ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Naveruclif 5 mg/ml powder for dispersion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles.

After reconstitution, each ml of dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for dispersion for infusion (powder for infusion).
The reconstituted dispersion has a pH of 6-7.5 and an osmolality of 300-380 mOsm/kg.
White to yellow coloured powder or lyophilized cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Naveruclif monotherapy is indicated for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated (see section 4.4).

Naveruclif in combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.

Naveruclif in combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.

4.2 Posology and method of administration

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

Posology

Breast cancer
The recommended dose of Naveruclif is 260 mg/m^2 administered intravenously over 30 minutes every 3 weeks.

Dose adjustments during treatment of breast cancer
Patients who experience severe neutropenia (neutrophil count < 500 cells/mm^3 for a week or longer) or severe sensory neuropathy during Naveruclif therapy should have the dose reduced to 220 mg/m^2 for subsequent courses. Following recurrence of severe neutropenia or severe sensory neuropathy, additional dose reduction should be made to 180 mg/m^2. Naveruclif should not be administered until neutrophil counts recover to >1500 cells/mm^3. For Grade 3 sensory neuropathy, withhold treatment until resolution to Grade 1 or 2, followed by a dose reduction for all subsequent courses.

Pancreatic adenocarcinoma
The recommended dose of Naveruclif in combination with gemcitabine is 125 mg/m^2 administered intravenously over 30 minutes on Days 1, 8 and 15 of each 28-day cycle. The concurrent recommended dose of gemcitabine is 1000 mg/m^2 administered intravenously over 30 minutes immediately after the completion of Naveruclif administration on Days 1, 8 and 15 of each 28- day cycle.

Dose adjustments during treatment of pancreatic adenocarcinoma

Table 1: Dose level reductions for patients with pancreatic adenocarcinoma

Dose level	**Naveruclif dose (mg/m^2)**	**Gemcitabine dose (mg/m^2)**
Full dose	125	1000
1st dose level reduction	100	800
2nd dose level reduction	75	600
If additional dose reduction required	Discontinue treatment	Discontinue treatment

Table 2: Dose modifications for neutropenia and/or thrombocytopenia at the start of a cycle or within a cycle for patients with pancreatic adenocarcinoma

Cycle Day	**ANC count (cells/mm^3)**		**Platelet count (cells/mm^3)**	**Naveruclif dose**	**Gemcitabine dose**
Day 1	< 1,500	OR	< 100,000	Delay doses until recovery	
Day 8	≥ 500 but < 1,000	OR	≥ 50,000 but < 75,000	Reduce doses 1 dose level	
	< 500	OR	< 50,000	Withhold doses	
Day 15: If Day 8 doses were given without modification:					
Day 15	≥ 500 but < 1,000	OR	≥ 50,000 but < 75,000	Treat with Day 8 dose level and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 8 doses	
	< 500	OR	< 50,000	Withhold doses	
Day 15: If Day 8 doses were reduced:					
Day 15	≥ 1,000	AND	≥ 75,000	Return to the Day 1 dose levels and follow with WBC Growth Factors OR Treat with same doses as Day 8	
	≥ 500 but < 1,000	OR	≥ 50,000 but < 75,000	Treat with Day 8 dose levels and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 8 doses	
	< 500	OR	< 50,000	Withhold doses	
Day 15: IF Day 8 doses were withheld:					
Day 15	≥ 1,000	AND	≥ 75,000	Return to Day 1 dose levels and follow with WBC Growth Factors OR Reduce doses 1 dose level from Day 1 doses	
	≥ 500 but < 1,000	OR	≥ 50,000 but < 75,000	Reduce 1 dose level and follow with WBC Growth Factors OR Reduce doses 2 dose levels from Day 1 doses	
	< 500	OR	< 50,000	Withhold doses	

Abbreviations: ANC=Absolute Neutrophil Count; WBC=white blood cell

Table 3: Dose modifications for other adverse drug reactions in patients with pancreatic adenocarcinoma

Adverse Drug Reaction (ADR)	Naveruclif Dose	Gemcitabine Dose
Febrile Neutropenia: Grade 3 or 4	Withhold doses until fever resolves and ANC ≥ 1500; resume at next lower dose level[a]	
Peripheral Neuropathy: Grade 3 or 4	Withhold dose until improves to ≤ Grade 1; resume at next lower dose level[a]	Treat with same dose
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level[a]; discontinue treatment if ADR persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhoea	Withhold doses until improves to ≤ Grade 1, resume at next lower dose level[a]	

a. See Table 1 for dose level reductions

Non-small cell lung cancer:
The recommended dose of Naveruclif is 100 mg/m^2 administered as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of each 21-day cycle. The recommended dose of carboplatin is AUC = 6 mg•min/mL on Day 1 only of each 21-day cycle, beginning immediately after the end of Naveruclif administration.

Dose adjustments during treatment of non-small cell lung cancer:
Naveruclif should not be administered on Day 1 of a cycle until absolute neutrophil count (ANC) is ≥1500 cells/mm^3 and platelet count is ≥100,000 cells/mm^3. For each subsequent weekly dose of Naveruclif, patients must have an ANC ≥500 cells/mm^3 and platelets >50,000 cells/mm^3 or the dose is to be withheld until counts recover. When counts recover, resume dosing the following week according to the criteria in Table 4. Reduce subsequent dose only if criteria in Table 4 are met.

Table 4: Dose reductions for haematologic toxicities in patients with non-small cell lung cancer

Haematologic Toxicity	**Occurrence**	Dose of **Naveruclif (mg/m^2)[1]**	Dose of carboplatin **(AUC mg•min/mL)[1]**
Nadir ANC <500/mm^3 with neutropenic fever > 38°C OR Delay of next cycle due to persistent neutropenia[2] (Nadir ANC <1500/mm^3) OR Nadir ANC <500/mm^3 for > 1 week	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Nadir platelets <50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	

[1]On Day 1 of the 21-day cycle reduce the dose of Naveruclif and carboplatin simultaneously. On Days 8 or 15 of the 21-day cycle reduce the dose of Naveruclif; reduce the dose of carboplatin in the subsequent cycle.
[2]Maximum of 7 days post scheduled Day 1 dose of next cycle.

For Grade 2 or 3 cutaneous toxicity, Grade 3 diarrhoea, or Grade 3 mucositis, interrupt treatment until the toxicity improves to ≤ Grade 1, then restart treatment according to the guidelines in Table 5. For ≥ Grade 3 peripheral neuropathy, withhold treatment until resolution to ≤ Grade 1. Treatment may be resumed at the next lower dose level in subsequent cycles according to the guidelines in Table 5. For any other Grade 3 or 4 non-haematologic toxicity, interrupt treatment until the toxicity improves to ≤ Grade 2, then restart treatment according to the guidelines in Table 5.

Table 5: Dose reductions for non-haematologic toxicities in patients with non-small cell lung cancer

Non-haematologic Toxicity	**Occurrence**	Dose of **Naveruclif (mg/m^2)**[1]	Dose of carboplatin **(AUC mg•min/mL)**[1]
Grade 2 or 3 cutaneous toxicity Grade 3 diarrhoea Grade 3 mucositis ≥ Grade 3 peripheral neuropathy Any other Grade 3 or 4 non-haematologic toxicity	First	75	4.5
	Second	50	3.0
	Third	Discontinue Treatment	
Grade 4 cutaneous toxicity, diarrhoea, or mucositis	First	Discontinue Treatment	

[1]On Day 1 of the 21-day cycle reduce the dose of Naveruclif and carboplatin simultaneously. On Days 8 or 15 of the 21-day cycle reduce the dose of Naveruclif; reduce the dose of carboplatin in the subsequent cycle.

Special populations

Hepatic impairment
For patients with mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x ULN and aspartate aminotransferase [AST] ≤ 10 x ULN), no dose adjustments are required, regardless of indication. Treat with same doses as patients with normal hepatic function.

For metastatic breast cancer patients and non-small cell lung cancer patients with moderate to severe hepatic impairment (total bilirubin > 1.5 to ≤ 5 x ULN and AST ≤ 10 x 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 metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment, there are insufficient data to permit dosage recommendations (see sections 4.4 and 5.2).

For patients with total bilirubin > 5 x ULN or AST > 10 x ULN, there are insufficient data to permit dosage recommendations regardless of indication (see sections 4.4 and 5.2).

Renal impairment
Adjustment of the starting Naveruclif dose is not required for patients with mild to moderate renal impairment (estimated creatinine clearance ≥30 to <90 ml/min). There are insufficient data available to recommend dose modifications of Naveruclif in patients with severe renal impairment or end stage renal disease (estimated creatinine clearance <30 ml/min) (see section 5.2).

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

Of the 229 patients in the randomized study who received human serum albumin-paclitaxel nanoparticles monotherapy for breast cancer, 13% were at least 65 years of age and < 2% were 75 years and older. No toxicities occurred notably more frequently among patients at least 65 years of age who received human serum albumin-paclitaxel nanoparticles. However, a subsequent analysis in 981 patients receiving human serum albumin-paclitaxel nanoparticles monotherapy for metastatic breast cancer, of which 15% were ≥ 65 years old and 2% were ≥ 75 years old, showed a higher incidence of epistaxis, diarrhoea, dehydration, fatigue and peripheral oedema in patients ≥ 65 years.

Of the 421 patients with pancreatic adenocarcinoma in the randomized study who received human

serum albumin-paclitaxel nanoparticles in combination with gemcitabine, 41% were 65 years and older and 10% were 75 years and older. In patients aged 75 years and older who received human serum albumin-paclitaxel nanoparticles and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation (see section 4.4). Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed before treatment is considered (see section 4.4).

Of the 514 patients with non-small cell lung cancer in the randomized study who received human serum albumin-paclitaxel nanoparticles in combination with carboplatin, 31% were 65 years or older and 3.5% were 75 years or older. Myelosuppression events, peripheral neuropathy events, and arthralgia were more frequent in patients 65 years or older compared to patients younger than 65 years of age. There is limited experience of human serum albumin-paclitaxel nanoparticles/carboplatin use in patients 75 years or older.

Pharmacokinetic/pharmacodynamic modelling using data from 125 patients with advanced solid tumours indicates that patients ≥ 65 years of age may be more susceptible to development of neutropenia within the first treatment cycle.

Paediatric population
The safety and efficacy of human serum albumin-paclitaxel nanoparticles in children and adolescents aged 0 to less than 18 years has not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made. There is no relevant use of human serum albumin-paclitaxel nanoparticles in the paediatric population for the indication of metastatic breast cancer or pancreatic adenocarcinoma or non-small cell lung cancer.

Method of administration

Naveruclif is for intravenous use. Administer reconstituted Naveruclif dispersion intravenously using an infusion set incorporating a 15 µm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Lactation (see section 4.6).
Patients who have baseline neutrophil counts < 1,500 cells/mm^3.

4.4 Special warnings and precautions for use

Naveruclif is an albumin-bound nanoparticle formulation of paclitaxel, which may have substantially different pharmacological properties compared to other formulations of paclitaxel (see sections 5.1 and 5.2). It should not be substituted for or with other paclitaxel formulations.

Hypersensitivity

Rare occurrences of severe hypersensitivity reactions, including very rare events of anaphylactic reactions with fatal outcome, have been reported. If a hypersensitivity reaction occurs, the medicinal product should be discontinued immediately, symptomatic treatment should be initiated, and the patient should not be rechallenged with paclitaxel.

Haematology

Bone marrow suppression (primarily neutropenia) occurs frequently with human serum

albumin-paclitaxel nanoparticles. Neutropenia is dose-dependent and a dose-limiting toxicity. Frequent monitoring of blood cell counts should be performed during Naveruclif therapy. Patients should not be retreated with subsequent cycles of Naveruclif until neutrophils recover to >1500 cells/mm^3 and platelets recover to >100,000 cells/mm^3 (see section 4.2).

Neuropathy

Sensory neuropathy occurs frequently with human serum albumin-paclitaxel nanoparticles, although development of severe symptoms is less common. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose reduction. When Naveruclif is used as monotherapy, if Grade 3 sensory neuropathy develops, treatment should be withheld until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent courses of Naveruclif is recommended (see section 4.2). For combination use of Naveruclif and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Naveruclif; continue treatment with gemcitabine at the same dose. Resume Naveruclif at reduced dose when peripheral neuropathy improves to Grade 0 or 1 (see section 4.2). For combination use of Naveruclif and carboplatin, if Grade 3 or higher peripheral neuropathy develops, treatment should be withheld until improvement to Grade 0 or 1 followed by a dose reduction for all subsequent courses of Naveruclif and carboplatin (see section 4.2).

Sepsis

Sepsis was reported at a rate of 5% in patients with or without neutropenia who received human serum albumin-paclitaxel nanoparticles in combination with gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Naveruclif and gemcitabine until fever resolves and ANC $\geq$ 1,500 cells/mm^3, then resume treatment at reduced dose levels (see section 4.2).

Pneumonitis

Pneumonitis occurred in 1% of patients when human serum albumin-paclitaxel nanoparticles was used as monotherapy and in 4% of patients when human serum albumin-paclitaxel nanoparticles were used in combination with gemcitabine. Closely monitor all patients for signs and symptoms of pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Naveruclif and gemcitabine and promptly initiate appropriate treatment and supportive measures (see section 4.2).

Hepatic impairment

Because the toxicity of paclitaxel can be increased with hepatic impairment, administration of Naveruclif in patients with hepatic impairment should be performed with caution. Patients with hepatic impairment may be at increased risk of toxicity, particularly from myelosuppression; such patients should be closely monitored for development of profound myelosuppression.

Naveruclif is not recommended in patients that have total bilirubin > 5 x ULN or AST > 10 x ULN. In addition, Naveruclif is not recommended in patients with metastatic adenocarcinoma of the pancreas that have moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and AST $\leq$ 10 x ULN) (see section 5.2).

Cardiotoxicity

Rare reports of congestive heart failure and left ventricular dysfunction have been observed among individuals receiving human serum albumin-paclitaxel nanoparticles. Most of the individuals were previously exposed to cardiotoxic medicinal products such as anthracyclines or had underlying cardiac history. Thus, patients receiving Naveruclif should be vigilantly monitored by physicians for the occurrence of cardiac events.

CNS metastases

The effectiveness and safety of human serum albumin-paclitaxel nanoparticles in patients with central nervous system (CNS) metastases has not been established. CNS metastases are generally not well controlled by systemic chemotherapy.

Gastrointestinal symptoms

If patients experience nausea, vomiting and diarrhoea following the administration of Naveruclif, they may be treated with commonly used anti-emetics and constipating agents.

Eye disorders

Cystoid macular oedema (CMO) has been reported in patients treated with human serum albumin-paclitaxel nanoparticles. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, Naveruclif treatment should be discontinued and appropriate treatment initiated (see section 4.8).

Patients 75 years and older

For patients of 75 years and older, no benefit for the combination treatment of human serum albumin-paclitaxel nanoparticles and gemcitabine in comparison to gemcitabine monotherapy has been demonstrated. In the very elderly (≥ 75 years) who received human serum albumin-paclitaxel nanoparticles and gemcitabine, there was a higher incidence of serious adverse reactions and adverse reactions that led to treatment discontinuation including haematologic toxicities, peripheral neuropathy, decreased appetite and dehydration. Patients with pancreatic adenocarcinoma aged 75 years and older should be carefully assessed for their ability to tolerate Naveruclif in combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections (see section 4.2 and 4.8).

Other

Although limited data is available, no clear benefit in terms of prolonged overall survival has been demonstrated in pancreatic adenocarcinoma patients with normal CA 19-9 levels prior to start of treatment with human serum albumin-paclitaxel nanoparticles and gemcitabine (see section 5.1).

Erlotinib should not be co-administered with Naveruclif plus gemcitabine (see section 4.5).

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per 100 mg, that is to say essentially ‘sodium free’.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4 (see section 5.2). Therefore, in the absence of a PK drug-drug interaction study, caution should be exercised when administering paclitaxel concomitantly with medicines 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 medicines 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.

Paclitaxel and gemcitabine do not share a common metabolic pathway. Paclitaxel clearance is

primarily determined by CYP2C8 and CYP3A4 mediated metabolism followed by biliary excretion, while gemcitabine is inactivated by cytidine deaminase followed by urinary excretion. Pharmacokinetic interactions between Naveruclif and gemcitabine have not been evaluated in humans.

A pharmacokinetic study was conducted with human serum albumin-paclitaxel nanoparticles and carboplatin in non-small cell lung cancer patients. There were no clinically relevant pharmacokinetic interactions between human serum albumin-paclitaxel nanoparticles and carboplatin.

Naveruclif is indicated as monotherapy for breast cancer, in combination with gemcitabine for pancreatic adenocarcinoma, or in combination with carboplatin for non-small cell lung cancer (see section 4.1).

Naveruclif should not be used in combination with other anticancer agents.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should use effective contraception during treatment and for at least six months after the last dose of Naveruclif. Male patients with female partners of reproductive potential are advised to use effective contraception and to avoid fathering a child during treatment with Naveruclif and for at least three months after the last dose of Naveruclif.

Pregnancy

There are very limited data on the use of paclitaxel in human pregnancy. Paclitaxel is suspected to cause serious birth defects when administered during pregnancy. Studies in animals have shown reproductive toxicity (see section 5.3). Women of childbearing potential should have a pregnancy test prior to starting treatment with Naveruclif. Naveruclif should not be used in pregnancy, and in women of childbearing potential not using effective contraception, unless the clinical condition of the mother requires treatment with paclitaxel.

Breast-feeding

Paclitaxel and/or its metabolites were excreted into the milk of lactating rats (see section 5.3). It is not known if paclitaxel is excreted in human milk. Because of potential serious adverse reactions in breast-feeding infants, Naveruclif is contraindicated during lactation. Breast-feeding must be discontinued for the duration of therapy.

Fertility

Human serum albumin-paclitaxel nanoparticles induced infertility in male rats (see section 5.3). Based on findings in animals, male and female fertility may be compromised. Male patients should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Naveruclif.

4.7 Effects on ability to drive and use machines

Paclitaxel has minor or moderate influence on the ability to drive and use machines. Paclitaxel may cause adverse reactions such as tiredness (very common) and dizziness (common) that may affect the ability to drive and use machinery. Patients should be advised not to drive and 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 human serum albumin-paclitaxel nanoparticles have been neutropenia, peripheral neuropathy, arthralgia/myalgia and gastrointestinal disorders.

Tabulated list of adverse reactions

Table 6 lists adverse reactions associated with human serum albumin-paclitaxel nanoparticles monotherapy at any dose in any indication during clinical trials (N = 789), human serum albumin-paclitaxel nanoparticles in combination with gemcitabine for pancreatic adenocarcinoma from the phase III clinical trial (N = 421), human serum albumin-paclitaxel nanoparticles in combination with carboplatin for non-small cell lung cancer from the phase III clinical trial (N = 514) and from post-marketing use.

Frequencies are defined as: 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), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse reactions reported with human serum albumin-paclitaxel nanoparticles

	Monotherapy (N=789)	**Combination therapy with gemcitabine (N =421)**	**Combination therapy with carboplatin (N = 514)**
Infections and infestations			
Common:	Infection, urinary tract infection, folliculitis, upper respiratory tract infection, candidiasis, sinusitis	Sepsis, pneumonia, oral candidiasis	Pneumonia, bronchitis, upper respiratory tract infection, urinary tract infection
Uncommon:	Sepsis1, neutropenic sepsis1, pneumonia, oral candidiasis, nasopharyngitis, cellulitis, herpes simplex, viral infection, herpes zoster, fungal infection, catheter-related infection, injection site infection		Sepsis, oral candidiasis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Uncommon:	Tumour necrosis, metastatic pain		
Blood and lymphatic system disorders			
Very common:	Bone marrow suppression, neutropenia, thrombocytopenia, anaemia, leukopenia, lymphopenia	Neutropenia, thrombocytopenia, anaemia	Neutropenia[3], thrombocytopenia[3], anaemia[3], leukopenia[3]
Common:	Febrile neutropenia	Pancytopenia	Febrile neutropenia, lymphopenia
Uncommon:		Thrombotic thrombocytopenic purpura	Pancytopenia
Rare:	Pancytopenia		
Immune system disorders			
Uncommon:	Hypersensitivity		Drug hypersensitivity, hypersensitivity
Rare:	Severe hypersensitivity[1]		

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Metabolism and nutrition disorders			
Very common:	Anorexia	Dehydration, decreased appetite, hypokalaemia	Decreased appetite
Common:	Dehydration, decreased appetite, hypokalaemia		Dehydration
Uncommon:	Hypophosphataemia, fluid retention, hypoalbuminaemia, polydipsia, hyperglycaemia, hypocalcaemia, hypoglycaemia, hyponatraemia		
Not known:	Tumour lysis syndrome[1]		
Psychiatric disorders			
Very common:		Depression, insomnia	
Common:	Depression, insomnia, anxiety	Anxiety	
Uncommon:	Restlessness		Insomnia
Nervous system disorders			
Very common:	Peripheral neuropathy, neuropathy, hypoaesthesia, paraesthesia	Peripheral neuropathy, dizziness, headache, dysgeusia	Peripheral neuropathy
Common:	Peripheral sensory neuropathy, dizziness, peripheral motor neuropathy, ataxia, headache, sensory disturbance, somnolence, dysgeusia		Dizziness, headache, dysgeusia
Uncommon:	Polyneuropathy, areflexia, syncope, postural dizziness, dyskinesia, hyporeflexia, neuralgia, neuropathic pain, tremor, sensory loss	VIIth nerve paralysis	
Not known:	Cranial nerve palsies multiple[1]		
Eye disorders			
Common:	Vision blurred, lacrimation increased, dry eye, keratoconjunctivitis sicca, madarosis	Lacrimation increased	Vision blurred
Uncommon:	Reduced visual acuity, abnormal vision, eye irritation, eye pain, conjunctivitis, visual disturbance, eye pruritus, keratitis	Cystoid macular oedema	
Rare:	Cystoid macular oedema[1]		
Ear and labyrinth disorders			
Common:	Vertigo		
Uncommon:	Tinnitus, ear pain		
Cardiac disorders			
Common:	Arrhythmia, tachycardia, supraventricular tachycardia	Cardiac failure congestive, tachycardia	
Rare:	Cardiac arrest, cardiac failure congestive, left ventricular dysfunction, atrioventricular block1, bradycardia		

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Vascular disorders			
Common:	Hypertension, lymphoedema, flushing, hot flushes	Hypotension, hypertension	Hypotension, hypertension
Uncommon:	Hypotension, orthostatic hypotension, peripheral coldness	Flushing	Flushing
Rare:	Thrombosis		
Respiratory, thoracic and mediastinal disorders			
Very common:		Dyspnoea, epistaxis, cough	Dyspnoea
Common:	Interstitial pneumonitis[2], dyspnoea, epistaxis, pharyngolaryngeal pain, cough, rhinitis, rhinorrhoea	Pneumonitis, nasal congestion	Haemoptysis, epistaxis, cough
Uncommon:	Pulmonary emboli, pulmonary thromboembolism, pleural effusion, exertional dyspnoea, sinus congestion, decreased breath sounds, productive cough, allergic rhinitis, hoarseness, nasal congestion, nasal dryness, wheezing	Dry throat, nasal dryness	Pneumonitis
Not known:	Vocal cord paresis[1]		
Gastrointestinal disorders			
Very common:	Diarrhoea, vomiting, nausea, constipation, stomatitis	Diarrhoea, vomiting, nausea, constipation, abdominal pain, abdominal pain upper	Diarrhoea, vomiting, nausea, constipation
Common:	Gastrooesophageal reflux disease, dyspepsia, abdominal pain, abdominal distension, abdominal pain upper, oral hypoaesthesia	Intestinal obstruction, colitis, stomatitis, dry mouth	Stomatitis, dyspepsia, dysphagia, abdominal pain
Uncommon:	Rectal haemorrhage, dysphagia, flatulence, glossodynia, dry mouth, gingival pain, loose stools, oesophagitis, abdominal pain lower, mouth ulceration, oral pain		
Hepatobiliary disorders			
Common:		Cholangitis	Hyperbilirubinaemia
Uncommon:	Hepatomegaly		
Skin and subcutaneous tissue disorders			
Very common:	Alopecia, rash	Alopecia, rash	Alopecia, rash
Common:	Pruritus, dry skin, nail disorder, erythema, nail pigmentation/discolouration, skin hyperpigmentation, onycholysis, nail changes	Pruritus, dry skin, nail disorder	Pruritus, nail disorder
Uncommon:	Photosensitivity reaction, urticaria, skin pain, generalised pruritus, pruritic rash, skin		Skin exfoliation, dermatitis allergic, urticaria

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
	disorder, pigmentation disorder, hyperhidrosis, onychomadesis, erythematous rash, generalised rash, dermatitis, night sweats, maculo-papular rash, vitiligo, hypotrichosis, nail bed tenderness, nail discomfort, macular rash, papular rash, skin lesion, swollen face		
Very rare:	Stevens-Johnson syndrome[1], toxic epidermal necrolysis[1]		
Not known:	Palmar-plantar erythrodysaesthesiae syndrome[1,4], scleroderma[1]		
Musculoskeletal and connective tissue disorders			
Very common:	Arthralgia, myalgia	Arthralgia, myalgia, pain in extremity	Arthralgia, myalgia
Common:	Back pain, pain in extremity, bone pain, muscle cramps, limb pain	Muscular weakness, bone pain	Back pain, pain in extremity, musculoskeletal pain
Uncommon:	Chest wall pain, muscular weakness, neck pain, groin pain, muscle spasms, musculoskeletal pain, flank pain, limb discomfort, muscle weakness		
Renal and urinary disorders			
Common:		Acute renal failure	
Uncommon:	Haematuria, dysuria, pollakiuria, nocturia, polyuria, urinary incontinence	Haemolytic uraemic syndrome	
Reproductive system and breast disorders			
Uncommon:	Breast pain		
General disorders and administration site conditions			
Very common:	Fatigue, asthenia, pyrexia	Fatigue, asthenia, pyrexia, oedema peripheral, chills	Fatigue, asthenia, oedema peripheral
Common:	Malaise, lethargy, weakness, peripheral oedema, mucosal inflammation, pain, rigors, oedema, decreased performance status, chest pain, influenza-like illness, hyperpyrexia	Infusion site reaction	Pyrexia, chest pain
Uncommon:	Chest discomfort, abnormal gait, swelling, injection site reaction		Mucosal inflammation, infusion site extravasation, infusion site inflammation, infusion site rash
Rare:	Extravasation		

	Monotherapy (N=789)	Combination therapy with gemcitabine (N =421)	Combination therapy with carboplatin (N = 514)
Investigations			
Very common:		Weight decreased, alanine aminotransferase increased	
Common:	Decreased weight, increased alanine aminotransferase, increased aspartate aminotransferase, decreased haematocrit, decreased red blood cell count, increased body temperature, increased gamma-glutamyltransferase, increased blood alkaline phosphatase	Aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased	Weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
Uncommon:	Increased blood pressure, increased weight, increased blood lactate dehydrogenase, increased blood creatinine, increased blood glucose, increased blood phosphorus, decreased blood potassium, increased bilirubin		
Injury, poisoning and procedural complications			
Uncommon:	Contusion		
Rare:	Radiation recall phenomenon, radiation pneumonitis		

[1]As reported in the post-marketing surveillance of human serum albumin-paclitaxel nanoparticles.
[2]The frequency of pneumonitis is calculated based on pooled data in 1,310 patients in clinical trials receiving human serum albumin-paclitaxel nanoparticles monotherapy for breast cancer and for other indications.
[3]Based on laboratory assessments: maximal degree of myelosuppression (treated population).
[4]In some patients previously exposed to capecitabine.

Description of selected adverse reactions

This section contains the most common and clinically relevant adverse reactions related to human serum albumin-paclitaxel nanoparticles injection.

Adverse reactions were assessed in 229 patients with metastatic breast cancer who were treated with 260 mg/m^2 human serum albumin-paclitaxel nanoparticles once every three weeks in the pivotal phase III clinical study (human serum albumin-paclitaxel nanoparticles monotherapy).

Adverse reactions were assessed in 421 patients with metastatic pancreatic cancer who were treated with serum albumin-paclitaxel nanoparticles in combination with gemcitabine (125 mg/m^2 human serum albumin-paclitaxel nanoparticles in combination with gemcitabine at a dose of 1000 mg/m^2 given on Days 1, 8 and 15 of each 28-day cycle) and 402 gemcitabine monotherapy-treated patients receiving first-line systemic treatment for metastatic adenocarcinoma of the pancreas (human serum albumin-paclitaxel nanoparticles /gemcitabine).

Adverse reactions were assessed in 514 patients with non-small cell lung cancer who were treated with human serum albumin-paclitaxel nanoparticles in combination with carboplatin (100 mg/m^2 human serum albumin-paclitaxel nanoparticles given on Days 1, 8 and 15 of each 21-day cycle in combination with carboplatin given on Day 1 of each cycle) in the phase III randomized, controlled clinical trial (human serum albumin-paclitaxel nanoparticles/carboplatin). Patient-reported taxane toxicity was

assessed using the 4 subscales of the Functional Assessment of Cancer Therapy (FACT)- Taxane questionnaire. Using repeated measure analysis, 3 of the 4 subscales (peripheral neuropathy, pain hands/feet and hearing) favoured human serum albumin-paclitaxel nanoparticles and carboplatin ($p \leq 0.002$). For the other subscale (oedema), there was no difference in the treatment arms.

Infections and infestations

Human serum albumin-paclitaxel nanoparticles/gemcitabine
Sepsis was reported at a rate of 5% in patients with or without neutropenia who received human serum albumin-paclitaxel nanoparticles in combination with gemcitabine during the conduct of a trial in pancreatic adenocarcinoma. Of the 22 cases of sepsis reported in patients treated with human serum albumin-paclitaxel nanoparticles in combination with gemcitabine, 5 had a fatal outcome. Complications due to the underlying pancreatic cancer, especially biliary obstruction or presence of biliary stent, were identified as significant contributing factors. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Naveruclif and gemcitabine until fever resolves and ANC $\geq$ 1,500 cells/mm^3, then resume treatment at reduced dose levels (see section 4.2).

Blood and lymphatic system disorders

Human serum albumin-paclitaxel nanoparticles monotherapy-metastatic breast cancer
In patients with metastatic breast cancer, neutropenia was the most notable important haematological toxicity (reported in 79% of patients) and was rapidly reversible and dose-dependent; leukopenia was reported in 71% of patients. Grade 4 neutropenia (< 500 cells/mm^3) occurred in 9% of patients treated with human serum albumin-paclitaxel nanoparticles. Febrile neutropenia occurred in four patients on human serum albumin-paclitaxel nanoparticles. Anaemia (Hb < 10 g/dl) was observed in 46% of patients on human serum albumin-paclitaxel nanoparticles and was severe (Hb < 8 g/dl) in three cases. Lymphopenia was observed in 45% of the patients.

Human serum albumin-paclitaxel nanoparticles/gemcitabine
Table 7 provides the frequency and severity of haematologic laboratory-detected abnormalities for patients treated with human serum albumin-paclitaxel nanoparticles in combination with gemcitabine or with gemcitabine.

Table 7: Haematologic laboratory-detected abnormalities in pancreatic adenocarcinoma trial

	Human serum albumin-paclitaxel nanoparticles (125 mg/ m^2)/Gemcitabine		**Gemcitabine**	
	Grades 1-4 (%)	**Grade 3-4 (%)**	**Grades 1-4 (%)**	**Grade 3-4 (%)**
Anaemia[a,b]	97	13	96	12
Neutropenia[a,b]	73	38	58	27
Thrombocytopenia[b,c]	74	13	70	9

[a]405 patients assessed in human serum albumin-paclitaxel nanoparticles/gemcitabine-treated group
[b]388 patients assessed in gemcitabine-treated group
[c]404 patients assessed in human serum albumin-paclitaxel nanoparticles/gemcitabine-treated group

Human serum albumin-paclitaxel nanoparticles/carboplatin
Anaemia and thrombocytopenia were more commonly reported in the human serum albumin-paclitaxel nanoparticles and carboplatin arm than in the Taxol and carboplatin arm (54% versus 28% and 45% versus 27% respectively).

Nervous system disorders

Human serum albumin-paclitaxel nanoparticles monotherapy-metastatic breast cancer
In general, the frequency and severity of neurotoxicity was dose-dependent in patients receiving human serum albumin-paclitaxel nanoparticles. Peripheral neuropathy (mostly Grade 1 or 2 sensory neuropathy) was observed in 68% of patients on human serum albumin-paclitaxel nanoparticles with

10% being Grade 3, and no cases of Grade 4.

Human serum albumin-paclitaxel nanoparticles/gemcitabine
For patients treated with human serum albumin-paclitaxel nanoparticles in combination with gemcitabine, the median time to first occurrence of Grade 3 peripheral neuropathy was 140 days. The median time to improvement by at least 1 grade was 21 days, and the median time to improvement from Grade 3 peripheral neuropathy to Grade 0 or 1 was 29 days. Of the patients with treatment interrupted due to peripheral neuropathy, 44% (31/70 patients) were able to resume human serum albumin-paclitaxel nanoparticles at a reduced dose. No patients treated with human serum albumin-paclitaxel nanoparticles in combination with gemcitabine had Grade 4 peripheral neuropathy.

Human serum albumin-paclitaxel nanoparticles/carboplatin
For non-small cell lung cancer patients treated with human serum albumin-paclitaxel nanoparticles and carboplatin, the median time to first occurrence of Grade 3 treatment-related peripheral neuropathy was 121 days, and the median time to improvement from Grade 3 treatment related peripheral neuropathy to Grade 1 was 38 days. No patients treated with human serum albumin-paclitaxel nanoparticles and carboplatin experienced Grade 4 peripheral neuropathy.

Eye disorders

There have been rare reports during post-marketing surveillance of reduced visual acuity due to cystoid macular oedema during treatment with human serum albumin-paclitaxel nanoparticles (see section 4.4).

Respiratory, thoracic and mediastinal disorders

Human serum albumin-paclitaxel nanoparticles/gemcitabine
Pneumonitis has been reported at a rate of 4% with the use of human serum albumin-paclitaxel nanoparticles in combination with gemcitabine. Of the 17 cases of pneumonitis reported in patients treated with human serum albumin-paclitaxel nanoparticles in combination with gemcitabine, 2 had a fatal outcome. Monitor patients closely for signs and symptoms of pneumonitis.
After ruling out infectious aetiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with Naveruclif and gemcitabine and promptly initiate appropriate treatment and supportive measures (see section 4.2).

Gastrointestinal disorders

Human serum albumin-paclitaxel nanoparticles monotherapy-metastatic breast cancer
Nausea occurred in 29% of the patients and diarrhoea in 25% of the patients.

Skin and subcutaneous tissue disorders

Human serum albumin-paclitaxel nanoparticles monotherapy-metastatic breast cancer
Alopecia was observed in >80% of the patients treated with human serum albumin-paclitaxel nanoparticles. The majority of alopecia events occurred less than one month after initiation of human serum albumin-paclitaxel nanoparticles. Pronounced hair loss ≥ 50% is expected for the majority of patients who experience alopecia.

Musculoskeletal and connective tissue disorders

Human serum albumin-paclitaxel nanoparticles monotherapy-metastatic breast cancer
Arthralgia occurred in 32% of patients on human serum albumin-paclitaxel nanoparticles and was severe in 6% of cases. Myalgia occurred in 24% of patients on human serum albumin-paclitaxel nanoparticles and was severe in 7% of cases. The symptoms were usually transient, typically occurred three days after human serum albumin-paclitaxel nanoparticles administration and resolved within a week.

General disorders and administration site conditions

Human serum albumin-paclitaxel nanoparticles monotherapy-metastatic breast cancer
Asthenia/Fatigue was reported in 40% of the patients.

Paediatric population

The study consisted of 106 patients, 104 of whom were paediatric patients aged from 6 months to less than 18 years (see section 5.1). Every patient experienced at least 1 adverse reaction. The most frequently reported adverse reactions were neutropenia, anaemia, leukopenia and pyrexia. Serious adverse reactions reported in more than 2 patients were pyrexia, back pain, peripheral oedema and vomiting. No new safety signals were identified in the limited number of paediatric patients treated with human serum albumin-paclitaxel nanoparticles and the safety profile was similar to that of the adult population.

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 bone marrow suppression, mucositis and peripheral neuropathy.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, plant alkaloids and other natural products, 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. This stability 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 abnormal arrays or “bundles” of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Naveruclif contains human serum albumin-paclitaxel nanoparticles of approximately 180 nm in size, where the paclitaxel is present in a non-crystalline, amorphous state. Upon intravenous administration, the nanoparticles dissociate rapidly into soluble, albumin bound paclitaxel complexes of approximately 10 nm in size. Albumin is known to mediate endothelial caveolar transcytosis of plasma constituents, and *in vitro* studies demonstrated that the presence of albumin enhances transport of paclitaxel across endothelial cells. It is hypothesised that this enhanced transendothelial caveolar transport is mediated by the gp-60 albumin receptor, and that there is enhanced accumulation of paclitaxel in the area of tumour due to the albumin-binding protein Secreted Protein Acidic Rich in Cysteine (SPARC).

Clinical efficacy and safety

Breast cancer

Data from 106 patients accrued in two single-arm open-label studies and from 454 patients treated in

a randomised Phase III comparative study are available to support the use of human serum albumin-paclitaxel nanoparticles in metastatic breast cancer. This information is presented below.

Single-arm open-label studies
In one study, human serum albumin-paclitaxel nanoparticles were administered as a 30-minute infusion at a dose of 175 mg/m^2 to 43 patients with metastatic breast cancer. The second trial utilised a dose of 300 mg/m^2 as a 30- minute infusion in 63 patients with metastatic breast cancer. Patients were treated without steroid pre-treatment or planned G-CSF support. Cycles were administered at 3-week intervals. The response rates in all patients were 39.5% (95% CI: 24.9%-54.2%) and 47.6% (95% CI: 35.3%-60.0%), respectively. The median time to disease progression was 5.3 months (175 mg/m^2; 95% CI: 4.6-6.2 months) and 6.1 months (300 mg/m^2; 95% CI: 4.2-9.8 months).

Randomised comparative study
This multi-centre trial was conducted in patients with metastatic breast cancer, who were treated every 3 weeks with single-agent paclitaxel, either as solvent-based paclitaxel 175 mg/m^2 given as a 3-hour infusion with premedication to prevent hypersensitivity (N = 225), or as human serum albumin-paclitaxel nanoparticles 260 mg/m^2 given as a 30 minute infusion without premedication (N = 229).

Sixty-four percent of patients had impaired performance status (ECOG 1 or 2) at study entry; 79% had visceral metastases; and 76% had > 3 sites of metastases. Fourteen percent of the patients had not received prior chemotherapy; 27% had received chemotherapy in the adjuvant setting only, 40% in the metastatic setting only, and 19% in both metastatic and adjuvant settings. Fifty-nine percent received study medicinal product as second or greater than second-line therapy. Seventy-seven percent of the patients had been previously exposed to anthracyclines.

Results for overall response rate and time to disease progression, and progression-free survival and survival for patients receiving > 1st-line therapy, are shown below.

Table 8: Results for overall response rate, median time to disease progression, and progression-free survival as assessed by the investigator

Efficacy variable	Human serum albumin-paclitaxel nanoparticles (260 mg/m^2)	Solvent-based paclitaxel (175 mg/m^2)	p-value
Response rate [95% CI] (%)			
> 1st-line therapy	26.5 [18.98, 34.05] (n = 132)	13.2 [7.54, 18.93] (n = 136)	0.006[a]
**Median time to disease progression [95% CI] (weeks)*			
> 1st-line therapy	20.9 [15.7, 25.9] (n = 131)	16.1 [15.0, 19.3] (n = 135)	0.011[b]
**Median progression free survival [95% CI] (weeks)*			
> 1st-line therapy	20.6 [15.6, 25.9] (n = 131)	16.1 [15.0, 18.3] (n = 135)	0.010[b]
**Survival [95% CI] (weeks)*			
> 1st-line therapy	56.4 [45.1, 76.9] (n = 131)	46.7 [39.0, 55.3] (n = 136)	0.020[b]

[*]This data is based on Clinical Study Report: CA012-0 Addendum dated Final (23 March-2005)
[a]Chi-squared test
[b]Log-rank test

Two hundred and twenty nine patients treated with human serum albumin-paclitaxel nanoparticles in the randomized, controlled clinical trial were evaluated for safety. Neurotoxicity to paclitaxel was evaluated through improvement by one grade for patients experiencing Grade 3 peripheral neuropathy at any time during therapy. The natural course of peripheral neuropathy to resolution to baseline due to cumulative toxicity of human serum albumin-paclitaxel nanoparticles after > 6 courses of treatment was not evaluated and remains unknown.

Pancreatic adenocarcinoma

A multicenter, multinational, randomized, open-label study was conducted in 861 patients to compare human serum albumin-paclitaxel nanoparticles/gemcitabine versus gemcitabine monotherapy as first-line treatment in patients with metastatic adenocarcinoma of the pancreas. Human serum albumin-paclitaxel nanoparticles were administered to patients (N = 431) as an intravenous infusion over 30-40 minutes at a dose of 125 mg/m^2 followed by gemcitabine as an intravenous infusion over 30-40 minutes at a dose of 1000 mg/m^2 given on Days 1, 8 and 15 of each 28-day cycle. In the comparator treatment arm, gemcitabine monotherapy was administered to patients (N = 430) in accordance with the recommended dose and regimen. Treatment was administered until disease progression or development of an unacceptable toxicity. Of the 431 patients with pancreatic adenocarcinoma who were randomized to receive human serum albumin-paclitaxel nanoparticles in combination with gemcitabine, the majority (93%) were white, 4% were black and 2% were Asian. 16% had a Karnofsky Performance Status of 100; 42% had a KPS of 90; 35% had a KPS of 80; 7% had a KPS of 70; and <1% of patients had a KPS of below 70. Patients with high cardiovascular risk, history of peripheral artery disease and/or of connective tissue disorders and/or interstitial lung disease were excluded from the study.

Patients received a median treatment duration of 3.9 months in the human serum albumin-paclitaxel nanoparticles/gemcitabine arm and 2.8 months in the gemcitabine arm. 32% of patients in the human serum albumin-paclitaxel nanoparticles/gemcitabine arm compared with 15% of patients in the gemcitabine arm received 6 or more months of treatment. For the treated population, the median relative dose intensity for gemcitabine was 75% in the human serum albumin-paclitaxel nanoparticles/gemcitabine arm and 85% in the gemcitabine arm. The median relative dose intensity of human serum albumin-paclitaxel nanoparticles was 81%. A higher median cumulative dose of gemcitabine was delivered in the human serum albumin-paclitaxel nanoparticles/gemcitabine arm (11400 mg/m^2) when compared with the gemcitabine arm (9000 mg/m^2).

The primary efficacy endpoint was overall survival (OS). The key secondary endpoints were progression- free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using RECIST guidelines (Version 1.0).

Table 9: Efficacy results from randomized study in patients with pancreatic adenocarcinoma (Intent-to-treat population)

	Human serum albumin-paclitaxel nanoparticles (125 mg/m^2)/gemcitabine (N=431)	**Gemcitabine (N=430)**
Overall Survival		
Number of deaths (%)	333 (77)	359 (83)
Median Overall Survival, months (95% CI)	8.5 (7.89, 9.53)	6.7 (6.01, 7.23)
$HR_{A+G/G}$ (95% CI) a	0.72 (0.617, 0.835)	
P-valueb	<0.0001	
Survival Rate % (95% CI) at		
1 Year	35% (29.7, 39.5)	22% (18.1, 26.7)
2 Year	9% (6.2, 13.1)	4% (2.3, 7.2)
75th Percentile Overall Survival (months)	14.8	11.4
Progression-free Survival		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free Survival, months (95% CI)	5.5 (4.47, 5.95)	3.7 (3.61, 4.04)
$HR_{A+G/G}$ (95% CI) [a]	0.69 (0.581, 0.821)	
P-value[b]	<0.0001	
Overall Response Rate		
Confirmed complete or partial	99 (23)	31 (7)

	Human serum albumin-paclitaxel nanoparticles (125 mg/m^2)/gemcitabine (N=431)	Gemcitabine (N=430)
overall response, n (%)		
95% CI	19.1, 27.2	5.0, 10.1
p_{A+G} /pG (95% CI)	3.19 (2.178, 4.662)	
P-value (chi-square test)	<0.0001	

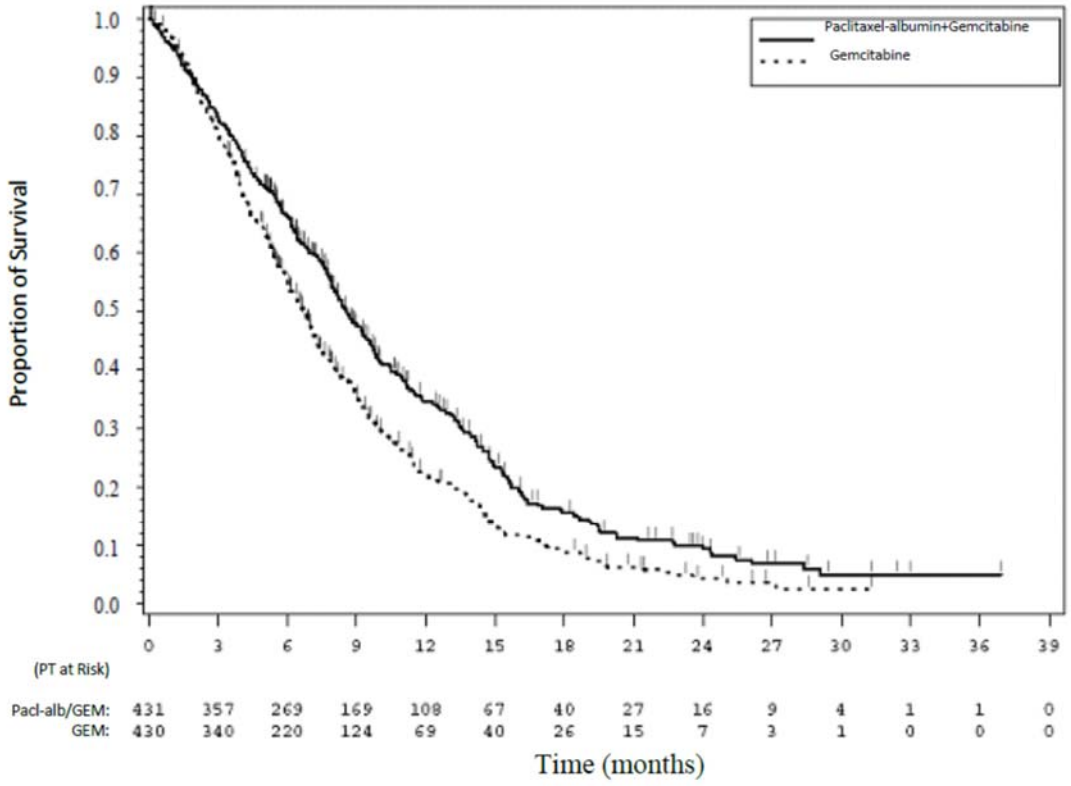
CI = confidence interval, $HR_{A+G/G}$ = hazard ratio of human serum albumin-paclitaxel nanoparticles+gemcitabine/gemcitabine, $p_{A+G/pG}$=response rate ratio of human serum albumin-paclitaxel nanoparticles+gemcitabine/gemcitabine

[a] stratified Cox proportional hazard model

[b] stratified log-rank test, stratified by geographic region (North America versus others), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no).

There was a statistically significant improvement in OS for patients treated with human serum albumin-paclitaxel nanoparticles/gemcitabine versus gemcitabine alone, with 1.8 months increase in median OS, 28% overall reduction in risk of death, 59% improvement in 1-year survival, and 125% improvement in 2-year survival rates.

Figure 1: Kaplan-Meier curve of overall survival (intent-to-treat population)



Treatment effects on OS favoured the human serum albumin-paclitaxel nanoparticles/gemcitabine arm across the majority of pre-specified subgroups (including gender, KPS, geographic region, primary location of pancreatic cancer, stage at diagnosis, presence of liver metastases, presence of peritoneal carcinomatosis, prior Whipple procedure, presence of biliary stent at baseline, presence of pulmonary metastases, and number of metastatic sites). For patients ≥ 75 years of age in the human serum albumin-paclitaxel nanoparticles/gemcitabine and gemcitabine arms the survival Hazard Ratio (HR) was 1.08

(95% CI 0.653, 1. 797). For patients with normal baseline CA 19-9 levels the survival HR was 1.07 (95% CI 0.692, 1.661).

There was a statistically significant improvement in PFS for patients treated with human serum albumin-paclitaxel nanoparticles /gemcitabine versus gemcitabine alone, with 1.8 months increase in median PFS.

Non-small cell lung cancer

A multicenter, randomized, open-label study was conducted in 1052 chemotherapy-naive patients with Stage IIIb/IV non-small cell lung cancer. The study compared human serum albumin-paclitaxel nanoparticles in combination with carboplatin versus solvent-based paclitaxel in combination with carboplatin as first-line treatment in patients with advanced non-small cell lung cancer. Over 99% of patients had an ECOG (Eastern Cooperative Oncology Group) performance status of 0 or 1. Patients with pre-existing neuropathy of Grade ≥ 2 or serious medical risk factors involving any of the major organ systems were excluded. Human serum albumin-paclitaxel nanoparticles were administered to patients (N=521) as an intravenous infusion over 30 minutes at a dose of 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle without any steroid premedication and without granulocyte colony stimulating factor prophylaxis. Beginning immediately after the end of human serum albumin-paclitaxel nanoparticles administration, carboplatin at a dose of AUC = 6 mg•min/mL was administered intravenously on Day 1 only of each 21-day cycle. Solvent- based paclitaxel was administered to patients (N=531) at a dose of 200 mg/m^2 as an intravenous infusion over 3 hours with standard premedication, immediately followed by carboplatin administered intravenously at AUC = 6 mg•min/mL. Each drug was administered on Day 1 of each 21-day cycle. In both study arms treatment was administered until disease progression or development of an unacceptable toxicity. Patients received a median of 6 cycles of treatment in both study arms.

The primary efficacy endpoint was overall response rate defined as the percentage of patients who achieved an objective confirmed complete response or partial response based on an independent, central, blinded radiological review using RECIST (Version 1.0). Patients in the human serum albumin-paclitaxel nanoparticles/carboplatin arm had a significantly higher overall response rate compared with patients in the control arm: 33% versus 25%, p = 0.005 (Table 10). There was a significant difference in overall response rate in the human serum albumin-paclitaxel nanoparticles/carboplatin arm compared to the control arm in patients with non-small cell lung cancer of squamous histology (N=450, 41% vs. 24%, p<0.001), however this difference did not translate into a difference in PFS or OS. There was no difference in ORR between the treatment arms in patients with non-squamous histology (N=602, 26% vs 25%, p=0.808).

Table 10: Overall response rate in randomized non-small cell lung cancer trial (intent-to-treat population)

Efficacy Parameter	**Human serum albumin-paclitaxel nanoparticles (100 mg/m^2/week) + carboplatin (N=521)**	**Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) + carboplatin (N=531)**
Overall Response Rate (independent review)		
Confirmed complete or partial overall response, n (%)	170 (33%)	132 (25%)
95% CI (%)	28.6, 36.7	21.2, 28.5
p_A/p_T (95.1% CI)	1.313 (1.082, 1.593)	
P-value[a]	0.005	

CI = confidence interval; $HR_{A/T}$ = hazard ratio of human serum albumin-paclitaxel nanoparticles/carboplatin to solvent-based paclitaxel/carboplatin;
p_A/p_T = response rate ratio of human serum albumin-paclitaxel nanoparticles/carboplatin to solvent-based paclitaxel/carboplatin.
[a]P-value is based on a chi-square test.

There was no statistically significant difference in progression-free survival (by blinded radiologist assessment) and overall survival between the two treatment arms. A non-inferiority analysis was conducted for PFS and OS, with a pre-specified non-inferiority margin of 15%. The non-inferiority criterion was met for both PFS and OS with the upper bound of the 95% confidence interval for the associated hazard ratios being less than 1.176 (Table 11).

Table 11: Non-inferiority analyses on progression-free survival and overall survival in randomized non-small cell lung cancer trial (intent-to-treat population)

Efficacy Parameter	**Human serum albumin-paclitaxel nanoparticles (100 mg/m^2/week) + carboplatin (N=521)**	**Solvent-based paclitaxel (200 mg/m^2 every 3 weeks) + carboplatin (N=531)**
Progression-free Survival[a] (independent review)		
Death or progression, n (%)	429 (82%)	442 (83%)
Median PFS (95% CI) (months)	6.8 (5.7, 7.7)	6.5 (5.7, 6.9)
$HR_{A/T}$ (95% CI)	0.949 (0.830, 1.086)	
Overall Survival		
Number of deaths, n (%)	360 (69%)	384 (72%)
Median OS (95% CI) (months)	12.1 (10.8, 12.9)	11.2 (10.3, 12.6)
$HR_{A/T}$ (95.1% CI)	0.922 (0.797, 1.066)	

CI = confidence interval; $HR_{A/T}$ = hazard ratio of human serum albumin-paclitaxel nanoparticles/carboplatin to solvent-based paclitaxel/carboplatin;
p_A/p_T = response rate ratio of human serum albumin-paclitaxel nanoparticles/carboplatin to solvent-based paclitaxel/carboplatin.
[a]Per EMA methodological considerations for PFS endpoint, missing observations or initiation of subsequent new therapy were not used for censoring.

Paediatric population

Safety and effectiveness in paediatric patients have not been established (see section 4.2).

Study ABI-007-PST-001, a Phase 1/2, multicenter, open-label, dose-finding study to assess the safety, tolerability and preliminary efficacy of weekly human serum albumin-paclitaxel nanoparticles in paediatric patients with recurrent or refractory solid tumours included a total of 106 patients aged ≥ 6 months to ≤ 24 years.

The Phase 1 portion of the study included a total of 64 patients aged from 6 months to less than 18 years old and determined the maximum tolerated dose (MTD) to be 240 mg/m^2, administered as an intravenous infusion over 30 minutes, on Days 1, 8, and 15 of each 28-day cycle.

The Phase 2 portion enrolled a total of 42 patients using a Simon two-stage minimax design, aged from 6 months to 24 years with recurrent or refractory Ewing's sarcoma, neuroblastoma or rhabdomyosarcoma for the evaluation of antitumour activity assessed by the overall response rate (ORR). Of the 42 patients, 1 patient was < 2, 27 were aged ≥ 2 to < 12, 12 were aged ≥12 to < 18 and 2 adult patients were aged ≥ 18 to 24 years old.

Patients were treated for a median of 2 cycles at the MTD. From the 41 patients eligible for efficacy evaluation in stage 1, 1 patient in the rhabdomyosarcoma group (N=14) had a confirmed partial response (PR) resulting in an ORR of 7.1% (95% CI: 0.2, 33.9). No confirmed complete response (CR) or PR was observed in either the Ewing's sarcoma group (N=13) or the neuroblastoma group (N=14). None of the study arms continued into stage 2 because the protocol-defined requirement of ≥ 2 patients to have a confirmed response was not met.

The median overall survival results, including the 1-year follow-up period were 32.1 weeks (95% CI: 21.4, 72.9), 32.0 weeks (95% CI: 12, not established) and 19.6 weeks (95% CI: 4, 25.7) for

the Ewing's sarcoma, neuroblastoma and rhabdomyosarcoma groups, respectively.

The overall safety profile of human serum albumin-paclitaxel nanoparticles in paediatric patients was consistent with the known safety profile of human serum albumin-paclitaxel nanoparticles in adults (see section 4.8). Based on these results, it was concluded that human serum albumin-paclitaxel nanoparticles as monotherapy does not have meaningful clinical activity or survival benefit that warrants further development in the paediatric population.

5.2 Pharmacokinetic properties

The pharmacokinetics of total paclitaxel following 30- and 180 minute infusions of human serum albumin-paclitaxel nanoparticles at dose levels of 80 to 375 mg/m^2 were determined in clinical studies. The paclitaxel exposure (AUC) increased linearly from 2653 to 16736 ng.hr/ml following dosing from 80 to 300 mg/m^2.

In a study in patients with advanced solid tumours, the pharmacokinetic characteristics of paclitaxel following human serum albumin-paclitaxel nanoparticles administered intravenously at 260 mg/m^2 over 30 minutes were compared with those following 175 mg/m^2 of the solvent-based paclitaxel injection administered over 3 hours. Based on non-compartmental PK analysis, the plasma clearance of paclitaxel with human serum albumin-paclitaxel nanoparticles was larger (43%) than that following a solvent-based paclitaxel injection and its volume of distribution was also higher (53%). There were no differences in terminal half-lives.

In a repeat dose study with 12 patients receiving human serum albumin-paclitaxel nanoparticles administered intravenously at 260 mg/m^2, intra-patient variability in AUC was 19% (range = 3.21%-37.70%). There was no evidence for accumulation of paclitaxel with multiple treatment courses.

Distribution

Following human serum albumin-paclitaxel nanoparticles administration to patients with solid tumours, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%).

The protein binding of paclitaxel following human serum albumin-paclitaxel nanoparticles was evaluated by ultrafiltration in a within-patient comparison study. The fraction of free paclitaxel was significantly higher with human serum albumin-paclitaxel nanoparticles (6.2%) than with solvent-based paclitaxel (2.3%). This resulted in significantly higher exposure to unbound paclitaxel with human serum albumin-paclitaxel nanoparticles compared with solvent-based paclitaxel, even though the total exposure is comparable. This is possibly due to paclitaxel not being trapped in Cremophor EL micelles as with solvent-based paclitaxel. Based on the published literature, *in vitro* studies of binding to human serum proteins, (using paclitaxel at concentrations ranging from 0.1 to 50 µg/ml), indicate that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel.

Based on population pharmacokinetic analysis, the total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

Biotransformation and elimination

Based on the published literature, *in vitro* studies with human liver microsomes and tissue slices show that paclitaxel is metabolised primarily to 6α-hydroxypaclitaxel; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α-3'-*p*-dihydroxypaclitaxel. The formation of these hydroxylated metabolites is catalysed by CYP2C8, CYP3A4, and both CYP2C8 and CYP3A4 isoenzymes, respectively.

In patients with metastatic breast cancer, after a 30-minute infusion of human serum albumin-paclitaxel nanoparticles at 260 mg/m^2, the mean value for cumulative urinary excretion of unchanged active

substance accounted for 4% of the total administered dose with less than 1% as the metabolites 6α-hydroxypaclitaxel and 3'-*p*-hydroxypaclitaxel, indicating extensive non-renal clearance. Paclitaxel is principally eliminated by hepatic metabolism and biliary excretion.

At the clinical dose range of 80 to 300 mg/m^2, the mean plasma clearance of paclitaxel ranges from 13 to 30 L/h/m^2, and the mean terminal half-life ranges from 13 to 27 hours.

Hepatic impairment

The effect of hepatic impairment on population pharmacokinetics of human serum albumin-paclitaxel nanoparticles was studied in patients with advanced solid tumours. This analysis included patients with normal hepatic function (n=130), and pre-existing mild (n=8), moderate (n=7), or severe (n=5) hepatic impairment (according to NCI Organ Dysfunction Working Group criteria). The results show that mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN) has no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin >1.5 to ≤3 x ULN) or severe (total bilirubin >3 to ≤5 x ULN) hepatic impairment have a 22% to 26% decrease in the maximum elimination rate of paclitaxel and approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function. Hepatic impairment has no effect on mean paclitaxel C_{max}. In addition, elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin.

Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for human serum albumin-paclitaxel nanoparticles exposure.

Pharmacokinetic data are not available for patients with total bilirubin >5 x ULN or for patients with metastatic adenocarcinoma of the pancreas (see section 4.2).

Renal impairment

Population pharmacokinetic analysis included patients with normal renal function (n=65), and pre-existing mild (n=61), moderate (n=23), or severe (n=l) renal impairment (according to draft FDA guidance criteria 2010). Mild to moderate renal impairment (creatinine clearance ≥30 to <90 ml/min) has no clinically important effect on the maximum elimination rate and systemic exposure (AUC and C_{max}) of paclitaxel. Pharmacokinetic data are insufficient for patients with severe renal impairment and not available for patients with end stage kidney disease.

Elderly

Population pharmacokinetic analysis for human serum albumin-paclitaxel nanoparticles included patients with ages ranging from 24 to 85 years old and shows that age does not significantly influence the maximum elimination rate and systemic exposure (AUC and C_{max}) of paclitaxel.

Pharmacokinetic/pharmacodynamic modelling using data from 125 patients with advanced solid tumours indicates that patients ≥ 65 years of age may be more susceptible to development of neutropenia within the first treatment cycle, although the plasma paclitaxel exposure is not affected by age.

Paediatric population

The pharmacokinetics of paclitaxel following 30 minutes of intravenous administration at dose levels of 120 mg/m^2 to 270 mg/m^2 were determined in 64 patients (2 to ≤ 18 years) in Phase 1 of a Phase 1/2 study in recurrent or refractory paediatric solid tumours. Following dosing increase from 120 to 270 mg/m^2, the paclitaxel mean $AUC_{(0\text{-}inf)}$ and C_{max} ranged from 8867 to 14361 ng*hr/ml and from 3488 to 8078 ng/ml, respectively.

Dose normalized peak drug exposure values were comparable across the dose range studied; however,

dose-normalized total drug exposure values were only comparable across 120 mg/m^2 to 240 mg/m^2; with lower dose-normalized AUC_∞ at the 270 mg/m^2 dose level. At the MTD of 240 mg/m^2, the mean CL was 19.1 L/h and the mean terminal half-life was 13.5 hours.

In children and adolescent patients, exposure to paclitaxel increased with higher dosing and weekly drug exposures were higher than in adult patients.

Other intrinsic factors

Population pharmacokinetic analyses for human serum albumin-paclitaxel nanoparticles indicate that gender, race (Asian vs. White), and type of solid tumours do not have a clinically important effect on systemic exposure (AUC and C_{max}) of paclitaxel. Patients weighing 50 kg had paclitaxel AUC approximately 25% lower than those weighing 75 kg. The clinical relevance of this finding is uncertain.

5.3 Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, based on the published literature, paclitaxel is a potentially carcinogenic and genotoxic agent at clinical doses, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel has been shown to be genotoxic *in vivo* (micronucleus test in mice), but it did not induce mutagenicity in the Ames test or the Chinese hamster ovary/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) gene mutation assay.

Paclitaxel at doses below the human therapeutic dose was associated with low fertility when administered prior and during mating in male and female rats and foetal toxicity in rats. Animal studies with human serum albumin-paclitaxel nanoparticles showed non-reversible, toxic effects on the male reproductive organs at clinically relevant exposure levels.

Paclitaxel and/or its metabolites were excreted into the milk of lactating rats. Following intravenous administration of radiolabelled paclitaxel to rats on days 9 to 10 postpartum, concentrations of radioactivity in milk were higher than in plasma and declined in parallel with the plasma concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Albumin (human) (containing sodium caprylate and N-acetyl-L-tryptophan).

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 vials

3 years

Stability of reconstituted dispersion in the vial

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C in the original carton when protected from light.

Stability of the reconstituted dispersion in the infusion bag

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C when protected from light followed by 4 hours at 25°C, when not protected from light.

However, from a microbiological point of view, unless the method of reconstituting and filling of the infusion bags precludes the risks of microbial contamination, the product should be used immediately after reconstitution and filling of the infusion bags.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

The total combined storage time of reconstituted medicinal product in the vial and in the infusion bag when refrigerated and protected from light is 24 hours. This may be followed by storage in the infusion bag for 4 hours below 25°C.

6.4 Special precautions for storage

Unopened vials

Keep the vial in the outer carton in order to protect from light. Neither freezing nor refrigeration adversely affects the stability of the product. This medicinal product does not require any special temperature storage conditions.

Reconstituted dispersion

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

6.5 Nature and contents of container

50 ml vial (type 1 glass) with a stopper (bromobutyl rubber), with an overseal (aluminium), containing 100 mg of paclitaxel formulated as albumin bound nanoparticles.

Pack size of one vial.

6.6 Special precautions for disposal and other handling

Preparation and administration precautions

Paclitaxel is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Naveruclif. The use of gloves, goggles and protective clothing is recommended. If the dispersion 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. Naveruclif should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Naveruclif.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during administration of the medicinal product. Limiting the infusion of Naveruclif to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.

Reconstitution and administration of the product

Naveruclif is supplied as a sterile lyophilised powder for reconstitution before use. After reconstitution, each ml of dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

100 mg vial: Using a sterile syringe, 20 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion should slowly be injected into a vial of Naveruclif over a minimum of 1 minute.

The solution should be directed onto the inside wall of the vial. The solution should not be injected directly onto the powder as this will result in foaming.

Once the addition is complete, the vial should be allowed to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, the vial should gently and slowly be swirled and/or inverted for at least 2 minutes until complete redispersion of any powder occurs. The generation of foam must be avoided. If foaming or clumping occurs, the dispersion must stand for at least 15 minutes until foam subsides.

The reconstituted dispersion should be milky and homogenous without visible precipitates. Some settling of the reconstituted dispersion may occur. If precipitates or settling are visible, the vial should be gently inverted again to ensure complete redispersion prior to use.

Inspect the dispersion in the vial for particulate matter. Do not administer the reconstituted dispersion if particulate matter is observed in the vial.

The exact total dosing volume of 5 mg/ml dispersion required for the patient should be calculated and the appropriate amount of reconstituted Naveruclif should be injected into an empty, sterile, PVC or non-PVC type intravenous bag.

The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer Naveruclif may result in the formation of proteinaceous strands. Administer Naveruclif using an infusion set incorporating a 15 µm filter to avoid administration of these strands. Use of a 15 µm filter removes strands and does not change the physical or chemical properties of the reconstituted product.

Use of filters with a pore size less than 15 µm may result in blockage of the filter.

The use of specialized di(2-ethylhexyl)phthalate (DEHP)-free solution containers or administration sets is not necessary to prepare or administer Naveruclif infusions.

Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center
Moll de Barcelona, s/n
Edifici Est 6ª planta
08039 Barcelona
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1778/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 January 2024.

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

Accord Healthcare Polska Sp.z.o.o.
Ul. Lutomierska 50,
95-200, Pabianice, Poland

Laboratori Fundació Dau
C/ C, 12-14 Pol. Ind.
Zona Franca, Barcelona, 08040, Spain

Accord Healthcare Single Member S.A.,
64th Km National Road, Athens,
Lamia, Schimatari, 32009, Greece

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

Naveruclif 5 mg/ml powder for dispersion for infusion
paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles.

After reconstitution, each ml of dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

3. LIST OF EXCIPIENTS

Albumin (human) (containing sodium caprylate and N-acetyl-L-tryptophan).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for dispersion for infusion.

1 vial

100 mg/20 ml

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

Do not substitute with other paclitaxel formulations.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened vials: Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution, see package leaflet

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1778/001

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

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

MINIMUM PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Naveruclif 5 mg/ml powder for infusion
paclitaxel

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles.

After reconstitution, each ml of dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.

3. LIST OF EXCIPIENTS

Albumin (human) (containing sodium caprylate and N-acetyl-L-tryptophan).

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for infusion.

1 vial

100 mg/20 ml

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

Do not substitute with other paclitaxel formulations.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened vials: 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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
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08039 Barcelona,
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1778/001

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Naveruclif 5 mg/ml powder for dispersion 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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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 Naveruclif is and what it is used for
2. What you need to know before you are given Naveruclif
3. How to use Naveruclif
4. Possible side effects
5. How to store Naveruclif
6. Contents of the pack and other information

1. What Naveruclif is and what it is used for

Naveruclif contains, as its active substance, paclitaxel attached to the human protein albumin, in the form of tiny particles known as nanoparticles. Paclitaxel belongs to a group of medicines called "taxanes" used in cancer.
- Paclitaxel is the part of the medicine that affects the cancer, it works by stopping cancer cells from dividing – this means that they die.
- Albumin is the part of the medicine that helps paclitaxel dissolve in the blood and get across the walls of the blood vessels into the tumour. This means that other chemicals that can cause side effects that can be life threatening are not needed. Such side effects occur far less with Naveruclif.

What Naveruclif is used for
Naveruclif is used to treat the following types of cancer:

Breast Cancer
- Breast cancer which has spread to other parts of the body (this is called "metastatic" breast cancer).
- Naveruclif is used in metastatic breast cancer when at least one other therapy has been tried but has not worked and you are unsuitable for treatments containing a group of medicines called "anthracyclines".
- People with metastatic breast cancer who received Naveruclif where another therapy had failed, were more likely to experience a reduction in tumour size, and lived longer than people who took an alternative therapy.

Pancreatic Cancer
- Naveruclif is used together with a medicine called gemcitabine if you have metastatic cancer of the pancreas. People with metastatic pancreatic cancer (pancreatic cancer that has spread to other parts of the body) who received Naveruclif with gemcitabine in a clinical trial lived longer than people who had only received gemcitabine.

Lung Cancer

- Naveruclif is also used together with a medicine called carboplatin if you have the most common type of lung cancer, called “non-small cell lung cancer”.
- Naveruclif is used in non-small cell lung cancer where surgery or radiotherapy would not be suitable to treat the disease.

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

Do not use Naveruclif

- if you are allergic to Paclitaxel or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding
- if you have a low white blood cell count (baseline neutrophil counts <1500 cells/mm^3 - your doctor will advise you on this).

Warnings and precautions

Talk to your doctor or nurse before using Naveruclif

- if you have poor kidney function;
- if you have severe liver problems;
- if you have heart problems.

Talk to your doctor or nurse if you experience any of these conditions whilst being treated with Naveruclif, your doctor may wish to stop treatment or reduce the dose:

- if you experience any abnormal bruising, bleeding, or signs of infections such as a sore throat or a fever;
- if you experience numbness, tingling, pricking sensations, sensitivity to touch, or muscle weakness;
- if you experience breathing problems, like shortness of breath or dry cough.

Children and adolescents

Naveruclif is only for adults and should not be taken by children and adolescents aged below 18 years.

Other medicines and Naveruclif

Tell your doctor if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because Naveruclif can affect the way some other medicines work. Also, some other medicines can affect the way Naveruclif works.

Take care and speak to your doctor when taking Naveruclif at the same time as any of the following:

- medicines for treating infections (i.e. antibiotics such erythromycin, rifampicin, etc.; ask your doctor, nurse or pharmacist if you are unsure whether the medicine you are taking is an antibiotic), and including medicines for treating fungal infections (e.g. ketoconazole)
- medicines used to help you stabilize your mood also sometimes referred to as anti-depressants (e.g. fluoxetine)
- medicines used to treat seizures (epilepsy) (e.g. carbamazepine, phenytoin)
- medicines used to help you lower blood lipid levels (e.g. gemfibrozil)
- medicine used for heartburn or stomach ulcers (e.g. cimetidine)
- medicines used to treat HIV and AIDS (e.g. ritonavir, saquinavir, indinavir, nelfinavir, efavirenz, nevirapine)
- a medicine called clopidogrel used to prevent blood clots.

Pregnancy, breast-feeding and fertility
Paclitaxel may cause serious birth defects and should therefore not be used if you are pregnant. Your doctor will arrange a pregnancy test before starting treatment with Naveruclif.

Women of childbearing age should use effective contraception during and for at least 6 months after receiving treatment with Naveruclif.

Do not breast feed when taking Naveruclif as it is not known if the active ingredient paclitaxel passes into the mother's milk.

Male patients are advised to use effective contraception and to avoid fathering a child during and for at least 3 months after treatment and should seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with Naveruclif.

Ask your doctor for advice before taking this medicine.

Driving and using machines
Some people may feel tired or dizzy after being given Naveruclif. If this happens to you, do not drive or use any tools or machines.

If you are given other medicines as part of your treatment, you should ask your doctor for advice on driving and using machines.

Naveruclif contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg, that is to say essentially 'sodium free'.

3. How to use Naveruclif

Naveruclif will be given to you by a doctor or nurse into a vein from an intravenous drip. The dose you receive is based on your body surface area and blood test results. The usual dose is for breast cancer is 260 mg/m^2 of body surface area given over a 30 minute period. The usual dose for advanced pancreatic cancer is 125 mg/m^2 of body surface area given over a 30 minute period. The usual dose for non-small cell lung cancer is 100 mg/m^2 of body surface area given over a 30 minute period.

How often will you receive Naveruclif?
For treatment of metastatic breast cancer, Naveruclif is usually given once every three weeks (on day 1 of a 21-day cycle).

For treatment of advanced pancreatic cancer, Naveruclif is given on days 1, 8 and 15 of each 28-day treatment cycle with gemcitabine being given immediately after the Naveruclif.

For treatment of non-small cell lung cancer Naveruclif is given once every week (i.e. on days 1, 8 and 15 of a 21-day cycle), with carboplatin being given once every three weeks (i.e. only on day 1 of each 21-day cycle), immediately after the Naveruclif dose has been given.

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.

The very common side effects may affect more than 1 in 10 people:

- Loss of hair (the majority of cases of hair loss happened less than one month after starting Naveruclif. When it happens, hair loss is pronounced (over 50%) in the majority of patients)

- Rash
- Abnormal decrease in the number of types of white blood cells (neutrophils, lymphocytes or leukocytes) in the blood
- Deficiency of red blood cells
- Reduction in the number of platelets in the blood
- Effect on peripheral nerves (pain, numbness, tingling or loss of feeling)
- Pain in a joint or joints
- Pain in the muscles
- Nausea, diarrhoea, constipation, sore mouth, loss of appetite
- Vomiting
- Weakness and tiredness, fever
- Dehydration, taste disturbance, weight loss
- Low levels of potassium in the blood
- Depression, sleep problems
- Headache
- Chills
- Difficulty in breathing
- Dizziness
- Swelling of mucosal and soft tissues
- Increased liver function tests
- Pain in extremities
- Cough
- Abdominal pain
- Nose bleeds

The **common** side effects may affect up to 1 in 10 people:

- Itching, dry skin, nail disorder
- Infection, fever with decrease in the number of a type of white blood cell (neutrophils) in the blood, flushing, thrush, severe infection in your blood which may be caused by reduced white blood cells
- Reduction in all blood cell counts
- Chest or throat pain
- Indigestion, abdominal discomfort
- Stuffy nose
- Pain in back, bone pain
- Diminished muscular coordination or difficulty in reading, increased or decreased tears, loss of eyelashes
- Changes in heart rate or rhythm, heart failure
- Decreased or increased blood pressure
- Redness or swelling at the site where the needle entered the body
- Anxiety
- Infection in the lungs
- Infection in the urinary tract
- Obstruction in the gut, inflammation of the large bowel, inflammation of the bile duct
- Acute kidney failure
- Increased bilirubin in the blood
- Coughing up blood
- Dry mouth, difficulty in swallowing
- Muscle weakness
- Blurred vision

The **uncommon** side effects may affect up to 1 in 100 people:

- Increased weight, increased lactate dehydrogenase in the blood, decreased kidney function, increased blood sugar, increased phosphorus in the blood
- Decreased or lack of reflexes, involuntary movements, pain along a nerve, fainting, dizziness when standing up, shaking, facial nerve paralysis
- Irritated eyes, painful eyes, red eyes, itchy eyes, double vision, reduced vision, or seeing flashing lights, blurred vision due to swelling of the retina (cystoid macular oedema)
- Ear pain, ringing in your ears
- Coughing with phlegm, shortness of breath when walking or climbing stairs, runny nose, or dry nose, decreased breath sounds, water on the lung, loss of voice, blood clot in the lung, dry throat
- Gas, stomach cramps, painful or sore gums, rectal bleeding
- Painful urination, frequent urination, blood in the urine, inability to hold your urine
- Fingernail pain, fingernail discomfort, loss of fingernails, hives, skin pain, red skin from sunlight, skin discolouration, increased sweating, night sweats, white areas on the skin, sores, swollen face
- Decreased phosphorus in the blood, fluid retention, low albumin in the blood, increased thirst, decreased calcium in the blood, decreased sugar in the blood, decreased sodium in the blood
- Pain and swelling in the nose, skin infections, infection due to catheter line
- Bruising
- Pain at site of tumour, death of the tumour
- Decreased blood pressure when standing up, coldness in your hands and feet
- Difficulty walking, swelling
- Allergic reaction
- Decreased liver function, increased size of liver
- Pain in the breast
- Restlessness
- Small bleedings in your skin due to blood clots
- A condition involving destruction of red blood cells and acute kidney failure

The **rare** side effects may affect up to 1 in 1,000 people:

- Skin reaction to another agent or lung inflammation following radiation
- Blood clot
- Very slow pulse, heart attack
- Leaking of drug outside the vein
- A disorder of the electrical conduction system of the heart (atrioventricular block)

The **very rare** side effects may affect up to 1 in 10,000 people:

- Severe inflammation/eruption of the skin and mucous membranes (Stevens-Johnson syndrome, toxic epidermal necrolysis)

Not known side effects (frequency cannot be estimated from the available data):

- Hardening/thickening of the skin (scleroderma)

Reporting of side effects
If you get any side effects, talk to your doctor 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 Naveruclif

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 carton and vial after EXP. The expiry date refers to the last day of that month.

Unopened vials: Keep the vial in the outer carton in order to protect from light.

After first reconstitution the dispersion should be used immediately. If not used immediately, the dispersion may be stored in a refrigerator (2°C-8°C) for up to 24 hours in the vial when kept in the outer carton in order to protect it from light.

The reconstituted dispersion in the intravenous drip may be stored in a refrigerator (2°C-8°C) for up to 24 hours protected from light.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C when protected from light followed by 4 hours at 25°C when not protected from light.

Your doctor or pharmacist is responsible for disposing of any unused Naveruclif correctly.

6. Contents of the pack and other information

What Naveruclif contains

- The active substance(s) is paclitaxel. Each vial contains 100 mg of paclitaxel formulated as albumin bound nanoparticles. After reconstitution, each ml of dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles.
- The other ingredient is albumin (human) (containing sodium caprylate and N-acetyl-L-tryptophan), see section 2 “Naveruclif contains sodium”.

What Naveruclif looks like and contents of the pack

Naveruclif is a white to yellow powder or lyophilized cake for dispersion for infusion. Naveruclif is available in glass vials containing 100 mg of paclitaxel formulated as albumin bound nanoparticles.

Each pack contains 1 vial.

Marketing Authorisation Holder and Manufacturer

Marketing Authorization Holder
Accord Healthcare S.L.U.
World Trade Center, Moll De Barcelona s/n,
Edifici Est, 6a Planta,
Barcelona, 08039,
Spain

Manufacturer
Accord Healthcare Polska Sp.z o.o.
ul. Lutomierska 50,
95-200 Pabianice, Poland

Or
Laboratori Fundació Dau
C/ C, 12-14 Pol. Ind.
Zona Franca, Barcelona, 08040,
Spain

Or

Accord Healthcare Single Member S.A.,
64th Km National Road, Athens,
Lamia, Schimatari, 32009, Greece

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT / BE / BG / CY / CZ / DE / DK / EE / ES / FI / FR / HR / HU / IE / IS / IT / LT / LV / LU / MT / NL / NO / PL / PT / RO / SE / SI / SK

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This leaflet was last revised in

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

Medical or healthcare professionals

The following information is intended for medical or healthcare professionals only:

Instructions for use, handling and disposal

Preparation and administration precautions
Paclitaxel is a cytotoxic anticancer medicinal product and, as with other potentially toxic compounds, caution should be exercised in handling Naveruclif. Gloves, goggles and protective clothing should be used. If Naveruclif dispersion contacts the skin, the skin should be washed immediately and thoroughly with soap and water. If Naveruclif contacts mucous membranes, the membranes should be flushed thoroughly with water. Naveruclif should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Naveruclif.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during administration of the medicinal product. Limiting the infusion of Naveruclif to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.

Reconstitution of the product and administration
Naveruclif should be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents.

Naveruclif is supplied as a sterile lyophilised powder for reconstitution before use. After reconstitution, each ml of dispersion contains 5 mg of paclitaxel formulated as albumin bound nanoparticles. Reconstituted Naveruclif dispersion is administered intravenously using an infusion set incorporating a 15 µm filter.

Using a sterile syringe, 20 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion should slowly be injected into a vial of Naveruclif over a minimum of 1 minute.

The solution should be directed onto the inside wall of the vial. The solution should not be injected directly onto the powder as this will result in foaming.

Once the addition is complete, the vial should be allowed to stand for a minimum of 5 minutes to ensure proper wetting of the solid. Then, the vial should gently and slowly be swirled and/or inverted for at least 2 minutes until complete redispersion of any powder occurs. The generation of foam must be avoided. If foaming or clumping occurs, the dispersion must stand for at least 15 minutes until foam subsides.

The reconstituted dispersion should be milky and homogenous without visible precipitates. Some settling of the reconstituted dispersion may occur. If precipitates or settling are visible, the vial should be gently inverted again to ensure complete redispersion prior to use.

Inspect the dispersion in the vial for particulate matter. Do not administer the reconstituted dispersion if particulate matter is observed in the vial.

The exact total dosing volume of 5 mg/ml dispersion required for the patient should be calculated and the appropriate amount of reconstituted Naveruclif should be injected into an empty, sterile, PVC or non-PVC type intravenous bag.

The use of medical devices containing silicone oil as a lubricant (i.e. syringes and IV bags) to reconstitute and administer Naveruclif may result in the formation of proteinaceous strands. Administer Naveruclif using an infusion set incorporating a 15 µm filter to avoid administration of these strands. Use of a 15 µm filter removes strands and does not change the physical or chemical properties of the reconstituted product.

Use of filters with a pore size less than 15 μm may result in blockage of the filter.

The use of specialized di(2-ethylhexyl)phthalate (DEHP)-free solution containers or administration sets is not necessary to prepare or administer Naveruclif infusions.

Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose.
Any unused product or waste material should be disposed of in accordance with local requirements.

Stability
Unopened vials of Naveruclif are stable until the date indicated on the package when the vial is kept in the outer carton in order to protect from light. Neither freezing nor refrigeration adversely affects the stability of the product. This medicinal product does not require any special temperature storage conditions.

Stability of the reconstituted dispersion in the vial
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C in the original carton, protected from light.

Stability of the reconstituted dispersion in the infusion bag
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C when protected from light followed by 4 hours at 25°C, when not protected from light.

However, from a microbiological point of view, unless the method of reconstituting and filling of the infusion bags precludes the risks of microbial contamination, the product should be used immediately after reconstitution and filling of the infusion bags.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

The total combined storage time of reconstituted medicinal product in the vial and in the infusion bag when refrigerated and protected from light is 24 hours. This may be followed by storage in the infusion bag for 4 hours below 25°C.