ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Apealea 60 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 60 mg of paclitaxel.

After reconstitution, each mL of solution contains 1 mg of paclitaxel (micellar).

Excipients with known effect

One vial contains 3.77 mg (0.164 mmol) sodium. After reconstitution, each mL of solution contains up to approximately 3.60 mg (0.157 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

Greenish-yellow to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Apealea in combination with carboplatin is indicated for the treatment of adult patients with first relapse of platinum-sensitive epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer (see section 5.1).

4.2 Posology and method of administration

Apealea should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents. It should not be interchanged with other paclitaxel formulations.

Posology

The recommended dose of Apealea is 250 mg/m^2 body surface area (BSA) given as an intravenous infusion over 1 hour followed by carboplatin every three weeks for six cycles. The recommended dose of carboplatin is AUC = 5–6 mg/mL×min.

Dose adjustments and delays during treatment
Patients who experience neutropenia (neutrophil count < 1.5 × 10^9/L), febrile neutropenia or thrombocytopenia (platelet count < 100 × 10^9/L) during treatment should have the next treatment cycle delayed until neutrophil counts recover to ≥ 1.5 × 10^9/L and platelets recover to ≥ 100 × 10^9/L. For Apealea, dose reductions of initially 50 mg/m^2 and additionally 25 mg/m^2 should be considered for subsequent courses (see Table 1).

In the case of febrile neutropenia or low platelet count (< 75 × 10^9/L), the dose of carboplatin should be reduced by 1 AUC unit in the treatment cycles following recovery. For appropriate use of carboplatin, the prescriber is advised to consult the prescribing information for carboplatin as well.

Dose reductions or/and delays should be considered as a result of any clinically significant adverse reaction as presented in Table 1.

Table 1. Treatment delay and dose level reductions for adverse drug reactions

Observation[a]	**Delay of next cycle Apealea/carboplatin**	**Apealea dose for subsequent courses (mg/m^2)**[b]
Haematological toxicity[b]		
neutrophil count < 1.5×10^9/L or platelet count < 100×10^9/L or febrile neutropenia	Withhold treatment until recovery	Standard dose: 250 <u>*Possible dose reductions:*</u> First dose level reduction: 200 Second dose level reduction: 175
Nervous system disorders		
grade ≥ 2 peripheral sensory neuropathy or grade ≥ 2 motor neuropathy	Withhold treatment until recovery to < grade 2	<u>*Dose reduction:*</u> First dose level reduction: 200 <u>*Possible dose reduction:*</u> Second dose level reduction: 175
All other adverse reactions		
Any grade 4 toxicity	Discontinue treatment	
Any grade 3 toxicity except nausea, vomiting and diarrhoea	Withhold treatment until symptoms resolve to grade ≤ 1	<u>*Possible dose reductions:*</u> First dose level reduction: 200 Second dose level reduction: 175

[a] Grade of the adverse reaction is defined according to Common Terminology Criteria for Adverse Events (CTCAE).
[b] The dose of carboplatin should be reduced by 1 AUC unit for treatment cycles following the occurrence of febrile neutropenia or low platelet count (< 75×10^9/L).

<u>*Special populations*</u>

Hepatic impairment
Patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 × upper limit of normal (ULN) and aspartate aminotransferase (AST) ≤ 10 × ULN) may be treated with the same doses as patients with normal hepatic function.

For patients with moderate to severe impairment (total bilirubin > 1.5 to ≤ 5 × ULN and AST ≤ 10 × ULN), a 20% reduction in dose is recommended. The reduced dose may be escalated to the dose for patients with normal hepatic function if the patient is tolerating the treatment for at least two cycles (see sections 4.4 and 5.2).

For patients with total bilirubin > 5 × ULN or AST > 10 × ULN, there are insufficient data to permit dose recommendations (see sections 4.4 and 5.2).

Renal impairment
Patients with mildly or moderately impaired renal function (glomerular filtration rate (GFR) 89−60 mL/min or GFR 59−30 mL/min, respectively) may be treated with Apealea without a dose modification. Patients with severe renal impairment (GFR < 30 mL/min) should not be treated with paclitaxel (see section 5.2).

Elderly
No additional dose reductions, other than those for all patients, are recommended for patients 65 years and older.

Of the 391 patients with ovarian cancer in the randomised study who received Apealea in combination with carboplatin, 13% were between 65 and 74 years old. In this limited number of patients, anorexia, fatigue, myalgia, arthralgia, peripheral sensory neuropathy, and diarrhoea were observed more frequently compared to patients younger than 65 years. Limited data are available on use in patients ≥ 75 years (2% of the patients in the study).

Non-Caucasian patients
There are limited data of Apealea in non-Caucasian patients and current data is insufficient to recommend additional dose adjustments (see section 4.4). If neuropathy is observed, follow dose reduction recommendations in Table 1.

Paediatric population
There is no relevant use of paclitaxel in the paediatric population for the indications of epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer. The safety and efficacy of Apealea in children and adolescents aged 0−17 years has not been established.

Method of administration

Apealea is for intravenous use.

After reconstitution of the powder, the solution for infusion is a clear, greenish-yellow solution. The solution should be administered by an intravenous infusion over approximately one hour (120−140 drops/min). Administration sets containing a 15 µm polyamide fluid filter should be used. It is important to flush the infusion set and catheter/cannula before and after the administration using the solution for reconstitution in order to avoid accidental administration into the surrounding tissue and to ensure administration of the complete dose.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Severe hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

Breast-feeding (see section 4.6).

Baseline neutrophil count < 1.5×10^9/L.

4.4 Special warnings and precautions for use

Haematology

Paclitaxel causes myelosuppression (primarily neutropenia). Neutropenia is a dose-dependent and dose-limiting adverse reaction. Therefore, frequent complete blood cell counts should be performed during treatment with Apealea. In the pivotal study, about a third of the patients received granulocyte colony stimulating factor (GCSF) to treat neutropenia and clinicians should consider whether individual cases could benefit from GCSF. Patients should not be treated with subsequent cycles until neutrophils recover to ≥ 1.5×10^9/L and platelets recover to ≥ 100×10^9/L. Patients with low neutrophil count should be made aware of the increased risk of infections. The risk of myelosuppression is increased due to the combination use with carboplatin. Dose recommendations for Apealea as well as for carboplatin in the case of myelosuppression should be followed (see section 4.2).

Neuropathy

Peripheral sensory neuropathy and peripheral neuropathy are very common adverse reactions. For CTCAE grade ≥ 2 sensory or motor neuropathy withhold treatment until resolution to < grade 2, followed by a dose reduction for all subsequent courses (see section 4.2).

Hepatic impairment

Patients with hepatic impairment have not been studied with Apealea but may be at increased risk of toxicity, particularly from myelosuppression. Administration in patients with hepatic impairment defined as total bilirubin > 1 to ≤ 5 × ULN and AST ≤ 10 × ULN (see section 4.2) should therefore be performed with caution and they should be closely monitored with regard to increased liver impairment and myelosuppression. Patients that have total bilirubin > 5 × ULN or AST > 10 × ULN should not be treated with paclitaxel.

Gastrointestinal symptoms

Gastrointestinal adverse reactions are very common. If patients experience nausea, vomiting and diarrhoea following the administration of Apealea, they may be treated with antiemetics and/or antidiarrhoeal agents. Premedication may be considered in patients who have previously experienced gastrointestinal symptoms when being treated with cytotoxic medicinal products.

Infusion-associated reactions

Local reactions at the infusion site are very common during Apealea infusions. The infusion site reactions observed include pain, phlebitis, discolouration, redness, oedema and rash. These reactions are more common on the first infusion and may be improved by slowing the rate of infusion. Patients who experience severe pain or other reactions to the infusion of Apealea are recommended to be considered for a central venous catheter. Care should be taken to avoid accidental administration into the surrounding tissue during intravenous administration. If any sign of extravasal injection occurs, take immediate action: terminate the infusion, aspirate fluid from the catheter/cannula before the needle is withdrawn, infuse the affected area with sterile saline or lactated or acetated Ringer's solution and closely monitor the area. To avoid accidental administration into the surrounding tissue and to ensure intravenous delivery of the complete dose, flush the infusion set and catheter/cannula before as well as after the administration.

Hypersensitivity

Most hypersensitivity reactions related to Apealea are mild to moderate and mainly occur as skin and subcutaneous tissue disorders, general disorders and administration site conditions, but serious hypersensitivity reactions including anaphylactic shock have been reported. Minor symptoms such as flushing or skin reactions do not require interruption of therapy. Moderate cases may require premedication with corticosteroids, antihistamines and/or H_2 antagonists for the following treatment cycles. Severe reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema or generalised urticaria require immediate discontinuation of paclitaxel and initiation of symptomatic treatment. Patients experiencing severe reactions should not be re-challenged with paclitaxel. Patients should be observed closely during treatment, particularly those patients who previously suffered hypersensitivity reactions with any taxane formulation.

The true incidence, severity and time to onset of hypersensitivity reactions due to Apealea could not be established during clinical development due to the combination treatment with carboplatin. Delayed reactions related to paclitaxel occurring during or after infusion of carboplatin cannot be excluded.

Alopecia

Alopecia is a very common adverse reaction and occurs early in treatment. It can have a marked impact on the patients' self-image and quality of life and patients should be counselled about the

likelihood of this adverse effect and on what measures might be available to mitigate it, for example the use of cold caps. In studies with Apealea, 45% of patients reported alopecia during therapy.

Cardiotoxicity

Heart failure has been observed in some patients receiving Apealea. In some of the cases, the patients had previously been exposed to cardiotoxic medicinal products such as doxorubicin or had underlying cardiac history. These patients should be vigilantly monitored by physicians for the occurrence of cardiac events.

Patients 65 years and older

There was no marked difference in overall tolerability between the 65–74 age group and younger patients. Limited data are available on use in patients ≥ 75 years. In view of this, and of the potential for frailty and co-morbidities, elderly patients should be carefully monitored.

Race

There are limited data on the use of Apealea in non-Caucasian patients. However, studies in breast cancer patients treated with paclitaxel-containing regimens indicate a possible increased risk of neuropathy in non-Caucasian patients (see section 4.2).

Excipients

When reconstituted, this medicinal product contains up to approximately 1.6 g sodium per dose (0.9 g/m^2 BSA; 3.6 mg per mL), equivalent to 80% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No studies have been performed to evaluate drug-drug interactions between Apealea and other medicinal products.

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see section 5.2). Therefore, caution should be exercised when administering paclitaxel concomitantly with medicinal products known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicinal products known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

Apealea contains a mixture of two retinoic acid derivatives as excipients. *In vitro* studies using human microsomes have shown these derivatives to have inhibitory activity on CYP2B6, CYP2C8, CYP2C9, and to a lesser extent on CYP2D6. In the absence of *in vivo* studies addressing inhibition of CYP2B6 and CYP2C9, the concomitant use of Apealea and substances metabolised primarily by these CYP enzymes should be exercised with caution.

Apealea is indicated to be used in combination with carboplatin (see section 4.1). Apealea should be administered first, then carboplatin. Based on literature data, no clinically relevant pharmacokinetic interaction between paclitaxel and carboplatin is expected.

Clinically relevant pharmacokinetic interaction has been observed between paclitaxel and cisplatin. When paclitaxel is given before cisplatin, the safety profile of solvent-based paclitaxel is consistent with that reported for single-agent use. When solvent-based paclitaxel was given after cisplatin, patients showed a more profound myelosuppression and an approximately 20% decrease in paclitaxel

clearance. A similar effect can be anticipated for Apealea (paclitaxel micellar). Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential must use effective contraception during treatment and for six months afterwards.

Pregnancy

There are very limited data on the use of paclitaxel in pregnant women. Paclitaxel is suspected to cause serious birth defects when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). Paclitaxel should not be used during pregnancy unless the clinical condition requires this treatment.

Breast-feeding

Paclitaxel is excreted in human milk. Because of potential serious adverse reactions in children being breast-fed, Apealea is contraindicated during lactation. Breast-feeding must be discontinued for the duration of therapy.

Fertility

Studies in animals being treated with paclitaxel have shown decreased fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Apealea has moderate influence on the ability to drive or use machines. Apealea may cause adverse reactions such as fatigue (very common) and dizziness (common) that may affect the ability to drive or use machines. Patients should be advised not to drive or use machines if they feel tired or dizzy.

4.8 Undesirable effects

Summary of the safety profile

The most common clinically significant adverse reactions associated with the use of Apealea are neutropenia, gastrointestinal disorders, peripheral neuropathy, arthralgia/myalgia, and infusion site reactions. Approximately 86% of patients experienced adverse reactions.

Tabulated list of adverse reactions

The frequency of undesirable effects listed in Table 2 is defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000), and not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 lists adverse reactions associated with the administration of Apealea in combination with carboplatin observed in a clinical study (N = 391) and adverse reactions from post-marketing experience. The latter ones may be attributed to paclitaxel regardless of the treatment regimen.

Table 2. Listing of adverse reactions

System organ class	Frequency	Preferred term
Infections and infestations	*Uncommon:*	Sepsis, abscess, pneumonia, influenza, respiratory tract infection viral, herpes simplex, infusion site cellulitis, tonsillitis, urinary tract infection, skin infection, cystitis
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	*Uncommon:*	Metastatic pain
Blood and lymphatic system disorders	*Very common:*	Neutropenia[a]
	Common:	Febrile neutropenia[a], leukopenia[a], thrombocytopenia[a], granulocytopenia, anaemia[a]
	Uncommon:	Disseminated intravascular coagulation[a], pancytopenia, haematotoxicity, coagulopathy
Immune system disorders	*Common:*	Hypersensitivity
	Uncommon:	Anaphylactic shock, drug hypersensitivity
Metabolism and nutrition disorders	*Very common:*	Anorexia
	Uncommon:	Hyponatraemia, hypokalaemia, hypomagnesaemia, dehydration, decreased appetite
Psychiatric disorders	*Uncommon:*	Depression, insomnia, anxiety
Nervous system disorders	*Very common:*	Peripheral sensory neuropathy[a,b], neuropathy peripheral[a,b]
	Common:	Hypoaesthesia, dizziness, paraesthesia, peripheral motor neuropathy, dysgeusia, headache
	Uncommon:	Status epilepticus, coma, cerebrovascular accident, peripheral sensorimotor neuropathy, lethargy, hypotonia, neurotoxicity, polyneuropathy, polyneuropathy in malignant disease, burning sensation, somnolence, cognitive disorder, facial palsy, encephalopathy, hydrocephalus
Eye disorders	*Uncommon:*	Vision blurred, eye irritation, ocular discomfort, lacrimation increased
Ear and labyrinth disorders	*Uncommon:*	Vertigo, deafness, inner ear disorder, tinnitus
Cardiac disorders	*Common:*	Angina pectoris, tachycardia
	Uncommon:	Cardiac arrest, cardiac failure chronic, cyanosis, atrial fibrillation, sinus tachycardia, palpitations, sinus bradycardia
Vascular disorders	*Common:*	Hypotension, flushing, phlebitis, vein pain, hyperaemia
	Uncommon:	Circulatory collapse, venous thrombosis, vasculitis, thrombosis, hypertension, deep vein thrombosis, lymphoedema, phlebitis superficial, thrombophlebitis, blood pressure fluctuation, haemorrhage, angiopathy, hot flush, pallor

System organ class	Frequency	Preferred term
Respiratory, thoracic and mediastinal disorders	*Common:*	Dyspnoea, nasal congestion
	Uncommon:	Respiratory failure, epistaxis, cough, rhinorrhoea, oropharyngeal pain, pharyngeal disorder, asphyxia, bronchospasm, dysphonia, rhinitis allergic, allergic cough, oropharyngeal discomfort
Gastrointestinal disorders	*Very common:*	Diarrhoea[a], nausea[a], vomiting[a]
	Common:	Abdominal pain, constipation, abdominal pain upper, flatulence, dry mouth, stomatitis
	Uncommon:	Abdominal distension, gastritis, abdominal discomfort, abdominal pain lower, dyspepsia, faecaloma, intestinal functional disorder, gingival bleeding, haematochezia, paraesthesia oral
Hepatobiliary disorders	*Uncommon:*	Hepatitis, liver disorder
Skin and subcutaneous tissue disorders	*Very common:*	Alopecia[a]
	Common:	Erythema, rash, pruritus, urticaria
	Uncommon:	Angioedema, rash generalised, skin discolouration, hyperhidrosis, rash papular, dermatitis bullous, swelling face, pigmentation disorder, dry skin, cold sweat, livedo reticularis, nail disorder, pruritus allergic, skin disorder
	Not known:	Palmar-plantar erythrodysesthesia syndrome[c]
Musculoskeletal and connective tissue disorders	*Very common:*	Arthralgia[a], myalgia[a]
	Common:	Back pain, bone pain, musculoskeletal pain, muscular weakness, pain in extremity
	Uncommon:	Haemarthrosis, musculoskeletal discomfort, sensation of heaviness
Renal and urinary disorders	*Uncommon:*	Azotaemia
Reproductive system and breast disorders	*Uncommon:*	Vaginal haemorrhage, pelvic pain, breast pain
General disorders and administration site conditions	*Very common:*	Asthenia[a], fatigue[a], infusion site reaction[a,d]
	Common:	Oedema peripheral, pain, pyrexia, chest discomfort, hyperthermia, face oedema
	Uncommon:	Death, multi-organ failure, oedema, administration site pain, catheter site haemorrhage, catheter site oedema, local swelling, generalised oedema, hernia, chest pain, influenza like illness, localised oedema, hypothermia, chills, feeling hot
Investigations	*Uncommon:*	Alanine aminotransferase increased

[a] See Description of selected adverse reactions.
[b] Can persist beyond 6 months of paclitaxel discontinuation.[c]
[c] As reported in the post-marketing surveillance of paclitaxel.

[d] Includes the following preferred terms: infusion site pain, infusion site phlebitis, infusion site reaction, infusion site discolouration, infusion site erythema, infusion site extravasation, infusion site inflammation, infusion site oedema, infusion site paraesthesia, infusion site irritation, and infusion site rash.

Description of selected adverse reactions

In the pivotal clinical study, patients were either treated with Apealea (paclitaxel micellar) at a dose of 250 mg/m^2 in combination with carboplatin or with solvent-based paclitaxel at a dose of 175 mg/m^2 in combination with carboplatin (N = 391 in each arm). Overall, there were higher rates of serious adverse reactions with paclitaxel micellar (41%) than with solvent-based paclitaxel (27%). In both groups, the majority of the serious adverse reactions were haematological toxicities. There were no differences in Eastern Cooperative Oncology Group (ECOG) performance score between the two study groups at any time during or after treatment (mainly score 0 or 1).

Blood and lymphatic system disorders
Almost all patients treated with Apealea had neutropenia of some grade, 79% of the patients had grade 3 or 4. Neutropenia as a serious adverse reaction occurred in 29% of the patients and febrile neutropenia occurred in 3% of the patients. Neutropenia resolved to $\geq 1.5 \times 10^9$/L before the next course of treatment. Almost all patients experienced anaemia, decreased platelet count and decreased white blood cell count of any grade during the treatment period (98%, 93% and 98%, respectively). Anaemia as serious adverse reaction occurred in 5% of the patients, thrombocytopenia and leukopenia in 3% and 6% of the patients, respectively.

In comparison to the patients receiving solvent-based paclitaxel, there were more patients in the group receiving paclitaxel micellar who experienced haematological toxicities with grade 3 and 4. Neutropenia occurred in 79% and 66%, leukopenia in 53% and 34%, thrombocytopenia in 18% and 10%, and anaemia in 24% and 14% of the patients in the treatment arms receiving either paclitaxel micellar or solvent-based paclitaxel, respectively.

Disseminated intravascular coagulation (DIC), often in association with sepsis or multi-organ failure, has been reported.

Gastrointestinal disorders
Nausea (38%), vomiting (22%) and diarrhoea (15%) were among the most commonly reported adverse reactions in the study.

Nervous system disorders
Peripheral neuropathies (including the preferred terms neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, and polyneuropathy in malignant disease) were reported in 29% of the patients and were mostly (98%) mild to moderate (CTCAE grade ≤ 2). The average time to onset was 53 days from the first dose. Peripheral sensory neuropathy represented the most common reaction and was reported in 16% of patients. Other associated reactions were reported in 10% of the patients and were mostly (98%) mild to moderate (CTCAE grade ≤ 2). Paraesthesia and hypoaesthesia were the most common ones. During the course of the pivotal study, 46% of the peripheral neuropathies as well as the majority (78%) of the associated reactions resolved. The dose-dependency of frequency and severity of neurotoxicity was not studied for Apealea, but has been observed for other paclitaxel formulations in other indications. Further, it has been demonstrated that peripheral neuropathies can persist beyond 6 months of paclitaxel discontinuation.

Hypersensitivity reactions
Most hypersensitivity reactions related to Apealea were mild to moderate (see section 4.4). The frequency of paclitaxel-related hypersensitivity reactions was similar in both groups (5% of the patients receiving paclitaxel micellar and 7% of the patients receiving solvent-based paclitaxel), whereas a higher frequency of carboplatin-related hypersensitivity reactions was observed in the group receiving paclitaxel micellar (12% vs 7%). As a result of the combined treatment, it is not possible to

determine whether this observation is due to Apealea or to other factors, and delayed reactions related to paclitaxel cannot be excluded.

Skin and subcutaneous tissue disorders
Alopecia was observed in 45% of patients and was abrupt in onset. Pronounced hair loss of ≥ 50% is expected for the majority of patients who experience alopecia.

Musculoskeletal and connective tissue disorders
Arthralgia occurred in 19% of patients and myalgia in 10%.

General disorders and administration site conditions
Asthenia and fatigue were very common and occurred in 23% and 11% of patients, respectively. Infusion site reactions, such as pain, phlebitis, and erythema, were seen in 12% of patients (see section 4.4).

There were more reports of infusion site pain in the group receiving paclitaxel micellar as compared to the group treated with solvent-based paclitaxel (8% and 1%, respectively).

Additional experience from clinical studies

Apealea has been given as monotherapy in a total of 132 patients at doses ranging between 90 mg/m^2 in a 3-week regimen to weekly doses of 250 mg/m^2 for various indications. Based on the combined data from monotherapy studies, very common adverse reactions and those of special interest were the following: neutropenia (45%), fatigue (37%), leukopenia (33%), alopecia (30%), nausea (27%), infusion site reaction[a] (23%), peripheral sensory neuropathy (20%), diarrhoea (17%), asthenia (15%), pyrexia (12%), constipation (12%), arthralgia (12%), paraesthesia (11%), pain (11%), vomiting (9%), myalgia (9%), peripheral motor neuropathy (5%), neuropathy (5%), neuropathy peripheral (5%), thrombocytopenia (4%), febrile neutropenia (2%), sepsis (2%), tachycardia (2%), phlebitis (2%), thrombosis (2%).

[a] Includes the following preferred terms: infusion site phlebitis, infusion site pain, injection site reaction, injection site inflammation, infusion site erythema, injection site extravasation, infusion site reaction, injection site oedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known antidote for paclitaxel overdose. In the event of an overdose, the patient should be closely monitored. Treatment should be directed at the major anticipated toxicities, which are nausea, vomiting, diarrhoea, myelosuppression, peripheral sensory neuropathy and peripheral neuropathy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, taxanes, ATC code: L01CD01

Mechanism of action

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. Stabilisation results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces microtubule bundle formation throughout the cell cycle and induces microtubule aster formation during mitosis.

Clinical efficacy and safety

An open, randomised, multicentre study was conducted in 789 women with recurrent epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer to compare Apealea (paclitaxel micellar) in combination with carboplatin with solvent-based paclitaxel in combination with carboplatin. Patients were treated every three weeks for six cycles, either with Apealea 250 mg/m^2 given as a 1-hour intravenous infusion (N = 391) or with solvent-based paclitaxel 175 mg/m^2 given as a 3-hour infusion (N = 391). The paclitaxel infusion was followed by carboplatin after an interval of 30 minutes in both treatment arms.

Patients were stratified based on relapse (first or second) and CA125 values. The proportions of patients treated at first or second relapse were then equal in both treatment groups (76% were treated at first relapse and 24% at second relapse). Patients who had pre-existing neuropathy of grade ≥ 2 or serious medical risk factors involving any of the major organ systems were not allowed to enter the study. The mean age was 56 years of age in both treatment groups (range 26–81). Most of the patients enrolled in the study had ECOG performance status of 0 or 1 (≥ 96%), in similar proportions between the treatment arms. Only a few patients had ECOG performance status of 2.

In the clinical study, the proportion of patients receiving six treatment cycles was 81% in the group treated with paclitaxel micellar and 87% in the group receiving solvent-based paclitaxel. The corresponding median number of cycles (min;max) for the two groups were 6 (1;12) and 6 (1;9), respectively.

Patients received premedication prior to infusion of solvent-based paclitaxel, paclitaxel micellar and carboplatin as summarised in Table 3 below. Premedication was not mandated prior to infusion of paclitaxel micellar.

Table 3. Proportions of patients who received premedication prior to infusion of paclitaxel or carboplatin or overall (safety population)

Type of premedication	**Apealea** (N = 391)			**Paclitaxel (solvent-based)** (N = 391)		
	Overall	Paclitaxel	Carboplatin	Overall	Paclitaxel	Carboplatin
Corticosteroids	43%	6%	39%	99%	97%	15%
Antihistamines	19%	4%	16%	85%	85%	9%
H_2 antagonists	5%	2%	2%	90%	90%	1%
Antiemetics and antinauseants	87%	8%	81%	92%	38%	63%

In the study, 35% of the patients in the paclitaxel micellar group and 30% of the patients in the solvent-based paclitaxel group, respectively, received GCSF to treat neutropenia. The median number of cycles with paclitaxel/carboplatin treatment for patients receiving GCSF was 6 in both groups. The median number of cycles with administration of GCSF was 3 (1;6) and the mean value 3.1, each in both groups.

The principle measures of efficacy were progression-free survival (PFS) and overall survival (OS). PFS as the primary endpoint was evaluated by blinded assessment of computerised tomography images using Response Evaluation Criteria in Solid Tumours (RECIST) 1.0.

There was no statistically significant difference in PFS or OS between the two treatment arms. A non-inferiority analysis was conducted for PFS in the per-protocol (PP) population with pre-specified non-inferiority margin. The non-inferiority criterion was met for PFS with the upper bound limit of the one-sided 97.5% confidence interval (CI) for the associated hazard ratio being less than 1.2. The non-inferiority criterion was met for OS in the PP population with the upper bound limit of the one-sided 97.5% CI for the associated hazard ratio being less than 1.185 (Table 4; Figures 1 and 2). In the intention-to-treat (ITT) population (n = 789), the hazard ratios for PFS and OS were 0.85 (95% CI: 0.72;1.00) and 1.02 (95% CI: 0.85;1.22), respectively. Thereby, non-inferiority was shown in the ITT population for PFS, but not for OS. At the time of analysis of the OS data, death had occurred in 56% of the patients in the group treated with paclitaxel micellar compared to 60% in the group treated with solvent-based paclitaxel (ITT population).

Table 4. Non-inferiority analyses on PFS and OS in a randomised trial in patients with recurrent epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer (PP population)[a]

	Apealea **Q3W** 250 mg/m^2 + carboplatin (N = 311)	**Solvent-based paclitaxel** **Q3W** 175 mg/m^2 + carboplatin (N = 333)
Progression free survival (independent review)		
Death or progression, n (%)	239 (77%)	270 (81%)
Median time to death or disease progression [months] (95% CI)	10.3 (10.1;10.7)	10.1 (9.9;10.2)
Hazard ratio (95% CI)	0.86 (0.72;1.03)	
Overall survival		
Number of deaths, n (%)	179 (58%)	206 (62%)
Median time to death [months] (95% CI)	25.7 (22.9;28.1)	24.8 (21.7;27.1)
Hazard ratio (95% CI)	0.95 (0.78;1.16)	

[a] Primary population in non-inferiority analysis was predefined as the PP population

Figure 1. Kaplan-Meier curve of PFS (PP population)

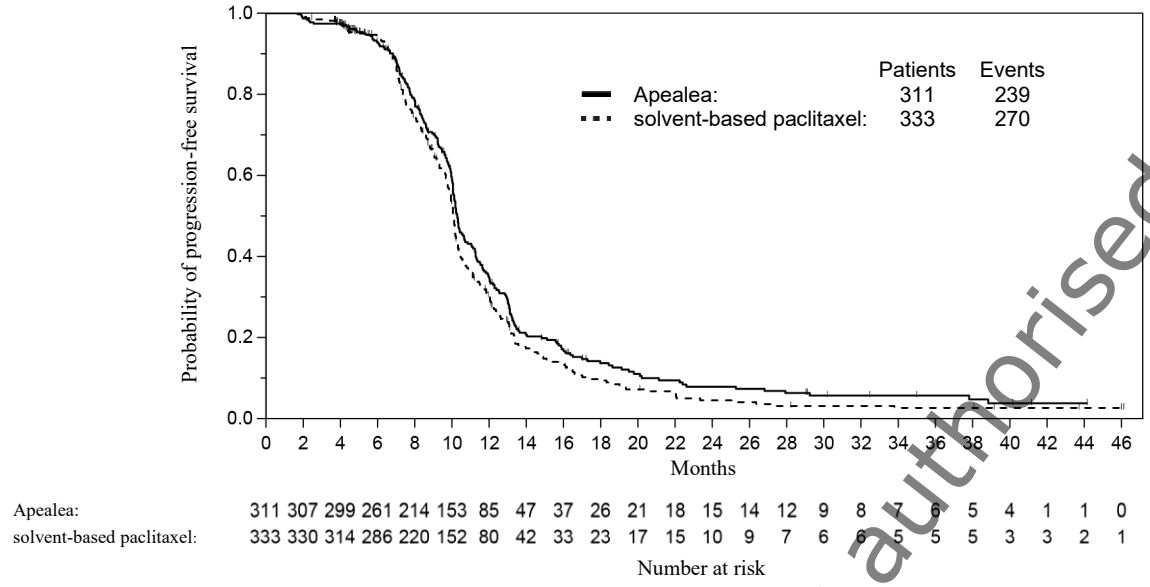
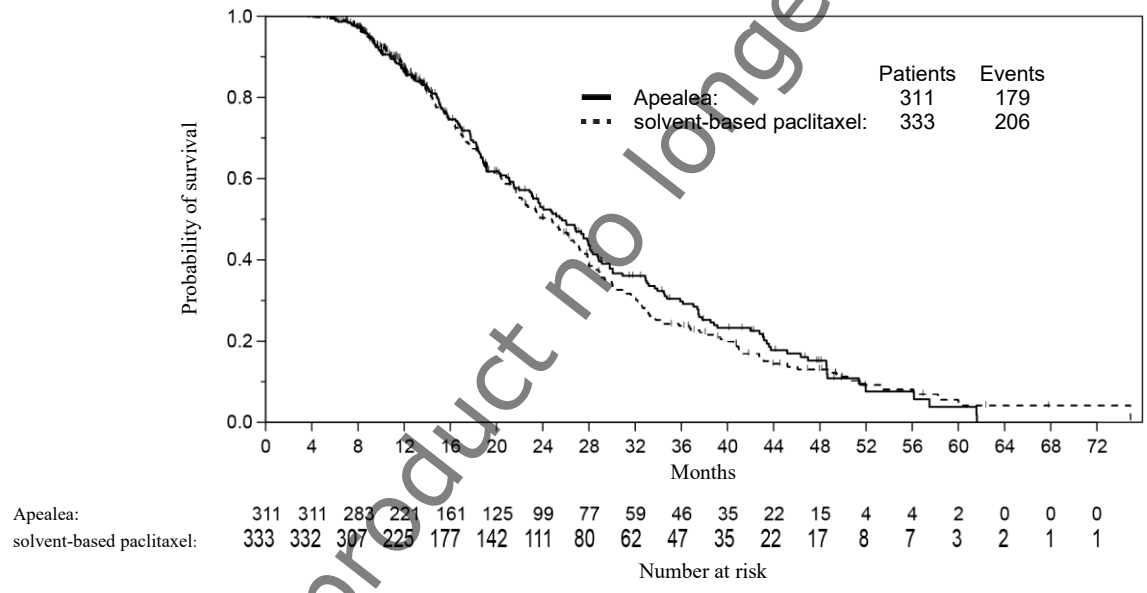


Figure 2. Kaplan-Meier curve of OS (PP population)



Post-hoc subgroup analysis by relapse

Additional subgroup analyses were conducted to investigate efficacy by relapse (first and second) in the PP and the ITT population. PFS and OS results in the PP population are summarised in Figures 3 and 4.

Figure 3. Forest plot for PFS by relapse (PP population)

Relapse	Apealea n	Apealea Events (%)	Apealea Median months (95% CI)	Solvent-based paclitaxel n	Solvent-based paclitaxel Events (%)	Solvent-based paclitaxel Median months (95% CI)	Hazard Ratio (95% CI)
All	311	239 (77%)	10.3 (10.1;10.7)	333	270 (81%)	10.1 (9.9;10.2)	0.86 (0.72;1.03)
First	240	180 (75%)	10.3 (10.2;11.3)	257	209 (81%)	10.1 (9.8;10.3)	0.82 (0.67;1.00)
Second	71	59 (83%)	9.9 (8.6;10.6)	76	61 (80%)	10.1 (9.7;10.4)	1.01 (0.69;1.46)

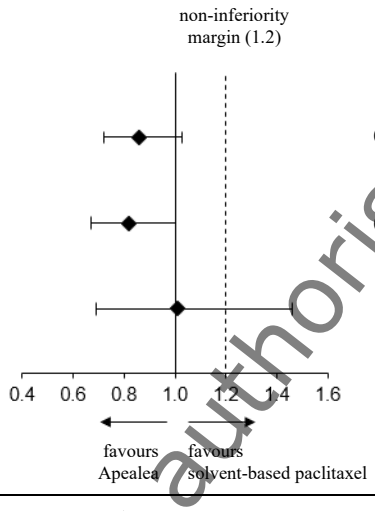
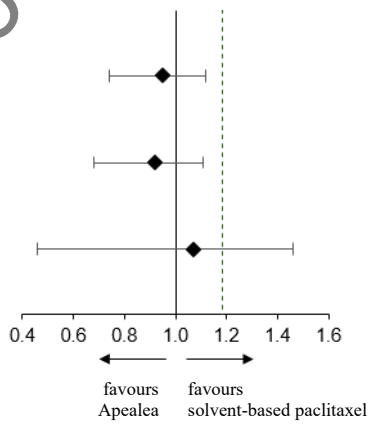


Figure 4. Forest plot for OS by relapse (PP population)

Relapse	Apealea n	Apealea Events (%)	Apealea Median months (95% CI)	Solvent-based paclitaxel n	Solvent-based paclitaxel Events (%)	Solvent-based paclitaxel Median months (95% CI)	Hazard Ratio (95% CI)
All	311	179 (58%)	25.7 (22.9;28.1)	333	206 (62%)	24.8 (21.7;27.1)	0.95 (0.78;1.16)
First	240	139 (58%)	26.1 (23.0;28.4)	257	162 (63%)	23.6 (21.3;27.1)	0.92 (0.73;1.16)
Second	71	40 (56%)	23.2 (18.3;28.9)	76	44 (58%)	24.8 (19.2;30.0)	1.07 (0.68;1.68)



In the ITT population, the hazard ratios for PFS in the subgroups of patients with first relapse and second relapse were 0.80 (95% CI: 0.66;0.97) and 1.04 (95% CI: 0.74;1.47), respectively. The hazard ratios for OS in patients with first and second relapse were 0.98 (95% CI: 0.79;1.21) and 1.18 (95% CI: 0.79;1.75), respectively. Thus, the results in the subgroup of patients with first relapse are consistent with the results in the overall population and in addition, there was an indication of PFS benefit for Apealea.

For safety data comparing the results of combination treatment with Apealea (paclitaxel micellar)/carboplatin and solvent-based paclitaxel/carboplatin, see section 4.8.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Apealea in all subsets of the paediatric population in the treatment of ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours), peritoneal carcinoma (excluding blastomas and sarcomas) and fallopian tube carcinoma (excluding rhabdomyosarcoma and germ cell tumours) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

When Apealea (paclitaxel micellar) is administered intravenously, its pharmacokinetic profile suggests that the formulation immediately releases paclitaxel into the blood. The pharmacokinetics of paclitaxel were studied in 22 patients with solid tumours after 1-hour infusions of Apealea (dose levels of 90 to 275 mg/m^2). In addition, a study with a crossover design compared total and unbound paclitaxel concentrations in plasma after a 1-hour infusion of Apealea 260 mg/m^2 with those after a 1-hour infusion of albumin-bound paclitaxel at the same dose. Total plasma levels of paclitaxel were similar after infusion of the two formulations. The plasma levels of unbound paclitaxel, i.e. the concentration that represents pharmacologically active paclitaxel in the body, were demonstrated to be bioequivalent (C_{max} and AUC) after administration of albumin-bound paclitaxel and Apealea. Based on limited data, C_{max} and AUC increased with dose after 1-hour infusions of Apealea in doses ranging from 150 to 275 mg/m^2. Dose-linearity could not be ascertained since a large inter-individual variability was observed.

Distribution

Paclitaxel is distributed equally between plasma and blood as described in published *in vitro* data. The mean unbound fraction of paclitaxel (fu) varied between 5.2% and 4.3% over time after Apealea infusion. This was in agreement with the mean fu after albumin-bound paclitaxel infusion which varied between 5.5% and 4.5% over time.

Binding of paclitaxel to both albumin and α_1-acid glycoprotein has been reported, but other binding proteins such as lipoproteins might be important. There are no reports of active substances able to displace protein-bound paclitaxel, nor is paclitaxel a likely candidate as a displacer of other active substances given its low molar concentrations in plasma. Based on the published literature, *in vitro* studies indicate that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine does not affect protein binding of paclitaxel. Paclitaxel has been shown *in vitro* to be a substrate for the influx transporter proteins OATP1B3 and OATP1A2.

During and after infusion of Apealea, paclitaxel rapidly leaves the plasma compartment with a distribution half-life of about 0.6 hours. Thus, the distribution phase is essentially complete at 2 hours after the end of infusion. The tissue distribution is extensive, with a volume of distribution on the terminal elimination phase of about 155 L/m^2 corresponding to about 280 L for an average patient with a body surface area of 1.8 m^2. Thus, only about 1% of the paclitaxel in the body is located in plasma during the elimination phase.

Biotransformation and elimination

The terminal half-life of paclitaxel after Apealea infusion varied about 5-fold between the subjects, 5–23 hours. Likewise, total plasma clearance varied about 5-fold from 8 to 41 L/hour. The high interindividual variability in clearance is believed to be a consequence of variability in hepatic enzyme activity.

The biotransformation and elimination of paclitaxel have been reported in published studies; paclitaxel is mainly eliminated by hepatic metabolism and biliary excretion. The main metabolite of paclitaxel is 6α-hydroxypaclitaxel. Other metabolites are 3'-*p*-hydroxypaclitaxel and 6α,3'-*p*-dihydroxypaclitaxel. The formation of these metabolites is catalysed by CYP2C8 and CYP3A4. No pharmacologically active metabolite has been found. *In vitro* and *in vivo* studies have demonstrated that paclitaxel is a substrate for the efflux protein P-glycoprotein. The major route of excretion of paclitaxel-derived material in humans is the faeces, where 6α-hydroxypaclitaxel constitutes the main material. Renal excretion accounts for a minor part, less than 15% of the dose.

Special populations

Hepatic impairment
No clinical studies in patients with hepatic impairment have been undertaken with Apealea (see sections 4.2 and 4.4). A population pharmacokinetics study with albumin-bound paclitaxel demonstrated that patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 × ULN) have an elimination rate in the normal range. In contrast, patients with moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3 × ULN) and severe hepatic impairment (total bilirubin > 3 to ≤ 5 × ULN) had a 22% or a 26% reduction in paclitaxel elimination rate, respectively. Compared to patients with normal hepatic function, hepatically impaired patients with total bilirubin > 1.5 × ULN have an increase in mean paclitaxel AUC of approximately 20%. Hepatic impairment has no effect on mean paclitaxel C_{max}. Pharmacokinetic data for patients with total bilirubin > 5 × ULN are not available.

Renal impairment
No clinical studies in patients with renal impairment have been undertaken with Apealea (see section 4.2 for dose recommendations). Since renal elimination is a minor pathway for paclitaxel, increased plasma levels are not expected in this patient group. A population pharmacokinetics study with albumin-bound paclitaxel demonstrated that patients with mild and moderate renal impairment (creatinine clearance ≥ 30 to < 90 mL/min) have an elimination rate similar to that of patients with normal renal function. Information is lacking for patients with severe renal impairment (GFR < 30 mL/min).

Effects of age, gender, race and body size
No analysis of the effect of age, gender or body size on the elimination of Apealea has been undertaken. However, a population pharmacokinetics study of 168 patients (86 males and 82 females) treated with solvent-based paclitaxel has been reported. On average, the paclitaxel elimination rate was 20% higher in males compared to in females. With regard to age, the population model indicated an approximate 5% decline in paclitaxel elimination rate for each 10-year increase in age compared to the median age of 56 years of the study. This amounted to a 14% decline in an 86-year-old patient compared to one aged 56. Further it has been shown that the rate of paclitaxel elimination increased with increasing body size. The model indicated that a 0.2 m^2 increase in BSA would lead to a 9% increase in the elimination rate. There is very little information available on whether the elimination of paclitaxel differs between races.

5.3 Preclinical safety data

Mutagenesis, carcinogenesis, impairment of fertility

In vitro studies using different cell systems have shown paclitaxel to be clastogenic inducing chromosomal aberrations, micronuclei and DNA damage. Chromosomal aberrations have also been detected in *in vivo* studies in mice and monkeys. Paclitaxel was devoid of mutagenic activity in the Ames test or the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay. The carcinogenic activity of paclitaxel has not been studied. However, paclitaxel is potentially carcinogenic based on its mechanism of action and demonstrated genotoxic activity. Paclitaxel at doses below the human therapeutic dose was associated with low fertility and foetal toxicity in rats. Repeat dose toxicity studies have shown non-reversible, toxic effects on male reproductive organs.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N-(*all-trans*-retinoyl)-L-cysteic acid methyl ester sodium salt
N-(13-*cis*-retinoyl)-L-cysteic acid methyl ester sodium salt
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

After reconstitution

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C in lactated and acetated Ringer's solution and for 4 hours at 2 °C to 8 °C in sodium chloride 9 mg/mL (0.9%) solution when protected from light. From a microbiological point of view, unless the method of opening and reconstituting precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear type I glass vial with a silicon coated butyl rubber stopper, an aluminium overseal and a plastic flip-off cap containing powder equivalent to 60 mg of paclitaxel.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Administration precautions

Paclitaxel is an antineoplastic medicinal product and as with other potentially toxic compounds, caution should be exercised in handling Apealea. The use of gloves, goggles and protective clothing is recommended. If the solution contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. Apealea should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant and breast-feeding staff should not handle Apealea. The reconstituted product should not be diluted.

Reconstitution of the medicinal product

Apealea is supplied as a sterile powder for reconstitution before use. After reconstitution, the solution contains 1 mg/mL of paclitaxel formulated as micellar nanoparticles. The reconstituted solution for infusion is a clear, greenish-yellow solution.

Protect from direct and/or bright light throughout the preparation process. The (reconstituted) product can only withstand short-term handling in absence of light protection.

Only reconstitute Apealea using one of the following commercially available solutions for reconstitution:

- sodium chloride 9 mg/mL (0.9%) solution suitable for infusion;
- lactated Ringer's solution suitable for infusion;
- acetated Ringer's solution suitable for infusion.

The pH of lactated or acetated Ringer's solution must be in the range of 5.0 to 7.5, and acceptable ion concentrations of calcium and magnesium are listed below (Table 5).

Table 5. Acceptable ion concentrations for calcium and magnesium in lactated and acetated Ringer's solutions suitable for reconstitution

Ion	Range (mmol/L)
Ca^{2+}	1.0–3.5*
Mg^{2+}	0.0–2.5*

* Solutions containing both Ca^{2+} and Mg^{2+} should have a total (combined) concentration of Ca^{2+} and Mg^{2+} within the range of 1.0 to 3.5 mmol/L.

Apealea should be reconstituted using either one of the three suitable solutions for reconstitution and according to the following steps:

a. Take the desired number of vials from the refrigerator. The powder should be greenish-yellow to yellow. In case of discolouration (orange), discard the vial. To reach room temperature, let the vials stand protected from light for approximately 15 to 20 minutes not above 25 °C.
b. Due to negative pressure in the vial, pressure must be equilibrated by a needle before and during injection of the solution for reconstitution. Using a sterile syringe, inject 60 mL of solution for reconstitution per vial. The solution should be injected during approximately one minute towards the inner wall of the vial and not directly onto the powder as this will result in foaming.
c. Swirl the vial in an upright position for approximately 20 seconds. To keep the generation of foam to a minimum, do not shake the vial.
d. Protect from light and allow the vial to stand for three to five minutes.
e. Swirl the vial again in upright position for approximately 20 seconds, then gently invert it five times. Do not shake.
f. Continue to swirl the vial until the powder is completely dissolved., Alternatively, the vial may be placed on a shaker and rotated for up to 20 minutes, while being protected from light (orbital shake pattern; 200–250 rpm). Steps c and to f should not be more than 30 minutes.
g. The solution should be clear and greenish-yellow without visible particles or precipitates. If particles, precipitates, discolouration (orange) or opalescence are observed, the solution should be discarded.
h. Inject the required amount of reconstituted Apealea into an empty, sterile ethylene-vinyl acetate (EVA) bag. Ensure that the solution is clear and place a light-protective bag over the EVA infusion bag.

Compatibility with administration sets made of DEHP-free PVC (i.e. polyvinyl chloride without the plasticizer di-(2-ethylhexyl) phthalate) has been demonstrated. However, compatibility with DEHP-containing administration sets has not been demonstrated. Administration sets containing a 15 µm polyamide fluid filter should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Inceptua AB
Gustavslundsv. 143
16751 Bromma

Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1292/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 November 2018
Date of latest renewal:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Inceptua AB
Gustavslundsv. 143
16751 Bromma
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Apealea 60 mg powder for solution for infusion
paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 60 mg paclitaxel.

After reconstitution, each mL of solution contains 1 mg of paclitaxel (micellar).

3. LIST OF EXCIPIENTS

Excipients: *N*-(*all-trans*-retinoyl)-L-cysteic acid methyl ester sodium salt, *N*-(13-*cis*-retinoyl)-L-cysteic acid methyl ester sodium salt, sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic: handle with caution.

Apealea should not be interchanged with other paclitaxel formulations.

8. EXPIRY DATE

EXP

After reconstitution: use immediately.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Single-use vial

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Inceptua AB
Gustavslundsv. 143
16751 Bromma
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1292/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Apealea 60 mg powder for solution for infusion
paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 60 mg paclitaxel.

After reconstitution, each mL of solution contains 1 mg of paclitaxel (micellar).

3. LIST OF EXCIPIENTS

Excipients: *N*-(*all-trans*-retinoyl)-L-cysteic acid methyl ester sodium salt, *N*-(13-*cis*-retinoyl)-L-cysteic acid methyl ester sodium salt, sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

Apealea should not be interchanged with other paclitaxel formulations.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Inceptua AB
Bromma, Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1292/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Apealea 60 mg powder for solution for infusion
paclitaxel

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Apealea is and what it is used for

Apealea is a cancer medicine containing the active substance paclitaxel, which belongs to a group of medicines called taxanes. Paclitaxel affects or stops growth of rapidly dividing cells, such as tumour cells.

Apealea is used to **treat** the following **cancers** in adults, in combination with another medicine called carboplatin:
- epithelial ovarian cancer – a cancer of the ovary, the organ that produces a woman's egg cells
- primary peritoneal cancer – a cancer of the cells lining the space between the wall of the belly and the internal organs
- cancer of the fallopian tubes (the connection between the ovaries and the womb)

It is used when other therapies have not worked.

2. What you need to know before you are given Apealea

Do not use Apealea if you:

- are allergic to paclitaxel or any of the other ingredients of this medicine (listed in section 6)
- are breast-feeding
- have a count of white blood cells called neutrophils below 1.5×10^9/L before start of the therapy

Talk to your doctor or nurse, if you are not sure if any of the above applies to you.

Warnings and precautions

Talk to your doctor or nurse **before you are given** Apealea if you have:
- reduced liver, kidney or heart function
  Apealea is not recommended for patients with severely reduced liver or kidney function.
- previously had nausea, vomiting and diarrhoea during cancer treatment

Contact your doctor immediately, if **during treatment** you develop:
- fever, pain, chills, weakness or other signs of infection
- severe nausea, vomiting or diarrhoea
- severe reactions at the site of infusion
- an allergic reaction
- numbness, tingling, pricking sensation, sensitivity to touch or muscle weakness

You may need additional medicines if you develop any of these symptoms. Your doctor may wish to delay further treatment with Apealea or reduce the dose.

Ask your doctor or nurse about hair loss and what can be done to avoid it.

You will be observed closely during treatment:
- regular blood tests to ensure it is safe for you to continue treatment
- symptoms of allergic reaction during the infusion, such as:
  - reddening and swelling at the site of infusion
  - low blood pressure
  - breathing difficulties
  - puffing of the face

Children and adolescents

Apealea is not recommended for children and adolescents under 18 years, because it has not been studied in this age group.

Other medicines and Apealea

Tell your doctor if you are using, have recently used or might use any other medicines.

In particular, tell your doctor or nurse before you are given Apealea if you are using:
- ketoconazole, or other medicines to treat fungal infections
- erythromycin, rifampicin: medicines to treat bacterial infections
- fluoxetine: a medicine to treat depression
- gemfibrozil: a medicine to lower blood fats
- clopidogrel: a medicine that reduces the chances of getting blood clots
- cimetidine: a medicine to reduce stomach acid
- efavirenz, nevirapine, ritonavir, saquinavir, indinavir, nelfinavir: medicines to treat HIV infection
- carbamazepine, phenytoin: medicines to treat epilepsy and certain pain conditions
- cisplatin: a medicine to treat cancer

Pregnancy and breast-feeding

Tell your doctor before treatment if you are pregnant, think you may be pregnant or are breast-feeding.

Apealea is **not recommended during pregnancy**, as paclitaxel may cause serious birth defects. Patients who can become pregnant should use effective contraception during treatment with Apealea and for six months afterwards.

Stop breast-feeding while being treated, as paclitaxel passes into breast milk and may harm the child.

Driving and using machines

Apealea may cause side effects such as tiredness or dizziness that may reduce your ability to drive or use machines. Do not drive or use machines if you have these symptoms.

Apealea contains sodium

After reconstitution, this medicine contains approximately up to 1.6 g sodium (component of cooking salt) per dose. This is equivalent to 80% of the recommended maximum daily dietary intake of sodium for an adult.

3. How Apealea is given

Apealea is given to you by a doctor or nurse by a slow drip (infusion) into a vein. This will take about one hour. The dose is based on your body surface area (worked out from your height and weight) and blood test results. The usual dose is 250 mg/m^2 body surface area given every three weeks for up to six treatments.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately if you have any of the following:
- **Very common** (may affect **more than 1 in 10** people):
  - nerve disorder in arms and legs which causes tingling, numbness or burning pain, which can persist beyond 6 months of paclitaxel discontinuation.
- **Common** (may affect **up to 1 in 10** people):
  - fever
  - muscle weakness, cramps or spasms
  - allergic reactions, such as breathing difficulties, fainting, swelling of the face, itching, feeling hot, chills, particularly during your infusion. Uncommonly these can lead to severe allergic shock.

Other side effects and their frequencies include:
Very common (may affect **more than 1 in 10** people):
- low level of white blood cells called neutrophils
- lack of appetite
- diarrhoea, nausea, vomiting
- hair loss
- joint or muscle pain or discomfort
- weakness, tiredness
- reactions at the infusion site such as pain, inflammation, discolouration, redness, swelling, tingling, rash, bleeding

Common (may affect **up to 1 in 10** people):
- low level of white blood cells called leukocytes and granulocytes
- low level of blood platelets or red blood cells
- reduced sense of touch or sensation
- abnormal sensation such as tingling, burning, pricking or numbness of the skin or in the mouth
- dizziness or feeling of spinning
- taste disturbance
- headache
- rapid heartbeat
- chest pain or discomfort
- low blood pressure, flushing, vein inflammation, vein pain, increased blood flow to some parts of the body
- breathing difficulties, nasal congestion

- abdominal pain, constipation, wind
- dry mouth, inflammation of the inner lining of the mouth
- skin reddening, rash, itching, nettle-rash
- pain for instance in arms, legs, breast or at site of tumour
- back pain, bone pain
- swelling of ankles, feet, face or fingers

Uncommon (may affect **up to 1 in 100** people):
- blood poisoning
- pus in body tissue
- lung inflammation, influenza, tonsil inflammation
- herpes simplex (a viral infection), viral airways infections
- urinary tract infection, inflammation of the bladder
- skin infections, including infections at the infusion site
- disturbed blood clotting mechanisms in the body
- lack of white and red blood cells, and blood platelets
- low blood levels of potassium, magnesium or sodium
- excessive water loss (dehydration)
- allergic reactions to other medicines, such as penicillin
- depression, sleeplessness, anxiety
- epileptic fit lasting longer than five minutes or more than one fit within five minutes
- coma, feeling very sleepy, drowsy and/or being deeply unresponsive
- low muscle tone, facial palsy
- toxicity to the nervous system
- cognitive disorder (difficulty thinking or processing thoughts, difficulty remembering)
- brain damage, abnormal fluid accumulation within the brain
- stroke
- blurred vision, eye discomfort or irritation, watery eyes
- deafness, inner ear disorder, ringing in the ears
- blood vessel disorders, such as:
  - formation of blood clots
  - blood vessel inflammation
  - build-up of water in tissue because of blocked lymph vessel
  - hot flushes
  - bleeding
- cardiac arrest, heart failure
- blue tinged lips or skin
- a heart rhythm disorder causing irregular rapid activity in the upper heart chambers
- feeling your heartbeat (palpitations), slow heartbeat
- blood circulation failure
- high blood pressure, blood pressure changes, paleness
- lung failure, narrowing of airways
- severe lack of oxygen, arising from abnormal breathing
- difficulty producing voice sounds
- nosebleed, allergic inflammation inside the nose, runny nose
- cough
- mouth and throat pain or discomfort, throat disorder, bleeding gums
- inflammation of the stomach lining, abdominal discomfort or bloating, lower abdominal pain
- indigestion, disorder of bowel function, very hard stools, bloody stool
- liver inflammation or disorder, raised liver enzyme in your blood
- painful severe swelling of deep skin layers, mainly in the face
- skin discolouration, pigmentation disorder
- skin inflammation with blisters
- increased sweating, cold sweat

- dry skin, nail disorder
- bleeding into a joint
- sensation of heaviness in the legs
- multi-organ failure which can lead to death
- tissue swelling caused by excess fluid
- hernia
- feeling hot
- low body temperature
- vaginal bleeding
- abnormally high levels of nitrogen-containing compounds in the blood

Frequency not known (cannot be estimated from the available data):
- redness and swelling of the palms of your hands or soles of your feet which may cause your skin to peel

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Apealea

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.

Unopened vial: Store in a refrigerator (2 °C – 8 °C). Keep the vial in the outer carton in order to protect from light.

Once opened, Apealea is recommended to be used immediately.

Any unused medicine or waste material should be disposed of in accordance with local requirements. Do not throw away any medicines via wastewater or household waste. These measures will help protect the environment.

6. Contents of the pack and other information

What Apealea contains

- The active substance is paclitaxel. One vial contains 60 mg of paclitaxel. After preparation, each millilitre of solution contains 1 mg of paclitaxel (micellar).
- The other ingredients are:
  - *N*-(*all-trans*-retinoyl)-L-cysteic acid methyl ester sodium salt
  - *N*-(13-*cis*-retinoyl)-L-cysteic acid methyl ester sodium salt
  - sodium hydroxide (for pH adjustment)

  See section 2 “Apealea contains sodium”.

What Apealea looks like and contents of the pack

Apealea is supplied as a greenish-yellow to yellow powder in a glass vial with a rubber stopper and aluminium seal.

Each carton contains 1 glass vial with powder equivalent to 60 mg of paclitaxel.

Marketing Authorisation Holder and Manufacturer
Inceptua AB
Gustavslundsv. 143
16751 Bromma
Sweden

For any information about this medicine, please contact the Marketing Authorisation Holder.

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Administration precautions
Paclitaxel is an antineoplastic medicinal product and as with other potentially toxic compounds, caution should be exercised in handling Apealea. The use of gloves, goggles and protective clothing is recommended. If the solution contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If it contacts mucous membranes, the membranes should be flushed thoroughly with water. Apealea should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant and breast-feeding staff should not handle Apealea. The reconstituted product should not be diluted.

Reconstitution of the medicinal product
Apealea is supplied as a sterile powder for reconstitution before use. After reconstitution, the solution contains 1 mg/mL of paclitaxel formulated as micellar nanoparticles. The reconstituted solution for infusion is a clear, greenish-yellow solution.

Protect from direct and/or bright light throughout the preparation process. The (reconstituted) product can only withstand short-term handling in absence of light protection.

Only reconstitute Apealea using one of the following commercially available solutions for reconstitution:
- sodium chloride 9 mg/mL (0.9%) solution suitable for infusion;
- lactated Ringer's solution suitable for infusion;
- acetated Ringer's solution suitable for infusion.

The pH of lactated or acetated Ringer's solution must be in the range of 5.0 to 7.5 and acceptable ion concentrations of calcium and magnesium are listed below (Table 1).

Table 1. Acceptable ion concentrations for calcium and magnesium in lactated and acetated Ringer's solutions suitable for reconstitution

Ion	Range (mmol/L)
Ca^{2+}	1.0–3.5*
Mg^{2+}	0.0–2.5*

* Solutions containing both Ca^{2+} and Mg^{2+} should have a total (combined) concentration of Ca^{2+} and Mg^{2+} within the range of 1.0 to 3.5 mmol/L.

Apealea should be reconstituted using either one of the three suitable solutions for reconstitution and according to the following steps:

1. Take the desired number of vials from the refrigerator. The powder should be greenish-yellow to yellow. In case of discolouration (orange), discard the vial. To reach room temperature, let the vials stand protected from light for approximately 15 to 20 minutes not above 25 °C.
2. Due to negative pressure in the vial, pressure must be equilibrated by a needle before and during injection of the solution for reconstitution. Using a sterile syringe, inject 60 mL of solution for reconstitution per vial. The solution should be injected during approximately one minute towards the inner wall of the vial and not directly onto the powder as this will result in foaming.
3. Swirl the vial in an upright position for approximately for 20 seconds. To keep the generation of foam to a minimum, do not shake the vial.
4. Protect from light and allow the vial to stand for three to five minutes.
5. Swirl the vial again in upright position for approximately 20 seconds, then gently invert it five times. Do not shake.
6. Continue to swirl the vial until the powder is completely dissolved. Alternatively, the vial may be placed on a shaker and rotated for up to 20 minutes, while being protected from light (orbital shake pattern; 200–250 rpm). Steps 3 to 6 should not be more than 30 minutes.
7. The solution should be clear and greenish-yellow without visible particles or precipitates. If particles, precipitates, discolouration (orange) or opalescence are observed, the solution should be discarded.
8. Inject the required amount of reconstituted Apealea into an empty, sterile ethylene-vinyl acetate (EVA) bag. Ensure that the solution is clear and place a light protective-bag over the EVA infusion bag.

Shelf life after reconstitution
Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C to 8 °C in lactated and acetated Ringer's solution and for 4 hours at 2 °C to 8 °C in sodium chloride 9 mg/mL (0.9%) solution when protected from light. From a microbiological point of view, unless the method of opening and reconstituting precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Intravenous administration
Compatibility with administration sets made of DEHP-free PVC (i.e. polyvinyl chloride without the plasticizer di-(2-ethylhexyl) phthalate) has been demonstrated. However, compatibility with DEHP-containing administration sets has not been demonstrated. Administration sets containing a 15 µm polyamide fluid filter should be used. It is important to flush the infusion set and catheter/cannula before and after the administration using the solution for reconstitution in order to avoid accidental administration into the surrounding tissue and to ensure administration of the complete dose.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.