Summary of risk management plan for Apealea (paclitaxel)

This is a summary of the risk management plan (RMP) for Apealea. The RMP details important risks of Apealea, how these risks can be minimised, and how more information will be obtained about Apealea's risks and uncertainties (missing information).

Apealea's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Apealea should be used.

This summary of the RMP for Apealea should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Apealea's RMP.

I. The medicine and what it is used for

Apealea in combination with carboplatin is authorised for the treatment of adult patients with first relapse of platinum-sensitive epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer (see SmPC for the full indication). It contains paclitaxel as the active substance and it is given by intravenous (i.v.) infusion.

Further information about the evaluation of Apealea's benefits can be found in Apealea's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004154/human_med_002297.jsp

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

Important risks of Apealea together with measures to minimise such risks and the proposed studies for learning more about Apealea's 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 Apealea is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Apealea 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 Apealea. 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	• Myelosuppression: Neutropenia, Anaemia, Thrombocytopenia • Infusion site reactions • Peripheral neuropathy • Hypersensitivity reactions •
Important potential risks	• Acute renal failure and haemolytic-uremic syndrome • Concomitant therapy and interactions requiring dose adjustment • Medication errors • Off-label use • Reproductive toxicity • Use in patients with hepatic impairment • Safety in patients 75 years or older •
Missing information	<u>Special Populations:</u> • Patients with impaired renal function • Non-Caucasian patients <u>Other Missing Information:</u> • Genotoxicity long-term effect

II.B Summary of important risks

Important identified risk: Myelosuppression (Neutropenia, Anaemia, Thrombocytopenia)	
Evidence for linking the risk to the medicine	Clinical study OAS-07OVA and literature search. Myelosuppression, particularly neutropenia, is considered an important identified risk since it represents the most common dose-limiting toxicity associated with the use of Apealea in combination with carboplatin. Both duration and severity of the neutropenia are factors that may lead to febrile neutropenia. The duration of neutropenia is particularly important in terms of the risk of infections.
Risk factors and risk groups	Lyman et al, 2005 suggested that age is a very important risk factor, not just age in itself, but also because of the comorbidities that accompany the ageing process. Other risk groups are patients with prior neutropenic event(s) and patients receiving a combination of chemotherapy and radiation therapy. Prior chemotherapy might also be a risk factor, and all patients in the study had been previously treated. In clinical study OAS-07OVA, neutropenia defined as serious (Grade 4 and lower if the patient was hospitalised) occurred in 29% of the patients treated with Apealea, while Grade 3 or higher leukopenia was less frequent (6%) in patients treated with Apealea, as was anaemia (5%). Febrile neutropenia occurred in 3% of the patients treated with Apealea.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> *SmPC Section 4.2* contains advice regarding treatment delay and dose reductions in the event of neutropenia and/or thrombocytopenia for Apealea in combination with carboplatin. *SmPC Section 4.4* contains special precautions regarding myelosuppression. Neutropenia, febrile neutropenia, leukopenia, thrombocytopenia, granulocytopenia, anaemia, disseminated intravascular coagulation, pancytopenia, haematotoxicity and coagulopathy are labelled in *SmPC Section 4.8*. Patients with low neutrophil counts or platelet counts are contraindicated, *SmPC Section 4.3*. Since myelosuppression may occur in the event of an overdose this is specified in *SmPC Section 4.9*. <u>Additional risk minimisation measures:</u> None proposed.

Important identified risk: Infusion site reactions	
Evidence for linking the risk to the medicine	Clinical study OAS-07OVA and literature search. Infusion site reactions are considered important identified risks since they were reported more frequently in patients receiving Apealea (12%) than Taxol (1%). The reactions were typically of low grade and transient.
Risk factors and risk groups	No subgroups of patients have been identified as being at a higher risk of developing an infusion site reaction.
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.4* advises that these reactions are common, but may be improved by slowing the infusion rate. At severe reactions, the patient is recommended to be considered for a central intravenous catheter. Infusion site reaction is labelled as a very common reaction in *SmPC Section 4.8*.

Important identified risk: Peripheral neuropathy	
Evidence for linking the risk to the medicine	Clinical study OAS-07OVA and literature search. Peripheral neuropathy is considered an important identified risk since it is associated with paclitaxel/carboplatin treatment. Chemotherapy induced neurotoxicity may affect patient's response to treatment due to the need for dose reduction or discontinuation and also affect quality of life.
Risk factors and risk groups	Several studies have attempted to identify risk factors for development of CIPN, which also vary with different chemotherapeutic agents. Some of the clinical factors implicated in the development of CIPN include baseline neuropathy (Dimopoulos et al, 2011; Badros et al 2007) the presence of diabetes (Badros et al 2007), smoking history and decreased creatinine clearance (Kawakami et al, 2012). In addition, there is interest in pharmacogenomics and identifying genes that may play a role in the development of CIPN. Although numerous genes have been investigated, such as GSTP1, CYP2C8, and AGXT, there have been no conclusive findings (Alberti and Cavaletti, 2014). Patients with cancer (Honnorat and Antoine, 2007). The risk of peripheral neuropathy may be increased if used in combination with other agents, depending upon the combination.
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.2* contains advice for delay during treatment and dose reduction in the event of signs of neuropathy.

	Peripheral sensory neuropathy and peripheral neuropathy are stated in Special warnings and precautions for use, *SmPC Section 4.4*. Peripheral sensory neuropathy and peripheral neuropathy are labelled in *SmPC Section 4.8*. Since peripheral sensory neuropathy and peripheral neuropathy may occur in the event of an overdose this is specified in *SmPC Section 4.9*. Additional risk minimisation measures: None proposed.

Important identified risk: Hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical study OAS-07OVA and literature search. Hypersensitivity reactions are considered important potential risks since they are not only reported for Cremophor-EL formulated paclitaxel but also have been reported for treatment with albumin-bound paclitaxel formulations. Even though most hypersensitivity reactions reported for Apealea were mild to moderate and mainly occur as skin and subcutaneous tissue disorders, general disorders and administration site conditions, serious hypersensitivity reactions including one anaphylactic shock were reported.
Risk factors and risk groups	Hypersensitivity reactions could appear in any cycle. Patients who previously suffered hypersensitivity reactions with a taxane formulation are at increased risk (see review by Picard and Castells, 2015).
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.3* states that severe hypersensitivity to the active substance or the excipients is a contraindication. *SmPC Section 4.4* cautions that patients should be observed closely during treatment. Moderate cases may require premedication. Delayed reactions related to paclitaxel occurring during or after infusion of carboplatin cannot be excluded. Hypersensitivity reactions are labelled in *SmPC Section 4.8*. Additional risk minimisation measures: None proposed.

Important potential risk: Acute renal failure and haemolytic-uremic syndrome	
Evidence for linking the risk to the medicine	Clinical study OAS-07OVA and literature search. Even though there were no reports of acute renal failure or haemolytic-uremic syndrome in the clinical trial of Apealea, acute renal failure is listed as a common, and haemolytic uraemic syndrome as an uncommon adverse reaction for albumin-bound paclitaxel in combination with gemcitabine. Since albumin-bound paclitaxel and Apealea belongs to the same pharmacological class, acute renal failure is considered an important potential risk.
Risk factors and risk groups	Illness requiring intensive care, impaired renal or hepatic function, diabetes, high blood pressure, heart failure.
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.2* states that patients with mildly or moderately impaired renal function may be treated without a dose modification. Patients with severe renal impairment should not be treated. Azotaemia is labelled in *SmPC Section 4.8*. Additional risk minimisation measures: None proposed.

Important potential risk: Concomitant therapy and interactions requiring dose adjustment	
Evidence for linking the risk to the medicine	Interactions with Inducers or Inhibitors of CYP2C8 and CYP3A4: OAS-REP-06, EMA/706621/2016 and literature search: Harris et al, 1994; Rahman et al, 1994; Michalets, 1998 Interaction with cisplatin: SmPC generic paclitaxel and literature search: Baker and Dorr 2001; Crul et al, 2002
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.5* provides details of potential interactions with other medicinal products. Additional risk minimisation measures: None proposed.

Important potential risk: Medication errors	
Evidence for linking the risk to the medicine	Medication errors is considered an important potential risk since there is a known risk for medication errors with medicinal products.
Risk factors and risk groups	Not applicable
Risk minimisation measures	Routine risk minimisation measures:

	SmPC Section 4.2 states that Apealea should only be administered under the supervision of a qualified oncologist and should not be interchanged with other paclitaxel formulations Administration precautions are included in *SmPC Section 6.6*. The therapeutic indications are clearly stated in *SmPC Section 4.1*. <u>Additional risk minimisation measures:</u> None proposed.

Important potential risk: Off-label use	
Evidence for linking the risk to the medicine	Off-label use is considered an important potential risk since there is a known risk for off-label use with medicinal products.
Risk factors and risk groups	Not applicable
Risk minimisation measures	<u>Routine risk minimisation measures:</u> The potential for off-label use should be monitored by routine pharmacovigilance. <u>Additional risk minimisation measures:</u> None proposed.

Important potential risk: Reproductive toxicity	
Evidence for linking the risk to the medicine	Paclitaxel is suspected to cause serious birth defects when administered during pregnancy. Studies in animals have shown reproductive toxicity. Paclitaxel should not be used during pregnancy unless the clinical condition requires this treatment.
Risk factors and risk groups	Women of childbearing potential not using effective contraception during treatment and up to one month after receiving treatment.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> *SmPC Section 4.6* provides information on the reproductive toxicity of paclitaxel, and includes a warning on the use of Apealea in fertility, during pregnancy, and in breast-feeding women. *SmPC Section 4.3* states that breast feeding is a contraindication. <u>Additional risk minimisation measures:</u> None proposed.

Important potential risk: Use in patients with hepatic impairment	
Evidence for linking the risk to the medicine	Clinical study OAS-07OVA and literature search
Risk factors and risk groups	In a study of the safety and pharmacology of paclitaxel in patients with impaired liver function (N = 37), a significantly increased haematological toxicity was seen in patients with increasing hepatic impairment, even with a lower paclitaxel exposure (AUC; Joerger et al, 2007). This study suggested that an individual's susceptibility to paclitaxel-related haematological toxicity, such as myelosuppression in cancer patients with moderate to severe hepatic impairment, could be predicted based on total bilirubin concentration (Joerger et al, 2007). More instances of mucositis and neutropenic fever were also seen in paclitaxel-treated patients in the higher liver impairment groups (Joerger et al, 2007). In a small study (N = 9) of high-dose paclitaxel (250 mg/m^2) in patients with advanced breast cancer, the 2 patients with hepatic function disturbances experienced more profound neuropathy (Huizing et al, 1995). However, a correlation between paclitaxel pharmacokinetic and sensory polyneuropathy was not seen in a more recent study (Joerger et al, 2007). A Phase 2 study of paclitaxel in patients with hepatocellular carcinoma (N = 20) showed that, in patients with hepatic impairment (N = 4 [toxicity data; N = 3 for PK data] according to indocyanine green test), the AUC was significantly increased ($p < 0.02$), clearance decreased ($p < 0.02$) and treatment-related deaths increased ($p = 0.03$) compared to those patients without hepatic impairment (Chao et al, 1998).
Risk minimisation measures	<u>Routine risk minimisation measures:</u> *SmPC Section 4.2* contains information of insufficient data for recommendation of dose modification for patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment should not be treated with paclitaxel. *SmPC Section 4.4* warns that the toxicity of paclitaxel may be increased with hepatic impairment and the patients should be closely monitored. <u>Additional risk minimisation measures:</u> None proposed.

Important potential risk: Safety in patients ≥75 years	
Evidence for linking the risk to the medicine	Clinical study OAS-07OVA and literature search
Risk factors and risk groups	No risk group or risk factor in this age group is identified.
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.2* advises that limited data are available on the use of Apealea in patients 75 years old or older. Additional risk minimisation measures: None proposed.

Missing information: Patients with impaired renal function	
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.2* states that patients with mildly or moderately impaired renal function may be treated without a dose modification. Patients with severe renal impairment should not be treated. Azotaemia is labelled in *SmPC Section 4.8* and *PL Section 4*. Additional risk minimisation measures: None proposed.

Missing information: Non-Caucasian patients	
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.2* contains information of insufficient data for recommendation of additional dose adjustments for non-Caucasian patients. *SmPC Section 4.4* warns that there are limited data on the use of Apealea in non-Caucasian patients, and studies in breast cancer patients treated with paclitaxel-containing regimens indicate a possible increased risk of neuropathy in non-Caucasian patients.Additional risk minimisation measures: None proposed.

Missing information: Genotoxicity long-term effect	
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 5.3* includes information on the genotoxic potential of paclitaxel. Additional risk minimisation measures: None proposed.

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 Apealea.

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

There are no studies planned for additional pharmacovigilance activities.