entire content, leading to a higher dose of Jevtana delivered*" (Jevtana DHPC, 2013). The risk of "drug preparation errors i.e. drug reconstitution errors" is specific for Jevtana® and is not considered necessary for the hybrid product containing cabazitaxel that was developed to avoid the intermediate step of dilution process that generated the safety signal for Jevtana® in 2013. The important identified risk "drug preparation errors i.e. reconstitution errors" is not considered relevant for Cabazitaxel ratiopharm. Therefore, the medication error risk for Cabazitaxel ratiopharm has a different scope and is downgraded to POTENTIAL.
Risk factors and risk groups	Underlying systems factors have been shown as crucial contributors to the occurrence of medication errors (Keers et al., 2013a). Human factors such as high perceived workload, staff health status (fatigue, stress) or interruptions/distractions during drug administration, and problems with ward-based equipment (access, functionality) have been reported as medication error general causes (Keers et al., 2013b). Regarding the specific intravenous medication error risk, a study conducted at a paediatric hospital that was using automated compounding identified four factors that were significantly ($p < 0.05$) associated with an increased risk of compounding errors in this setting: dose preparation during the morning shift (relative risk [RR], 1.84; 95% CI, 1.68-2.02) or on a Sunday (RR, 1.28; 95% CI, 1.11-1.47), preparation of doses for use in critical care units (RR, 1.17; 95% CI, 1.07-1.28), and technician versus pharmacist compounding (RR, 1.17; 95% CI, 1.04-1.32) (Deng et al., 2016).
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2 and 6.6. Prescription only medicine. Additional risk minimisation measures None.
Missing information: Ethnicity other than Caucasian	
Evidence source	Racial distribution of patients involved in studies that evaluated clinical efficacy and safety of cabazitaxel was: 83.9% Caucasian, 6.9%

	Asian/Oriental, 5.3% Black and 4% Others.
Population in need of further characterisation	Patients that are not of Caucasian ethnicity.
Risk minimisation measures	Routine risk minimisation measures Prescription only medicine. Additional risk minimisation measures None.

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 specific obligation of Cabazitaxel.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Cabazitaxel.