SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Paclitaxel Albumin Teva 5 mg/ml powder for suspension for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

After reconstitution, each ml of suspension 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 suspension for infusion.

The reconstituted dispersion has a pH of 6-7.5 and an osmolality of 300-360 mOsm/kg.

The powder is white to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Paclitaxel Albumin Teva 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).

4.2 Posology and method of administration

Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva 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. Paclitaxel Albumin Teva 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.

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 who 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 Paclitaxel Albumin Teva 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 human serum albumin-paclitaxel nanoparticles 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

Paclitaxel Albumin Teva is not indicated for children and adolescents under 18 years old.

The safety and efficacy of human serum albumin-paclitaxel nanoparticles in children and adolescents aged 0 to less than 18 years have not been established. 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

Paclitaxel Albumin Teva is for intravenous use. Administer reconstituted Paclitaxel Albumin Teva 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 <1500 cells/mm^3.

4.4 Special warnings and precautions for use

Paclitaxel Albumin Teva 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 human serum albumin-paclitaxel nanoparticles therapy. Patients should not be retreated with subsequent cycles of human serum albumin-paclitaxel nanoparticles 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 Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva is recommended (see section 4.2). For combination use of Paclitaxel Albumin Teva and gemcitabine, if Grade 3 or higher peripheral neuropathy develops, withhold Paclitaxel Albumin Teva; continue treatment with gemcitabine at the same dose. Resume Paclitaxel Albumin Teva at reduced dose when peripheral neuropathy improves to Grade 0 or 1 (see section 4.2). For combination use of Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva and gemcitabine until fever resolves and ANC ≥1500 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 were 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 Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva 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.

Paclitaxel Albumin Teva is not recommended in patients who have total bilirubin >5 x ULN or AST >10 x ULN.

In addition, Paclitaxel Albumin Teva is not recommended in patients with metastatic adenocarcinoma of the pancreas who have moderate to severe hepatic impairment (total bilirubin >1.5 x ULN and AST ≤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 Paclitaxel Albumin Teva 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 have 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 Paclitaxel Albumin Teva, 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, Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva in combination with gemcitabine with special consideration to performance status, co-morbidities and increased risk of infections (see sections 4.2 and 4.8).

Other

Although limited data are 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 Paclitaxel Albumin Teva 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 Interactions 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 human serum albumin-paclitaxel nanoparticles 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.

Paclitaxel Albumin Teva 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).

Paclitaxel Albumin Teva should not be used in combination with other anticancer agents.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Women of childbearing potential should use effective contraception during treatment and up to 1 month after receiving treatment with Paclitaxel Albumin Teva. Male patients treated with Paclitaxel Albumin Teva are advised to use effective contraception and to avoid fathering a child during and up to six months after treatment.

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 Paclitaxel Albumin Teva. Paclitaxel Albumin Teva 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, Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva.

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:	Sepsis[1], neutropenic sepsis[1], 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]		
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	Insomnia
Uncommon:	Restlessness		
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	VII[th] 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 block[1], bradycardia		
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, upper abdominal pain	Diarrhoea, vomiting, nausea, constipation
Common:	Gastrooesophageal reflux disease, dyspepsia, abdominal pain, abdominal distension, upper abdominal pain, 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, lower abdominal pain, 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 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		Skin exfoliation, dermatitis allergic, urticaria
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		
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 1310 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.

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 human 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) favored 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 human serum albumin-paclitaxel nanoparticles and gemcitabine until fever resolves and ANC ≥1500 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 etiology and upon making a diagnosis of pneumonitis, permanently discontinue treatment with human serum albumin-paclitaxel nanoparticles 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.

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.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" that appears on the homepage of the Ministry of Health's website (www.health.gov.il) which links to an online form for reporting side effects, or by following this link: https://sideeffects.health.gov.il

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.

Paclitaxel Albumin Teva contains human serum albumin-paclitaxel nanoparticles of approximately 130 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 was 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]

*These 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 was 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).

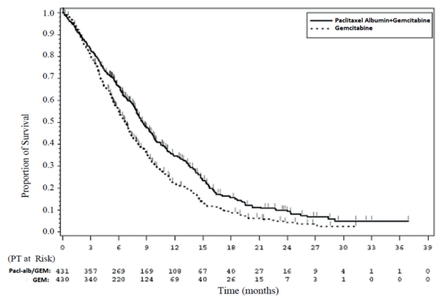
Table 9: Efficacy results from randomized study in patients with pancreatic adenocarcinoma (Intent-to-treat population)

	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-value[b]	<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 overall response, n (%)	**99** (23)	**31** (7)
95% CI	19.1, 27.2	5.0, 10.1
p_{A+G}/p_G (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}/p_G = 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 a 1.8 month 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 a 1.8 month 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 was 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

Paclitaxel Albumin Teva is not indicated for children and adolescents under 18 years old.

The safety and efficacy of human serum albumin-paclitaxel nanoparticles in children and adolescents aged 0 to less than 18 years have not been established. 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.

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 was 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, intrapatient 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 = 1) 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.

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)
Sodium caprylate
N-acetyl-DL-tryptophan
Sodium chloride
Hydrochloric acid
Sodium hydroxide

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

The expiry date of the product is indicated on the packaging materials.

Stability of reconstituted dispersion in the vial

Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8°C when the vial is in the original carton, and protected from bright light. Alternative light protection may be used in the clean room. From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the product should be filled into an infusion bag immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

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, protected from light followed by 4 hours at 15°C-25°C. From a microbiological point of view, unless the method of opening/reconstituting/dilution precludes the risks of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Unopened vials

Store below 25°C.
Keep the container in the outer carton in order to protect from light.
Neither freezing nor refrigeration adversely affects the stability of the product.

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 (butyl 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 Paclitaxel Albumin Teva. 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. Paclitaxel Albumin Teva should only be prepared and administered by personnel appropriately trained in the handling of cytotoxic agents. Pregnant staff should not handle Paclitaxel Albumin Teva.

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 Paclitaxel Albumin Teva to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.

Reconstitution and administration of the product

Paclitaxel Albumin Teva 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.

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 Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva may result in the formation of proteinaceous strands. Administer Paclitaxel Albumin Teva 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 Paclitaxel Albumin Teva 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. MANUFACTURER AND LICENCE HOLDER:

Teva Israel Ltd.,
124 Dvora HaNevi'a St., Tel Aviv 6944020

8. MARKETING AUTHORISATION NUMBER(S):

166.86.36321

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